CHAPTER 2

Corticothalamic Rhythms during States of Reduced Vigilance

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Since the discovery of the first rhythmic activity in the human electroencephalogram (EEG) by Hans Berger in the late 1920s (Berger, 1929), neuroscientists and laymen alike have been fascinated by the variety and complexity of the electrical waves that the human brain is able to express during clearly defined behavioral states (Brismar, 2007; Dijk, 2009; Krueger, Rector, Roy, Van Dongen, Belenky, & Panksepp, 2008; Monto, Palva, Voipio, & Palva, 2008; Siegel, 2008; Tallon-Baudry, 2009), from the attentive states of perception and decision-making to the unconscious states of non-rapid-eye-movement (NREM) sleep, anesthesia, and coma. This has been particularly true in the last 20 years with the advent of full band and high density EEG recordings (Vanhatalo, Voipio, & Kaila, 2005; Monto et al., 2008). At the same time, our understanding of the physiological and pathological significance of these EEG biomarkers recorded from the human scalp has benefited greatly from the ability to correlate them with noninvasive functional imaging of deep brain structures (Dang-Vu, Schabus, Desseilles, Sterpenich, Bonjean, & Maquet, 2010; Desseilles, Dang-Vu, Schabus, Sterpenich, Maquet, & Schwartz, 2008; Salek-Haddadi, Friston, Lemieux, & Fish, 2003). Our knowledge of the molecular, cellular, synaptic, and network processes underlying these waves and rhythms has also greatly progressed, though at a relatively slower speed, such that more than 80 years after Berger's pioneering observations we still lack a fully comprehensive mechanistic picture of some of these EEG activities and thus refer to them using long-standing, frequency band-based classifications.

As far as sleep rhythms are concerned, however, two notable exceptions need to be stressed. First is the discovery of powerful reciprocal connections between neocortex and thalamus, both with respect to the sensory thalamus and primary cortices as well as to intralaminar thalamic nuclei and association cortices (Jones, 2008; Sherman & Guillery, 1996): this

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has focused relevant research not only to the neocortex but also to the thalamus when searching for potential generator(s) of sleep-related EEG rhythms. In this respect, particular emphasis has been given to the corticothalamic synapses on thalamocortical (TC) neurons in sensory thalamic nuclei, which well outnumber those of afferents from the periphery and represent more than 50% of the overall synaptic count onto these neurons (Godwin, Van Horn, Sesma, Romano, & Sherman, 1996; Sherman & Guillery, 1996). Second is the identification of a key modulatory role for the ascending cholinergic and monoaminergic systems, which are the main determinants of the membrane potential of cortical and thalamic neurons (McCormick, 1992). In particular, during the progression from the waking attentive state to deep NREM sleep there is an overall net decrease in the tone of these afferents, which leads to a progressively more negative membrane potential in almost all types of cortical and thalamic neurons (Hirsch, Fourment, & Marc, 1983; Crunelli & Hughes, 2010; Steriade, Amzica, & Nuñez, 1993a).

In this chapter, we summarize current views on the cellular and network mechanisms of three EEG rhythms: the classical posterior alpha rhythm, the theta waves of light NREM sleep, and the slow (<1 Hz) sleep oscillation. The emerging picture in all these activities is one that highlights a smooth interplay between cortical and thalamic networks as the essential element that underlies the full expression of each of these brain waves in the EEG: this finding, we believe, is key in achieving a comprehensive knowledge of brain function in health and disease states. The other important point that arises from these studies is that the now classical textbook dichotomy of TC neuron electrophysiology (Sherman & Guillery, 1996; Llinas & Steriade, 2006) as expressing two firing modes, i.e., tonic single action potential firing in wakefulness and T-type Ca^{2+} channel-mediated high frequency burst firing in sleep, appears today to be highly restrictive and often an impediment for a full understanding of thalamic physiology: as illustrated in detail throughout this chapter, TC neurons express a much richer repertoire of intrinsic and synaptically driven firing activities than previously thought (Fig. 2.1).

THE ALPHA RHYTHM OF RELAXED WAKEFULNESS AND THE THETA WAVES OF EARLY NREM SLEEP

A section dealing with the classical posterior alpha rhythm may seem out of place in a book dedicated to brain activities during sleep. However,

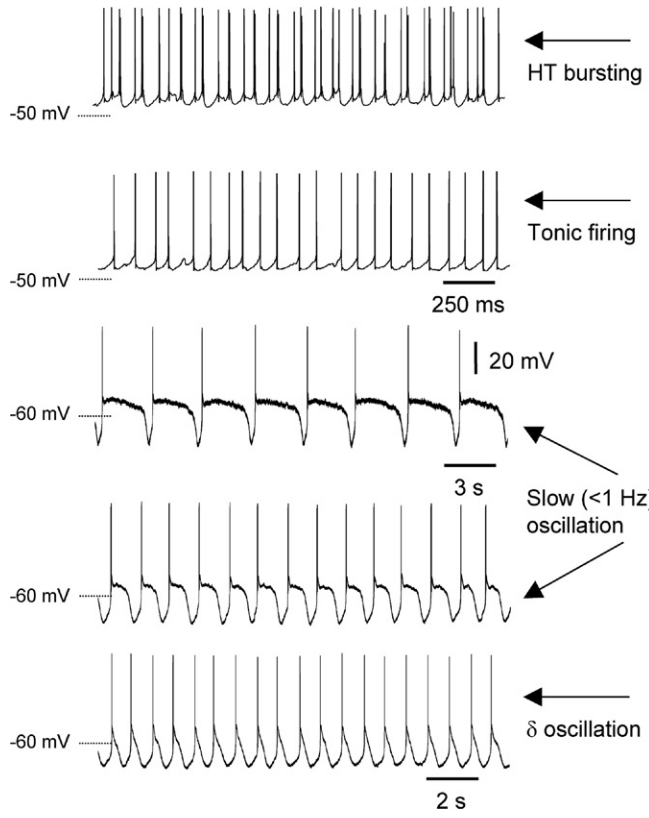

Figure 2.1 ***Repertoire of intrinsic activities of TC neurons.*** Intracellular recordings from a single TC neuron in the presence of a metabotrobic glutamate receptor agonist (t-ACPD, 50 μM) *in vitro* show the variety of intrinsic activities that can be elicited by TC neurons with different levels of increasing steady hyperpolarization (from top to bottom) mimicking the decrease in depolarizing tone that occurs during progression from relaxed wakefulness, when high threshold (HT) bursting is observed at the cellular level, to deep NREM sleep, where slow (<1 Hz) and delta oscillations are present. The addition of the glutamate metabotropic receptor agonist is used to mimic the effect of the cortical input on TC neurons. Note, however, that identical activities can be obtained *in vitro* in the absence of a glutamate metabotropic receptor agonist by electrically stimulating the cortical afferent present in the slice (for further details, see Blethyn et al., 2006; Crunelli & Hughes, 2010; Hughes et al., 2002b, 2004; Zhu et al., 2006).

