



Cellular and molecular connections between sleep and synaptic plasticity

Joel H. Benington^{a,*}, Marcos G. Frank^{b,1}

^a Department of Biology, St. Bonaventure University, St. Bonaventure, NY 14778, USA

^b Department of Neuroscience, University of Pennsylvania School of Medicine, 215 Stemmler Hall, 35th Hamilton Walk, Philadelphia, PA 19104-6074, USA

Received 5 December 2002; accepted 7 February 2003

Abstract

The hypothesis that sleep promotes learning and memory has long been a subject of active investigation. This hypothesis implies that sleep must facilitate synaptic plasticity in some way, and recent studies have provided evidence for such a function. Our knowledge of both the cellular neurophysiology of sleep states and of the cellular and molecular mechanisms underlying synaptic plasticity has expanded considerably in recent years. In this article, we review findings in these areas and discuss possible mechanisms whereby the neurophysiological processes characteristic of sleep states may serve to facilitate synaptic plasticity. We address this issue first on the cellular level, considering how activation of T-type Ca²⁺ channels in nonREM sleep may promote either long-term depression or long-term potentiation, as well as how cellular events of REM sleep may influence these processes. We then consider how synchronization of neuronal activity in thalamocortical and hippocampal–neocortical networks in nonREM sleep and REM sleep could promote differential strengthening of synapses according to the degree to which activity in one neuron is synchronized with activity in other neurons in the network. Rather than advocating one specific cellular hypothesis, we have intentionally taken a broad approach, describing a range of possible mechanisms whereby sleep may facilitate synaptic plasticity on the cellular and/or network levels. We have also provided a general review of evidence for and against the hypothesis that sleep does indeed facilitate learning, memory, and synaptic plasticity.

© 2003 Elsevier Science Ltd. All rights reserved.

Contents

1. Introduction	72
2. The neurobiology of sleep and waking	72
3. Cellular and molecular mechanisms of synaptic plasticity	74
3.1. Long-term potentiation (LTP)	74
3.2. Long-term depression (LTD)	75
3.3. Spike-timing-dependent plasticity (STDP)	76
3.4. Retrograde signaling in synaptic plasticity	76
4. Evidence for a link between sleep and synaptic plasticity	77
4.1. Learning, memory, and sleep	78
4.1.1. Learning and REM-sleep augmentation	78
4.1.2. Sleep deprivation and learning	79

Abbreviations: AP, action potential; BDNF, brain-derived neurotrophic factor; CaM, Ca²⁺-calmodulin; CaMKII, CaM kinase II; CICR, Ca²⁺-induced Ca²⁺ release; CREB, cyclic AMP response element-binding protein; I_h, hyperpolarization-activated cation channel; IP₃/DAG, inositol-triphosphate/diacylglycerol; LGN, lateral geniculate nucleus; LTD, long-term depression; LTP, long-term potentiation; MD, monocular deprivation; mGlu, metabotropic glutamate receptor; NGF, nerve growth factor; NO, nitric oxide; nNOS, neuronal nitric oxide synthase; NonREM, non-rapid-eye-movement; P, postnatal day; PCR, polymerase chain reaction; PET, positron emission tomography; PGO, ponto-geniculo-occipital; PSP, postsynaptic potential; REM, rapid-eye-movement; RSD, REM-sleep deprivation; SD, sleep deprivation; SS–PS, transition from nonREM sleep to REM sleep; STDP, spike-timing-dependent plasticity; VGCCs, voltage-gated Ca²⁺ channels

* Corresponding author. Tel.: +1-716-375-2564; fax: +1-716-375-7618.

E-mail addresses: jbening@sbu.edu (J.H. Benington), mgf@mail.med.upenn.edu (M.G. Frank).

¹ Co-corresponding author. Tel.: +1-215-746-0388.

4.2. Neurochemical changes in sleep	80
4.2.1. Sleep and RNA/DNA synthesis	80
4.2.2. Sleep and gene expression	81
4.2.3. Sleep and protein synthesis	81
4.3. Reactivation of neuronal activity patterns in sleep	82
4.4. Sleep, sleep deprivation, and synaptic plasticity	83
4.5. Sleep and developmentally regulated synaptic plasticity	84
5. Facilitating synaptic plasticity on the cellular level	85
5.1. Ca ²⁺ influx in sleep and synaptic plasticity	85
5.2. T-type Ca ²⁺ channels and LTD	86
5.3. T-type Ca ²⁺ channels and LTP	87
5.4. Cellular events of REM sleep and synaptic plasticity	87
6. Facilitating synaptic plasticity on the network level	87
6.1. Synchronized neuronal activity in nonREM sleep	88
6.2. Synchronized neuronal activity in REM sleep	89
6.3. Network-level models of sleep and synaptic plasticity	89
6.3.1. Thalamocortical interactions	90
6.3.2. Hippocampal–neocortical interactions	90
6.3.2.1. Two-stage models of hippocampal functioning	91
6.4. General evaluation of network-level models	92
7. Summary and conclusions	92
7.1. Facilitation of synaptic plasticity as the primary function of sleep	93
7.2. Future directions	94
References	95

1. Introduction

Recent studies have rekindled interest in a possible link between sleep and synaptic plasticity. The idea that sleep may in some way facilitate synaptic plasticity has been proposed a number of times, and has long been supported by studies showing impaired consolidation of learned responses following sleep deprivation (SD), but only recently have there been findings suggesting such a connection on the cellular and network level. While these new findings are stimulating, less attention has been paid to the question of how the cellular and molecular events associated with sleep states could cause modulation of synaptic strength and the formation and elimination of synapses.

We begin by reviewing the cellular neurophysiology and network properties of sleep and waking, and current ideas regarding the cellular and molecular mechanisms of synaptic plasticity. We then discuss the evidence suggesting that sleep may indeed facilitate synaptic plasticity. These sections in turn provide a basis for considering possible ways in which neural events taking place in sleep may facilitate the cellular and molecular processes underlying synaptic plasticity. We present hypotheses for causal connections between sleep and synaptic plasticity first in terms of events taking place within single neurons, and then in terms of network interactions among neurons of the cerebral cortex and other brain regions. Our discussion of these matters is by design quite broad and speculative, as there is as yet little evidence that strongly supports one particular mechanism whereby sleep could facilitate synaptic plasticity,

and we therefore catalog the widest range of candidate mechanisms.

This article synthesizes material from a number of fields in neurobiology, each one of which comprises a considerable body of research work. To facilitate the reader's further investigation of these diverse fields, we have restricted citations of original research articles to those situations in which: (1) a specific point is being made for which there exist a manageable number of pertinent studies; (2) noteworthy research articles have been published since the most recent review of the subject; or (3) the material being reviewed is central to the hypotheses presented in this article. In all other cases, citations are to the best and most recent review articles so that readers may most efficiently explore in more depth the body of work in question.

2. The neurobiology of sleep and waking

Sleep in eutherian mammals comprises two distinct states, nonREM sleep and REM sleep, which alternate at fairly regular intervals throughout each sleep period (Carskadon and Dement, 2000). In most species, nonREM sleep makes up about 4/5 of total sleep time, and the interval between REM-sleep episodes varies as a function of brain size, from less than 10 min in mice to about 90 min in humans (Zepelin, 2000).

Neuronal activity in REM sleep is substantially similar to that seen in waking (Hobson and Steriade, 1986). Neocortical pyramidal neurons are tonically depolarized

(Hirsch et al., 1983), producing single action potentials at irregular intervals. The EEG consists of low-amplitude fast activity, indicating desynchronization of neuronal activity (Carskadon and Dement, 2000). In the hippocampus, neurons are also tonically depolarized, but as a result they produce synchronized rhythmic activity in the theta (4–8 Hz) frequency range (Buzsaki, 2002; Kahana et al., 2001; Steriade, 2000). This activity pattern is also seen during more active waking states, in rodents involving exploratory motor activity. REM sleep is further characterized by high levels of ponto-geniculo-occipital (PGO) waves in some species. These are caused by bursts of action potentials originating in specific pontine regions and propagating through the lateral geniculate nucleus to the occipital cortex and other brain regions (Calvo and Fernandez-Guardiola, 1984; Datta, 1997; Siegel, 2000).

In nonREM sleep, neocortical pyramidal neurons are less active and responsive than in waking or REM sleep, generally firing single action potentials or bursts at fairly regular intervals, with a long after-hyperpolarization following each depolarization (Steriade, 1999, 2000; Steriade et al., 1993a). The EEG consists of high amplitude waves in the delta (0.5–4 Hz) and sigma (7–14 Hz) frequency ranges, indicating synchronous bursts of neuronal activity at these frequencies, involving large populations of neurons in the cerebral cortex and other brain regions. Rhythmic neuronal activity in the delta frequency range appears to be intrinsic to neurons of the cerebral cortex and thalamus, as well as other brain regions (Steriade et al., 1993b). Generation and synchronization of sigma activity depends on a network involving the reticular nucleus of the thalamus, thalamocortical neurons in thalamic relay nuclei, and corticothalamic neurons, as well as intrinsic interneurons in both thalamus and cortex (Destexhe et al., 1999a; Steriade et al., 1987). Synchronized neuronal oscillations in the delta and sigma frequency ranges are in turn organized by a slower rhythm (<1 Hz) of depolarization followed by hyperpolarization, which appears to be generated in the cerebral cortex (Sanchez-Vives and McCormick, 2000; Steriade et al., 1993b).

Synchronous neuronal activity also occurs in the hippocampus during nonREM sleep, producing sharp waves at irregular intervals ($0.02\text{--}3\text{ s}^{-1}$), during which time a large fraction of hippocampal pyramidal neurons fire bursts of action potentials within a 40–120 ms window (Buzsaki, 1996). In association with these sharp waves, phase-locked oscillations of hippocampal interneurons produce brief 200 Hz ripples in hippocampal field potential recordings. Both sharp waves and ripples are also observed during quiescent waking in rodents.

These state-specific changes in neuronal response properties appear to be driven primarily by differential release of neuromodulators such as acetylcholine, norepinephrine, serotonin, and histamine (McCormick, 1992; McCormick and Bal, 1997). In waking, these neuromodulators are released at high levels, activating the inositol-triphosphate/diacylglycerol (IP_3/DAG) and cyclic AMP

second-messenger systems, thereby reducing neuronal K^+ , causing neurons to be tonically depolarized (Hirsch et al., 1983). In REM sleep, this same result is achieved by release of acetylcholine alone, as release of serotonin and norepinephrine in REM sleep is minimal (Aston-Jones and Bloom, 1981; Jacobs, 1986; Lydic et al., 1987; McGinty and Harper, 1976). In nonREM sleep, these neuromodulators are all released at relatively low levels, hence neurons are relatively hyperpolarized in this state.

The synchronized, rhythmic neuronal activity characteristic of nonREM sleep is produced largely by the coordinated opening of two types of ion channel: the T-type depolarization-activated Ca^{2+} channel and a hyperpolarization-activated cation channel (I_h) (McCormick and Bal, 1997; Steriade et al., 1993a). Action potentials occur during membrane depolarization, when T-type Ca^{2+} channels are activated. The resultant influx of Ca^{2+} activates SK K^+ channels (Sah and Louise Faber, 2002; Vergara et al., 1998), causing an after-hyperpolarization lasting hundreds of milliseconds following each burst. This after-hyperpolarization is critical to the maintenance of rhythmic neuronal activity, as T-type Ca^{2+} channels spontaneously inactivate and require membrane hyperpolarization to be de-inactivated (McCormick and Bal, 1997). In addition, I_h is activated during this period of hyperpolarization and facilitates a return to a depolarized potential, thus again activating the T-type Ca^{2+} channels. Rhythmic bursts of action potentials in populations of neurons in the cerebral cortex and thalamus are synchronized during the occurrence of sleep spindles through direct interconnections within the population, and through reciprocal projections with GABAergic neurons of the thalamic reticular nucleus (Steriade, 1999).

Acetylcholine released in waking and REM sleep blocks the above-described sequence of events because activation of the IP_3/DAG second-messenger system activates protein kinase C and Ca^{2+} -calmodulin-dependent protein kinases (CaM kinases), which phosphorylate various K^+ channels, including the Ca^{2+} -dependent SK channels (Schulman and Hyman, 1999). As a result, neurons are tonically depolarized, thus preventing de-inactivation of T-type Ca^{2+} channels and thereby suppressing rhythmic neuronal activity entirely (McCormick and Bal, 1997). Acetylcholine release during waking also causes I_h to be activated at more depolarized potentials (McCormick, 1992), further preventing the hyperpolarization needed for de-inactivation of T-type Ca^{2+} channels.

While all stages of nonREM sleep are associated with synchronized EEG waveforms and rhythmic neuronal activity, stages 3 and 4 differ from stage 2 in that delta activity predominates over sigma activity in the EEG. This is significant because EEG delta activity and the occurrence of stages 3 and 4 nonREM sleep are promoted by sleep loss (Borbely and Achermann, 2000), and may contribute to discharge of sleep propensity (Beersma et al., 1990; Brunner et al., 1990, 1993). If facilitating synaptic plasticity is an

important function of nonREM sleep then that function is likely to be homeostatically regulated (Benington, 2000), and is therefore likely to be linked to the increased EEG delta activity that is characteristic of homeostatic increases in sleep intensity. Thus, should the above-described patterns of neuronal activity characteristic of nonREM sleep be involved in facilitating synaptic plasticity, that process may be promoted more by synchronized activity in the delta frequency range than in the sigma frequency range.

3. Cellular and molecular mechanisms of synaptic plasticity

Synaptic plasticity consists of any changes in the synaptic connections between neurons, including strengthening and weakening of synapses, changes in the distribution of receptor proteins and postsynaptic signal transduction mechanisms, and even changes in the number and distribution of synapses formed between pairs of neurons. The nervous system is most plastic in early ontogenetic development, but synaptic plasticity continues throughout life and is the physical substrate of learning and long-term memory formation.

Synaptic plasticity largely occurs as a function of differential activity at synapses. The dominant conceptual model for activity-dependent synaptic plasticity is the Hebbian synapse. Hebb (1949) postulated that neural networks would have learning-related properties if only those synaptic inputs which contribute more significantly to activating the postsynaptic neuron were strengthened, while others were weakened. In other words, the occurrence of coincident release of transmitter by the presynaptic neuron and generation of an action potential in the postsynaptic neuron should contribute to strengthening the synapse, while presynaptic release of transmitter in the absence of a postsynaptic action potential should either have no effect on synaptic strength or should contribute to weakening the synapse.

In experimental preparations, synaptic responses can be either potentiated or depressed, depending on the pattern of stimulated neuronal activity and the chemical treatments used. Potentiation and depression are measured in terms of the size of the postsynaptic potential (PSP) induced in response to a constant presynaptic stimulus regimen (the test pulse). Experimentally induced potentiation and depression have been shown to last hours to weeks, and are therefore referred to as long-term potentiation (LTP) and long-term depression (LTD). Commonly used LTP and LTD protocols increase/decrease synaptic strength typically by about 40%. LTP and LTD have been most extensively studied *in vitro*, but they have both been produced *in vivo* as well. The relevance of these cellular phenomena to learning has been supported by an increasing number of studies in which genetic or pharmacological manipulations that affect LTP or LTD produce parallel changes in learning abilities in experimental animals (e.g. Miller and Mayford, 1999; Tang et al., 1999; Yin and Tully, 1996).

In the following sections, we will discuss each of these protocols in turn. LTP and LTD have been studied in the hippocampus, various neocortical areas, the cerebellum, and elsewhere. The essential properties of LTP and LTD and many of the underlying molecular mechanisms are substantially similar in different brain regions. In our discussion, we will emphasize the commonalities while identifying regional distinctions where appropriate. This discussion is largely restricted to forms of synaptic plasticity found in neocortical and hippocampal areas; cerebellar LTD shares many features with neocortical and hippocampal plasticity mechanisms but is also different in a number of ways. It has been the subject of a recent detailed review (Ito, 2001).

3.1. Long-term potentiation (LTP)

LTP was originally induced in the hippocampus, by stimulating axons of the perforant path and potentiating the PSPs in dentate gyrus neurons (Bliss and Lomo, 1973). The potentiation was found to be input-specific, in that stimulation of medial perforant path did not potentiate lateral perforant path PSPs, and vice versa (McNaughton et al., 1978). Because LTP stimulus protocols often involved high-frequency stimulation (up to 100 Hz), LTP was viewed with suspicion in some quarters, since the stimulus was so obviously unphysiological (Barnes, 1995). However, subsequent studies have demonstrated that LTP can be produced by low-frequency pairing of anterograde stimulation of an axonal input with retrograde stimulation of the axons of the postsynaptic CA1 neurons (Paulsen and Sejnowski, 2000). This demonstrated that the relevant event, even in the case of the original stimulus protocol, is the pairing of a PSP at a specific synapse with generation of an action potential (AP) in the postsynaptic neuron. It has since become clear that the relative timing of PSP and AP is critical (see Section 3.3).

The key molecular mechanism underlying LTP is activation of the NMDA glutamate receptor (Elgersma and Silva, 1999), a $\text{Na}^+/\text{Ca}^{2+}$ channel that is activated by glutamate only when the postsynaptic cell membrane is depolarized from resting potential. Consequently, Ca^{2+} influx through the NMDA receptor occurs only when a glutamate synapse is activated simultaneously with significant depolarization of the postsynaptic neuron. The resultant increase in $[\text{Ca}^{2+}]_i$ generates the postsynaptic responses that result in synaptic potentiation (see below).

In vertebrate neurons, the vast majority (90%) of synapses occur on dendritic spines, which are small outpocketings off the dendritic shaft (Hering and Sheng, 2001; Nimchinsky et al., 2002). Dendritic spines vary from one to several micrometers in length, and are typically no more than 1 μm wide, with a narrower neck where the spine connects to the dendritic shaft. Spines volume varies from ~ 0.01 to 1 μm^3 . Dendritic spines are highly labile in embryonic and early neonatal neurons (Dailey and Smith, 1996), and become more stable in adult tissue (Dunaevsky et al., 1999; Lendvai et al., 2000). But even in tissues slices derived from adult

brain, changes in spine size and configuration have been observed in response to stimulated activity.

Dendritic spines are thought to serve chiefly as small enclosed spaces providing a microenvironment within which $[Ca^{2+}]_i$ can locally reach high levels with a minimum of transmembrane Ca^{2+} flux (Hering and Sheng, 2001; Nimchinsky et al., 2002). Optical imaging of $[Ca^{2+}]_i$ has shown that levels are indeed higher in the dendritic spines than in the dendritic shaft, and increases in $[Ca^{2+}]_i$ resulting from activation of individual synapses are largely restricted to single dendritic spines (Sabatini et al., 2001; Yuste et al., 2000). Diffusion of Ca^{2+} from spine to shaft is thought to be attenuated by the narrowness of spine necks and the presence of Ca^{2+} buffers in the spine cytosol (Yuste et al., 2000).

The levels of $[Ca^{2+}]_i$ achieved as a result of synaptic activation are not entirely a result of direct Ca^{2+} influx through the NMDA receptor ion channel. In addition, voltage-gated Ca^{2+} channels (VGCCs) in dendritic spines and shafts open as a result of postsynaptic depolarization, further increasing $[Ca^{2+}]_i$ (Sabatini et al., 2001; Sjöstrom and Nelson, 2002; Yuste et al., 2000). These include: (1) high-voltage-activated R-type and L-type Ca^{2+} channels which open only in response to strong depolarization to above AP threshold; and (2) low-voltage-activated T-type Ca^{2+} channels which open transiently in response to smaller, subthreshold depolarization. These Ca^{2+} channel types are differentially distributed throughout the dendritic arbor (Magee and Johnston, 1995a,b). L-type Ca^{2+} channels predominate in the cell soma and proximal dendrites (within about 100 μ m of the cell soma). T-type and R-type Ca^{2+} channels predominate in more distal dendrites, more than 100 μ m from the cell soma. In dendritic spines, R-type Ca^{2+} channels appear to predominate in CA1 neurons in the hippocampus (Sabatini and Svoboda, 2000), while N-type, P/Q-type, and T-type channels are found in layer V neocortical pyramidal neurons (Schiller et al., 1998).

Increases in $[Ca^{2+}]_i$ may further be augmented by Ca^{2+} -induced release of Ca^{2+} from intracellular stores. Smooth endoplasmic reticulum is found in dendritic shafts and even some dendritic spines (Spacek and Harris, 1997), thus Ca^{2+} -induced Ca^{2+} release (CICR) can theoretically be specific to individual spines. The degree to which CICR contributes to stimulus-induced increases in $[Ca^{2+}]_i$ is still controversial, perhaps because the contribution varies among cell types and brain regions (Rizzuto, 2001; Svoboda and Mainen, 1999).

Increases in $[Ca^{2+}]_i$ cause potentiation of PSPs by activating protein kinases in the postsynaptic density. The most important protein kinase in this regard is Ca^{2+} -calmodulin-dependent protein kinase II (CaMKII) (Malenka and Nicoll, 1999; Soderling, 2000), which is activated by autophosphorylation in the presence of Ca^{2+} , and phosphorylates other proteins for as long as it itself remains phosphorylated (Fink and Meyer, 2002; Lisman et al., 2002). Other protein kinases are also thought to be

involved in the phosphorylation cascade associated with LTP, including MAP kinase, PI3 kinase, tyrosine kinases, protein kinase C, and CaM kinase IV (Sanes and Lichtman, 1999; Sheng and Kim, 2002).

Activation of these and possibly other protein kinases triggers a complex molecular response comprising both short-term and long-term mechanisms. Phosphorylation of AMPA glutamate receptors immediately increases Na^+ flux during synaptic activation, and insertion of additional AMPA receptors into the postsynaptic membrane further augments this effect (Barry and Ziff, 2002; Carroll et al., 2001; Lisman et al., 2002; Luscher and Frerking, 2001). The phosphorylation cascade also induces translation of particular mRNAs already resident in the vicinity of the postsynaptic density, resulting in immediate synthesis of a number of proteins including CaMKII (Job and Eberwine, 2001; Soderling, 2000). Phosphorylation of transcription factors such as cyclic AMP response element-binding protein (CREB) activates nuclear transcription of relevant genes and thus increases protein synthesis (Chawla et al., 1998; Silva et al., 1998; Yin and Tully, 1996). These newly synthesized proteins must then be transported to specific synapses targeted for potentiation, a process that may involve tagging of the relevant synapses (Frey and Morris, 1998). The targeted synthesis of new proteins in turn makes possible long-term changes in synapse size, shape, and number (Cohen-Cory, 2002). Further details of the response mechanisms thought to be involved in LTP can be found in the articles cited throughout this section.

3.2. Long-term depression (LTD)

Stimulation of neocortical and hippocampal presynaptic inputs at low frequency (1–5 Hz for several minutes) induces not LTP but LTD (Kemp and Bashir, 2001). The exact protocol for inducing maximal LTD differs according to the age of the animal and the brain region, but the capacity for LTD is present in adult tissue and in a wide variety of brain regions. The necessary condition for inducing LTD is activation of a specific synapse *without* generation of an AP in the postsynaptic neuron.