as will be become evident later, the reason for this inclusion stems from the discovery that the alpha rhythm of relaxed wakefulness and the theta waves that are observed in the EEG during the early stages of NREM sleep rely on a very similar cellular mechanism (Hughes, Lőrincz, Cope, Blethyn, Kekesi, Parri, Juhasz, & Crunelli, 2004). Indeed, a discussion of

these rhythms provides the opportunity to highlight the full spectrum of intrinsic activities that TC neurons can generate at different membrane potentials, i.e., from the tonic action potential firing and high threshold (HT) bursts at depolarized potentials, to the intrinsically generated slow (<1 Hz) sleep oscillation and delta oscillation at progressively more hyperpolarized potentials (Fig. 2.1).

In contrast to other brain rhythms, for which extensive investigations have been carried out both in cortical and thalamic territories, the analysis of the mechanisms underlying the alpha rhythm has mainly focused, in part for historical reasons, on the thalamus (Hughes & Crunelli, 2005). Thus, following attempts to investigate the alpha rhythm mechanism by the use of an inappropriate model, i.e., the barbiturate-induced spindles (Andersen & Andersson, 1968), the work of Buser (Buser & Rougeul-Buser, 1995), Lopes Da Silva (Lopes da Silva, van Lierop, Schrijer, & van Leeuwen, 1973; Lopes da Silva, Vos, Mooibroek, & Van Rotterdam, 1980), and others (Basar E, Schurmann M, Basar-Eroglu C, & Karakas S. 1997; Bouyer, Tilquin, & Rougeul, 1983; Feige, Scheffler, Esposito, Di Salle, Hennig, & Seifritz, 2005; Isaichev, Derevyankin, Koptelov, & Sokolov, 2001), together with more recent noninvasive imaging investigations (Danos, Guich, Abel, & Buchsbaum, 2001; Goldman, Stern, Engel, & Cohen, 2002; Larson, Davidson, Abercrombie, Ward, Schaefer, Jackson, Holden, & Perlman, 1998; Lindgren, Larson, Schaefer, Abercrombie, Ward, Oakes, Holden, Perlman, Benca, & Davidson, 1999), have pointed to this subcortical structure as the potential rhythm generator for the alpha rhythm that is observed in the primary visual cortex of both humans and higher mammals during periods of relaxed wakefulness. Nevertheless, in freely behaving cats the alpha rhythm is clearly driven by a novel firing pattern, i.e., HT bursting, that is present in a subset (about 30%) of TC neurons in the visual thalamus, i.e., the dorsal lateral geniculate nucleus (LGN) (Figs. 2.1 and 2.2A) (Hughes et al., 2004; Lőrincz, Kékesi, Juhász, Crunelli, & Hughes, 2009). These HT bursts are very different from the classical high frequency bursts of action potentials that are elicited on the crest of T-type Ca^{2+} channel-mediated, low threshold Ca^{2+} potentials (LTCPs) (Figs. 2.1 and 2.2) (Hughes et al., 2004; Lőrincz et al., 2009). First, HT bursts occur when the membrane potential is in the range of −50 to −55 mV (Fig. 2.2D), whereas LTCP-mediated bursts are evoked only from membrane potentials <−60 mV. Second, the interspike intervals of HT bursts do not change as the burst progresses (Fig. 2.2C), whereas those of LTCP-mediated bursts show a characteristic increase within a

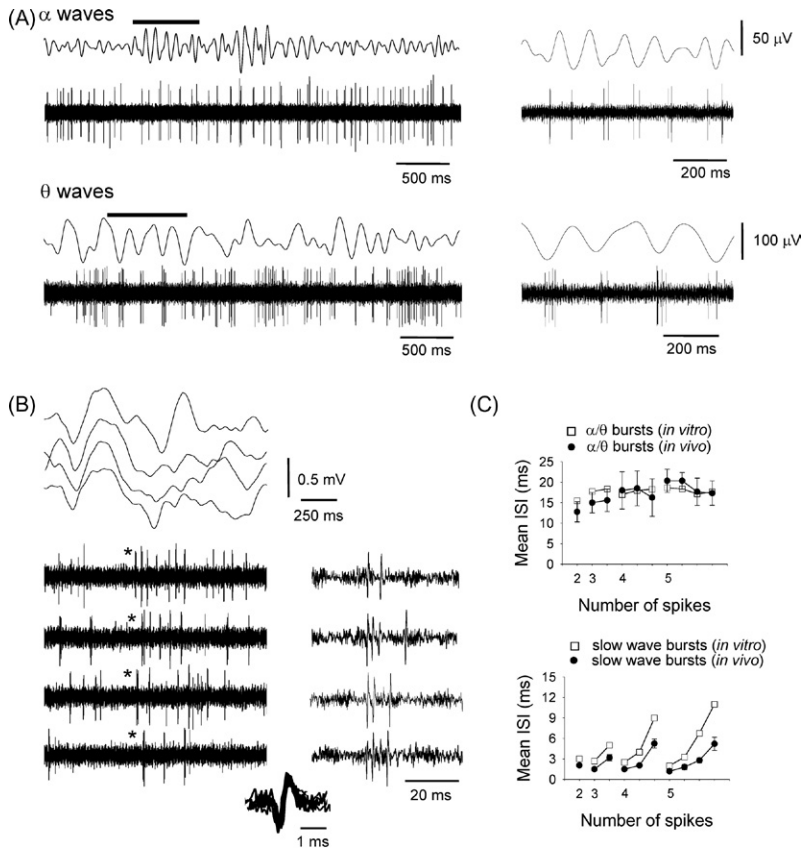

Figure 2.2 ***High threshold (HT) bursts in TC neurons and their role in the generation of alpha rhythm and sleep theta waves.*** A. Simultaneous field and single-unit recording in the LGN of a freely behaving animal showing correlated activity with both α (upper traces) and θ (lower traces) field oscillations during a period of relaxed wakefulness and in the early stage of NREM sleep, respectively. Marked sections are enlarged on the right. B. Four consecutive slow waves recorded from the LGN of a freely behaving animal during deep NREM sleep *in vivo* (upper 4 traces) and the corresponding single unit activity (lower 4 traces). Note that the high frequency burst of action potentials with interspike intervals that increase as the burst progresses. The bursts marked by asterisks are enlarged on the right, and the bottom inset is an overlay of all spikes in these bursts. C. Average interspike intervals (ISI) for action potentials in HT bursts correlated to α and θ activity *in vivo* (•) and *in vitro* (□) (top plot). Average interspike interval (ISI) for action potentials correlated to slow wave activity *in vivo* (•) and *in vitro* (□) (bottom plot) (note the contrasting pattern to that occurring during α and θ rhythms shown in the top plot). *In vitro* data were obtained in the presence of a glutamate metabotropic receptor agonist (t-ACPD).

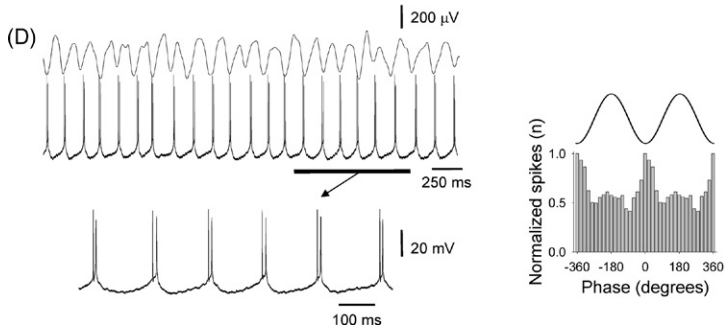

Figure 2.2 (*Continued*) D. Local field potential (top trace) and intracellular recordings (bottom trace) showing the waveform of HT bursts during alpha waves recorded *in vitro*. Spike timing histogram of the intracellular activity is shown to the right (for further details, see Hughes et al., 2004; Hughes & Crunelli, 2005).

burst (Fig. 2.2D). Third, the interspike intervals of HT bursts are rarely less than ~10 msec, whereas those at the start of an LTCP-mediated burst are typically in the range 2–5 ms (Fig. 2.2C, D). Fourth, HT bursts are partially sensitive to both high- and low-voltage activated Ca^{2+} channel blockers, whereas LTCP-mediated events are exclusively generated by the activation of low-voltage activated T-type Ca^{2+} channels.

Importantly, the frequency of HT bursting progressively increases with increasing membrane hyperpolarization (Hughes et al., 2004). It is therefore not surprising that when an animal transitions from a state of relaxed wakefulness (with prominent EEG alpha activity) to the early stage of sleep the occasional sequences of theta waves that are recorded from the occipital cortex in this behavioral condition are also correlated with HT bursts, which now show a larger number of action potentials per burst (generally 3 to 7) than during the alpha rhythm (Figs. 2.1 and 2.2A) (Hughes et al., 2004).

HT bursts are locally synchronized within the thalamus, since HT bursting TC neurons are coupled by gap junctions (Hughes, Blethyn, Cope, & Crunelli, 2002a; Hughes, Lőrincz, Blethyn, Kékesi, Juhász, Turmaine, Parnavelas, & Crunelli, 2011), leading to a powerful thalamic output to cortex, as indicated by the presence of a large local field potential (LFP) in the alpha frequency band in slices of the LGN following activation of either metabotropic glutamate receptors (mGluRs) or muscarinic acetylcholine receptors (mAchRs) (Hughes et al., 2004; Lőrincz, Crunelli, & Hughes, 2008b; Lőrincz et al., 2009). Indeed, blocking either mGluRs or mAchRs as well as gap-junction coupling by reverse

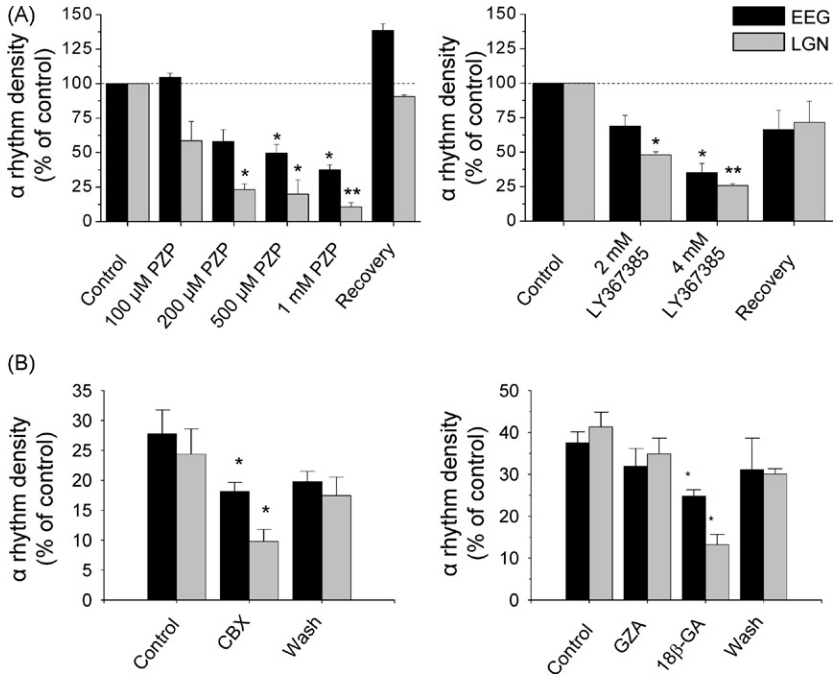

Figure 2.3 ***Gap-junction blockers and metabotropic cholinergic and glutamatergic receptor antagonists block alpha rhythm.*** A. Histograms summarizing the effect of bilateral thalamic injection by reverse microdialysis of pirenzipine (mAchR antagonist) (left) and LY367385 (mGluR1a antagonist) (right) on EEG (black bars) and LGN (gray bars) alpha rhythm density. B. Histograms summarizing the effect of bilateral thalamic injection by reverse microdialysis of two gap-junction blockers, carbenoxolone (CBX) (left plot) and 18β-glycyrrhetinic acid (18β-GA) (right plot) on EEG (black bars) and LGN (gray bars) alpha rhythm density. Note the lack of action of glycyrrhizic acid (GZA) (right plot), a glycyrrhetinic acid derivative that is inactive at gap-junction blockers (for further details, see Hughes et al., 2011; Lőrincz et al., 2009).