Two main classes of LTD have been identified, one dependent on activation of NMDA glutamate receptors and the other dependent on activation of metabotropic glutamate (mGlu) receptors (Cho and Bashir, 2002; Nicoll et al., 1998; Oliet et al., 1997). Both of these forms of LTD are Ca^{2+} -dependent, but the source of Ca^{2+} differs. In NMDA-dependent LTD, release of glutamate activates NMDA receptors, apparently triggering low levels of Ca^{2+} influx even when postsynaptic depolarization is below the threshold for AP generation (Kemp and Bashir, 2001). Activation of VGCCs also contributes to the levels of $[Ca^{2+}]_i$ associated with this form of LTD (Christie et al., 1997; Otani et al., 2002; Wang et al., 1997). Group II mGlu-dependent LTD has likewise been shown to depend on activation of T-type VGCCs (Oliet et al., 1997), as well

as inositol-triphosphate mediated release of intracellular Ca^{2+} (Otani et al., 2002).

The increases in $[\text{Ca}^{2+}]_i$ associated with LTD are both smaller and longer lasting than those associated with LTP (Cho et al., 2001; Cormier et al., 2001). It is currently hypothesized that LTD occurs when the $[\text{Ca}^{2+}]_i$ is in the high nanomolar range, while micromolar concentrations of Ca^{2+} produce LTP (Kemp and Bashir, 2001). Lower levels of $[\text{Ca}^{2+}]_i$ cause synaptic depression because at these concentrations Ca^{2+} predominantly activates protein phosphatases rather than protein kinases (Elgersma and Silva, 1999; Isaac, 2001; Moulton et al., 2002; Winder and Sweatt, 2001). As a result, phosphorylation of the proteins associated with the above-described postsynaptic molecular cascade (see Section 3.1) reduces their activity (van Dam et al., 2002), thus producing a molecular response that is equivalently complex to that of LTP but in the opposite direction, including, for example, internalization of AMPA glutamate receptors (Beattie et al., 2000; Snyder et al., 2001). And indeed, LTD-inducing stimulations applied immediately after LTP have been shown to reverse the LTP, a phenomenon referred to as depotentiation (Kemp and Bashir, 2001).

If the critical difference between LTP and LTD is indeed that smaller increases in $[\text{Ca}^{2+}]_i$ activate phosphatases, thereby producing LTD, then an involvement of T-type Ca^{2+} channels in LTD is reasonable. As noted in Section 2, these channels are activated transiently by small depolarizations of the neuronal membrane. They are therefore ideally suited to produce small increases in $[\text{Ca}^{2+}]_i$ in response to subthreshold depolarizations that occur when a synapse or group of excitatory synapses is activated, without thereby depolarizing the cell to the threshold for generating an action potential.

3.3. Spike-timing-dependent plasticity (STDP)

As noted in Section 3.1, LTP can be induced by pairing PSPs in specific synapses with generation of an AP in the postsynaptic neuron. To be effective, this pairing must occur within a narrow time window, with the AP occurring within 20 ms after the PSP. If, on the other hand, the AP occurs less than 20 ms before the PSP, LTD is induced instead (Magee and Johnston, 1997; Markram et al., 1997; Sjostrom and Nelson, 2002). This phenomenon, referred to as spike-timing-dependent plasticity (STDP) is consistent with the idea of a Hebbian synapse in that a PSP is only likely to contribute to generation of an AP when it occurs immediately before the AP (Bi and Poo, 2001). Occurrence of a PSP milliseconds after an AP instead indicates that the presynaptic neuron is not effectively synchronized with the circuits which are effective in triggering an AP in the postsynaptic neuron.

The phenomena of STDP are thought to be consequences of the nature of AP backpropagation through the dendritic arbor. According to one hypothesis, production of PSPs in dendrites briefly inactivates A-type voltage-gated K^+ chan-

nels (Hoffman et al., 1997). Before they are inactivated, these channels open in response to depolarization of the dendritic membrane, and the resultant efflux of K^+ attenuates the depolarization. The presence of activateable A-type K^+ channels in dendrites interferes with AP backpropagation both by reducing the magnitude of depolarization and by increasing membrane conductance. When, however, these channels are inactivated, AP backpropagation spreads more efficiently from the cell soma to the most distal dendrites. The duration of inactivation of A-type K^+ channels is roughly consistent with the duration of the time window within which an AP must occur following a PSP in order to induce LTD.

Optical imaging of $[\text{Ca}^{2+}]_i$ has shown that levels increase in individual dendritic spines in association with subthreshold PSPs (Kovalchuk et al., 2000; Mainen et al., 1999), while AP backpropagation causes more widespread increases in both spines and the dendritic shaft (Koester and Sakmann, 1998; Schiller et al., 1998). Increases in $[\text{Ca}^{2+}]_i$ caused by AP backpropagation are, however, higher in the dendritic spines than in the adjacent shaft (Koester and Sakmann, 1998), suggesting that the Ca^{2+} influx occurs largely as a result of VGCCs in the spines themselves (Sabatini and Svoboda, 2000; Schiller et al., 1998). When an AP follows immediately after a PSP, there is supralinear summation of the increases in $[\text{Ca}^{2+}]_i$, producing levels that are significantly higher than those produced by either stimulus alone (Koester and Sakmann, 1998). Occurrence of an AP immediately before a PSP, on the other hand, causes the PSP-induced increase in $[\text{Ca}^{2+}]_i$ to be attenuated. Thus, the phenomena associated with STDP are consistent with the above-described relationship between $[\text{Ca}^{2+}]_i$ and induction of LTP or LTD.

3.4. Retrograde signaling in synaptic plasticity

The above-described mechanisms of LTP, LTD, and STDP all involve changes in the postsynaptic neuron in response to coincidence or non-coincidence of PSPs and APs. There is, however, increasing evidence that changes to presynaptic nerve terminals also occur in association with synaptic plasticity. If these presynaptic changes are Hebbian, then the postsynaptic neuron must secrete some signaling molecule in response to coincidence or non-coincidence of PSPs and APs, which diffuses across the synaptic cleft and acts on the presynaptic terminal—a mechanism known as retrograde signaling. Given that synaptic vesicles are not observed in postsynaptic densities, retrograde signaling must involve molecules that are released by a non-vesicular mechanism. A number of such molecules have been identified, some of which have been shown to be involved in synaptic plasticity. More presumably await identification.

Nitric oxide (NO) is synthesized in neuronal postsynaptic densities, diffuses in all directions away from the site of synthesis, and readily crosses cell membranes. It is therefore not dependent on cell-surface receptor proteins, like most neurotransmitters, but instead acts directly on intracellular

molecules (Bogdan, 2001; Kiss and Vizi, 2001). Its actions in target cells are complex, being mediated through a number of NO-related free radicals, and acting on a variety of proteins, the full extent of which is presumably still unknown (Bogdan, 2001). Among the known target proteins are a number of transcription factors, and therefore NO release influences gene expression in nearby cells. NO has been implicated in mechanisms of synaptic plasticity, particularly during brain development (Bicker, 2001; Contestabile, 2000; Grassi and Pettorossi, 2001; Mize and Lo, 2000).

Given the freedom with which NO diffuses, its rate of release from a cell is a simple function of the rate at which it is synthesized. NO is synthesized from L-arginine by nitric oxide synthase. The neuronal form of this enzyme (nNOS) is activated by increases in $[Ca^{2+}]_i$ (Griffith and Stuehr, 1995), such as those mediated by NMDA glutamate receptors (Garthwaite and Boulton, 1995). nNOS is closely associated with NMDA receptors in the postsynaptic density because they are both attached to the postsynaptic density protein PSD95 (Brenman and Brecht, 1997). Thus, NO appears to be merely one more element of the molecular response mechanism associated with NMDA-mediated LTP.

Endocannabinoids are a family of molecules that are synthesized from membrane phospholipids (Ameri, 1999; Elphick and Egertova, 2001), and thus pass to the outside of the cell membrane without being packaged in vesicles. They act predominantly by binding to G-protein-coupled receptors in target cell membranes (Matsuda, 1997). CB1 endocannabinoid receptors have been identified in presynaptic terminals (Katona et al., 1999, 2001), enabling endocannabinoids to function as retrograde messengers (Ohno-Shosaku et al., 2001). Synthesis of endocannabinoids is driven by increases in $[Ca^{2+}]_i$ resulting from activation of NMDA and/or metabotropic glutamate receptors (Di Marzo et al., 1998).

Endocannabinoids have been implicated in both short-term and long-term synaptic plasticity. They appear to be largely responsible for mediating a phenomenon known as depolarization-induced suppression of inhibition, in which depolarization of a postsynaptic neuron inhibits further release of GABA from a presynaptic terminal (Kreitzer and Regehr, 2001; Wilson and Nicoll, 2001). Endocannabinoids have also recently been implicated in extinction of aversive memories (Marsicano et al., 2002) and in mediating presynaptic mechanisms of LTD (Gerdeman et al., 2002; Robbe et al., 2002). Given the dependence of endocannabinoid release on $[Ca^{2+}]_i$, this demonstration of the involvement of endocannabinoids in LTD may once again merely elaborate the molecular response mechanism associated with NMDA-mediated and/or metabotropic glutamate receptor-mediated LTD.

Neurotrophins comprise a group of molecules that are required for the establishment and maintenance of synaptic connections during brain development, and are also involved in synaptic plasticity in the adult brain (Lewin and Barde, 1996; Poo, 2001). The most thoroughly investigated neu-

rotrophins are nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT3). These molecules act on target cells by binding to tyrosine kinase (Trk) receptors and a pan-neurotrophin (p75) receptor (Barker and Shooter, 1994; Greene and Kaplan, 1995).

There is evidence that neurotrophins act in both an anterograde manner and a retrograde manner (Altar and DiStefano, 1998; Tao and Poo, 2001). Retrograde release is involved in the maintenance of synaptic connections, as postsynaptic neurons release neurotrophins, which then bind to receptors on the presynaptic nerve terminal (Heerssen and Segal, 2002). One mechanism of action involves internalization of a ligand–Trk receptor complex that is transported down the axon to the cell body, where the presence of this complex activates synthesis of proteins involved in maintaining synaptic connections (Watson et al., 1999). Release of neurotrophins by postsynaptic neurons is activity-dependent, and there is evidence that neurotrophin release plays a permissive role in LTP (Schinder and Poo, 2000).

The retrograde actions of NO, endocannabinoids, and neurotrophins have been reviewed because these molecules have attracted attention as mediators of synaptic plasticity. In the case of NO and endocannabinoids, the role of postsynaptic $[Ca^{2+}]_i$ in triggering release suggests that these molecules are components of the molecular response mechanism associated with NMDA receptor-mediated LTP. Since NMDA receptor-mediated increases in $[Ca^{2+}]_i$ are currently the only known mechanism for signaling coincidence between presynaptic and postsynaptic activation, it has been suggested that the activity-dependent release of neurotrophins is similarly Ca^{2+} -dependent (Poo, 2001), although it should be noted that other as-yet-undescribed mechanisms for signaling coincidence may exist. In support of that possibility, a form of LTP observed in mossy fiber synapses in the hippocampus exhibits a weak dependence on postsynaptic membrane potential, and yet is independent of postsynaptic $[Ca^{2+}]_i$ (Zalutsky and Nicoll, 1990).

A number of recent studies have suggested that presynaptic mechanisms are involved in LTP (Antonova et al., 2001; Arancio et al., 2001; Castillo et al., 2002; Eder et al., 2002; Zakharenko et al., 2001) and group I mGlu receptor-mediated LTD (Faas et al., 2002; Fitzjohn et al., 2001; Watabe et al., 2002; Zakharenko et al., 2002). In only one of these studies has it been suggested that the effects are independent of postsynaptic $[Ca^{2+}]_i$ (Fitzjohn et al., 2001), and so these findings are largely consistent with the idea that retrograde mechanisms are merely part of the above-described Ca^{2+} -dependent molecular response cascade.

4. Evidence for a link between sleep and synaptic plasticity

There are several categories of experiments suggesting a role for sleep in synaptic plasticity. These include findings

suggesting that: (1) learning procedures, which presumably promote synaptic plasticity, alter subsequent sleep; (2) sleep enhances or sleep loss diminishes processes such as learning and memory that entail synaptic plasticity; (3) synthesis of genes and proteins required for synaptic plasticity actually takes place in sleep; and (4) sleep and sleep loss modify synaptic strengths and patterns of synaptic connectivity. Our review of these experiments focuses primarily on results in experimental animals, since mechanisms of synaptic plasticity have best been described in these species.

4.1. Learning, memory, and sleep

The idea that sleep somehow reorganizes or consolidates memories acquired during waking has been hotly debated by researchers for many years (Block et al., 1981; Ellman et al., 1991; Fishbein and Gutwein, 1981; Hobson and Stickgold, 1995; Horne, 2000; Maquet, 2001; Siegel, 2001; Stickgold et al., 2001; Vertes and Eastman, 2000). Beginning in the 1970s, a large number of studies (primarily in rodents) suggested a positive effect of sleep on learning and memory (Fishbein and Gutwein, 1981; Hennevin et al., 1995; Pearlman, 1981). Undoubtedly influenced by the perceived association between REM sleep and dreaming popular at the time, the majority of these investigations focused on REM sleep. Findings from these studies can be generally organized into two broad categories that are most germane to post-learning synaptic plasticity. First, sleep amounts—in particular REM sleep—are reported to increase following a learning task, or exposure to “enriched” environments known to trigger synaptic remodeling. Second, SD following a learning task, particularly during periods when augmented REM sleep is predicted to occur, impairs task acquisition.

4.1.1. Learning and REM-sleep augmentation

Following Lucero's initial demonstration of increased REM sleep after maze learning in the rat (Lucero, 1970), a number of investigators have reported REM-sleep augmentation in animals following a variety of learning or exposure to enriched environments tasks (Block et al., 1981; Fishbein and Gutwein, 1981; Hennevin et al., 1995; Pearlman, 1981; Smith, 1985, 1995). Hennevin and colleagues reported post-learning increases in REM sleep in rats and cats following both massed and distributed learning, in negatively reinforced (aversive stimuli paired with incorrect choice) and positively reinforced (reward paired with correct choice) tasks, indicating a general effect of learning demands on subsequent REM sleep. The post-learning increase in REM sleep appeared to be associated with task acquisition, as it was no longer observed once the task was mastered. Increases in REM sleep also appear to be triggered by ‘challenging’ tasks, since simple learning paradigms generally failed to induce REM-sleep augmentation (Hennevin et al., 1995). Many of these findings have been replicated in the rat and mouse by other investigators (Pearlman, 1981;

Smith, 1985, 1995). More recently, Datta (2000) reported increases in REM sleep and nonREM–REM transitional states following conditioned avoidance learning in the rat. Interestingly, task acquisition was positively correlated with the number of PGO waves occurring in both REM and nonREM–REM transitional sleep, suggesting that the putative beneficial effects of REM sleep on mnemonic processes may depend more on changes in REM-sleep phasic events than on absolute REM-sleep amounts.

There is less consensus, however, regarding the timing of post-learning REM-sleep augmentation. Hennevin reported that the increases in REM sleep were most acute in the first 90 min following a learning task. Other investigators, however, have reported more prolonged post-learning enhancements of REM sleep in mice and rats (Block et al., 1981; Hennevin et al., 1995; Smith, 1985, 1995). Smith, for example, reported 4 h ‘windows’ of REM-sleep augmentation occurring as much as 17–20 h after a learning task (Smith, 1985, 1995). Indeed, precisely when REM-sleep windows occur has varied dramatically depending on the strain of rat, the type of learning task, and whether a massed or distributed learning protocol has been used (Smith, 1985, 1995).

To a lesser extent, rodent studies have also shown changes in nonREM-sleep amounts and architecture following exposure to enriched environments (Smith, 1985, 1995) or learning tasks, in some cases coincident with increases in REM sleep (Giuditta et al., 1995; Horne, 2000; Piscopo et al., 2001). Rats trained on a two-way active avoidance task displayed longer episodes of nonREM sleep, particularly those episodes that contained a subsequent transition to REM sleep (‘SS–PS’: slow-wave sleep to paradoxical sleep), in the post-learning period. This effect was most pronounced in rats that quickly learned the task, although it was also observed to a lesser degree (and occurred at slightly different times) in ‘non-learning’ rats (Ambrosini et al., 1992; Giuditta et al., 1995). The increases in SS–PS episodes were positively correlated with task acquisition in the learning rats (Langella et al., 1992). These increases in SS–PS episodes, and their correlation with task acquisition, were more pronounced at certain times than others, in a manner reminiscent of the REM-sleep windows reported by Smith (1985, 1995). Subsequent studies by these investigators showed that transitional sleep states also correlated with task acquisition (Mandile et al., 2000), which is in general agreement with the results of other investigators (Datta, 2000; Schiffelholz and Aldenhoff, 2002).

Some studies have shown similar augmentation in sleep amounts or sleep architecture in humans following learning tasks, although in general these effects tend to be more variable and smaller in size than those reported in animals. For example, increases in REM-sleep amounts and REM density have been reported following learning in several human studies (Peigneux et al., 2001). Evidence for REM-sleep windows in humans is less commonly reported, but studies from two different laboratories have shown similar REM-sleep enhancements within a single night and across several nights

following learning tasks (Smith and Rose, 2000; Stickgold, 1998). Changes in nonREM sleep, however, are less frequently reported in humans. Positive correlations between the number of nonREM–REM sleep cycles and memorization of word lists are reported by Mazzoni (Mazzoni et al., 1999). Maze learning has been shown to increase stage 2 sleep and EEG spindles in subsequent sleep (reviewed in Peigneux et al., 2001), and similar increases in EEG spindles are reported following memorization of word lists (Gais et al., 2002) and are positively correlated with memory performance. Interestingly, stage 2 nonREM sleep, which is particularly rich in EEG spindles, is reported to be positively correlated with the acquisition of a motor skill (Walker et al., 2002). Fischer et al. (2002), however, using a similar motor skill learning task, found performance positively correlated with REM sleep time.

While the effects of learning on sleep are intriguing, a number of caveats are worth considering. First, as pointed out by several investigators, the learning environment may be stressful, especially in cases of aversive-conditioning, and stress has been shown to increase sleep amounts (Horne, 2000; Siegel, 2001). This appears to be a potential confound in some of the earlier studies, but more recent findings are not so easily explained in terms of stress. For example, Hennevin and colleagues reported that the increases in REM sleep in learning rats were not found in non-learning rats exposed to similar environmental stimuli (pseudo-conditioned), suggesting that non-specific effects of the learning task (stress, motor activity) were unrelated to REM-sleep augmentation (Hennevin et al., 1995; Smith, 1995). Similar findings were reported by Datta (2000), who found that pseudo-conditioned animals receiving the same number of aversive stimuli as conditioned animals did not display similar changes in PGO-wave activity. Nor does stress appear to be an important factor in human studies, where in general small amounts of SD and benign tasks have been used.

A second issue is whether the reported correlation between learning and subsequent change in sleep reflects a functionally important link between the two events. In the case of REM-sleep enhancements, for example, heightened cholinergic activity in some rat strains might lead to increased learning ability and heightened REM sleep, without the augmentation in post-learning REM sleep being in any way involved in consolidating learning. This alternative explanation would explain the strain-dependencies in REM-sleep windows, and the observation that baseline REM-sleep time is positively correlated with learning ability in specific inbred lines of mice (Pagel et al., 1973). A co-segregation of functionally unrelated behaviors may also account for other changes in sleep architecture observed after learning. For example, the specific sleep sequences shown to correlate with learning are observed in post-learning *and* baseline sleep, suggesting that changes in post-acquisition sleep reflect innate patterns of sleep architecture that co-segregate, but are not necessarily func-

tionally related, with more rapid task acquisition (Mandile et al., 2000; Vescia et al., 1996).

4.1.2. Sleep deprivation and learning

A more direct approach to establishing a role for sleep in mnemonic processes is to deprive animals of sleep following a learning task. If sleep is necessary for memory consolidation, then learning should be impaired in sleep-deprived animals. In fact, with a few notable exceptions (Gisquet-Verrier and Smith, 1989; Smith, 1996), SD appears to profoundly interfere with learning and memory consolidation in mice and rats, with the greatest effects reported in ‘demanding’ learning tasks that presumably require more complex cognitive processing (Block et al., 1981; Pearlman, 1981; Smith, 1985, 1995). A large, but somewhat less consistent, body of findings suggests that SD can also impair human learning and memory (Peigneux et al., 2001).

To what extent sleep loss per se accounts for the reported learning deficits has been, and continues to be, fiercely debated (Fishbein, 2000; Maquet, 2001; Siegel, 2001; Stickgold et al., 2001; Vertes and Eastman, 2000). For example, the above studies are often criticized because controls for the secondary effects of SD or training, the specificity of the effect (e.g. REM sleep versus nonREM sleep) and additional factors (circadian effects, time-dependent versus sleep-dependent processes) are not always incorporated in the experimental design (Horne, 2000; Siegel, 2001; Vertes and Eastman, 2000). In addition, the effects of sleep on learning are highly task-dependent, and vary considerably within and across animal species (Peigneux et al., 2001; Smith, 1985, 1995). Nor is it yet clear what sorts of memories are specifically accessed and/or possibly consolidated in REM sleep and nonREM sleep (Peigneux et al., 2001; Siegel, 2001); a problem only compounded by the difficulty in generalizing learning/memory tasks across animals and humans.

The chief criticism of the animal studies is that SD is stressful, and stress has dramatic effects on learning and synaptic plasticity. The technique commonly used to deprive animals of REM sleep (the ‘pedestal’ or ‘flower-pot’ technique) involves placing the animal on an elevated platform over a pan of water. While on the pedestal, the animals are able to obtain nonREM sleep, but REM sleep is suppressed, since at onset of REM-sleep atonia, the animal contacts the water. Other techniques of SD, such as gentle handling or forced locomotion are also associated with increases in glucocorticoid release (Tobler et al., 1983).

A second concern is that the observed deficits in learning tasks following SD may merely reflect deficits in performance at re-test due to fatigue, depressed motivation or a state-dependent failure to recall material learned in one state (REM-sleep-deprived) while in another (post-deprived) (Horne, 2000; Siegel, 2001; Vertes and Eastman, 2000). Indeed, as reviewed by Coenan (2000), studies using more innocuous methods of SD fail to show sleep-deprivation-related deficits in learning and memory,

and in some cases strong state-dependency of learning and retrieval/recall at re-test was reported in sleep-deprived animals (Siegel, 2001).

In response to this criticism, investigators have attempted to control for the non-specific effects of SD in their experiments. Pearlman (1981) reported that simply immersing rodents in cold water (following a learning task) did not produce the deficits in learning obtained from selective REM-sleep deprivation (RSD). In subsequent studies, Pearlman was able to separate performance and state-dependent factors by using shorter periods of RSD, spaced at various times distant from the learning task (an extinction paradigm following bar-press learning in the rat). Presumably, if the reported deficits in learning following SD were due to non-specific effects on performance or retrieval, then they should be most acute when the SD is closer to re-test. Pearlman reported that 5 h of RSD immediately after training impaired learning to levels seen after three days of RSD. However, rats allowed to sleep for 5 h before the RSD showed no impairments at re-test. In other experiments, the deficits in learning did not appear to be due to state-dependent differences at test and re-test, since RSD during the extinction phase of the experiment did not restore normal performance.