microdialyis application of appropriate antagonists directly in the LGN of freely moving animals almost abolishes the alpha rhythm locally and markedly decreases the alpha waves recorded from the occipital cortex (Fig. 2.3) (Hughes et al., 2011; Lőrincz et al., 2009). Moreover, in LGN slices transient elimination of HT bursts in a single TC neuron by membrane hyperpolarization abolishes alpha rhythm-related firing in closely surrounding neurons (Hughes et al., 2004) and decreases the amplitude of the thalamic LFP measured in the vicinity of the recorded neuron (Lõrincz et al., 2008b). Conversely, inhibition of firing in a single TC neuron that does not fire HT bursts leaves the output activity of the surrounding neurons and the thalamic LFP unchanged (Lőrincz et al., 2008, 2009).

During both alpha and theta waves in freely moving animals, the activity of the local GABAergic interneurons in the LGN and that of the remaining 70% of TC neurons that do not fire HT bursts but single action potentials is determined by the HT bursting TC neurons (Fig. 2.4) (Lőrincz et al., 2009). Interestingly, the type of firing expressed by LGN interneurons during the alpha rhythm strictly depends on their level of membrane polarization; thus, interneurons that are in a less depolarized state elicit single action potentials while those in a more depolarized state fire in a peculiar manner that consists of a single action potential followed some 20–50 msec later by a short burst of 3–5 action potentials (Fig. 2.4). These two interneuron firing modes in turn lead to two distinct patterns of $GABA_A$ receptor-mediated inhibitory postsynaptic potentials (IPSPs) in tonic firing TC neurons, thus splitting the tonic firing TC neuron population into two groups: one where a few isolated IPSPs are in phase with the negative peak of the LFP and another one where a short burst of IPSPs is in an anti-phase relation with the LFP (Fig. 2.4). These two patterns of phasic inhibition tightly control the output of the tonic firing TC neurons, giving rise to a short period of suppression of firing that is either in an in-phase or an anti-phase relationship with the negative peak of the thalamic LFP (Fig. 2.4) (Lőrincz et al., 2009). Importantly, the GABAergic neurons in the visual sector of the nucleus reticularis thalami (NRT), the other main GABAergic input to TC neurons in the LGN, are either silent during alpha rhythm episodes in freely moving animals or their occasional firing is not correlated to the ongoing thalamic or EEG alpha waves, indicating that NRT neurons are unlikely to contribute to the generation of this rhythm of relaxed wakefulness (Lőrincz et al., 2009).

Thus, although phasic inhibition onto TC neurons is also a key component in the generation of another sleep rhythm, i.e., sleep spindles (Andersen & Andersson, 1968; von Krosigk et al., 1993), fundamental differences exist between this activity of early NREM sleep and the alpha rhythm. Most notably, phasic inhibition during alpha activity is derived from probably one or very few LGN interneurons leading to small amplitude IPSPs (~0.5–1 mV) that delicately control the single action potential output of tonic firing TC neurons (Fig. 2.4) (Lőrincz et al., 2009), whereas inhibition during spindles originates from widespread LTCP-mediated bursting in the perigeniculate nucleus (the visual sector of the NRT) leading to large amplitude IPSPs (~10–15 mV) in the entire population of TC neurons (von Krosigk et al., 1993). Moreover, during the alpha rhythm

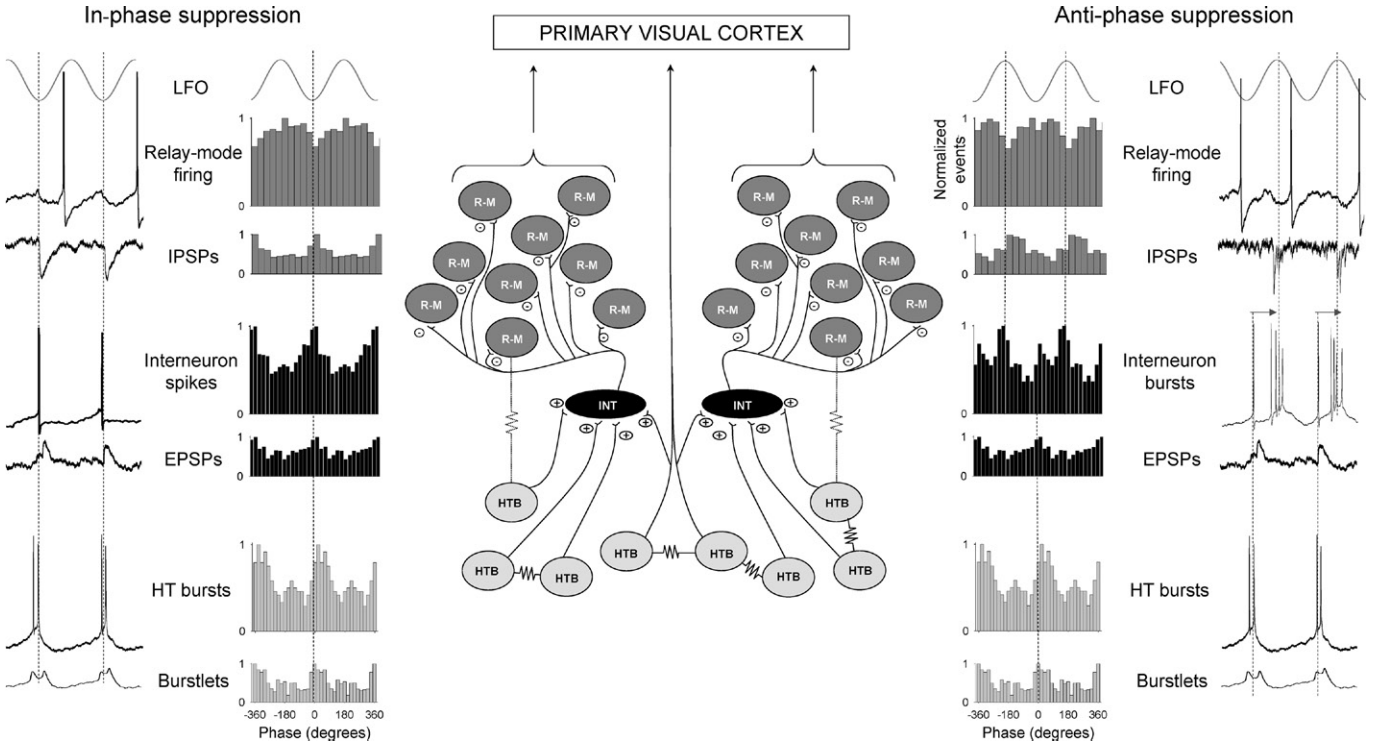

Figure 2.4 ***Cellular and network mechanism of alpha and theta wave generation.*** HT bursting TC neurons (light gray filled circles, HTB) form a gap-junction coupled network in the LGN that generates synchronized oscillations at alpha/theta frequencies. These cells may also couple via weak gap junctions (thin dotted lines) to a subset of TC neurons that exhibit conventional tonic single action potential firing, i.e., relay mode firing (dark gray filled circles, R-M). The main sequence of alpha/theta rhythm-related events that shape relay-mode firing, however, is as follows. First, HT bursting TC neurons provide a convergent excitation of local GABAergic interneurons (black filled circles, INT), probably via axon collaterals. This convergent excitation rhythmically drives interneuron firing, which can consist of either primarily single spike output (left side) or bursting (right), with bursting occurring when interneurons occupy a more depolarized state. During single spike output, action potentials in interneurons occur predominantly close to the negative LFP peak. In contrast, during bursting, a large interval between the first and second spikes in individual bursts means that action potentials are translated to occur mainly close to the positive LFP peak. These two forms of interneuron firing are then reflected in relay-mode TC neurons as mainly single IPSPs that occur near the negative LFP peak or IPSP bursts that occur near the positive LFP peak, respectively. Ultimately, these two forms of inhibition lead to a differential temporal framing of output from relay-mode TC neurons (for further details, see Lőrincz et al., 2009).

TC neurons are relatively depolarized and can thus only generate either HT bursts or single action potentials (Lőrincz et al., 2009), whereas during sleep spindles TC neurons are hyperpolarized and produce action potentials as LTCP-mediated high frequency bursts (von Krosigk et al., 1993). These differences are clearly commensurate with the fact that spindle waves are mostly pervasive brain oscillations that occur during sleep (and certain types of anesthesia) whereas alpha waves are a more localized, responsive rhythm of the awake, albeit "relaxed" brain (Hughes & Crunelli, 2005).

Another important feature of alpha waves is that HT bursting TC neurons often spontaneously switch between an in-phase and anti-phase association with the LFP (Hughes et al,, 2004; Hughes & Crunelli, 2005). This dynamic phase relationship contrasts markedly with that which occurs in other brain areas, such as the hippocampus, where the firing patterns of neurons of a similar type exhibit a reproducible monophasic relationship with respect to the ongoing field oscillations (Klausberger & Somogyi, 2004). The dynamic phase shifting in the thalamus during alpha waves dictates that at any point in time the local network state essentially reflects the destructive interference between two populations of neurons that oscillate in an essentially anti-phase relationship to each other (Hughes et al., 2004; Hughes & Crunelli, 2005). Because phase shifting appears to be a response to increasing depolarization, one prediction of this scheme is that the reduction of alpha waves that occurs in the intact brain with increased attention, and particularly upon eye opening, may not necessarily reflect a decrease in cellular alpha activity but, at least at the thalamic level, a new dynamic condition with increased contribution of anti-phase HT bursts (Hughes et al., 2004; Hughes & Crunelli, 2005).

In summary, the alpha rhythm of relaxed wakefulness and the theta waves of early NREM sleep are mainly driven by thalamic pacemaker units comprising a small number of HT bursting TC neurons that are connected by gap junctions and entrain local GABAergic interneurons and the remaining TC neurons that fire in a classical relay mode, i.e., with a tonic single action potential output (Fig. 2.4). It remains unclear whether the failure of pharmacological inactivation of the thalamic HT burst pacemaker units to fully abolish alpha and theta waves in the EEG results from the inability of this procedure to affect the entire visual thalamus or whether the primary visual cortex is also capable of its own independent output in these frequency bands. In the latter case, it will be important to establish whether the underlying mechanism of any putative

alpha rhythm pacemaker unit in primary visual cortex is mainly driven by cortical neurons intrinsically generating alpha and sleep theta waves or by synaptic interactions across local networks.

THE SLOW (<1 HZ) EEG RHYTHM OF NREM SLEEP

The pioneering work of Steriade's group in the early 1990s identified the slow (<1 Hz) rhythm as one of the key EEG waves of NREM sleep and demonstrated that it is underpinned by the rhythmic sequences of depolarizations (associated with neuronal firing, i.e., UP states) and hyperpolarizations (associated with neuronal quiescence, i.e., the DOWN states) that occur in a quasi-synchronous manner in all cortical and thalamic neurons during this behavioral state (Fig. 2.5) (Steriade et al., 1993a; Steriade, Nuñez, & Amzica, 1993b; Steriade, Contreras, Curró Dossi, & Nuñez, 1993c; Steriade, Timofeev, & Grenier, 2001). It is now well established that this slow (<1 Hz) EEG rhythm, and the underlying cellular activity, i.e., the slow (<1 Hz) sleep oscillation, permeates all stages of natural NREM sleep in humans (Achermann & Borbély, 1997; Cash, Halgren, Dehghani, Rossetti, Thesen, Wang, Devinsky, Kuzniecky, Doyle, Madsen, Bromfield, Eross, Halász, Karmos, Csercsa, Wittner, & Ulbert, 2009; Clemens, Mölle, Eross, Barsi, Halász, & Born, 2007; Dang-Vu et al., 2010; Simon, Manshanden, & Lopes da Silva, 2000) and other mammals (Destexhe, Contreras, & Steriade, 1999). Thus, the K-complex (of stage 2 sleep) represents the EEG manifestation of a single cycle of the slow oscillation (Cash et al., 2009; Amzica & Steriade, 1997, 2002), but as sleep deepens, the frequency of the slow oscillation, and thus that of K-complexes, increases until a proper slow rhythm develops, occupying an increasingly larger component of the EEG signal (Amzica & Steriade, 1997, 1998, 2002). Thus, in contrast to the original observation in ketamine-xylazine anesthetized animals, the frequency of the slow rhythm during sleep progression is not set at a given frequency but changes from 0.03 Hz in the early sleep stages to about 0.6–1 Hz in deep NREM sleep. In contrast, during anesthesia the frequency of the slow sleep rhythm is determined by the anesthetic agent and the depth of anesthesia; for example, the ketamine-xylazine combination elicits a slow oscillation with a higher frequency (0.6–1 Hz) than that observed under urethane (0.3–0.4 Hz) (Steriade et al., 1993a), and isoflurane drastically lowers the slow oscillation frequency (Doi, Mizuno, Katafuchi, Furue, Koga, & Yoshimura, 2007), whereas barbiturates abolish the characteristic UP and DOWN state fluctuations