The former results from these studies are consistent with results from Smith, who found that RSD during 4 h REM-sleep windows, but not during other times, impaired learning. This was true even when the total amount of RSD in animals deprived at times other than the REM-sleep window exceeded the 4 h of RSD during the window (Smith, 1995; Smith and Rose, 2000). These effects were unlikely due to performance deficits at re-test since the effects were noted several days after the RSD, which would seem to provide ample time for the secondary effects (fatigue, motivation) to subside. Fishbein (2000) has also reported that, in contrast to the findings cited by Coenan (2000), more benign forms of SD still result in learning deficits or changes in memory processing that are independent of performance confounds at re-test. Recent preliminary findings from La Hoste et al. (2002), indicate that sleep-deprivation-induced stress is not related to Morris water maze learning in the rat. In this study, investigators controlled stress hormone release using adrenalectomy combined with corticosterone pellet implantation. The pelleted rats showed learning deficits following SD, despite the total absence of increases in stress-hormone release.

In contrast to studies in animals, stress appears to be an unlikely factor in human studies employing SD. With the exception of some early studies that used prolonged SD, the majority of recent studies use small amounts of SD that are unlikely to produce large amounts of stress (Gais et al., 2000; Kami et al., 1994; Stickgold et al., 2000). In addition, as opposed to rodents, motivational and emotional factors are more easily assessed and controlled in humans. A more salient and unresolved issue in the human literature is determining the precise role of each sleep state in

different forms of memory processing. Disruption of either REM sleep or nonREM sleep can impair learning of both declarative and non-declarative tasks (Peigneux et al., 2001; Stickgold, 1998; Stickgold et al., 2001), but the exact contribution of each state to each form of learning is not yet clear. For example, REM-sleep disruption across a night of sleep has been reported to impair non-declarative learning (Karni et al., 1994), but similar results have been reported following 'early' SD, which primarily reduces nonREM sleep (Gais et al., 2000). Contradictory findings are also reported for non-declarative motor skill learning, with some investigators finding positive correlations between performance and stage 2 nonREM sleep (Walker et al., 2002), while others find similar correlations only with REM sleep (Fischer et al., 2002). Other findings in human indicate that stage 2 nonREM sleep, nonREM and REM sleep, or the number of nonREM-REM cycles participate in non-declarative and declarative learning, respectively (Peigneux et al., 2001). A second troubling finding from the human literature is the apparent absence of cognitive deficits in individuals who, either through medication, or brain lesions, have no or little REM sleep (reviewed in (Siegel, 2001; Vertes and Eastman, 2000)). In response to this criticism, other investigators have pointed out these individuals have rarely been tested in learning tasks that appear to be primarily REM-sleep dependent (Stickgold et al., 2001); an argument that is somewhat undermined by the contradictory findings described above.

4.2. Neurochemical changes in sleep

Sleep may also contribute to synaptic plasticity by promoting the synthesis of biomolecules necessary for the consolidation of waking experience. Although sleep is generally associated with decreases in neurotransmitters known to promote plasticity, it is possible that neurohumoral factors important for synaptic reorganization are preferentially released during sleep (Krueger and Obal, 2002). As suggested by Buzsaki (1996), the transient elevations of neuronal Ca^{2+} concentrations typical of nonREM sleep may trigger the transcription of genes important for synaptic remodeling. In other tissues, sleep is associated with the release of growth factors that trigger growth and gene expression (Cauter and Spiegel, 1999). To what extent sleep exerts similar effects on the brain is unknown, but we consider this possibility in the following sections.

4.2.1. Sleep and RNA/DNA synthesis

A possible role for sleep in the synthesis of biomolecules important for synaptic plasticity was initially investigated by studying the synthesis of DNA and RNA during different vigilance states or after SD (Ambrosini et al., 1988; Balestrieri et al., 1980; Giuditta et al., 1980a,b, 1985; Vitale-Neugebauer et al., 1970). Estimates of DNA and RNA synthesis were based on measurements of the turnover of radioactive elements incorporated into nuclear or cytoplasmic

nucleotides. Studies in rabbits showed positive correlations between RNA synthesis in purified nuclear fractions of neocortical neurons and EEG synchronization during sleep. The increase in RNA synthesis was observed in the large, nuclear portion of the fractions, indicating that the sleep effects were restricted to neurons and astroglia, but the relative contribution of each cell type could not be determined (Giuditta et al., 1980a). Further investigations in the neuronal fractions showed that the positive correlations between EEG synchronization and RNA synthesis were primarily restricted to the nucleus of the cell (Giuditta et al., 1980b).

Less consistent findings were reported in studies investigating the relationship between DNA synthesis, SD, and post-learning sleep amounts. In one study using shuttle-box avoidance training, post-learning REM-sleep amounts were negatively associated with DNA synthesis (primarily in the cerebellum and brainstem) in *non-learning* rats (Giuditta et al., 1985). These studies were extended in a series of investigations that examined the effects of sleep, total SD (via amphetamine), or selective REM SD (via clomipramine) on DNA synthesis during two-way active avoidance learning (Ambrosini et al., 1988). Although a number of significant correlations were reported between DNA metabolism and certain sleep parameters, the investigators were unable to replicate their earlier results in non-learning rats.

While intriguing, the interpretation of these studies is less than straightforward. The presence of increased RNA following sleep does not a priori indicate a sleep-dependent increase in substances involved in synaptic remodeling since the identity of the mRNA transcripts is unknown. The post-hoc treatments of the data, though exhaustive, generally do not reveal clear connections between sleep and DNA/RNA metabolism. Moreover, the use of aversive conditioning indicates that stress may account for some of the purported sleep effects in non-learning rats because these animals receive more aversive stimuli than learning animals. The interpretation of the Ambrosini et al. (1988) data are further complicated by the use of pharmacological agents that may directly impact DNA/RNA metabolism. Nevertheless, these studies are noteworthy because they represent some of the first attempts to link sleep to molecular changes in the brain.

4.2.2. Sleep and gene expression

More recent investigations have used modern molecular techniques, such as polymerase chain reaction (PCR), in situ hybridization, and microarray technology, to investigate a role for sleep in the synthesis of substances important for synaptic plasticity. Studies using a combination of mRNA differential display and cDNA microarrays have shown that many genes known to influence synaptic plasticity are up-regulated by wakefulness or SD and down-regulated by sleep (Cirelli, 2002; Tononi and Cirelli, 2001a,b). These include genes for subunits of the AMPA and NMDA glutamate receptors, two protein kinases, calmodulin, BDNF, the TrkB receptor, and others (Cirelli and Tononi, 1998b,

2000a,b). Similar results have been reported in studies using in situ hybridization (Pompeiano et al., 1997) and RT-PCR and PCR techniques (Taishi et al., 2001). The expression of many of these plasticity-related genes is mediated by norepinephrine, which is released at its lowest levels during sleep (Cirelli and Tononi, 2000a). Moreover, the phosphorylated form of the CREB transcription factor protein is present at higher levels after periods of waking than periods of sleep (Cirelli and Tononi, 2000a), as are general levels of protein phosphorylation at serine and threonine residues (Cirelli and Tononi, 1998a). Based on these results, some investigators have concluded that sleep does not promote synaptic remodeling (Tononi and Cirelli, 2001b).

Other findings, however, suggest that under certain conditions sleep can promote the expression of genes important in plasticity. While the majority of transcripts are up-regulated by waking, a small fraction are up-regulated by sleep (Cirelli and Tononi, 2000a). The function of these mRNAs is unknown, but it is plausible that some of them may influence synaptic plasticity. For example, Taishi et al. (2001) reported that warm ambient temperatures known to increase sleep in the rodent increased expression in hippocampus and cerebral cortex of the plasticity-related gene *MMP-9*. Although vigilance states were not directly assessed in this study, the up-regulation of *MMP-9* mRNAs appeared to require sleep, since its expression was decreased by gentle handling. A REM-sleep-dependent activation of *zif-268* has been reported in rats following exposure to enriched environments, and following hippocampal LTP (Ribeiro et al., 2002). Interestingly, the expression of *zif-268* in the latter study was observed in several extrahippocampal areas, suggesting a progressive activation of this gene along the hippocampal–neocortical network during REM sleep. Thus, it is possible that while basal expression of plasticity-related genes predominantly occurs during wakefulness, a more restricted up-regulation of these genes may occur during sleep in circuits undergoing synaptic remodeling.

4.2.3. Sleep and protein synthesis

In addition to influencing gene transcription, sleep may also promote the translation of these genes into their active proteins. This was initially investigated by measuring the incorporation of radioactive amino acids into newly formed proteins during REM SD (Bobillier et al., 1971; Shapiro and Girdwood, 1981). The results of these studies were somewhat contradictory, with Bobillier et al. reporting that REM SD had no effects on in vitro protein synthesis, while Shapiro and Girdwood using a similar REM SD paradigm found small decreases in in vivo protein synthesis, chiefly in the cerebellum. Further studies in rodents and monkeys demonstrated positive correlations between cerebral protein synthesis and nonREM sleep (Nakanishi et al., 1997; Ramm and Smith, 1990).

Several findings indicate that some proteins synthesized during sleep can influence synaptic plasticity. Neurogranin is a member of the calpactin protein family, and through its

interactions with Ca^{2+} and calmodulin is thought to modulate synaptic plasticity (Gerendasy, 1999; Gerendasy and Sutcliffe, 1997). Dendrin, like neurogranin, is densely concentrated in dendrites in neocortical and hippocampal neurons. While the function of dendrin is unknown, its close association with postsynaptic densities in dendritic spines strongly suggests an important role for dendrin in synaptic plasticity (Neuner-Jehle et al., 1996). A sleep-dependent increase in the synthesis of these proteins has not been demonstrated conclusively, but is suggested by findings that 24 h sleep deprivation reduces neurogranin and dendrin proteins in the cerebral cortex (Neuner-Jehle et al., 1995, 1996).

Sleep loss has also been reported to affect concentrations of the neurotrophins NGF and BDNF (Brandt et al., 2001; Sei et al., 2000). In one study, 6 h total SD combined with whisker trim in the rodent (a stimulus for synaptic remodeling in sensory cortex) had differential effects on NGF expression in neocortical neurons. NGF expression was up-regulated in the hemisphere receiving input from the intact whiskers, but was unchanged (relative to basal levels) in the hemisphere receiving input from the cut whiskers. The interpretation of these findings is difficult, but they do suggest an interaction between sleep, synaptic remodeling and NGF expression (Brandt et al., 2001). A specific role for REM sleep in the synthesis of neurotrophins was reported by Sei et al. (2000). In this study, 6 h of REM SD (using gentle handling) reduced BDNF protein in the cerebellum and brainstem, and decreased NGF protein in the hippocampus. However, as was true for the studies of neurogranin and dendrin, a direct sleep-dependent increase in the synthesis of BDNF and NGF during sleep was not reported.

4.3. Reactivation of neuronal activity patterns in sleep

The case for a role for sleep in promoting synaptic plasticity has been strengthened in recent years by reports that patterns of neuronal activity (or metabolism) present during waking are “reactivated” during subsequent sleep in birds (Dave and Margoliash, 2000; Dave et al., 1998), rodents (Hirase, 2001; Kudrimoti et al., 1999; Lee and Wilson, 2002; Louie and Wilson, 2001; Nadasky et al., 1999; Pavlides and Winson, 1989; Poe et al., 2000; Qin et al., 1997; Skaggs and McNaughton, 1996; Wilson and McNaughton, 1994), primates (Hoffman and McNaughton, 2002) and humans (Laureys et al., 2001; Maquet et al., 2000). This sleep-dependent “reactivation” has been hypothesized to contribute to the consolidation of changes in neuronal circuitry triggered by waking experience (Hoffman and McNaughton, 2002; Wilson and McNaughton, 1994).

Interest in sleep-dependent reactivation of previously active circuits increased following an initial report in rats that hippocampal neurons activated during a waking period displayed increased activity during subsequent REM sleep and nonREM sleep (Pavlides and Winson, 1989). Subsequent studies in the rodent hippocampus have failed to replicate these findings (Hirase, 2001; Kudrimoti et al., 1999;

Wilson and McNaughton, 1994), but have shown that pairs of hippocampal neurons whose activity is correlated during a learned behavior are more likely to show correlated activity in nonREM sleep subsequent to than prior to the training period (Kudrimoti et al., 1999; Wilson and McNaughton, 1994), and that the temporal sequence of neuronal firing during waking is preserved in subsequent nonREM sleep (Lee and Wilson, 2002; Skaggs and McNaughton, 1996). Interestingly, the replay of hippocampal firing during nonREM sleep has been reported to occur at an accelerated rate (“time-compressed”) during nonREM sleep, and can be detected as long as 24 h after the task-specific activation of these neurons during prior waking (Hirase, 2001; Kudrimoti et al., 1999; Lee and Wilson, 2002; Nadasky et al., 1999). Sleep-dependent neuronal reactivation may also occur in the cerebral cortex. Vyazovskiy et al. (2000) reported that unilateral whisker stimulation in the rat increased EEG spectral energies in the hemisphere contralateral to the stimulated whiskers during subsequent sleep. Reactivation of specific waking patterns of neuronal firing has been reported in the cortex in rodents (Qin et al., 1997) and primates (Hoffman and McNaughton, 2002), and in related structures in the zebra finch brain (Dave and Margoliash, 2000), although in the latter two studies the type of sleep necessary for this reactivation was not determined.

To what extent reactivation occurs during REM sleep is not yet clear. For example, Pavlides and Winson (1989) reported increased firing of previously active neurons during subsequent REM sleep. It has also been reported that activity patterns in multiple neurons over periods of 1–2 min of REM sleep are significantly correlated with activity patterns in the same set of neurons during a *subsequent* training session, and in most cases the REM-sleep spike trains are temporally compressed or expanded (“speeded up” or “slowed down”) by factors of up to 2.5 (Louie and Wilson, 2001). Other investigators, however, have found no evidence for enhanced neuronal firing or reactivation during REM sleep following (or preceding) waking experience (Kudrimoti et al., 1999), and no evidence for a temporal expansion of REM-sleep spike trains (Kudrimoti et al., 1999; Nadasky et al., 1999; Poe et al., 2000). One possible explanation for these contradictory findings may be that neuronal reactivation during REM sleep is modulated by the background hippocampal theta oscillation. Poe et al. (2000) reported that hippocampal neurons previously active during waking are reactivated during REM sleep in a manner that is highly dependent upon their temporal phase position in theta oscillations. Neurons that were activated during a well-rehearsed, maze-running task tended to fire at the troughs of the theta wave in subsequent REM sleep. However, when a new maze-running task was introduced to the same animals, neurons that were activated during the novel task tended to fire at the peaks of the theta wave. These results suggest that neuronal connections are modified during REM sleep in a manner that provides for the strengthening of newly acquired memories and the eroding of older ones.

Several recent studies in humans have provided additional evidence for use-dependent neuronal reactivation during sleep. In an experiment quite similar to that performed in the rat, [Kattler et al. \(1994\)](#) have shown that mechanical stimulation of one hand leads to an increase in EEG slow-wave activity in corresponding somatosensory cortex during subsequent nonREM sleep. A similar enhancement of EEG spectral energies in temporal cortex in nonREM sleep has also been reported following acoustic stimulation during waking ([Cantero et al., 2002](#)). Other investigators using functional neuroimaging have extended these EEG-based findings. Studies using positron emission tomography (PET) have shown that brain areas previously active during a serial reaction time task are reactivated in subsequent REM sleep ([Maquet et al., 2000](#)). Subsequent PET studies have also shown greater functional connectivity between several neocortical areas during REM sleep following learning, suggesting a sleep-dependent “optimization” of neocortical networks dedicated to particular learning tasks ([Laureys et al., 2001](#)).

These findings, while interesting, should be interpreted with some caution. With regard to the ensemble recordings of single-unit activity in the hippocampus and neocortex, the effects are statistically significant but often small. For example, during sleep-dependent reactivation, the amount of variance in neuronal activity that can be statistically accounted for by prior waking experience (explained variance) represents a fraction of the total variance (12–15%), and this explained variance rapidly diminishes during subsequent sleep episodes ([Hoffman and McNaughton, 2002](#); [Kudrimoti et al., 1999](#)). [Nadasky et al. \(1999\)](#), using similar ensemble recordings in the hippocampus, but different analytical techniques, also showed statistically significant but small effects. The fact that only a fraction of ongoing neuronal activity patterns during sleep represents reactivation does not preclude an important role for this activity in mnemonic functions. However, there is presently no evidence that reactivation during sleep is *functionally* involved in synaptic remodeling or processes dependent on synaptic remodeling. The reactivation that does occur could be a mere epiphenomenon of changes in synaptic strengths achieved during prior learning activity, without contributing to further consolidation of those changes. For example, the strongest nonREM-sleep reactivations demonstrated typically decay over a period of 10–30 min following training sessions, which is consistent with the idea that these associations represent an effect of the molecular mechanisms linked to early-LTP but not late-LTP.

4.4. Sleep, sleep deprivation, and synaptic plasticity

Another line of evidence suggesting a role for sleep in synaptic plasticity comes from studies examining the effects of sleep and sleep loss on LTP and LTD. [Leonard et al. \(1987\)](#), using white-matter stimulation of the perforant path combined with granule cell recording in the dentate gyrus of the hippocampus in vivo, reported that stimulation

during wakefulness induced LTP, while stimulation during slow-wave sleep did not. Slightly different results were reported by [Bramham and Srebro \(1989\)](#), who found highly variable changes in dentate gyrus responses when perforant path stimulation was delivered during slow-wave sleep. In most cases, this stimulation produced no change in neuronal firing, but in some cases LTD, or more rarely LTP, was observed. In contrast, perforant path stimulation routinely produced LTP in the dentate gyrus when applied during waking and REM sleep, and this change in neuronal efficacy was detected during subsequent sleep states, suggesting a transfer of neuronal changes elicited during REM sleep to other vigilance states ([Bramham and Srebro, 1989](#)). In subsequent studies, [Bramham et al. \(1994\)](#) also showed that perforant path stimulation during post-learning REM-sleep-induced LTP, while similar stimulation during post-learning waking did not, suggesting that REM sleep may especially facilitate changes in neuronal circuitry following learning.

Taking a slightly different approach, [Hennevin et al. \(1995\)](#) and [Maho and Hennevin \(2002\)](#) showed that changes in neuronal firing elicited by a classical conditioning paradigm could be reinstated during REM sleep upon presentation of the conditioned stimulus, indicating that information acquired during waking was ‘available’ to the brain during REM sleep. Moreover, associative learning can be induced during REM sleep (using non-awakening conditioned and unconditioned stimuli), but not in slow-wave sleep ([Hennevin et al., 1995](#); [Maho and Hennevin, 2002](#)). In agreement with the results from [Bramham and Srebro \(1989\)](#), this associative learning was in some instances transferred to the waking state ([Hennevin et al., 1995](#)).

The fact that LTP can be induced during sleep is particularly important in light of recent genetic findings that suggest that synaptic plasticity can only occur during waking ([Cirelli and Tononi, 2000a](#)). Nevertheless, a few points are worth considering. First, the fact that plasticity can be artificially induced during REM sleep does not, of course, indicate that synaptic remodeling normally occurs during natural REM sleep. Second, the findings that LTP, or associative learning, can be induced in REM sleep and transferred across similar states (waking and REM sleep) might be explained in terms of state-dependent storage and access of memory. Given that REM sleep and waking are quite similar in terms of neuronal activity and acetylcholine levels, one might expect that information acquired in one state would be available to the other, without there being any particular functional relationship between the two.

There is currently only one published report (in adult animals) on the effects of SD on LTP. [Campbell et al. \(2002\)](#) investigated the effects of 12 h SD on CA1 hippocampal LTP evoked by stimulation of Schaffer collaterals in vitro. LTP was significantly reduced in brain slices obtained from sleep-deprived rats compared to control rats. To what extent this diminishment of LTP was due to sleep loss per se, or to non-specific effects of the sleep-deprivation is not clear. Stress hormones were significantly elevated in the

sleep-deprived rats to levels known to impair this form of synaptic plasticity.

4.5. Sleep and developmentally regulated synaptic plasticity

In a variety of mammalian species, sleep amounts are greater during neonatal periods of rapid brain development and synaptic plasticity than at any other time of life (Frank and Heller, 1997; Jouvet-Mounier et al., 1970; Roffwarg et al., 1966). Consequently, if sleep contributes to synaptic plasticity, one would expect this to be especially true in developing animals. This issue has been investigated primarily in the developing visual system, which is exquisitely sensitive to experience during critical periods of development.

Pompeiano et al. (1995) reported that total SD (nonREM+REM sleep) combined with monocular deprivation (MD) augmented the effects of MD on lateral geniculate (LGN) cell morphology. The results of this study, however, are difficult to interpret since the amount of visual experience was not equal across sleeping and sleep-deprived cats, and very little quantitative data on sleep architecture were presented. More persuasive evidence for a role for sleep in subcortical plasticity was provided by combining various forms of selective RSD, or deprivation of REM-sleep PGO waves, with MD. Using the pedestal technique of RSD, Oksenberg et al. (1996) demonstrated that 1 week of RSD in kittens enhanced the effects of MD on cell morphology in the binocular segment of the LGN. LGN neurons innervated from the deprived eye were smaller when RSD was combined with MD compared to MD alone, resulting in a greater disparity in the size of LGN cells activated by the open and deprived eyes. An increase in LGN cell-size disparity has also been reported when MD is combined with brainstem lesions that eliminate PGO waves—in this case, LGN cells receiving input from the open eye were reported to increase in size (Shaffery et al., 1999). RSD combined with MD also reduces cell sizes in the monocular segment of the LGN, which is normally unaffected by competitive interactions between the two eyes (Shaffery et al., 1998). In addition, RSD for 1 week decreases immunoreactivity for the Ca²⁺-binding protein parvalbumin in GABAergic interneurons in the developing LGN (Hogan et al., 2001). Interestingly, neuronal stores of parvalbumin influence certain forms of synaptic plasticity (Caillard et al., 2000). Together these results indicate that REM sleep may influence plasticity in the LGN during critical periods of visual-system development.

A role for REM sleep has also been found in a developmentally regulated form of LTP during the critical period for visual-system development. In this type of LTP, high-frequency white-matter stimulation in neocortical slices obtained from juvenile rats (postnatal days (P) 28–30) produces LTP in upper neocortical layers, an effect that wanes with age (P35+), and is not observed in adult neocortex (Kirkwood et al., 1995). Using a less stressful version of the pedestal technique of RSD (“multiple

small-platform”), Shaffery et al. (2002) reported that 1 week of RSD extended the critical period for this developmentally regulated form of LTP in visual cortex. This type of LTP was readily observed slices of visual cortex from RSD rats at ages P34–40, when it is not normally found. An extension of the critical period was not observed in neocortical slices from control rats that were left in their nests, or from rats placed on slightly larger platforms that have in other studies been shown to permit REM sleep. However, a non-developmentally regulated form of LTP evoked by layer IV stimulation was not affected by RSD. The effects of RSD on developmentally regulated LTP were similar to effects produced by dark-rearing, which also prolongs the period of susceptibility to this form of LTP (Shaffery et al., 2002).