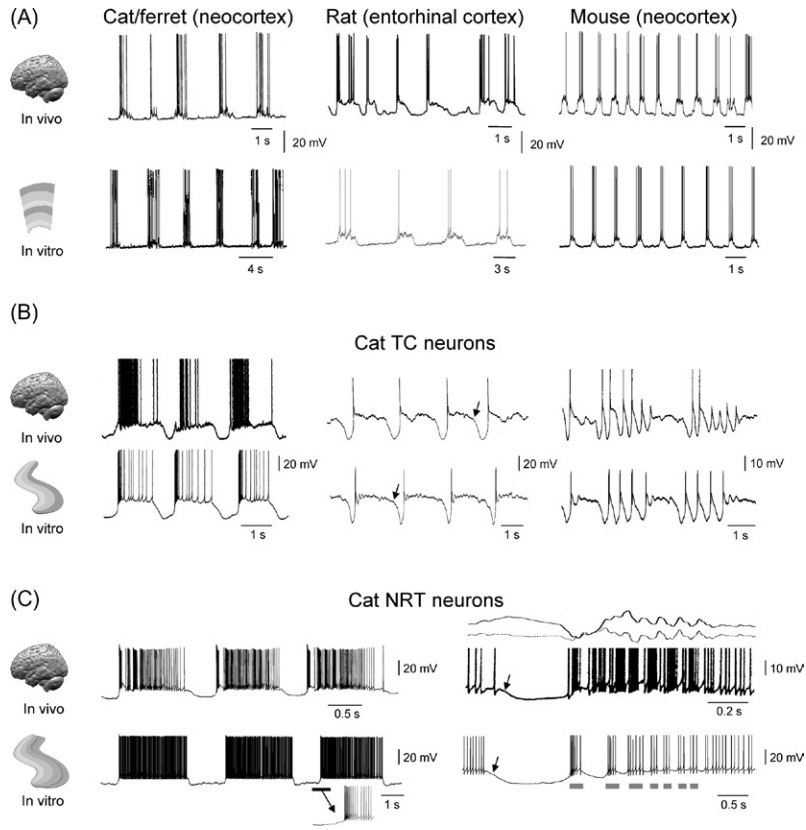

Figure 2.5 ***The slow (<1 Hz) sleep oscillation in cortical and thalamic neurons.*** A. Comparison of the slow (<1 Hz) sleep oscillation recorded in the indicated species and cortical areas *in vivo* during anesthesia (top traces) and in slices (bottom traces). B. Comparison of the slow oscillation recorded *in vivo* in three TC neurons of anesthetized cats (top traces) with that observed in slices of the cat dorsal lateral geniculate nucleus (LGN) *in vitro* in the presence of a metabotropic glutamate agonist (t-ACPD) (bottom traces). Arrows mark inflection points in the membrane potential at the transition from the UP to the DOWN state. C. Comparison of the slow oscillation recorded *in vivo* in two NRT neurons of anesthetized cats (top traces) with that observed in NRT neurons from cat LGN-perigeniculate nucleus slices *in vitro* in the presence of an mGluR agonist (bottom traces). Note the presence of sleep spindle activity in the top two traces on the right (surface and depth EEG records) (for further details, see Crunelli & Hughes, 2010). *Reproduced with permission from Crunelli & Hughes, 2010.*

(Steriade et al., 1993a; Destexhe et al., 1999). Another important feature is that both in anesthesia and during natural sleep the frequency of the slow oscillation is higher in lower mammals (reaching up to 2 Hz in mice) than in humans (Crunelli, Lőrincz, Errington, & Hughes, 2011; Fellin, Halassa,

Terunuma, Succol, Takano, Frank, Moss, & Haydon, 2009; Isomura, Sirota, Ozen, Montgomery, Mizuseki, Henze, & Buzsáki, 2006; Ruiz-Mejias, Ciria-Suarez, Mattia, & Sanchez-Vives, 2011; Sirota, Csicsvari, Buhl, & Buzsáki, 2003).

Despite many claims to the contrary, the most parsimonious view of the mechanism of the slow (<1 Hz) sleep oscillation is one that considers this activity as resulting from the intricate interplay of cortical and thalamic neurons (Crunelli & Hughes, 2010). In fact, the original view of this sleep rhythm as being exclusively of cortical origin has been strongly challenged by the results of recent *in vivo* and *in vitro* experiments showing that both an isolated cortex as well as an isolated thalamus are unable to express the variety, complexity, and periodicity of this brain wave as it is observed in the intact brain. Thus, in a cortical slab (i.e., a small block of cortical tissue in anesthetized animals where thalamic and other cortical inputs are severed) or in an intact cortex following pharmacological inactivation of a limited thalamic territory the slow oscillation is abolished in some neurons while in others its periodicity is drastically compromised (Lemieux & Timofeev, 2010; Timofeev, Grenier, Bazhenov, Sejnowski, & Steriade, 2000) (see also Chapter 1, I. Timofeev's chapter in this book). Similarly, neither *in vitro* nor *in vivo* recordings from thalamic neurons that lack their cortical afferents are able to show the slow sleep oscillation (Hughes et al., 2002b; Steriade et al., 1993b; Timofeev & Steriade, 1996). On the other hand, both an isolated cortex maintained under certain *in vitro* conditions (Beierlein, Fall, Rinzel, & Yuste, 2002; Cossart, Aronov, & Yuste, 2003; Sanchez-Vives &, McCormick, 2000; Shu, Hasenstaub &, McCormick, 2003) as well as an isolated thalamus where the impact of missing cortical afferents is compensated for by reactivation of mGluRs (Hughes, Cope, Blethyn, & Crunelli, 2002b; Blethyn, Hughes, Tóth, Cope, & Crunelli, 2006; Zhu, Blethyn, Cope, Tsomaia, Crunelli, & Hughes, 2006) can both generate slow oscillations in their respective cellular types that are almost identical to those observed *in vivo*. More specifically, in cortical slices modifications of the Ca^{2+} concentration of the perfusing solution (Cossart et al., 2003; Sanchez-Vives & McCormick, 2000) or addition of the cholinergic agonist, carbachol (Lőrincz, Bao, Crunelli, & Hughes, 2007; Lőrincz et al., 2008a), are required for any type of cortical neuron to elicit an activity that closely reproduces the slow oscillation of NREM sleep and anesthesia, while activation of mGluRs is essential for both TC and NRT neurons to express the slow sleep oscillation because it is these receptors that are targeted by corticothalamic

fibers in the intact brain (McCormick & von Krosigk, 1992; Sherman & Guillery, 1996; Turner & Salt, 2000).