A role for sleep in developmental cortical plasticity has also been demonstrated in vivo. In addition to its anatomical effects in the LGN, MD during the critical period for visual-system development induces rapid changes in neocortical responses to the two eyes. Frank et al. (2001) investigated the role of sleep in this process by combining MD with periods of ad lib sleep or SD. Cats at the peak of the critical period were divided into four groups, all of which had one eye closed and were kept awake in a lighted environment for 6 h. This MD period provided a standard stimulus for the induction of plasticity in all groups. The four groups differed in their experience thereafter. Cats in the first group (MD6) were immediately prepared for physiological measurement of ocular dominance in primary visual cortex using extracellular unit recordings and optical imaging of intrinsic neocortical signals. Cats in a second group (MDS) were allowed to sleep for an additional 6 h in complete darkness before physiological measurements were made. Cats in the third group (MDSD) were treated identically to those in the MDS group except that they were gently sleep deprived in complete darkness during the 6 h before the physiological measurements were made. Cats in the fourth group (MD12) were also kept awake for additional 6 h but remained in a lighted environment, giving them additional 6 h of monocular deprivation before physiological measurements.

These experiments determined: (1) whether the effects of MD were enhanced by subsequent sleep (MD6 compared to MDS); (2) whether the enhancement of plasticity observed was due to sleep or merely a time dependent process that could occur in any vigilance state (MDS compared to MDSD); and (3) whether the procedure used to sleep deprive the cats itself directly inhibited ocular dominance plasticity (MD12 compared to MDSD).

Both extracellular unit recordings and optical imaging of intrinsic neocortical signals showed that sleep greatly enhanced the synaptic changes induced by a preceding period of MD, while wakefulness in complete darkness did not. Moreover, no brain state other than sleep is known have such enhancing effects on ocular dominance plasticity, since anesthetic states and neocortical inactivation actually *suppress* ocular dominance plasticity (Freeman, 1979; Imamura and Kasamatsu, 1991; Rauschecker and Hahn, 1987; Reiter

et al., 1986). While it was not possible to determine the precise contribution of REM sleep and nonREM sleep in this effect, the enhancement of neocortical plasticity was positively correlated with nonREM-sleep amounts, suggesting an important role for nonREM sleep in the rapid neocortical synaptic remodeling elicited by MD (Frank et al., 2001).

Although the findings discussed in this section suggest that sleep may influence synaptic plasticity, a number of considerations should be kept in mind. First, manipulations performed in one sleep state may also influence neural processing in other vigilance states as well, making it difficult to determine which vigilance state is responsible for the observed effects. For example, RSD increases noradrenergic activity in the central nervous system (Irwin et al., 1999; Porkka-Heiskanen et al., 1995), which increases signal detection in sensory neurons during waking (Aston-Jones et al., 1999; Smiley, 1996). RSD can also alter nonREM-sleep architecture (increasing sleep fragmentation and suppressing deeper stages of nonREM sleep) even when total nonREM-sleep amounts are preserved (Beersma et al., 1990; Brunner et al., 1993; Endo et al., 1997). Thus, in experimental designs that use prolonged RSD combined with periods of sensory input, the observed changes in plasticity may result from RSD itself, altered neural processing during waking, or disruption of nonREM sleep.

A second consideration is the role of non-specific effects of SD on developmental synaptic plasticity. As discussed above, even gentle forms of SD can increase stress hormones that in turn can alter plasticity depending on the timing, duration and intensity of the stressful event (Abraham and Kovacs, 2000; Sapolsky, 1996). Consequently, it is not clear if the effects of selective RSD in the kitten reflect purely sleep-dependent processes, or the non-specific effects of stress. Stress, however, does not appear to be a factor in studies using SD combined with in situ LTP, immunohistochemical assays of Ca^{2+} -binding proteins (parvalbumin) or neocortical plasticity in vivo. In the case of the Shaffery et al. (2002) study, the chronic stress hormone release induced by long-term RSD might be expected to impair susceptibility to LTP. It is also unlikely that stress associated with RSD down-regulates parvalbumin in the LGN. Increases in stress hormones have no effect on parvalbumin concentrations in the hippocampus—a brain area highly sensitive to circulating glucocorticoid levels (Krugers et al., 1996; Sapolsky, 1996). Moreover, the acute release of stress hormones elicited by very short periods of SD tends to enhance, not impair synaptic plasticity, and is probably unrelated to the loss of plasticity in sleep-deprived cats and the enhancement of plasticity in cats allowed to sleep reported by Frank et al. (2001).

5. Facilitating synaptic plasticity on the cellular level

Having briefly reviewed the neurobiology of sleep and waking, the molecular mechanisms of synaptic plasticity,

and the evidence that sleep may facilitate synaptic plasticity, we will now consider possible explanations for how sleep could facilitate synaptic plasticity. In this section, we will consider possible connections between neural events in sleep and the molecular mechanisms of synaptic plasticity, focusing only on events taking place within single neurons. In Section 6, we will then consider how the network interactions among neurons characteristic of nonREM sleep and REM sleep could be involved in the process. Throughout our discussion, we will intentionally describe a range of hypothetical explanations, without advocating narrowly for any particular one. Our intent in doing so is to map out as many potential connections as possible, each one of which could then be tested experimentally. A broad approach such as this is appropriate given that there is at present little specific evidence to establish the validity of any particular connection between sleep and synaptic plasticity on the level of molecular mechanisms.

5.1. Ca^{2+} influx in sleep and synaptic plasticity

In light of the material reviewed in Sections 2 and 3, the obvious connection between neural events in sleep and the molecular mechanisms of synaptic plasticity is Ca^{2+} influx. The key ion channel responsible for producing rhythmic neuronal activity in nonREM sleep is the T-type Ca^{2+} channel, which is open at the peak of each rhythmic cycle. The key protein in mediating activity-dependent synaptic plasticity is the NMDA glutamate receptor, which produces synapse-specific Ca^{2+} influx associated with both LTP and LTD.

The potential role of Ca^{2+} in linking these two processes has of course been alluded to by other writers in the field (Buzsaki, 1998; Sejnowski and Destexhe, 2000). But given the complexity of molecular mechanisms of synaptic plasticity, it is not at all obvious how Ca^{2+} influx through T-type Ca^{2+} channels in nonREM sleep would influence ongoing plasticity processes. As noted in Section 3.1, Ca^{2+} influx underlying synaptic plasticity is synapse-specific, and involves a particular combination of Ca^{2+} sources, including NMDA receptors, VGCCs, and possibly CICR from smooth endoplasmic reticulum. Locally high levels of $[\text{Ca}^{2+}]_i$ produce LTP, as when PSPs immediately precede APs, while lower and longer-lasting levels of $[\text{Ca}^{2+}]_i$ are thought to produce LTD, as when APs immediately precede PSPs.

Ca^{2+} influx during rhythmic activity in nonREM sleep occurs because neurons are tonically hyperpolarized in that state and T-type Ca^{2+} channels are therefore able to de-inactivate. Ca^{2+} influx occurs at fairly regular intervals in each neuron during the depolarized phase of the rhythmic response sequence. The effect of this pattern of Ca^{2+} influx on synaptic plasticity will depend on a number of factors of which we are still largely uncertain. How high is $[\text{Ca}^{2+}]_i$ during periods of Ca^{2+} influx when neurons are rhythmically active? How exactly is Ca^{2+} influx distributed throughout a neuron's dendritic arbor? Are T-type Ca^{2+}

channels located in dendritic spines, on dendritic shafts, or in both places? Do a high proportion of a neuron's T-type Ca^{2+} channels open during each rhythmic depolarization or is there a more heterogeneous distribution of Ca^{2+} influx? Answers to these questions will determine whether Ca^{2+} influx during rhythmic neuronal activity is likely to produce LTP, LTD, a combination of both, or neither. And the distribution of LTP and/or LTD in a neuron in relation to ongoing plasticity processes initiated during prior waking will determine whether synaptic plasticity driven by rhythmic neuronal activity in sleep reinforces or antagonizes waking-related synaptic plasticity.

5.2. T-type Ca^{2+} channels and LTD

There is some evidence for an involvement of T-type Ca^{2+} channels in LTP (see Section 3.1), but the preponderance of evidence links T-type Ca^{2+} channels to the mechanisms of LTD (see Section 3.2). Experiments have demonstrated a requirement for functioning T-type Ca^{2+} channels in both NMDA-related and mGlu-related forms of LTD. As noted earlier, this makes sense given that T-type Ca^{2+} channels are activated transiently by small, subthreshold depolarization, and so are ideally suited to producing a low-level Ca^{2+} signal when PSPs are not immediately followed by APs.

It should be noted that the experiments reviewed in Section 3 may not reveal the full role of T-type Ca^{2+} channels, since those channels inactivate rapidly and are only de-inactivated following membrane hyperpolarization. Thus, these channels are only functionally available under specific circumstances. In many *in vitro* studies, experimental conditions are such that resting membrane potential is too depolarized to permit T-type Ca^{2+} channels to de-inactivate. The plasticity processes produced using such protocols manifestly do not rely on the involvement of T-type Ca^{2+} channels, but it is nevertheless entirely possible that T-type Ca^{2+} channels would modulate plasticity were they functional. *In vivo* studies of LTP and LTD in unanesthetized animals are most commonly performed during waking, when T-type Ca^{2+} channels are inactivated by acetylcholine and other neuromodulators. In anesthetized animals, T-type Ca^{2+} channels may or may not be activated, depending on the anesthesia used and treatment conditions. Two studies which have assessed synaptic plasticity in nonREM sleep *in vivo* have reported suppression of LTP and/or some occurrence of synaptic depression following a relatively mild stimulus (eight spikes at 400 Hz) which in waking produced LTP (Bramham and Srebro, 1989; Leonard et al., 1987).

Given that one obviously distinctive feature of nonREM sleep is that T-type Ca^{2+} channels are active (in fact, the occurrence of rhythmic activity maximizes and regularizes the involvement of these channels), one possible hypothesis is that *in vivo*, LTD occurs predominantly in nonREM sleep. The fact that both NMDA-related and mGlu-related forms of LTD appear to require T-type Ca^{2+} channels (see Section 3.2) suggests that the occurrence of LTD should

be reduced or eliminated during waking, when these channels are inactive. LTD is as important as LTP for plasticity in neural circuits, as what matters is *differential* strengthening of synapses (Hebb, 1949). Hence, the occurrence of LTP at some synapses is functionally unremarkable unless there is an absence of potentiation and even depression at other synapses. So hypothetically, plasticity processes operative during waking may potentiate synapses in proportion to their efficacy in promoting APs, with little or no depression of inefficacious synapses. In nonREM sleep, by contrast, T-type Ca^{2+} channel-mediated LTD of synapses that are least effective in promoting APs may then restore the proper balance of synaptic strength in neural circuits. The occurrence of synchronized activity in neural circuits during nonREM sleep would presumably enhance this process by more markedly differentiating between more versus less efficacious synapses (see Section 6).

The hypothesis that LTD is more prevalent during sleep than waking is consistent with the findings reviewed in Section 4.2.2. concerning gene expression in sleep and waking. In those studies, reductions in expression of a number of genes associated with LTP, as well as reductions in the phosphorylation of the CREB transcription factor protein and in general levels of protein phosphorylation, have been taken as evidence that synaptic plasticity is inhibited in sleep relative to waking (Tononi and Cirelli, 2001b). But these findings are equally compatible with the hypothesis that sleep promotes synaptic plasticity by enabling the occurrence of LTD, as all of the molecular phenomena associated with the phosphorylation cascade of LTP would be *antagonized* by promotion of LTD. This hypothesis is also consistent with the findings described in Section 4.5, suggesting that synaptic remodeling induced by MD is specifically enhanced by nonREM sleep (Frank et al., 2001), since the process of MD-induced synaptic remodeling is thought to require LTD (Rittenhouse et al., 1999).

One caveat concerning the above hypothesis is that T-type Ca^{2+} channels are not by any means ubiquitous in the mammalian central nervous system. They are found on CA1 pyramidal neurons in the hippocampus (Fisher et al., 1990; Kay and Wong, 1987; Magee and Johnston, 1995a; Mogul and Fox, 1991), which have been the focus of much research on synaptic plasticity. In piriform cortex, they are found in a high proportion of principle neurons in deep layers (III and IV) but in few pyramidal neurons in layer II (Brevi et al., 2001; Magistretti and de Curtis, 1998). The laminar distribution of these channels in other cortical areas requires further study. Any direct, sleep-related modulation of synaptic plasticity involving these channels would necessarily be restricted to those neurons in which they are expressed.

The cellular localization of T-type Ca^{2+} channels varies in different classes of neurons. In neurons of thalamic relay nuclei, a large fraction of T-type Ca^{2+} channels appear to be localized to the cell soma, as substantial T-type conductances can be recorded from neurons with truncated dendritic arbors (Coulter et al., 1989; Hernandez-Cruz and Pape,

1989; Suzuki and Rogawski, 1989). In neurons of the reticular nucleus of the thalamus, however, conductances mediated by T-type Ca^{2+} channels are substantially reduced in neurons with truncated dendritic arbors, suggesting a predominantly dendritic localization in these cells (Huguenard and Prince, 1992). In CA1 pyramidal cells in the hippocampus, T-type and/or R-type Ca^{2+} channels also appear to be largely dendritic, and are preferentially located in more distal parts of apical dendrites, 100 μm and more from the cell soma (Christie et al., 1995; Isomura et al., 2002; Magee and Johnston, 1995a,b). More work needs to be done to establish the cellular localization of T-type Ca^{2+} channels in other cell types, particularly in neocortical pyramidal neurons, but these findings already suggest that the functional roles of these channels may vary among different classes of neurons. Thus, the effects on synaptic plasticity of activating these channels during rhythmic neuronal activity in nonREM sleep may vary as well.

5.3. T-type Ca^{2+} channels and LTP

While there is more evidence linking T-type Ca^{2+} channels to LTD than LTP, we should not entirely neglect the possibility that these channels play a more subtle, permissive role in synaptic plasticity, perhaps modulating the process in specific ways when they are active in nonREM sleep. As noted above, T-type and/or R-type Ca^{2+} channels are preferentially located in more distal parts of apical dendrites in CA1 pyramidal cells in the hippocampus (Christie et al., 1995; Isomura et al., 2002; Magee and Johnston, 1995a,b). It has been hypothesized that the small increase in Ca^{2+} influx produced by activation of these channels may help to overcome the biophysical implications of having synapses situated so far from the soma (Magee and Johnston, 1995a). This hypothesis is consistent with recent reports that in CA1 hippocampal pyramidal neurons, effective synaptic strength does not scale with distance from the soma as it has been theoretically expected to (Stricker, 2002; Stricker et al., 1996).

It is therefore possible, that under the specific cellular physiological conditions of nonREM sleep, activation of T-type Ca^{2+} channels subtly increases the degree of depolarization and Ca^{2+} influx produced by both PSPs and back-propagating APs, thereby promoting LTP under conditions in which it would not normally occur. However, the small amount of available evidence concerning the occurrence of LTP in nonREM sleep contradicts this hypothesis (Bramham and Srebro, 1989; Leonard et al., 1987).

5.4. Cellular events of REM sleep and synaptic plasticity

As noted in Section 2, REM sleep is electrophysiologically very similar to waking. In both states, neurons throughout the thalamus, cerebral cortex, and other brain regions are tonically depolarized and produce APs at a high rate. In both states, high levels of acetylcholine release block K^+ chan-

nels, depolarizing membrane potential and increasing membrane resistance, thereby making neurons more active and responsive. In waking, norepinephrine and serotonin release further contribute to this effect, while in REM sleep neurons are activated by acetylcholine alone. In the hippocampus, high levels of acetylcholine release produces theta frequency activity in both REM sleep and periods of waking characterized by exploratory behaviors. While levels of acetylcholine release are similar in waking and REM sleep, release in REM sleep is slightly higher in the hippocampus and slightly lower in the neocortex, relative to waking (Marrosu et al., 1995).

Given the above, cellular mechanisms of synaptic plasticity in REM sleep should be fairly equivalent to those occurring in waking. As such, it is difficult to imagine how, on the cellular level, REM sleep could serve a special function in facilitating synaptic plasticity. Conceivably, the slight differences in neuronal activity (Hobson and Steriade, 1986), metabolic activity (Franzini, 1992), and acetylcholine release (Marrosu et al., 1995) between waking and REM sleep could be significant, but it appears at present that those differences are rather subtle. Alternatively, the dramatic decrease in release of norepinephrine and serotonin in REM sleep (Aston-Jones and Bloom, 1981; Jacobs, 1986; Lydic et al., 1987; McGinty and Harper, 1976) could influence the cellular mechanisms of synaptic plasticity in REM sleep. As noted in Section 4.2.2, expression of plasticity-related genes appears to be reduced in the absence of norepinephrine release in cerebral cortex, suggesting that decreased norepinephrine release in REM sleep would be unlikely to promote LTP, but it could (by analogy to our discussion in Section 5.2) promote a greater degree of LTD relative to LTP. The fact that LTP can be produced during REM sleep (Bramham and Srebro, 1989; Hennevin et al., 1995) does however indicate that, at the very least, reduced norepinephrine release in that state does not eliminate LTP altogether.

The above considerations do not preclude possible roles for REM sleep in facilitating synaptic plasticity on the *network* level. These are discussed in Section 6.2.

6. Facilitating synaptic plasticity on the network level

The hypotheses presented in Section 5 address the neurophysiological characteristics of nonREM sleep and REM sleep only from the cellular perspective. This is worthwhile as a starting point, but it is only part of the picture. The rhythmic activity produced in each neuron during nonREM sleep by the activation of T-type Ca^{2+} channels and their interactions with other ion channels causes in turn a heightened synchronization of activity in neuronal networks in the thalamus, cerebral cortex, and other brain regions. This synchronization is the cause of the characteristic high-amplitude waveforms observable in the EEG

during nonREM sleep, which were reviewed in [Section 2](#). Synchronization of neuronal activity in networks also occurs during REM sleep, when oscillations in the theta range occur in the hippocampus and other brain regions. REM sleep is also characterized by the irregular bursts of synchronized activity known as PGO waves.

Synchronization of presynaptic release of transmitter and postsynaptic depolarization is, as noted in [Section 3](#), the hallmark of Hebbian synaptic plasticity. It is therefore reasonable to suppose that the heightened synchronization which occurs in specific neural circuits in nonREM sleep and REM sleep may promote synaptic plasticity in ways that potentiate or antagonize the plasticity initiated in waking in response to specific patterns of sensory stimulation. This basic idea has been the inspiration for some rather complex models of memory functions performed by sleep, involving interconnections among multiple brain regions ([Buzsaki, 1989, 1996, 1998; Hasselmo, 1995; Sejnowski and Destexhe, 2000](#)). Before we consider these models, let us first discuss on a more elemental level how synchronized activity in nonREM sleep and/or REM sleep could be expected to influence synaptic plasticity initiated during waking.

6.1. Synchronized neuronal activity in nonREM sleep

NonREM sleep is characterized by a variety of forms of synchronized, rhythmic activity in neurons in the cerebral cortex, thalamus, and other brain regions (see [Section 2](#)). Slow waves in the delta frequency range (0.5–4 Hz) predominate in the deepest stages of nonREM sleep, but in lighter stages of nonREM sleep, these are mixed with sigma waves (7–14 Hz) and very slow oscillations (<1 Hz). Delta and sigma oscillations are characterized by depolarization-induced Ca^{2+} influx through T-type Ca^{2+} channels, alternating with hyperpolarizations lasting up to hundreds of milliseconds. During each period of Ca^{2+} influx, neurons generate one action potential or a burst of several action potentials at high frequency (up to 800 Hz). High-amplitude voltage deflections are produced in surface EEG recordings because the depolarizations and bursts of action potentials are synchronized in networks of neurons ([Destexhe et al., 1999b](#)), as a result of excitatory and inhibitory interactions.

In [Section 5.2](#), we introduced the hypothesis that T-type Ca^{2+} channels may be required for LTD, and therefore that de-inactivation of these channels as a result of the hyperpolarization that occurs in nonREM sleep may permit LTD to occur in nonREM sleep at a level not found in waking. But the synchronization of single action potentials and bursts that also occurs in nonREM sleep should additionally cause LTP to occur in synapses between neurons whose activity is maximally synchronized. In such cases, coincidence of PSPs and APs in synapses of the postsynaptic neuron will cause NMDA-mediated Ca^{2+} influx, increasing $[\text{Ca}^{2+}]_i$ to levels far above that produced by T-type Ca^{2+} channels alone, just as it does in waking or any other brain state.

According to this model, LTP will occur in synapses between more highly synchronized pairs of neurons (as a result of NMDA-mediated Ca^{2+} influx in the postsynaptic neuron), while LTD will occur in synapses between less highly synchronized pairs of neurons (in which Ca^{2+} influx in the postsynaptic neuron is mediated only by T-type Ca^{2+} channels). The precise timing of presynaptic versus postsynaptic AP generation should further determine whether synapses are potentiated or depressed, as a result of the occurrence of STDP (reviewed in [Section 3.3](#)). Synapses will be potentiated when release of transmitter by a presynaptic neuron immediately precedes generation of an AP in the postsynaptic neuron, and depressed when release of transmitter immediately follows generation of an AP in the postsynaptic neuron.

Thus, the resultant plasticity in neural circuits during synchronized activity could be determined by rather subtle resonances that emerge as excitatory and inhibitory interactions between neurons produce specific temporal patterns of synchronization. And it is worth noting that synaptic plasticity resulting from such network interactions would not necessarily be restricted to those neurons with intrinsically bursting properties. It may also occur in other neuronal types that are recruited, as a consequence of network events, into the large scale oscillations typical of nonREM sleep ([Sanchez-Vives and McCormick, 2000](#)). This is in contrast to the cellular-level hypothesis discussed in [Section 5](#), according to which promotion of LTD in nonREM sleep would be limited to those neurons expressing T-type Ca^{2+} channels.

A number of recent findings are consistent with the above-described hypothesis. The delta waves of nonREM sleep are preferentially observed in extragranular layers of the cortex ([Rappelsberger et al., 1982](#)), which appear to be sites of heightened plasticity (LTP and LTD) in both the developing and adult brain ([Heynen and Bear, 2001; Trachtenberg et al., 2000](#)). Spontaneous waves of synchronized activity similar to nonREM-sleep oscillations contribute to synaptic remodeling during early development ([Penn and Shatz, 1999](#)) and axonal sprouting following neocortical lesions in adult animals ([Carmichael and Chesselet, 2002](#)). Artificially induced and spontaneous spindles in thalamocortical relay cells produce augmenting responses in target neocortical neurons, both in vivo and in vitro ([Houweling et al., 2002; Steriade, 1999; Steriade and Amzica, 1998; Timofeev et al., 2002](#)). Moreover, artificially induced patterns of stimuli reappear spontaneously in the frequency of spindle oscillations, indicating that, at least under these conditions, ‘memories’ of previous activity patterns can be transiently stored in neocortical circuits ([Steriade, 2001](#)). It also appears that thalamocortical spindles powerfully depolarize postsynaptic dendrites in neocortical neurons, a situation that favors Ca^{2+} entry in the activated dendrite ([Sejnowski and Destexhe, 2000](#)). Although the effects of delta waves on dendritic Ca^{2+} dynamics are still undetermined, it is likely that they too result in dendritic depolarization and inward Ca^{2+} currents.

What would be the significance of this type of network-level plasticity for the cognitive function of sleep? Cognitively oriented hypotheses have been proposed in which sleep either reinforces patterns of synaptic activity developed in waking (Kavanau, 1994, 1996, 1997) or serves to maintain synapses that were relatively unstimulated in prior waking (Krueger and Obal, 1993; Krueger et al., 1995, 1999). Which of these would occur depends on whether the patterns of spike-timing produced by synchronized neuronal activity in nonREM sleep tend to replicate patterns observed in prior waking or run counter to waking-related patterns. The findings reviewed in Section 4.3 demonstrate that, in some instances at least, activity patterns observed in prior waking are indeed “reactivated” in subsequent non-REM sleep. On the face of it, these findings would appear to support the idea that network events in nonREM sleep reinforce synaptic plasticity initiated in waking, but it is not yet clear whether the reactivation observed is in fact functionally significant.

6.2. Synchronized neuronal activity in REM sleep

In our discussion in Section 5.4 of how REM sleep may facilitate synaptic plasticity on the cellular level, we argued that neuronal response properties in REM sleep and waking are so similar that it is difficult to imagine what could be accomplished in REM sleep that could not be accomplished equally well in waking. This same argument applies to a lesser extent on a network level as well. In the hippocampus and some associated brain regions, synchronized activity in the theta (4–8 Hz) frequency range dominates in REM sleep. Theta activity is also observed in waking, during exploratory behaviors.

Synaptic plasticity could be facilitated in REM sleep in much the same way as is described in Section 6.1. That is, synchronization of APs at theta-wave peaks should increase the number of opportunities for the occurrence of STDP, and the precise timing of APs in presynaptic versus postsynaptic neuron would determine whether each synapse is potentiated or depressed. The temporal association of APs during theta activity is a function of the phase of the theta rhythm at which APs occur. During STDP, potentiation should occur when the presynaptic AP is slightly phase-advanced relative to the postsynaptic AP. Phase has recently been shown to be correlated with AP frequency and to be advanced at the offset of periods of activity, relative to onset (Harris et al., 2002). These relationships hold during both spatial and non-spatial behaviors, and during REM sleep. During all of these conditions, phase relationships could therefore finely tune the occurrence of synaptic plasticity in hippocampal circuits.

However, such a mechanism would be expected to operate whenever theta activity is observed in the hippocampus—during REM sleep, but also during periods of exploratory behavior in waking. Moreover, the dynamics of phase–activity relationships in REM sleep parallel those observed during active waking (Harris et al., 2002), suggesting that to the

extent we are yet able to analyze neuronal activity in hippocampal circuits, REM sleep appears to exhibit network properties similar to those of waking. So it is not clear how synaptic plasticity occurring during REM sleep could serve a special function unlike that of the synaptic plasticity occurring during exploratory waking. The fact that serotonin and norepinephrine are released in hippocampal circuits in waking but not in REM sleep could conceivably cause the process of synaptic plasticity to function somewhat differently in the two states, but what exactly this difference would be, if any, is not yet clear. And the findings of Cirelli and Tononi in the neocortex (see Section 4.2.2) suggest that decreases in norepinephrine release should inhibit rather than promote synaptic plasticity. At best, therefore, the only advantage of theta activity in REM sleep, as regards facilitation of synaptic plasticity, appears to be an incremental increase in the daily duration of this process. Whether 1–2 h of REM sleep per day accomplishes anything noteworthy in this regard remains to be determined.

Another form of synchronized neuronal activity observed in REM sleep is PGO waves, which are driven by intense bursts of synchronized activity in pontine neurons that propagate through excitatory connections to the lateral geniculate nucleus and visual cortex (Calvo and Fernandez-Guardiola, 1984; Datta, 1997; Siegel, 2000). Datta has proposed that these may facilitate network-level synaptic plasticity in the regions to which they propagate, based on the findings that prior training in an avoidance task increases PGO-wave density in subsequent REM sleep (Datta, 2000). Certainly, such bursts of activity are well suited to increase $[Ca^{2+}]_i$ in target neurons, both through synapse-specific mechanisms and by increasing the probability of AP backpropagation. However, electrophysiological phenomena resembling PGO waves are observed during eye movements in waking as well (Brooks, 1968; Jeannerod and Sakai, 1970). These may not be identical to those of REM sleep, but there is at least a strong family relationship (Brooks and Gershon, 1971). So once again, it is not clear whether this mode of synchronized activity observed in REM sleep differs enough from the synchronized activity of waking to justify a special role of REM sleep in synaptic plasticity.

6.3. Network-level models of sleep and synaptic plasticity

Our discussion of network-level connections between sleep and synaptic plasticity in Sections 6.1 and 6.2 has intentionally emphasized the simplest and most general level of analysis. The networks of neurons being considered could consist of neurons within one cortical column, within one neocortical area or thalamic nucleus, within the hippocampus, and/or projection neurons between thalamus and cortex, cortex and hippocampus, etc. Given the wide distribution of synchronized activity within the brain, particularly in nonREM sleep, network-level facilitation of synaptic plasticity could occur virtually everywhere.

A number of models have been proposed in which sleep is hypothesized to facilitate synaptic plasticity as a result of higher-level network connections, involving information exchange between thalamus, neocortex, and hippocampus. In this section, we will briefly describe a sampling of these models and consider how the general principles enunciated above apply thereto.

6.3.1. *Thalamocortical interactions*

Sejnowski and Destexhe (2000) have proposed two different models by which synchronized activity in neurons of the thalamus and neocortex during nonREM sleep could facilitate synaptic plasticity. Both of these models represent specific applications of the general principles described in Section 6.2, incorporating additional experimental findings to justify additional and more specific hypotheses concerning what form of network interactions facilitate what forms of synaptic plasticity.

Using computational models to analyze the responses of neocortical neurons to thalamic stimulation during sigma frequency oscillations, Contreras et al. (1997) concluded that inhibitory mechanisms must exist in neocortical pyramidal cells to keep their firing rates low in the face of burst discharges from thalamocortical neurons. Evidence in support of this conclusion includes the measurement of large GABAergic conductances in neocortical neurons (Borg-Graham et al., 1998) and the observation that inhibitory synapses on these neurons are concentrated on the cell soma, while excitatory synapses are found mostly on dendrites (DeFelipe and Farinas, 1992). The implication of these findings is that, during sigma frequency oscillations, bursts of action potentials by thalamocortical neurons could promote localized Ca^{2+} influx in the dendrites of neocortical pyramidal neurons, while inhibitory potentials at the cell soma suppress discharge by those pyramidal neurons (Sejnowski and Destexhe, 2000).

Sejnowski and Destexhe (2000) hypothesize that this dendritic Ca^{2+} influx produces high enough levels of $[\text{Ca}^{2+}]_i$ to activate protein kinases and thereby produce LTP. They suggest that sigma frequency oscillations in nonREM sleep may function to maximize LTP in neocortical pyramidal neurons without causing excessive generation of APs in neocortical networks. Ordinarily, levels of $[\text{Ca}^{2+}]_i$ high enough to produce LTP occur only when PSPs are paired with AP backpropagation. However, the bursts of APs produced by the thalamocortical neurons during sigma frequency activity could conceivably stimulate sufficient localized Ca^{2+} influx in dendrites even in the absence of AP generation. An alternative hypothesis that these authors do not consider is that $[\text{Ca}^{2+}]_i$ in neocortical pyramidal neurons reaches levels sufficient for LTD but not LTP. If LTD occurs systematically in response to thalamocortical stimulation during sigma frequency activity, sleep spindles could equally well serve to facilitate synaptic plasticity.

Sejnowski and Destexhe (2000) further hypothesize that in deeper stages of nonREM sleep, an alternating occur-

rence of delta frequency oscillations with fast oscillations that are similar to neuronal activity patterns characteristic of waking produces a cyclic process that facilitates memory consolidation. According to this model, brief periods of fast oscillations for a few seconds reactivate patterns of neuronal activity reflective of the cognitive experiences of prior waking. The subsequent occurrence of synchronized delta frequency oscillations may then reinforce LTP and/or LTD resulting from those neuronal activity patterns, by means of network interactions such as are described in Section 6.2, and thus help to permanently establish new memories.

In Sejnowski and Destexhe's (2000) general model, the above two hypotheses work synergistically to enable nonREM sleep to facilitate synaptic plasticity. They propose that the wholesale occurrence of LTP in neocortical pyramidal neurons during light stages of nonREM sleep preliminarily activates protein kinases and thereby prepares those neurons for synaptic plasticity. The subsequent reactivation of waking-specific patterns of neuronal activity and reinforcing of Hebbian plasticity in deep stages of nonREM sleep in turn generates the specific potentiation and depression of synapses required for consolidation of memories.

6.3.2. *Hippocampal–neocortical interactions*

There is a large body of literature suggesting that the hippocampus and other temporal lobe structures play an important role in memory consolidation (Eichenbaum et al., 1999; Squire, 1992). The first evidence for this hypothesis was the effect of hippocampal damage or removal on consolidation of new memories. The role of the hippocampal formation in memory consolidation has since been further explored in animal models.

While it is clear that temporal lobe structures play an important role in memory consolidation, it is not as clear exactly what that role is. Damage to the hippocampal formation preserves already established memories but impairs the formation of new ones. Episodic memory (the capacity to remember events and situations) and semantic memory (the capacity to form new associations, including cognitive processes as simple as remembering telephone numbers or combinations of words) can be eliminated entirely with sufficiently large lesions. However, the same lesions preserve procedural memory, the capacity to learn new sensorimotor tasks. The preservation of procedural memory following hippocampal damage demonstrates that synaptic plasticity in neocortical tissue occurs independently of the hippocampal formation. The role of the hippocampus in the consolidation of episodic and semantic memory (collectively termed declarative memory) must therefore involve more sophisticated cognitive, associative processes.

Damage to the hippocampal formation in humans also produces retrograde amnesia for events dating from up to 2 years before the time of the damage (and to a lesser extent for even earlier events), suggesting that the hippocampal formation is somehow involved in consolidation of memories for some time following the initiation of new memory traces

(Squire and Alvarez, 1995). A similar phenomenon has been observed in monkeys, although the retrograde amnesia affects a considerably shorter time period (Zola-Morgan and Squire, 1990). But the persistence of older memories following hippocampal damage supports the generally accepted idea that ultimately memories are stored in a distributed fashion throughout the brain. And in each area involved in the storage of a memory, the long-term physical substrate of that memory presumably involves changes in synaptic strengths resulting from the cellular and molecular mechanisms of synaptic plasticity discussed throughout this article.

One model of the role of the hippocampal formation in memory consolidation is that it rapidly and temporarily stores new neuronal activity patterns, and then gradually transfers them to the neocortex, which alone is able to integrate each new memory with others already established (Marr, 1971; McClelland et al., 1995). An alternative model is that the hippocampus does not store and then transfer memories appropriate to specific neocortical areas, but rather functions as particularly high-level association cortex, assisting diverse neocortical areas in the formation of associations between components of a memory, and between one memory and another (Eichenbaum, 2000). This hypothesis is consistent with the fact that the hippocampal formation is required for consolidation of declarative but not procedural memories, since procedural memories involve implicit knowledge and largely unconscious cognitive processing, and so may not need the hypothesized association functions of the hippocampus.

Whatever may be its exact functional role, the involvement of the hippocampal formation in memory consolidation has made it an attractive model system in studies of cellular mechanisms of synaptic plasticity. LTP was first described in hippocampal circuits, and even now synaptic plasticity has been more extensively characterized in those circuits than in any other brain region. But it should be emphasized that synaptic plasticity occurring in the hippocampus is relevant only to the local plasticity needs of those circuits. If Marr's (1971) hypothesis is correct, LTP and LTD temporarily effected in hippocampal circuits could in turn influence more permanent synaptic plasticity occurring elsewhere. But ultimately, the formation of detailed and enduring memories reflects the synaptic plasticity that occurs throughout the neocortex and other brain regions.

The established involvement of the hippocampal formation in memory consolidation does not necessarily imply sleep-related modulation of that process. But coupled with evidence that sleep itself facilitates learning and memory, a role for sleep in the functioning of the hippocampal formation has seemed plausible to a number of researchers. That role is generally taken to entail state-dependent differences in how hippocampal circuits interact with those of the cerebral cortex, differences which are assumed to influence synaptic plasticity in hippocampus and/or cerebral cortex.

6.3.2.1. Two-stage models of hippocampal functioning. Buzsaki has, in a series of articles, developed a hypothesis of hippocampal–neocortical interactions in which the flow of information into and out of the hippocampus is dependent on behavioral state (Buzsaki, 1989, 1996, 1998). In this model, the hippocampus during active waking behavior predominantly *receives* information from the cerebral cortex via superficial layers (I–III) of entorhinal cortex and other retrohippocampal structures. During quiet waking and nonREM sleep, the occurrence of synchronized sharp waves characteristic of that state causes the direction of information flow to change, so that synaptic associations laid down in waking are transferred through deep layers (IV–VI) of entorhinal cortex and other retrohippocampal structures to the appropriate neocortical areas. In both states, synchronized activity (in the theta frequency during active waking and in association with sharp waves in nonREM sleep) maximizes the association of presynaptic and postsynaptic activity.

Buzsaki's model is based on the observation that superficial layer (I–IV) retrohippocampal neurons exhibit activity that is correlated with theta waves but not synchronized sharp waves, while deep layer (V–VI) retrohippocampal neurons exhibit activity that is correlated with synchronized sharp waves but not theta waves (Chrobak and Buzsaki, 1994). Because layers I–III of retrohippocampal structures are thought to receive afferent projections *from* neocortical areas (Amaral, 1987; Van Hoesen et al., 1991), while layer IV of retrohippocampal structures projects *to* neocortical areas (Swanson and Kohler, 1986), these associations have been taken to imply that information is predominantly relayed from neocortex to hippocampus in association with theta activity and in the reverse direction in association with sharp waves. This hypothesis is dependent on the inference that associated activity in hippocampus and retrohippocampal structures implies that neurons in one area are being driven by neurons in the other. Moreover, the layer IV retrohippocampal neurons that predominantly project to neocortical areas (Swanson and Kohler, 1986) are *not* active in association with hippocampal sharp waves—only layer V/VI neurons are—somewhat weakening the anatomical justification for this hypothesis. And the involvement of these state-dependent activity patterns in memory processing is largely a matter of conjecture.

Hasselmo (1999) has adapted and extended Buzsaki's model, retaining the basic idea of state-dependent information flow patterns and a two-stage mechanism of synaptic plasticity, and emphasizing the effects of neuromodulators in determining the nature of patterned neuronal activity and thus the direction of information flow. He has described cellular mechanisms whereby acetylcholine, which is predominantly responsible for producing theta frequency activity in active waking and REM sleep, may promote information flow into the hippocampus during those states and the temporary formation of synaptic associations. He has further proposed a unique role for REM sleep in this process, based on the absence of release of norepinephrine

during theta activity in this state. Another two-stage model of memory consolidation, involving interactions between hippocampus and neocortical areas, has been discussed recently by [Sejnowski and Destexhe \(2000\)](#).

6.4. General evaluation of network-level models

In our discussion of potential connections between sleep and synaptic plasticity on the network level, we have attempted to work from the simplest to the most complex types of hypothesis. In [Sections 6.1 and 6.2](#), we considered possible network-level roles for sleep involving anatomically unspecified circuits, which could be local or wide ranging, and which are based only on the dominant modes of synchronized activity characteristic of those states. In [Section 6.3](#), we then considered some recently proposed models of sleep-dependent mechanisms of synaptic plasticity, which are more complex and more specifically articulated, and which involve anatomically defined interconnections between neocortex and other brain regions. These more complex models incorporate simpler network-level processes based on synchronized activity such as were discussed in [Sections 6.1 and 6.2](#), but attempt to explain sleep-dependent memory processing based on further hypotheses beyond those presented in [Sections 6.1 and 6.2](#).

This hierarchical presentation of potential hypotheses is intended to emphasize the fact that the more complex hypotheses reviewed in [Section 6.3](#) are only examples of a multitude of possible mechanisms whereby network-level activity during nonREM sleep and/or REM sleep could facilitate synaptic plasticity. Those hypotheses are all based on electrophysiological observations but also involve a certain measure of bold speculation. While one of them may prove to be substantially correct, we should consider the very real possibility that synchronized activity in neuronal networks during nonREM sleep and/or REM sleep may indeed facilitate synaptic plasticity, and yet no one of these complex hypotheses may describe the specific neuronal interactions that accomplish this.

Given the present uncertain nature of the evidence establishing a connection between sleep and synaptic plasticity, we believe the matter will be best addressed by focusing on more basic hypotheses such as are discussed in [Sections 6.1 and 6.2](#) (and, on the cellular level, in [Section 5](#)). These are, after all, elements of the more complex models discussed in [Section 6.3](#), and so the testing of these more simple hypotheses could provide evidence consistent with the more complex models as well. Moreover, facilitation of synaptic plasticity by synchronized activity in local networks could be studied using reduced preparations *in vitro* (e.g. [Sanchez-Vives and McCormick, 2000](#)), permitting aspects of the question to be addressed by means of simpler and more feasible experiments. If facilitation on this level is established, then incrementally more elaborate experiments could in turn provide evidence for specific hypotheses involving interactions between anatomically distributed brain regions.

7. Summary and conclusions

While a role for sleep in synaptic plasticity has by no means been conclusively established, the findings reviewed in this article indicate at least that the idea merits serious consideration. As reviewed in [Section 4](#), there is evidence on the behavioral, physiological, and cellular and molecular levels that alterations in sleep produce concomitant alterations in processes associated with synaptic plasticity. There are of course alternative interpretations of these findings, but at the very least this substantial body of work establishes a solid *prima facie* case.

As reviewed in [Sections 5 and 6](#), the neurophysiological processes occurring during sleep are in many respects ideally suited to promoting synaptic plasticity. The unique forms of plasticity that may result from neural events occurring in sleep on the cellular and network levels could complement the activity-dependent plasticity initiated during waking by specific patterns of sensory stimulation and cognitive processing. Needless to say, the validity of the hypothetical scenarios offered in [Sections 5 and 6](#) still remains to be established, but our review of the literature demonstrates at least that there is considerable potential for fruitful connections between the cellular and molecular processes associated with sleep and those associated with synaptic plasticity.

It is worth noting in this regard that much of the evidence for a link between sleep and synaptic plasticity concerns REM sleep, while the most promising connections between sleep and synaptic plasticity on the cellular and molecular level arguably concern events taking place in nonREM sleep, and in fact the cellular physiology of nonREM sleep has received more attention from those advancing hypotheses on the cellular and molecular level. This may merely reflect current ignorance of the full significance of synchronized activity in REM sleep, in particular in the hippocampus. Alternatively, experiments designed to establish a link involving REM sleep may in reality have produced nonREM-sleep-related effects as well. The vast majority of such experiments involve selective RSD, the supposed selectivity of which is in most studies based largely on the observation that nonREM-sleep duration is not reduced by the intervention that suppresses REM sleep. However, even when an intervention only interrupts sleep at the onset of REM-sleep episodes, there is nevertheless a marked increase in sleep fragmentation and suppression of EEG delta power in nonREM sleep during the deprivation period ([Benington et al., 1994](#)), as well as a suppression of EEG delta power in nonREM sleep for hours afterwards ([Beersma et al., 1990](#); [Brunner et al., 1990, 1993](#)). Thus, even the most “selective” RSDs may compromise nonREM sleep as well. Consequently, the effects on processes associated with synaptic plasticity resulting from RSD protocols may in fact be caused by interference with nonREM-sleep processes during the deprivation period.

As noted in the introduction, we have by design discussed possible cellular and molecular connections between sleep

and synaptic plasticity in a broad and speculative manner. While there is not yet compelling evidence in support of a specific cellular/molecular process linking sleep and synaptic plasticity, it is nevertheless essential that the question be addressed on the cellular and molecular level. To that end, we have sought to lay out the widest range of possible hypotheses that would be at least consistent with available data. Our hope is that an awareness of the possible cellular and molecular connections among investigators active in this field will stimulate experiments that may ultimately provide evidence substantiating one particular hypothesis from among those currently possible.

7.1. Facilitation of synaptic plasticity as the primary function of sleep

If sleep does indeed facilitate synaptic plasticity, this function could either be the primary function of sleep or merely a secondary one. The primary function of sleep can be defined as the main reason that sleep is necessary, that sleep loss is attended with such disastrous consequences, and that the occurrence of sleep has been universally maintained in mammalian evolution. Secondary functions would be additional benefits associated with the occurrence of sleep, of varying degrees of importance in different organisms. While the most parsimonious hypothesis is that the current primary function of sleep is also the function for which sleep was originally adapted in whatever form it first evolved, it is at least conceivable that a sleep-like process originally designed for one function was at some point co-opted for a new primary function.

The primary function of sleep will also be the one which has exerted the greatest selective influence during mammalian evolution on the physiological phenomena associated with sleep and on the homeostatic mechanisms regulating sleep (Benington, 2000). If facilitation of synaptic plasticity is that function, then the physiological phenomena of sleep and the mechanisms of sleep homeostasis should be specifically adapted to accomplishing such facilitation. The considerable literature that has accumulated concerning sleep physiology and sleep homeostasis may therefore provide important insights into possible mechanisms whereby sleep may facilitate synaptic plasticity.

As noted in earlier sections, neuronal activity in nonREM sleep involves synchronized, oscillatory activity in at least three frequency bands—delta (0.5–4 Hz), sigma (7–14 Hz), and <1 Hz. These forms of oscillatory activity each result from distinct rhythmic properties of neurons in the thalamus and cerebral cortex, involving distinct populations of pacemaker neurons and distinct network interactions by means of which the oscillations are propagated and synchronized. Moreover, the occurrence of these species of oscillatory activity is organized on a time-scale of seconds within each stage of nonREM sleep and on a time-scale of minutes within each nonREM-sleep episode. It is highly unlikely that such elaborate neurophysiological mechanisms could exist purely

by chance, and so it is reasonable to hypothesize that the intrinsic properties of neurons and network connections which cause these oscillations to occur in the precise manner in which they do are largely the result of specific adaptations related to the primary function of sleep.