These studies have also demonstrated that the slow oscillation expressed by cortical neurons mainly results from the regular recurrence of intense, but balanced, intracortical excitatory and inhibitory synaptic barrages, which generate the UP state, and their absence, that constitutes the DOWN state (Cossart et al., 2003; Haider, Duque, Hasenstaub, & McCormick 2006; Sanchez-Vives & McCormick, 2000; Shu et al., 2003). There are, however, pyramidal neurons in layers 2/3 and 5, and Martinotti cells in layer 5 that can intrinsically generate UP and DOWN states (Le Bon-Jego & Yuste, 2007). In the latter case the persistent Na^+ current (I_{NaP}) appears to be particularly important for generating UP states whereas in a general sense $I_{K(Ca)}$, $I_{K(Na)}$, and $I_{K(ATP)}$ (Ca^{2+}-, Na^+-, and ATP dependent, K^+ currents, respectively) play an essential role in bringing about the DOWN state (Compte, Sanchez-Vives, McCormick, & Wang, 2003; Cunningham, Pervouchine, Racca, Kopell, Davies, Jones, Traub, & Whittington, 2006; Le Bon-Jego & Yuste, 2007). Importantly, although complex interactions among intracortical neuronal ensembles within a cortical slice allow potential multiple foci (layer 2/3, 4, and/or 5 in different studies) of initiation for the slow oscillation (MacLean, Watson, Aaron & Yuste 2005; Sanchez-Vives & McCormick, 2000), many investigations both *in vitro* and *in vivo* have consistently demonstrated that stimulation of thalamic afferents more efficiently and reliably triggers UP and DOWN state dynamics in cortical networks than intracortical stimulation (Cossart et al., 2003; Rigas & Castro-Alamancos, 2007; Shu et al., 2003; Steriade, Timofeev, Grenier, & Dürmüller, 1998).

The most striking difference in the slow oscillation between cortical and thalamic neurons is that in thalamic neurons recorded *in vivo* and *in vitro* this activity shows a highly stereotypical appearance and a conserved waveform from cycle to cycle (Fig. 2.5B, C) (Contreras & Steriade, 1996; Steriade et al., 1993c; Rudolph, Pospischil, Timofeev, & Destexhe, 2007; Hughes et al., 2002; Blethyn et al., 2006; Crunelli et al., 2011), properties which are clearly suggestive of an underlying intrinsic mechanism. In particular, there is a large (15–20 mV) and constant voltage difference between the UP and DOWN states, and the evolution of the membrane potential during the slow oscillation is characterized by two unmistakable signatures at the transition between states. Thus, the transition from DOWN to UP state is punctuated by an LTCP and associated high frequency (150–300 Hz) burst of action potentials (Fig. 2.5B, C), whereas the

transition between the UP and DOWN state is marked by a clear inflection point in the membrane potential (arrows in Fig. 2.5B). Moreover, the slow oscillation recorded from single TC and NRT neurons *in vitro* is not blocked by tetrodotoxin, $GABA_A$ and $GABA_B$ antagonists, and ionotropic glutamate receptor blockers, and its frequency is strictly governed by the amount of steady intracellular current injection (Hughes et al., 2002b; Blethyn et al., 2006; Zhu et al., 2006), confirming that it is intrinsically generated as a pacemaker activity. In fact, it results from the membrane potential bistability (Hughes et al., 1999; Tóth, Hughes, & Crunelli, 1998; Williams, Turner, Tóth, Hughes, & Crunelli, 1997) that is generated by the interplay of I_{Leak} and the window component of the low threshold Ca^{2+} current I_T ($I_{Twindow}$), such that the UP state essentially corresponds to the condition when $I_{Twindow}$ is active and the DOWN state to when $I_{Twindow}$ is inactive (Figs. 2.6 and 2.7) (for a detailed description of the biophysics underlying thalamic neuron bistability, see Crunelli, Tóth, Cope, Blethyn, & Hughes, 2005). Other membrane currents that are essential for

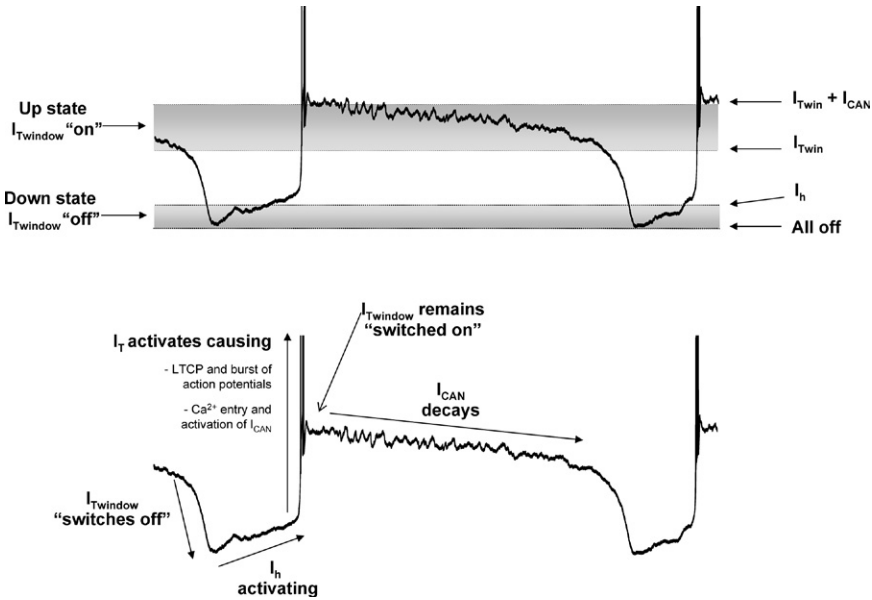

Figure 2.6 ***Cellular mechanism of slow (<1 Hz) sleep oscillation in TC neurons.*** The upper diagram illustrates the different ionic currents that are active at various points during the slow sleep oscillation in a TC neuron, whereas the lower diagram depicts the sequence of ionic events that shape this oscillation. The presence of UP and DOWN states is primarily due to the presence and absence of $I_{Twindow}$, respectively (for further details, see Hughes et al., 2002; Crunelli et al., 2005, 2006; Crunelli & Hughes, 2010).