The implications of this hypothesis for the idea that the primary function of sleep is to facilitate synaptic plasticity are daunting. At present, it is not clear exactly how oscillatory activity in general may facilitate synaptic plasticity either within single cells or as a result of network interactions. To extend this inquiry to involve at least three categories of oscillatory activity and network connections among the reticular thalamic nucleus, thalamic relay nuclei, and cerebral cortex makes the issue even more challenging. This is especially so if we further suppose that the temporal distribution of these forms of oscillatory activity may itself be significant. But unless we are to assume that the variety of forms of rhythmic neuronal activity observed in nonREM sleep is largely epiphenomenal, these possibilities should eventually be considered.

This situation may be simplified somewhat if we suppose that discharge of sleep propensity is primarily driven by the occurrence of delta frequency oscillations. The main argument for this hypothesis is the fact that EEG delta activity and hence stages 3 and 4 of nonREM sleep are enhanced following sleep deprivation, and that nonREM-sleep EEG delta activity is a reasonably consistent measure of the momentary level of sleep propensity (Borbely and Achermann, 2000). A regulated increase in EEG slow waves following sleep deprivation suggests that the occurrence of slow waves is directly or indirectly linked to the sleep recovery process, though it should be noted that there is at best suggestive evidence that enhancements of EEG delta activity speed discharge of sleep propensity (Dijk et al., 1987). Moreover, discharge of sleep propensity appears to be unimpeded under some circumstances in which EEG slow-waves are suppressed, such as administration of benzodiazepine hypnotics (Achermann and Borbely, 1987; Borbely et al., 1985), indicating that the association between EEG delta activity and discharge of sleep propensity is not absolute. Nevertheless, under most circumstances, EEG slow waves dominate when sleep drive is greatest, suggesting that synchronized activity in that frequency range is most closely associated with the sleep recovery process.

Assuming that changes in EEG delta activity are at least measures of the accumulation and discharge of sleep propensity, there is increasing evidence that these processes occur locally, such that rates of accumulation and discharge can vary among brain regions (Cajochen et al., 1999; Huber et al., 2000), and that the accumulation of sleep propensity in any given area is a function of the metabolic or cognitive demands placed on that part of the brain (Achermann et al., 2001; Kattler et al., 1994). These findings are consistent with the hypothesis that sleep facilitates synaptic plasticity, as demands for synaptic reorganization will vary from region to region in an experience-dependent manner,

and the satisfaction of those demands will also be accomplished locally, as new connections are formed in each part of the brain's networks (Krueger et al., 1999). This consideration suggests that the question should be amenable to study using reduced preparations *in vitro*, so long as the reduced circuits being studied exhibit the forms of oscillatory activity normally characteristic of particular sleep states.

If facilitation of synaptic plasticity is the primary and thus homeostatically regulated function of sleep, then there should exist negative feedback control mechanisms which register a level of demand for facilitation of synaptic plasticity and increase or decrease sleep propensity in response (Benington, 2000; Krueger and Obal, 2002). In other homeostatically regulated physiological systems, the negative feedback mechanisms entail biochemical and/or biophysical changes which trigger release of a paracrine or endocrine signaling molecule which stimulates the appropriate responses in target cells.

The question of what component of the molecular response cascade involved in synaptic plasticity could serve as such a feedback signal is indeed a challenge. As reviewed recently by Benington (2000), the known physiological effects of signaling molecules associated with LTP tend to depolarize rather than hyperpolarize neurons, implying that they would decrease rather than increase the tendency to sleep. However, intraventricular administration of the neurotrophins NGF and BDNF has been shown to produce small increases in sleep expression (Kushikata et al., 1999; Takahashi and Krueger, 1999), suggesting that these molecules may contribute to the negative feedback signal. There could also exist as-yet unknown components of this molecular response cascade and/or as-yet unknown physiological effects of components that have already been identified.

7.2. Future directions

We would like to close by considering some experiments which could help to resolve questions raised in this article. In our opinion, the conclusive demonstration of a role of sleep in synaptic plasticity will require experimental findings establishing the cellular and molecular mechanisms of this process, and not merely learning-related correlates of sleep or sleep deprivation. The broad, speculative approach we have taken in this article has been necessary precisely because the details of such a mechanism are still largely unclear. However, the discussions in Sections 5 and 6 demonstrate that the cellular and network-level neurophysiological processes of nonREM sleep and REM sleep provide numerous opportunities for facilitation of synaptic plasticity, and so a number of attractive candidate mechanisms are available. Experimental techniques and model systems developed by researchers investigating sleep neurophysiology and cellular and molecular mechanisms of synaptic plasticity can be adapted to test these candidate mechanisms.

While some experiments have been performed to test for the occurrence of LTP and LTD in nonREM sleep and REM sleep, these have really only scratched the surface. Both LTP and LTD are sensitive to specific experimental conditions. For example, a protocol that effectively produces LTD at one developmental stage will not at another, even though LTD can be produced using the appropriate protocol at all developmental stages (Kemp and Bashir, 2001, Section 2.1). Two studies have demonstrated a reduction in LTP during nonREM sleep, using relatively mild LTP-inducing stimuli (Bramham and Srebro, 1989; Leonard et al., 1987). It remains to be seen whether other LTP-inducing protocols have the same effects, and therefore whether LTP is indeed altogether suppressed in nonREM sleep. One of these studies (Bramham and Srebro, 1989) reported depression of the population response in nonREM sleep using a protocol that causes potentiation in waking, but there have not yet been systematic studies of the effects of LTD-inducing protocols in different behavioral states.

As discussed in Section 3.1, both forms of LTD appear to be dependent on activation of T-type Ca^{2+} channels *in vitro*. However, this dependence has been demonstrated only by selective pharmacological blockade of T-type Ca^{2+} channels using low concentrations of Ni^{+} . Stronger evidence for the hypothesis that LTD is promoted by activation of T-type Ca^{2+} channels during synchronized rhythmic neuronal activity in nonREM sleep would come from experiments in which T-type Ca^{2+} channels were activated or blocked in roughly the same manner as occurs naturally in nonREM sleep and waking. *In vitro*, this could be accomplished by adjusting the ionic composition of the bath medium and administering neuromodulatory molecules. By this means, neurons in neocortical and thalamic tissue slices could be systematically made to exhibit the modes of activity characteristic of waking versus nonREM sleep, and the relative efficacy of LTP and LTD protocols under these two conditions could be tested. The relevance of REM sleep to synaptic plasticity could be assessed by activating neurons *in vitro* either with acetylcholine alone or with acetylcholine plus norepinephrine and serotonin. Such experiments would permit the evaluation of cellular-level hypotheses such as are discussed in Section 5.

In vitro studies of the effects on synaptic plasticity of the various types of synchronized rhythmic activity that occur in nonREM sleep may also be possible. While some aspects of synchronized rhythmic activity are dependent upon distributed network interactions involving widely distributed brain regions (Steriade, 1999), others have been produced in isolated slice preparations *in vitro* and in deafferented nuclei *in vivo* (Steriade et al., 1987; von Krosigk et al., 1993). Using *in vitro* preparations, one could assess whether: (1) the occurrence of synchronized activity promotes LTP and/or LTD; (2) increases in the degree of synchronization accentuate the process; and (3) LTP is specifically promoted at synapses between pairs of neurons whose activity is more highly synchronized. The effects of synchronization could

be further assessed at the molecular level, by characterizing the protein phosphorylation, gene expression, and other postsynaptic effects associated with synaptic plasticity.

This is only a sampling of experiments that could be performed to test the hypotheses proposed in this article. As discussed in Section 6.4, relatively simple experiments such as these could provide evidence for the elements of more complex network-level models. To distinguish between the more detailed predictions of such models, a series of incrementally more elaborate experiments would eventually be required.

References

- Abraham, I.M., Kovacs, K.J., 2000. Postnatal handling alters the activation of stress-related neuronal circuitries. *Eur. J. Neurosci.* 12, 3003–3014.
- Achermann, P., Borbely, A.A., 1987. Dynamics of EEG slow wave activity during physiological sleep and after administration of benzodiazepine hypnotics. *Hum. Neurobiol.* 6, 203–210.
- Achermann, P., Finelli, L.A., Borbely, A.A., 2001. Unihemispheric enhancement of delta power in human frontal sleep EEG by prolonged wakefulness. *Brain Res.* 913, 220–223.
- Altar, C.A., DiStefano, P.S., 1998. Neurotrophin trafficking by anterograde transport. *Trends Neurosci.* 21, 433–437.
- Amaral, D.G., 1987. Memory: anatomical organization of candidate brain regions. In: Plum, V. (Eds.), *Handbook of physiology, Section 1: The Nervous System*, vol. V. American Physiological Society, Bethesda, MD, pp. 211–294.
- Ambrosini, M.V., Sadile, A.G., Gironi Carnevale, U.A., Mattiaccio, A., Giuditta, A., 1988. The sequential hypothesis on sleep function. II. A correlative study between sleep variables and newly synthesized brain DNA. *Physiol. Behav.* 43, 339–350.
- Ambrosini, M.V., Langella, M., Gironi Carnevale, U.A., Giuditta, A., 1992. The sequential hypothesis of sleep function. III. The structure of postacquisition sleep in learning and nonlearning rats. *Physiol. Behav.* 51, 217–226.
- Ameri, A., 1999. The effects of cannabinoids on the brain. *Prog. Neurobiol.* 58, 315–348.
- Antonova, I., Arancio, O., Trillat, A.C., Wang, H.G., Zablow, L., Udo, H., Kandel, E.R., Hawkins, R.D., 2001. Rapid increase in clusters of presynaptic proteins at onset of long-lasting potentiation. *Science* 294, 1547–1550.
- Arancio, O., Antonova, I., Gambaryan, S., Lohmann, S.M., Wood, J.S., Lawrence, D.S., Hawkins, R.D., 2001. Presynaptic role of cGMP-dependent protein kinase during long-lasting potentiation. *J. Neurosci.* 21, 143–149.
- Aston-Jones, G., Bloom, F.E., 1981. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep–waking cycle. *J. Neurosci.* 1, 876–886.
- Aston-Jones, G., Rajkowski, J., Cohen, J., 1999. Role of locus coeruleus in attention and behavioral flexibility. *Biol. Psychiatr.* 46, 1309–1320.
- Balestrieri, S., D’Onofrio, G., Giuditta, A., 1980. Deprivation of paradoxical sleep. Effect on weight and nucleic acid content of liver and brain. *Neurochem. Res.* 5, 1251–1264.
- Barker, P.A., Shooter, E.M., 1994. Disruption of NGF binding to the low affinity neurotrophin receptor p75LNTFR reduces NGF binding to TrkA on PC12 cells. *Neuron* 13, 203–215.
- Barnes, C.A., 1995. Involvement of LTP in memory: are we “searching under the street light”? *Neuron* 15, 751–754.
- Barry, M.F., Ziff, E.B., 2002. Receptor trafficking and the plasticity of excitatory synapses. *Curr. Opin. Neurobiol.* 12, 279–286.
- Beattie, E.C., Carroll, R.C., Yu, X., Morishita, W., Yasuda, H., von Zastrow, M., Malenka, R.C., 2000. Regulation of AMPA receptor endocytosis by a signaling mechanism shared with LTD. *Nat. Neurosci.* 3, 1291–1300.
- Beersma, D.G.M., Dijk, D.J., Blok, C.G.H., Everhardus, I., 1990. REM sleep deprivation during 5 h leads to an immediate REM sleep rebound and to suppression of non-REM sleep intensity. *Electroencephalogr. Clin. Neurophysiol.* 76, 114–122.
- Benington, J.H., 2000. Sleep homeostasis and the function of sleep. *Sleep* 23, 959–966.
- Benington, J.H., Woudenberg, M.C., Heller, H.C., 1994. REM-sleep propensity accumulates during 2-h REM-sleep deprivation in the rest period in rats. *Neurosci. Lett.* 180, 76–80.
- Bi, G., Poo, M., 2001. Synaptic modification by correlated activity: Hebb’s postulate revisited. *Annu. Rev. Neurosci.* 24, 139–166.
- Bicker, G., 2001. Sources and targets of nitric oxide signalling in insect nervous systems. *Cell Tissue Res.* 303, 137–146.
- Bliss, T.V., Lomo, T., 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J. Physiol. (Lond.)* 232, 331–356.
- Block, V., Hennevin, E., Leconte, P., 1981. The phenomenon of paradoxical sleep augmentation after learning: experimental studies of its characteristics and significance. In: Fishbein, W. (Ed.), *Sleep, Dreams and Memory*, vol. 6. Medical & Scientific Books, New York, pp. 1–18.
- Bobillic, P., Sakai, F., Seguin, S., Jouvet, M., 1971. Deprivation of paradoxical sleep and in vitro cerebral protein synthesis in the rat. *Life Sci.* 10, 1349–1357.
- Bogdan, C., 2001. Nitric oxide and the regulation of gene expression. *Trends Cell Biol.* 11, 66–75.
- Borbely, A.A., Achermann, P., 2000. Sleep homeostasis and models of sleep regulation. In: Kryger, M.H., Roth, T., Dement, W.C. (Eds.), *Principles and Practice of Sleep Medicine*. Saunders, Philadelphia, pp. 377–390.
- Borbely, A.A., Mattmann, P., Loepfe, M., Strauch, I., Lehmann, D., 1985. Effect of benzodiazepine hypnotics on all-night sleep EEG spectra. *Hum. Neurobiol.* 4, 189–194.
- Borg-Graham, L.J., Monier, C., Fregnac, Y., 1998. Visual input evokes transient and strong shunting inhibition in visual cortical neurons. *Nature* 393, 369–373.
- Bramham, C.R., Srebro, B., 1989. Synaptic plasticity in the hippocampus is modulated by behavioral state. *Brain Res.* 493, 74–86.
- Bramham, C.R., Maho, C., Laroche, S., 1994. Suppression of long-term potentiation during alert wakefulness but not during ‘enhanced’ REM sleep after avoidance learning. *Neuroscience* 59, 501–509.
- Brandt, J.A., Churchill, L., Guan, Z., Fang, J., Chen, L., Krueger, J.M., 2001. Sleep deprivation but not a whisker trim increases nerve growth factor within barrel cortical neurons. *Brain Res.* 898, 105–112.
- Brennan, J.E., Bredt, D.S., 1997. Synaptic signaling by nitric oxide. *Curr. Opin. Neurobiol.* 7, 374–378.
- Brevi, S., de Curtis, M., Magistretti, J., 2001. Pharmacological and biophysical characterization of voltage-gated calcium currents in the endopiriform nucleus of the guinea pig. *J. Neurophysiol.* 85, 2076–2087.
- Brooks, D.C., 1968. Waves associated with eye movement in the awake and sleeping cat. *Electroencephalogr. Clin. Neurophysiol.* 24, 532–541.
- Brooks, D.C., Gershon, M.D., 1971. Eye movement potentials in the oculomotor and visual systems of the cat: a comparison of reserpine induced waves with those present during wakefulness and rapid eye movement sleep. *Brain Res.* 27, 223–239.
- Brunner, D.P., Dijk, D.-J., Tobler, I., Borbely, A.A., 1990. Effect of partial sleep deprivation on sleep stages and EEG power spectra: evidence for non-REM and REM sleep homeostasis. *Electroencephalogr. Clin. Neurophysiol.* 75, 492–499.
- Brunner, D.P., Dijk, D.-J., Borbely, A.A., 1993. Repeated partial sleep deprivation progressively changes the EEG during sleep and wakefulness. *Sleep* 16, 100–113.
- Buzsaki, G., 1989. Two-stage model of memory trace formation: a role for “noisy” brain states. *Neuroscience* 31, 551–570.
- Buzsaki, G., 1996. The hippocampo-neocortical dialogue. *Cereb. Cortex* 6, 81–92.

- Buzsaki, G., 1998. Memory consolidation during sleep: a neurophysiological perspective. *J. Sleep Res.* 7 (Suppl. 1), 17–23.
- Buzsaki, G., 2002. Theta oscillations in the hippocampus. *Neuron* 33, 325–340.
- Caillard, O., Moreno, H., Schwaller, B., Llano, I., Celio, M.R., Marty, A., 2000. Role of the calcium-binding protein parvalbumin in short-term synaptic plasticity. *Proc. Natl. Acad. Sci. U.S.A.* 97, 13372–13377.
- Cajochen, C., Foy, R., Dijk, D.J., 1999. Frontal predominance of a relative increase in sleep delta and theta EEG activity after sleep loss in humans. *Sleep Res. Online* 2, 65–69.
- Calvo, J.M., Fernandez-Guardiola, A., 1984. Phasic activity of the basolateral amygdala, cingulate gyrus, and hippocampus during REM sleep in the cat. *Sleep* 7, 202–210.
- Campbell, I.G., Guinan, M.J., Horowitz, J.M., 2002. Sleep deprivation impairs long-term potentiation in the rat hippocampal slices. *J. Neurophysiol.* 88, 1073–1076.
- Cantero, J.L., Atienza, M., Salas, R.M., Dominguez-Marin, E., 2002. Effects of prolonged waking-auditory stimulation on electroencephalogram synchronization and cortical coherence during subsequent slow-wave sleep. *J. Neurosci.* 22, 4702–4708.
- Carmichael, S.T., Chesselet, M.-F., 2002. Synchronous neuronal activity is a signal for axonal sprouting after cortical lesions in the adult. *J. Neurosci.* 22, 6062–6070.
- Carroll, R.C., Beattie, E.C., von Zastrow, M., Malenka, R.C., 2001. Role of AMPA receptor endocytosis in synaptic plasticity. *Nat. Rev. Neurosci.* 2, 315–324.
- Carskadon, M.A., Dement, W.C., 2000. Normal human sleep: an overview. In: Kryger, M.H., Roth, T., Dement, W.C. (Eds.), *Principles and Practice of Sleep Medicine*. Saunders, Philadelphia, pp. 15–25.
- Castillo, P.E., Schoch, S., Schmitz, F., Sudhof, T.C., Malenka, R.C., 2002. RIM1alpha is required for presynaptic long-term potentiation. *Nature* 415, 327–330.
- Cauter, E.V., Spiegel, K., 1999. Circadian and sleep control of hormonal secretions. In: Turek, F.W. (Ed.), *Regulation of Sleep and Circadian Rhythms*, vol. 133. Marcel Dekker, New York, pp. 397–425.
- Chawla, S., Hardingham, G.E., Quinn, D.R., Bading, H., 1998. CBP: a signal-regulated transcriptional coactivator controlled by nuclear calcium and CaM kinase IV. *Science* 281, 1505–1509.
- Cho, K., Bashir, Z.I., 2002. Cooperation between mGlu receptors: a depressing mechanism? *Trends Neurosci.* 25, 405–411.
- Cho, K., Aggleton, J.P., Brown, M.W., Bashir, Z.I., 2001. An experimental test of the role of postsynaptic calcium levels in determining synaptic strength using perirhinal cortex of rat. *J. Physiol. (Lond.)* 532, 459–466.
- Christie, B.R., Eliot, L.S., Ito, K., Miyakawa, H., Johnston, D., 1995. Different Ca²⁺ channels in soma and dendrites of hippocampal pyramidal neurons mediate spike-induced Ca²⁺ influx. *J. Neurophysiol.* 73, 2553–2557.
- Christie, B.R., Schexnayder, L.K., Johnston, D., 1997. Contribution of voltage-gated Ca²⁺ channels to homosynaptic long-term depression in the CA1 region in vitro. *J. Neurophysiol.* 77, 1651–1655.
- Chrobak, J.J., Buzsaki, G., 1994. Selective activation of deep layer (V–VI) retrohippocampal cortical neurons during hippocampal sharp waves in the behaving rat. *J. Neurosci.* 14, 6160–6170.
- Cirelli, C., 2002. Functional genomics of sleep and circadian rhythm. Invited review: how sleep deprivation affects gene expression in the brain: a review of recent findings. *J. Appl. Physiol.* 92, 394–400.
- Cirelli, C., Tononi, G., 1998a. Changes in anti-phosphoserine and anti-phosphothreonine antibody binding during the sleep–waking cycle and after lesions of the locus coeruleus. *Sleep Res. Online* 1, 11–18.
- Cirelli, C., Tononi, G., 1998b. Differences in gene expression between sleep and waking as revealed by mRNA differential display. *Brain Res. Mol. Brain Res.* 56, 293–305.
- Cirelli, C., Tononi, G., 2000a. Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. *J. Neurosci.* 20, 9187–9194.
- Cirelli, C., Tononi, G., 2000b. Gene expression in the brain across the sleep–waking cycle. *Brain Res.* 885, 303–321.
- Coenan, A., 2000. The divorce of REM sleep and dreaming. *Behav. Brain Sci.* 23, 922–924.
- Cohen-Cory, S., 2002. The developing synapse: construction and modulation of synaptic structures and circuits. *Science* 298, 770–776.
- Contestabile, A., 2000. Roles of NMDA receptor activity and nitric oxide production in brain development. *Brain Res. Brain Res. Rev.* 32, 476–509.
- Contreras, D., Destexhe, A., Steriade, M., 1997. Intracellular and computational characterization of the intracortical inhibitory control of synchronized thalamic inputs in vivo. *J. Neurophysiol.* 78, 335–350.
- Cormier, R.J., Greenwood, A.C., Connor, J.A., 2001. Bidirectional synaptic plasticity correlated with the magnitude of dendritic calcium transients above a threshold. *J. Neurophysiol.* 85, 399–406.
- Coulter, D.A., Huguenard, J.R., Prince, D.A., 1989. Calcium currents in rat thalamocortical relay neurones: kinetic properties of the transient, low-threshold current. *J. Physiol. (Lond.)* 414, 587–604.
- Dailey, M.E., Smith, S.J., 1996. The dynamics of dendritic structure in developing hippocampal slices. *J. Neurosci.* 16, 2983–2994.
- Datta, S., 1997. Cellular basis of pontine ponto-geniculo-occipital wave generation and modulation. *Cell. Mol. Neurobiol.* 17, 341–365.
- Datta, S., 2000. Avoidance task training potentiates phasic pontine-wave density in the rat: a mechanism for sleep-dependent plasticity. *J. Neurosci.* 20, 8607–8613.
- Dave, A.S., Margoliash, D., 2000. Song replay during sleep and computational rules of sensorimotor vocal learning. *Science* 290, 812–816.
- Dave, A.S., Yu, A.C., Margoliash, D., 1998. Behavioral state modulation of auditory activity in a vocal motor system. *Science* 282, 2250–2254.
- DeFelipe, J., Farinas, I., 1992. The pyramidal neuron of the cerebral cortex: morphological and chemical characteristics of the synaptic inputs. *Prog. Neurobiol.* 39, 563–607.
- Destexhe, A., Contreras, D., Steriade, M., 1999a. Cortically-induced coherence of a thalamic-generated oscillation. *Neuroscience* 92, 427–443.
- Destexhe, A., Contreras, D., Steriade, M., 1999b. Spatiotemporal analysis of local field potentials and unit discharges in cat cerebral cortex during natural wake and sleep states. *J. Neurosci.* 19, 4595–4608.
- Dijk, D.J., Beersma, D.G., Daan, S., Bloem, G.M., Van den Hoofdakker, R.H., 1987. Quantitative analysis of the effects of slow wave sleep deprivation during the first 3 h of sleep on subsequent EEG power density. *Eur. Arch. Psychiatr. Neurol. Sci.* 236, 323–328.
- Di Marzo, V., Melck, D., Bisogno, T., De Petrocellis, L., 1998. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends Neurosci.* 21, 521–528.
- Dunaevsky, A., Tashiro, A., Majewska, A., Mason, C., Yuste, R., 1999. Developmental regulation of spine motility in the mammalian central nervous system. *Proc. Natl. Acad. Sci. U.S.A.* 96, 13438–13443.
- Eder, M., Zieglensberger, W., Dodt, H.U., 2002. Neocortical long-term potentiation and long-term depression: site of expression investigated by infrared-guided laser stimulation. *J. Neurosci.* 22, 7558–7568.
- Eichenbaum, H., 2000. A cortical–hippocampal system for declarative memory. *Nature Rev. Neurosci.* 1, 41–50.
- Eichenbaum, H.B., Cahill, L.F., Gluck, M.A., Hasselmo, M.E., Keil, F.C., Martin, A.J., McGaugh, J.L., Murre, J., Myers, C., Petrides, M., Roozendaal, B., Schacter, D.L., Simons, D.J., Smith, W.C., Williams, C.L., 1999. Learning and memory: systems analysis. In: Zigmond, M.J., Bloom, F.E., Landis, S.C., Roberts, J.R., Squire, L.R. (Eds.), *Fundamental Neuroscience*. Academic Press, San Diego, pp. 1411–1454.
- Elgersma, Y., Silva, A.J., 1999. Molecular mechanisms of synaptic plasticity and memory. *Curr. Opin. Neurobiol.* 9, 209–213.
- Ellman, S.J., Spielman, A.J., Luck, D., Steiner, S.S., Halperin, R., 1991. REM deprivation: a review. In: Antrobus, J.S. (Ed.), *The Mind in Sleep*. Wiley, New York, pp. 329–369.
- Elphick, M.R., Egertova, M., 2001. The neurobiology and evolution of cannabinoid signalling. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 381–408.

- Endo, T., Schwierin, B., Borbely, A.A., Tobler, I., 1997. Selective and total sleep deprivation: effect on the sleep EEG in the rat. *Psychiatr. Res.* 66, 97–110.
- Faas, G.C., Adwanikar, H., Gereau, R.W.T., Saggau, P., 2002. Modulation of presynaptic calcium transients by metabotropic glutamate receptor activation: a differential role in acute depression of synaptic transmission and long-term depression. *J. Neurosci.* 22, 6885–6890.
- Fink, C.C., Meyer, T., 2002. Molecular mechanisms of CaMKII activation in neuronal plasticity. *Curr. Opin. Neurobiol.* 12, 293–299.
- Fischer, S., Hallschmid, M., Elsner, A.L., Born, J., 2002. Sleep forms memory for finger skills. *Proc. Natl. Acad. Sci. U.S.A.* 99, 11987–11991.
- Fishbein, W., 2000. The case against memory consolidation in REM sleep: balderdash!. *Behav. Brain Sci.* 23, 934–936.
- Fishbein, W., Gutwein, B.M., 1981. Paradoxical sleep and a theory of long-term memory. In: Fishbein, W. (Ed.), *Sleep, Dreams and Memory*, vol. 6. Spectrum Publications, New York, pp. 147–182.
- Fisher, R.E., Gray, R., Johnston, D., 1990. Properties and distribution of single voltage-gated calcium channels in adult hippocampal neurons. *J. Neurophysiol.* 64, 91–104.
- Fitzjohn, S.M., Palmer, M.J., May, J.E., Neeson, A., Morris, S.A., Collingridge, G.L., 2001. A characterisation of long-term depression induced by metabotropic glutamate receptor activation in the rat hippocampus in vitro. *J. Physiol. (Lond.)* 537, 421–430.
- Frank, M.G., Heller, H.C., 1997. Development of REM and slow wave sleep in the rat. *Am. J. Physiol.* 272, R1792–R1799.
- Frank, M.G., Issa, N.P., Stryker, M.P., 2001. Sleep enhances plasticity in developing visual cortex. *Neuron* 30, 275–287.
- Franzini, C., 1992. Brain metabolism and blood flow during sleep. *J. Sleep Res.* 1, 3–16.
- Freeman, R.D., 1979. Effects of brief unioocular ‘patching’ on kitten visual cortex. *Trans. Ophthalm. Soc. U.K.* 99, 382–385.
- Frey, U., Morris, R.G., 1998. Synaptic tagging: implications for late maintenance of hippocampal long-term potentiation. *Trends Neurosci.* 21, 181–188.
- Gais, S., Plihal, W., Wagner, U., Born, J., 2000. Early sleep triggers memory for early visual discrimination skills. *Nat. Neurosci.* 3, 1335–1339.
- Gais, S., Molle, M., Helms, K., Born, J., 2002. Learning-dependent increases in sleep spindle density. *J. Neurosci.* 22, 6830–6834.
- Garthwaite, J., Boulton, C.L., 1995. Nitric oxide signaling in the central nervous system. *Annu. Rev. Physiol.* 57, 683–706.
- Gerdeman, G.L., Ronesi, J., Lovinger, D.M., 2002. Postsynaptic endocannabinoid release is critical to long-term depression in the striatum. *Nat. Neurosci.* 5, 446–451.
- Gerendasy, D.D., 1999. Homeostatic tuning of Ca²⁺ signal transduction by members of the calpacitin protein family. *J. Neurosci. Res.* 58, 107–119.
- Gerendasy, D.D., Sutcliffe, J.G., 1997. RC3/neurogranin, a postsynaptic calpacitin for setting the response threshold to calcium influxes. *Mol. Neurobiol.* 15, 131–163.
- Gisquet-Verrier, P., Smith, C., 1989. Avoidance performance in rat enhanced by postlearning paradoxical sleep deprivation. *Behav. Neural Biol.* 52, 152–169.
- Giuditta, A., Rutigliano, B., Vitale-Neugebauer, A., 1980a. Influence of synchronized sleep on the biosynthesis of RNA in neuronal and mixed fractions isolated from rabbit cerebral cortex. *J. Neurochem.* 35, 1267–1272.
- Giuditta, A., Rutigliano, B., Vitale-Neugebauer, A., 1980b. Influence of synchronized sleep on the biosynthesis of RNA in two nuclear classes isolated from rabbit cerebral cortex. *J. Neurochem.* 35, 1259–1266.
- Giuditta, A., Ambrosini, M.V., Scaroni, R., Chiurulla, C., Sadile, A., 1985. Effect of sleep on cerebral DNA synthesized during shuttle-box avoidance training. *Physiol. Behav.* 34, 769–778.
- Giuditta, A., Ambrosini, M.V., Montangnese, P., Mandile, P., Cotugno, M., Zucconi, G.G., Vescia, S., 1995. The sequential hypothesis of the function of sleep. *Behav. Brain Res.* 69, 157–166.
- Grassi, S., Pettorossi, V.E., 2001. Synaptic plasticity in the medial vestibular nuclei: role of glutamate receptors and retrograde messengers in rat brainstem slices. *Prog. Neurobiol.* 64, 527–553.
- Greene, L.A., Kaplan, D.R., 1995. Early events in neurotrophin signalling via Trk and p75 receptors. *Curr. Opin. Neurobiol.* 5, 579–587.
- Griffith, O.W., Stuehr, D.J., 1995. Nitric oxide synthases: properties and catalytic mechanism. *Annu. Rev. Physiol.* 57, 707–736.
- Harris, K.D., Henze, D.A., Hirase, H., Leinekugel, X., Dragoi, G., Czurko, A., Buzsaki, G., 2002. Spike train dynamics predicts theta-related phase precession in hippocampal pyramidal cells. *Nature* 417, 738–741.
- Hasselmo, M.E., 1995. Neuromodulation and cortical function: modeling the physiological basis of behavior. *Behav. Brain Res.* 67, 1–27.
- Hasselmo, M.E., 1999. Neuromodulation: acetylcholine and memory consolidation. *Trends Cogn. Sci.* 3, 351–359.
- Hebb, D.O., 1949. *The Organization of Behavior: A Neuropsychological Theory*. Wiley, New York.
- Heerssen, H.M., Segal, R.A., 2002. Location, location, location: a spatial view of neurotrophin signal transduction. *Trends Neurosci.* 25, 160–165.
- Hennevin, E., Hars, B., Maho, C., Bloch, V., 1995. Processing of learned information in paradoxical sleep: relevance for memory. *Behav. Brain Res.* 69, 125–135.
- Hering, H., Sheng, M., 2001. Dendritic spines: structure, dynamics and regulation. *Nat. Rev. Neurosci.* 2, 880–888.
- Hernandez-Cruz, A., Pape, H.C., 1989. Identification of two calcium currents in acutely dissociated neurons from the rat lateral geniculate nucleus. *J. Neurophysiol.* 61, 1270–1283.
- Heynen, A.J., Bear, M.F., 2001. Long-term potentiation of thalamocortical transmission in the adult visual cortex in vivo. *J. Neurosci.* 21, 9801–9813.
- Hirase, H., 2001. Firing rates of hippocampal neurons are preserved during subsequent sleep episodes and modified by novel experience. *Proc. Natl. Acad. Sci. U.S.A.* 98, 9286–9390.
- Hirsch, J.C., Fourment, A., Marc, M.E., 1983. Sleep-related variations of membrane potential in the lateral geniculate body relay neurons of the cat. *Brain Res.* 259, 308–312.
- Hobson, J.A., Steriade, M., 1986. Neuronal basis of behavioral state control. In: Mountcastle, V.B., Bloom, F.E., Geiger, S.R. (Eds.), *Handbook of Physiology, Section 1: The Nervous System*, vol. IV. Intrinsic Regulatory Systems of the Brain. American Physiological Society, Bethesda, pp. 701–826.
- Hobson, J.A., Stickgold, R., 1995. Sleep the beloved teacher? *Curr. Biol.* 5, 35–36.
- Hoffman, K.L., McNaughton, B.L., 2002. Coordinated reactivation of distributed memory traces in primate cortex. *Science* 297, 2070–2073.
- Hoffman, D.A., Magee, J.C., Colbert, C.M., Johnston, D., 1997. K⁺ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. *Nature* 387, 869–875.
- Hogan, D., Roffwarg, H.P., Shaffery, J.P., 2001. The effects of 1 week of REM sleep deprivation on parvalbumin and calbindin immunoreactive neurons in central visual pathways of kittens. *J. Sleep Res.* 10, 285–296.
- Horne, J.A., 2000. REM sleep—by default? *Neurosci. Biobehav. Rev.* 24, 777–797.
- Houweling, A.R., Bazhenov, M., Timofeev, I., Grenier, F., Steriade, M., Sejnowski, T.J., 2002. Frequency-selective augmenting responses by short-term synaptic depression in cat neocortex. *J. Physiol.* 542, 599–617.
- Huber, R., Deboer, T., Tobler, I., 2000. Topography of EEG dynamics after sleep deprivation in mice. *J. Neurophysiol.* 84, 1888–1893.
- Huguenard, J.R., Prince, D.A., 1992. A novel T-type current underlies prolonged Ca²⁺-dependent burst firing in GABAergic neurons of rat thalamic reticular nucleus. *J. Neurosci.* 12, 3804–3817.
- Imamura, K., Kasamatsu, T., 1991. Ocular dominance plasticity restored by NA infusion to aplastic visual cortex of anesthetized and paralyzed kittens. *Exp. Brain Res.* 87, 309–318.

- Irwin, M., Thompson, J., Miller, C., Gillin, J.C., Ziegler, M., 1999. Effects of sleep and sleep deprivation on catecholamine and interleukin-2 levels in humans: clinical implications. *J. Clin. Endocrinol. Metab.* 84, 1979–1985.
- Isaac, J., 2001. Protein phosphatase 1 and LTD: synapses are the architects of depression. *Neuron* 32, 963–966.
- Isomura, Y., Fujiwara-Tsukamoto, Y., Imanishi, M., Nambu, A., Takada, M., 2002. Distance-dependent Ni^{2+} -sensitivity of synaptic plasticity in apical dendrites of hippocampal CA1 pyramidal cells. *J. Neurophysiol.* 87, 1169–1174.
- Ito, M., 2001. Cerebellar long-term depression: characterization, signal transduction, and functional roles. *Physiol. Rev.* 81, 1143–1195.
- Jacobs, B.L., 1986. Single unit activity of locus coeruleus neurons in behaving animals. *Prog. Neurobiol.* 27, 183–194.
- Jeanerod, M., Sakai, K., 1970. Occipital and geniculate potentials related to eye movements in the unanaesthetized cat. *Brain Res.* 19, 361–377.
- Job, C., Eberwine, J., 2001. Localization and translation of mRNA in dendrites and axons. *Nat. Rev. Neurosci.* 2, 889–898.
- Jouvet-Mounier, D., Astic, L., Lacote, D., 1970. Ontogenesis of the states of sleep in rat, cat and guinea pig during the first postnatal month. *Dev. Psychobiol.* 2, 216–239.
- Kahana, M.J., Seelig, D., Madsen, J.R., 2001. Theta returns. *Curr. Opin. Neurobiol.* 11, 739–744.
- Karni, A., Tanne, D., Rubenstein, B.S., Askenasy, J.J.M., Sagi, D., 1994. Dependence of REM sleep of overnight improvement of a perceptual skill. *Science* 265, 679–682.
- Katona, I., Sperlagh, B., Sik, A., Kafalvi, A., Vizi, E.S., Mackie, K., Freund, T.F., 1999. Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. *J. Neurosci.* 19, 4544–4558.
- Katona, I., Rancz, E.A., Acsady, L., Ledent, C., Mackie, K., Hajos, N., Freund, T.F., 2001. Distribution of CB1 cannabinoid receptors in the amygdala and their role in the control of GABAergic transmission. *J. Neurosci.* 21, 9506–9518.
- Kattler, H., Dijk, D.-J., Borbely, A.A., 1994. Effect of unilateral somatosensory stimulation prior to sleep on the sleep EEG in humans. *J. Sleep Res.* 3, 159–164.
- Kavanau, J.L., 1994. Sleep and dynamic stabilization of neural circuitry: a review and synthesis. *Behav. Brain Res.* 63, 111–126.
- Kavanau, J.L., 1996. Memory, sleep, and dynamic stabilization of neural circuitry: evolutionary perspectives. *Neurosci. Biobehav. Rev.* 20, 289–311.
- Kavanau, J.L., 1997. Memory, sleep and the evolution of mechanisms of synaptic efficacy. *Neuroscience* 79, 7–44.
- Kay, A.R., Wong, R.K., 1987. Calcium current activation kinetics in isolated pyramidal neurones of the CA1 region of the mature guinea-pig hippocampus. *J. Physiol. (Lond.)* 392, 603–616.
- Kemp, N., Bashir, Z.I., 2001. Long-term depression: a cascade of induction and expression mechanisms. *Prog. Neurobiol.* 65, 339–365.
- Kirkwood, A., Lee, H.K., Bear, M.F., 1995. Co-regulation of long-term potentiation and experience-dependent synaptic plasticity in visual cortex. *Nature* 375, 328–331.
- Kiss, J.P., Vizi, E.S., 2001. Nitric oxide: a novel link between synaptic and nonsynaptic transmission. *Trends Neurosci.* 24, 211–215.
- Koester, H.J., Sakmann, B., 1998. Calcium dynamics in single spines during coincident pre- and postsynaptic activity depend on relative timing of back-propagating action potentials and subthreshold excitatory postsynaptic potentials. *Proc. Natl. Acad. Sci. U.S.A.* 95, 9596–9601.
- Kovalchuk, Y., Eilers, J., Lisman, J., Konnerth, A., 2000. NMDA receptor-mediated subthreshold Ca^{2+} signals in spines of hippocampal neurons. *J. Neurosci.* 20, 1791–1799.
- Kreitzer, A.C., Regehr, W.G., 2001. Cerebellar depolarization-induced suppression of inhibition is mediated by endogenous cannabinoids. *J. Neurosci.* 21, RC174.
- Krueger, J.M., Obal, F.J., 1993. A neuronal group theory of sleep function. *J. Sleep Res.* 2, 63–69.
- Krueger, J.M., Obal, F., 2002. Function of sleep. In: Carskadon, M.A. (Ed.), *Sleep Medicine*. Hanley & Belfus, Philadelphia, pp. 23–30.
- Krueger, J.M., Obal, F.J., Kapas, L., Fang, J., 1995. Brain organization and sleep function. *Behav. Brain Res.* 69, 177–185.
- Krueger, J.M., Obal, F.J., Fang, J., 1999. Why we sleep: a theoretical view of sleep function. *Sleep Med. Rev.* 3, 119–129.
- Krugers, H.J., Koolhaas, J.M., Medema, R.M., Korf, J., 1996. Prolonged subordination stress increases calbindin-D28k immunoreactivity in the rat hippocampal CA1 area. *Brain Res.* 729, 289–293.
- Kudrimoti, H.S., Barnes, C.A., McNaughton, B.L., 1999. Reactivation of hippocampal cell assemblies: effects of behavioral state, experience and EEG dynamics. *J. Neurosci.* 19, 4090–4101.
- Kushikata, T., Fang, J., Krueger, J.M., 1999. Brain-derived neurotrophic factor enhances spontaneous sleep in rats and rabbits. *Am. J. Physiol.* 276, R1334–R1338.
- La Hoste, G.J., Gordon, W.C., Bazan, N.G., 2002. Role of stress hormones in sleep deprivation-induced memory impairments in rats. Program No. 375.9. 2002 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience. Online.
- Langella, M., Colarieti, L., Ambrosini, M.V., Giuditta, A., 1992. The sequential hypothesis of sleep function. IV. A correlative analysis of sleep variables in learning and non-learning rats. *Physiol. Behav.* 51, 227–238.
- Laureys, S., Peigneux, P., Phillips, C., Fuchs, S., Degueldre, C., Aerts, J., Del Fiore, G., Petiau, C., Luxen, A., Van Der Linden, M., Cleeremans, A., Smith, C., Maquet, P., 2001. Experience-dependent changes in cerebral functional connectivity during human rapid-eye-movement sleep. *Neuroscience* 105, 521–525.
- Lee, A.K., Wilson, M.A., 2002. Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron* 36, 1183–1194.
- Lendvai, B., Stern, E.A., Chen, B., Svoboda, K., 2000. Experience-dependent plasticity of dendritic spines in the developing rat barrel cortex in vivo. *Nature* 404, 876–881.
- Leonard, B.J., McNaughton, B.L., Barnes, C.A., 1987. Suppression of hippocampal synaptic plasticity during slow-wave sleep. *Brain Res.* 425, 174–177.
- Lewin, G.R., Barde, Y.A., 1996. Physiology of the neurotrophins. *Annu. Rev. Neurosci.* 19, 289–317.
- Lisman, J., Schulman, H., Cline, H., 2002. The molecular basis of CaMKII function in synaptic and behavioural memory. *Nat. Rev. Neurosci.* 3, 175–190.
- Louie, K., Wilson, M.A., 2001. Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron* 29, 145–156.
- Lucero, M., 1970. Lengthening of REM sleep duration consecutive to learning in the rat. *Brain Res.* 20, 319–322.
- Luscher, C., Frerking, M., 2001. Restless AMPA receptors: implications for synaptic transmission and plasticity. *Trends Neurosci.* 24, 665–670.
- Lydic, R., McCarley, R.W., Hobson, J.A., 1987. Serotonin neurons and sleep. I. long term recordings of dorsal raphe discharge frequency and PGO waves. *Arch. Ital. Biol.* 125, 317–343.
- Magee, J.C., Johnston, D., 1995a. Characterization of single voltage-gated Na^+ and Ca^{2+} channels in apical dendrites of rat CA1 pyramidal neurons. *J. Physiol. (Lond.)* 487 (Part 1), 67–90.
- Magee, J.C., Johnston, D., 1995b. Synaptic activation of voltage-gated channels in the dendrites of hippocampal pyramidal neurons. *Science* 268, 301–304.
- Magee, J.C., Johnston, D., 1997. A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* 275, 209–213.
- Magistretti, J., de Curtis, M., 1998. Low-voltage activated T-type calcium currents are differently expressed in superficial and deep layers of guinea pig piriform cortex. *J. Neurophysiol.* 79, 808–816.
- Maho, C., Hennevin, E., 2002. Appetitive conditioning-induced plasticity is expressed during paradoxical sleep in the medial geniculate, but not in the lateral amygdala. *Behav. Neurosci.* 116, 807–823.

- Mainen, Z.F., Malinow, R., Svoboda, K., 1999. Synaptic calcium transients in single spines indicate that NMDA receptors are not saturated. *Nature* 399, 151–155.
- Malenka, R.C., Nicoll, R.A., 1999. Long-term potentiation—a decade of progress? *Science* 285, 1870–1874.
- Mandile, P., Vescia, S., Montagnese, P., Piscopo, S., Cotugno, M., Giuditta, A., 2000. Post-trial sleep sequences including transition sleep are involved in avoidance learning of adult rats. *Behav. Brain Res.* 112, 23–31.
- Maquet, P., 2001. The role of sleep in learning and memory. *Science* 294, 1048–1051.
- Maquet, P., Laureys, S., Peigneux, P., Fuchs, S., Petiau, C., Phillips, C., Aerts, J., Del Fiore, G., Degueldre, C., Meulemans, T., Luxen, A., Franck, G., Van Der Linden, M., Smith, C., Cleeremans, A., 2000. Experience-dependent changes in cerebral activation during human REM sleep. *Nat. Neurosci.* 3, 831–836.
- Markram, H., Lubke, J., Frotscher, M., Sakmann, B., 1997. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 275, 213–215.
- Marr, D., 1971. Simple memory: a theory for archicortex. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 262, 23–81.
- Marrosu, F., Portas, C., Mascia, M.S., Casu, M.A., Fa, M., Giagheddu, M., Imperato, A., Gessa, G.L., 1995. Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep–wake cycle in freely moving cats. *Brain Res.* 671, 329–332.
- Marsicano, G., Wotjak, C.T., Azad, S.C., Bisogno, T., Rammes, G., Cascio, M.G., Hermann, H., Tang, J., Hofmann, C., Zieglgansberger, W., Di Marzo, V., Lutz, B., 2002. The endogenous cannabinoid system controls extinction of aversive memories. *Nature* 418, 530–534.
- Matsuda, L.A., 1997. Molecular aspects of cannabinoid receptors. *Crit. Rev. Neurobiol.* 11, 143–166.
- Mazzoni, G., Sori, S., Formicola, G., Gneri, G., Massetani, R., Murri, L., Salzarulo, P., 1999. Word recall correlates with sleep cycles in elderly subjects. *J. Sleep Res.* 8, 185–188.
- McClelland, J.L., McNaughton, B.L., O'Reilly, R.C., 1995. Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* 102, 419–457.
- McCormick, D.A., 1992. Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. *Prog. Neurobiol.* 39, 337–388.
- McCormick, D.A., Bal, T., 1997. Sleep and arousal: thalamocortical mechanisms. *Annu. Rev. Neurosci.* 20, 185–215.
- McGinty, D.J., Harper, R.M., 1976. Dorsal raphe neurons: depression of firing during sleep in cats. *Brain Res.* 101, 569–575.
- McNaughton, B.L., Douglas, R.M., Goddard, G.V., 1978. Synaptic enhancement in fascia dentata: cooperativity among coactive afferents. *Brain Res.* 157, 277–293.
- Miller, S., Mayford, M., 1999. Cellular and molecular mechanisms of memory: the LTP connection. *Curr. Opin. Genet. Dev.* 9, 333–337.
- Mize, R.R., Lo, F., 2000. Nitric oxide, impulse activity, and neurotrophins in visual system development. *Brain Res.* 886 (1), 15–32.
- Mogul, D.J., Fox, A.P., 1991. Evidence for multiple types of Ca²⁺ channels in acutely isolated hippocampal CA3 neurones of the guinea-pig. *J. Physiol. (Lond.)* 433, 259–281.
- Moult, P.R., Schnabel, R., Kilpatrick, I.C., Bashir, Z.I., Collingridge, G.L., 2002. Tyrosine dephosphorylation underlies DHPG-induced LTD. *Neuropharmacology* 43, 175–180.
- Nadasky, Z., Hirase, H., Czurko, A., Csicsvari, J., Buzsáki, G., 1999. Replay and time compression of recurring spike sequences in the hippocampus. *J. Neurosci.* 19, 9497–9507.
- Nakanishi, H., Sun, Y., Nakamura, R.K., Mori, K., Ito, M., Suda, S., Namba, H., Storch, F.I., Dang, T.P., Mendelson, W., 1997. Positive correlations between cerebral protein synthesis rates and deep sleep in *Macaca mulatta*. *Eur. J. Neurosci.* 9, 271–279.
- Neuner-Jehle, M., Rhyner, T.A., Borbely, A.A., 1995. Sleep deprivation differentially affects the mRNA and protein levels of neurogranin in rat brain. *Brain Res.* 685, 143–153.
- Neuner-Jehle, M., Denizot, J.P., Borbely, A.A., Mallet, J., 1996. Characterization and sleep deprivation-induced expression modulation of dendrin, a novel dendritic protein in rat brain neurons. *J. Neurosci. Res.* 46, 138–151.
- Nicoll, R.A., Oliet, S.H.R., Malenka, R.C., 1998. NMDA receptor-dependent and metabotropic glutamate receptor-dependent forms of long-term depression coexist in CA1 hippocampal pyramidal cells. *Neurobiol. Learn. Mem.* 70, 62–72.
- Nimchinsky, E.A., Sabatini, B.L., Svoboda, K., 2002. Structure and function of dendritic spines. *Annu. Rev. Physiol.* 64, 313–353.
- Ohno-Shosaku, T., Maejima, T., Kano, M., 2001. Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals. *Neuron* 29, 729–738.
- Oksenberg, A., Shaffery, J.P., Marks, G.A., Speciale, S.G., Mihailoff, G., Roffwarg, H.P., 1996. Rapid eye movement sleep deprivation in kittens amplifies LGN cell-size disparity induced by monocular deprivation. *Dev. Brain Res.* 97, 51–61.
- Oliet, S.H., Malenka, R.C., Nicoll, R.A., 1997. Two distinct forms of long-term depression coexist in CA1 hippocampal pyramidal cells. *Neuron* 18, 969–982.
- Otani, S., Daniel, H., Takita, M., Crepel, F., 2002. Long-term depression induced by postsynaptic group II metabotropic glutamate receptors linked to phospholipase C and intracellular calcium rises in rat prefrontal cortex. *J. Neurosci.* 22, 3434–3444.
- Pagel, J., Pegram, V., Vaughn, S., Donaldson, P., Bridgers, W., 1973. The relationship of REM sleep with learning and memory in mice. *Behav. Biol.* 9, 383–388.
- Paulsen, O., Sejnowski, T.J., 2000. Natural patterns of activity and long-term synaptic plasticity. *Curr. Opin. Neurobiol.* 10, 172–179.
- Pavlidis, C., Winson, J., 1989. Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep. *J. Neurosci.* 9, 2907–2918.
- Pearlman, C.A., 1981. Rat models of the adaptive function of REM sleep. In: Fishbein, W. (Ed.), *Sleep, Dreams and Memory*, vol. 6. Spectrum Publications, New York, pp. 37–45.
- Peigneux, P., Laureys, S., Delbeuck, X., Maquet, P., 2001. Learning brain. The role of sleep for memory systems. *NeuroReport* 12, A111–A124.
- Penn, A.A., Shatz, C.J., 1999. Brain waves and brain wiring: the role of endogenous and sensory-driven neural activity in development. *Pediatr. Res.* 45, 447–458.
- Piscopo, S., Mandile, P., Montagnese, P., Cotugno, M., Giuditta, A., Vescia, S., 2001. Trains of sleep sequences are indices of learning capacity in rats. *Behav. Brain Res.* 120, 13–21.
- Poe, G.R., Nitz, D.A., McNaughton, B.L., Barnes, C.A., 2000. Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. *Brain Res.* 855, 176–180.
- Pompeiano, O., Pompeiano, M., Corvaja, N., 1995. Effects of sleep deprivation on the postnatal development of visual-deprived cells in the cat's lateral geniculate nucleus. *Arch. Ital. Biol.* 134, 121–140.
- Pompeiano, M., Cirelli, C., Ronca-Testoni, S., Tononi, G., 1997. NGF1-A expression in the rat brain after sleep deprivation. *Mol. Brain Res.* 46, 143–153.
- Poo, M.M., 2001. Neurotrophins as synaptic modulators. *Nat. Rev. Neurosci.* 2, 24–32.
- Porkka-Heiskanen, T., Smith, S.E., Taira, T., Urban, J.H., Levine, J.E., Turek, F.W., Stenberg, D., 1995. Noradrenergic activity in rat brain during rapid eye movement sleep deprivation and rebound sleep. *Am. J. Physiol.* 268, R1456–R1463.
- Qin, Y.L., McNaughton, B.L., Skaggs, W.E., Barnes, C.A., 1997. Memory reprocessing in corticocortical and hippocampal cortical neuronal ensembles. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 352, 1525–1533.
- Ramm, P., Smith, C.T., 1990. Rates of cerebral protein synthesis are linked to slow-wave sleep in the rat. *Physiol. Behav.* 48, 749–753.
- Rappelsberger, P., Pockberger, H., Petsche, H., 1982. The contribution of the cortical layers to the generation of the EEG: field potential and current source density analyses in the rabbit's visual cortex. *Electroencephalogr. Clin. Neurophysiol.* 53, 254–269.

- Rauschecker, J.P., Hahn, S., 1987. Ketamine–xylazine anesthesia blocks consolidation of ocular dominance changes in kitten visual cortex. *Nature* 326, 183–185.
- Reiter, H.O., Waitzman, D.M., Stryker, M.P., 1986. Cortical activity blockade prevents ocular dominance plasticity in the kitten visual cortex. *Exp. Brain Res.* 65, 182–188.
- Ribeiro, S., Mello, C.V., Velho, T., Gardner, T.J., Jarvis, E.D., Pavlides, C., 2002. Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal *zif-268* expression during ensuing rapid-eye-movement sleep. *J. Neurosci.* 22, 10914–10923.
- Rittenhouse, C.D., Shouval, H.Z., Paradiso, M.A., Bear, M.F., 1999. Monocular deprivation induces homosynaptic long-term depression in visual cortex. *Nature* 397, 347–350.
- Rizzuto, R., 2001. Intracellular Ca^{2+} pools in neuronal signalling. *Curr. Opin. Neurobiol.* 11, 306–311.
- Robbe, D., Kopf, M., Remaury, A., Bockaert, J., Manzoni, O.J., 2002. Endogenous cannabinoids mediate long-term synaptic depression in the nucleus accumbens. *Proc. Natl. Acad. Sci. U.S.A.* 99, 8384–8388.
- Roffwarg, H.P., Muzio, J.N., Dement, W.C., 1966. Ontogenetic development of the human sleep–dream cycle. *Science* 152, 604–619.
- Sabatini, B.L., Svoboda, K., 2000. Analysis of calcium channels in single spines using optical fluctuation analysis. *Nature* 408, 589–593.
- Sabatini, B.L., Maravall, M., Svoboda, K., 2001. Ca^{2+} signaling in dendritic spines. *Curr. Opin. Neurobiol.* 11, 349–356.
- Sah, P., Louise Faber, E.S., 2002. Channels underlying neuronal calcium-activated potassium currents. *Prog. Neurobiol.* 66, 345–353.
- Sanchez-Vives, M.V., McCormick, D.A., 2000. Cellular and network mechanisms of rhythmic recurrent activity in neocortex. *Nat. Neurosci.* 3, 1027–1034.
- Sanes, J.R., Lichtman, J.W., 1999. Can molecules explain long-term potentiation? *Nat. Neurosci.* 2, 597–604.
- Sapolsky, R.M., 1996. Stress, glucocorticoids, and damage to the nervous system: the current state of confusion. *Stress* 1, 1–19.
- Schiffelholz, T., Aldenhoff, J.B., 2002. Novel object presentation affects sleep–wake behavior in rats. *Neurosci. Lett.* 328, 41–44.
- Schiller, J., Schiller, Y., Clapham, D.E., 1998. NMDA receptors amplify calcium influx into dendritic spines during associative pre- and postsynaptic activation. *Nat. Neurosci.* 1, 114–118.
- Schinder, A.F., Poo, M., 2000. The neurotrophin hypothesis for synaptic plasticity. *Trends Neurosci.* 23, 639–645.
- Schulman, H., Hyman, S.E., 1999. Intracellular signaling. In: Zigmond, M.J., Bloom, F.E., Landis, S.C., Roberts, J.L., Squire, L.R. (Eds.), *Fundamental Neuroscience*. Academic Press, San Diego, pp. 269–316.
- Sei, H., Saitoh, D., Yamamoto, K., Morita, K., Morita, Y., 2000. Differential effect of short-term REM sleep deprivation on NGF and BDNF protein levels in the rat brain. *Brain Res.* 877, 387–390.
- Sejnowski, T.J., Destexhe, A., 2000. Why do we sleep? *Brain Res.* 886, 208–223.
- Shaffery, J.P., Oksenberg, A., Marks, G.A., Speciale, S.G., Mihailoff, G., Roffwarg, H.P., 1998. REM sleep deprivation in monocularly occluded kittens reduces the size of cells in LGN monocular segment. *Sleep* 21, 837–945.
- Shaffery, J.P., Roffwarg, H.P., Speciale, S.G., Marks, G.A., 1999. Pontogeniculo-occipital wave suppression amplifies lateral geniculate nucleus cell-size changes in monocularly deprived kittens. *Dev. Brain Res.* 114, 109–119.
- Shaffery, J.P., Sinton, C.M., Bisette, G., Roffwarg, H.P., A., M.G., 2002. Rapid eye movement sleep deprivation modifies expression of long-term potentiation in visual cortex of immature rats. *Neuroscience* 110, 431–443.
- Shapiro, C., Girdwood, P., 1981. Protein synthesis in rat brain during sleep. *Neuropharmacology* 20, 457–460.
- Sheng, M., Kim, M.J., 2002. Postsynaptic signaling and plasticity mechanisms. *Science* 298, 776–780.
- Siegel, J.M., 2000. Brainstem mechanisms generating REM sleep. In: Kryger, M.H., Roth, T., Dement, W.C. (Eds.), *Principles and Practice of Sleep Medicine*. Saunders, Philadelphia, pp. 112–133.
- Siegel, J.M., 2001. The REM sleep–memory consolidation hypothesis. *Science* 294, 1058–1063.
- Silva, A.J., Kogan, J.H., Frankland, P.W., Kida, S., 1998. CREB and memory. *Annu. Rev. Neurosci.* 21, 127–148.
- Sjostrom, P.J., Nelson, S.B., 2002. Spike timing, calcium signals and synaptic plasticity. *Curr. Opin. Neurobiol.* 12, 305–314.
- Skaggs, W.E., McNaughton, B.L., 1996. Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science* 271, 1870–1873.
- Smiley, J.F., 1996. Monoamines and acetylcholine in primate cerebral cortex: what anatomy tells us about function. *Rev. Bras. Biol.* 56 (Suppl. 1 (Part 1)), 153–164.
- Smith, C., 1985. Sleep states and learning: a review of the animal literature. *Neurosci. Biobehav. Rev.* 9, 157–168.
- Smith, C., 1995. Sleep states and memory processes. *Behav. Brain Res.* 69, 137–145.
- Smith, C., 1996. Paradoxical sleep deprivation and sleep recording following training in a brightness discrimination avoidance task in Sprague–Dawley rats: paradoxical effects. *Neurobiol. Learn. Mem.* 66, 283–294.
- Smith, C., Rose, G.M., 2000. Evaluating the relationship between REM sleep and memory consolidation: a need for scholarship and hypothesis testing. *Behav. Brain Sci.* 23, 1007–1008.
- Snyder, E.M., Philpot, B.D., Huber, K.M., Dong, X., Fallon, J.R., Bear, M.F., 2001. Internalization of ionotropic glutamate receptors in response to mGluR activation. *Nat. Neurosci.* 4, 1079–1085.
- Soderling, T.R., 2000. CaM-kinases: modulators of synaptic plasticity. *Curr. Opin. Neurobiol.* 10, 375–380.
- Spacek, J., Harris, K.M., 1997. Three-dimensional organization of smooth endoplasmic reticulum in hippocampal CA1 dendrites and dendritic spines of the immature and mature rat. *J. Neurosci.* 17, 190–203.
- Squire, L.R., 1992. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* 99, 195–231.
- Squire, L.R., Alvarez, P., 1995. Retrograde amnesia and memory consolidation: a neurobiological perspective. *Curr. Opin. Neurobiol.* 5, 169–177.
- Steriade, M., 1999. Coherent oscillations and short-term plasticity in corticothalamic networks. *Trends Neurosci.* 22, 337–345.
- Steriade, M., 2000. Brain electrical activity and sensory processing during waking and sleep states. In: Kryger, M.H., Roth, T., Dement, W.C. (Eds.), *Principles and Practice of Sleep Medicine*. Saunders, Philadelphia, pp. 93–111.
- Steriade, M., 2001. Impact of network activities on neuronal properties in corticothalamic systems. *J. Neurophysiol.* 86, 1–39.
- Steriade, M., Amzica, F., 1998. Coalescence of sleep rhythms and their chronology in corticothalamic networks. *Sleep Res. Online* 1, 1–10.
- Steriade, M., Domich, L., Oakson, G., Deschenes, M., 1987. The deafferented reticular thalamic nucleus generates spindle rhythmicity. *J. Neurophysiol.* 57, 260–273.
- Steriade, M., McCormick, D.A., Sejnowski, T.J., 1993a. Thalamocortical oscillations in the sleeping and aroused brain. *Science* 262, 679–685.
- Steriade, M., Nunez, A., Amzica, F., 1993b. Intracellular analysis of relations between the slow (<1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. *J. Neurosci.* 13, 3266–3283.
- Stickgold, R., 1998. Sleep: off-line memory reprocessing. *Trends Cogn. Sci.* 2, 484–492.
- Stickgold, R., LaTanya, J., Hobson, J.A., 2000. Visual discrimination learning requires sleep after training. *Nat. Neurosci.* 3, 1237–1238.
- Stickgold, R., Hobson, J.A., Fosse, R., Fosse, M., 2001. Sleep, learning and dreams: off-line memory reprocessing. *Science* 294, 1052–1057.
- Stricker, C., 2002. Central synaptic integration: linear after all? *News Physiol. Sci.* 17, 138–143.
- Stricker, C., Field, A.C., Redman, S.J., 1996. Statistical analysis of amplitude fluctuations in EPSCs evoked in rat CA1 pyramidal neurones in vitro. *J. Physiol. (Lond.)* 490 (Part 2), 419–441.

- Suzuki, S., Rogawski, M.A., 1989. T-type calcium channels mediate the transition between tonic and phasic firing in thalamic neurons. *Proc. Natl. Acad. Sci. U.S.A.* 86, 7228–7232.
- Svoboda, K., Mainen, Z.F., 1999. Synaptic $[Ca^{2+}]$: intracellular stores spill their guts. *Neuron* 22, 427–430.
- Swanson, L.W., Kohler, C., 1986. Anatomical evidence for direct projections from the entorhinal area to the entire cortical mantle in the rat. *J. Neurosci.* 6, 3010–3023.
- Taishi, P., Sanchez, C., Wang, Y., Fang, J., Harding, J.W., Krueger, J.M., 2001. Conditions that affect sleep alter the expression of molecules associated with synaptic plasticity. *Am. J. Physiol.* 281, R839–R845.
- Takahashi, S., Krueger, J.M., 1999. Nerve growth factor enhances sleep in rabbits. *Neurosci. Lett.* 264, 149–152.
- Tang, Y.P., Shimizu, E., Dube, G.R., Rampon, C., Kerchner, G.A., Zhuo, M., Liu, G., Tsien, J.Z., 1999. Genetic enhancement of learning and memory in mice. *Nature* 401, 63–69.
- Tao, H.W., Poo, M., 2001. Retrograde signaling at central synapses. *Proc. Natl. Acad. Sci. U.S.A.* 98, 11009–11015.
- Timofeev, I., Grenier, F., Bazhenov, M., Houweling, A.R., Sejnowski, T.J., Steriade, M., 2002. Short- and medium-term plasticity associated with augmenting responses in cortical slabs and spindles in intact cortex of cats in vivo. *J. Physiol. (Lond.)* 542, 583–598.
- Tobler, I., Murrison, R., Ursin, R., Ursin, H., Borbely, A.A., 1983. The effect of sleep deprivation and recovery sleep on plasma corticosterone in the rat. *Neurosci. Lett.* 35, 297–300.
- Tononi, G., Cirelli, C., 2001a. Modulation of brain gene expression during sleep and wakefulness: a review of recent findings. *Neuropsychopharmacology* 25, S28–S35.
- Tononi, G., Cirelli, C., 2001b. Some considerations on sleep and neural plasticity. *Arch. Ital. Biol.* 139, 221–241.
- Trachtenberg, J.T., Trepel, C., Stryker, M.P., 2000. Rapid extragranular plasticity in the absence of thalamocortical plasticity in the developing primary visual cortex. *Science* 287, 2029–2032.
- van Dam, E.J., Ruiter, B., Kamal, A., Ramakers, G.M., Gispen, W.H., de Graan, P.N., 2002. *N*-Methyl-D-aspartate-induced long-term depression is associated with a decrease in postsynaptic protein kinase C substrate phosphorylation in rat hippocampal slices. *Neurosci. Lett.* 320, 129–132.
- Van Hoesen, G.W., Hyman, B.T., Damasio, A.R., 1991. Entorhinal cortex pathology in Alzheimer's disease. *Hippocampus* 1, 1–8.
- Vergara, C., Latorre, R., Marrion, N.V., Adelman, J.P., 1998. Calcium-activated potassium channels. *Curr. Opin. Neurobiol.* 8, 321–329.
- Vertes, R.P., Eastman, K.E., 2000. The case against memory consolidation in REM sleep. *Behav. Brain Sci.* 23, 867–876.
- Vescia, S., Mandile, P., Montagnese, P., Romano, F., Cataldo, G., Cotugno, M., Giuditta, A., 1996. Baseline transition sleep and associated sleep episodes are related to the learning ability of rats. *Physiol. Behav.* 60, 1513–1525.
- Vitale-Neugebauer, A., Giuditta, A., Vitale, B., Giaquinto, S., 1970. Pattern of RNA synthesis in rabbit cortex during sleep. *J. Neurochem.* 17, 1263–1273.
- von Krosigk, M., Bal, T., McCormick, D.A., 1993. Cellular mechanisms of a synchronized oscillation in the thalamus. *Science* 261, 361–364.
- Vyazovskiy, V., Borbely, A.A., Tobler, I., 2000. Unilateral vibrissae stimulation during waking induces interhemispheric asymmetry during subsequent sleep. *J. Sleep Res.* 9, 367–371.
- Walker, M.P., Brakefield, T., Morgan, A., Hobson, J.A., Stickgold, R., 2002. Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron* 35, 205–211.
- Wang, Y., Rowan, M.J., Anwyl, R., 1997. Induction of LTD in the dentate gyrus in vitro is NMDA receptor independent, but dependent on Ca^{2+} influx via low-voltage-activated Ca^{2+} channels and release of Ca^{2+} from intracellular stores. *J. Neurophysiol.* 77, 812–825.
- Watabe, A.M., Carlisle, H.J., O'Dell, T.J., 2002. Postsynaptic induction and presynaptic expression of group 1 mGluR-dependent LTD in the hippocampal CA1 region. *J. Neurophysiol.* 87, 1395–1403.
- Watson, F.L., Heerssen, H.M., Moheban, D.B., Lin, M.Z., Sauvageot, C.M., Bhattacharyya, A., Pomeroy, S.L., Segal, R.A., 1999. Rapid nuclear responses to target-derived neurotrophins require retrograde transport of ligand–receptor complex. *J. Neurosci.* 19, 7889–7900.
- Wilson, M.A., McNaughton, B.L., 1994. Reactivation of hippocampal ensemble memories during sleep. *Science* 265, 676–682.
- Wilson, R.I., Nicoll, R.A., 2001. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. *Nature* 410, 588–592.
- Winder, D.G., Sweatt, J.D., 2001. Roles of serine/threonine phosphatases in hippocampal synaptic plasticity. *Nat. Rev. Neurosci.* 2, 461–474.
- Yin, J.C.P., Tully, T., 1996. CREB and the formation of long-term memory. *Curr. Opin. Neurobiol.* 6, 264–268.
- Yuste, R., Majewska, A., Holthoff, K., 2000. From form to function: calcium compartmentalization in dendritic spines. *Nat. Neurosci.* 3, 653–659.
- Zakharenko, S.S., Zablow, L., Siegelbaum, S.A., 2001. Visualization of changes in presynaptic function during long-term synaptic plasticity. *Nat. Neurosci.* 4, 711–717.
- Zakharenko, S.S., Zablow, L., Siegelbaum, S.A., 2002. Altered presynaptic vesicle release and cycling during mGluR-dependent LTD. *Neuron* 35, 1099–1110.
- Zalutsky, R.A., Nicoll, R.A., 1990. Comparison of two forms of long-term potentiation in single hippocampal neurons. *Science* 248, 1619–1624.
- Zepelin, H., 2000. Mammalian sleep. In: Kryger, M.H., Roth, T., Dement, W.C. (Eds.), *Principles and Practice of Sleep Medicine*. Saunders, Philadelphia, pp. 82–92.
- Zola-Morgan, S.M., Squire, L.R., 1990. The primate hippocampal formation: evidence for a time-limited role in memory storage. *Science* 250, 288–290.