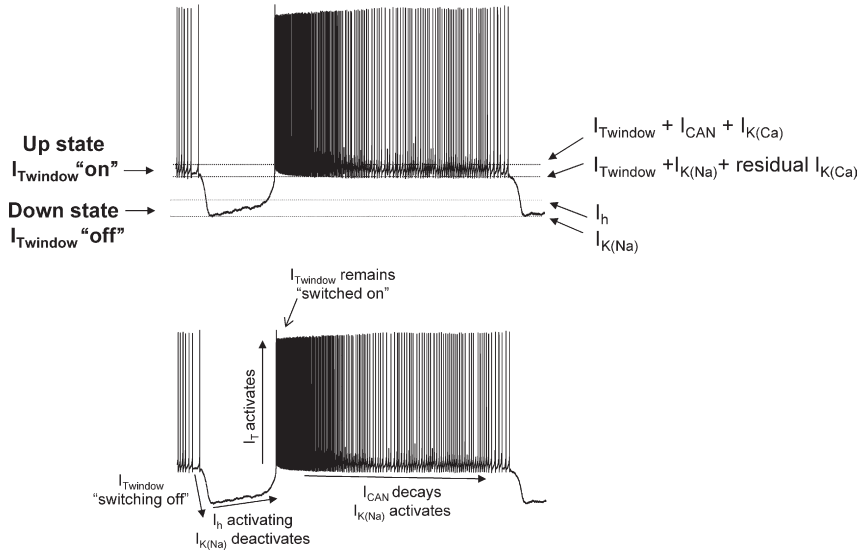

Figure 2.7 ***Cellular mechanism of slow (<1 Hz) sleep oscillation in NRT neurons.*** The upper diagram illustrates the different ionic currents that are active at various points during the slow (<1 Hz) sleep oscillation in an NRT neuron whereas the lower diagram depicts the sequence of ionic events that shape this oscillation. The presence of UP and DOWN states is primarily due to the presence and absence of $I_{Twindow}$, respectively (for further details, see Blethyn et al., 2006; Crunelli et al., 2005, 2006; Crunelli & Hughes, 2010).

the expression of the slow oscillation in TC and NRT neurons include the Ca^{2+}-activated nonselective cation current, I_{CAN}, and the hyperpolarization-activated mixed cation current, I_h (Hughes et al., 2002b; Blethyn et al., 2006; Crunelli et al., 2005; Crunelli, Cope, & Hughes, 2006), which in the absence of synaptic inputs are the main determinants of the duration of the UP and DOWN states, respectively. In NRT neurons, the slow oscillation is also shaped by $I_{K(Ca)}$ and $I_{K(Na)}$ (Fig. 2.7) (Blethyn et al., 2006). Importantly, in a thalamic slice a slow oscillation can also be recorded as a large LFP (see Fig. 1B in Hughes et al., 2004), indicating the ability of the thalamus to produce a synchronized output even in the absence of the cortical input. Whether the synchronization underlying these thalamic LFPs depends on TC neuron axon collaterals onto other TC neurons or interneurons (Cox, Reichova, & Sherman, 2003; Soltesz & Crunelli, 1992; Lorincz et al., 2009) and/or on gap junction-based electrical synapses among TC neurons (Hughes et al., 2002b; Lorincz et al., 2009; Hughes et al., 2011) remains to be determined. In summary,

a <1 Hz neocortical rhythm is not necessary for the expression of the slow oscillation in either TC or NRT neurons, which instead can be generated by each of these neuronal types operating as "conditional oscillators," i.e., by the dynamic interplay of their intrinsic voltage-dependent membrane currents, with sustained mGluRs (subtype 1) providing the necessary "condition" for these oscillators to function (Crunelli & Hughes, 2010).

Thus, contrary to the pervading corticocentric view, we believe that the EEG slow (<1 Hz) rhythm of NREM sleep is an emergent property of corticothalamic networks, which originates from the dynamic interplay of three cardinal oscillators: the mainly, but not necessarily exclusively, synaptically based cortical oscillator (with a layer 4 thalamofugal input and a layer 5/6 corticofugal output), and two intrinsic, conditional thalamic oscillators, i.e., TC and NRT neurons (Fig. 2.8) (Crunelli & Hughes, 2010). Although each of these three oscillators is capable of producing its own slow oscillation, the full EEG manifestation of the slow sleep rhythm requires the essential dynamic tuning provided by their complex synaptic interactions. Since two of the oscillators (i.e., the cortical network and the TC neuron population) are capable of an independent synchronized output when isolated from each other, the start of a new UP state within the intact brain will depend on the relative strength and timing of both the TC neuron and the cortical network oscillator. Although this question has not been directly addressed *in vivo*, the available indirect *in vivo* and *in vitro* evidence strongly points to the TC neuron output (i.e., the LTCP-mediated burst of action potentials that is invariably present at the onset of the TC neuron UP states) as being at least as frequent and effective a signal for eliciting the start of a new cortical UP state in a given thalamocortical module as an intracortical input (for a full discussion of the evidence supporting this point, see Crunelli and Hughes, 2010). This three-oscillator model that we have proposed does not diminish the important contribution played by astrocytic networks in modulating the strength and periodicity of the slow sleep oscillation, as recently shown using transgenic mice with impaired gliotransmission (Fellin et al., 2009) (see Chapter 3 in this book).

A key issue that originates from the above studies and which we believe has not received due attention by researchers in the field is that the frequency of the slow sleep oscillation clearly overlaps with the lower portion of the frequency band of the delta waves. This raises the questions of whether the classical definition of delta waves (as encompassing rhythms between 0.5 and 4 Hz) needs to be revised since it may be possible

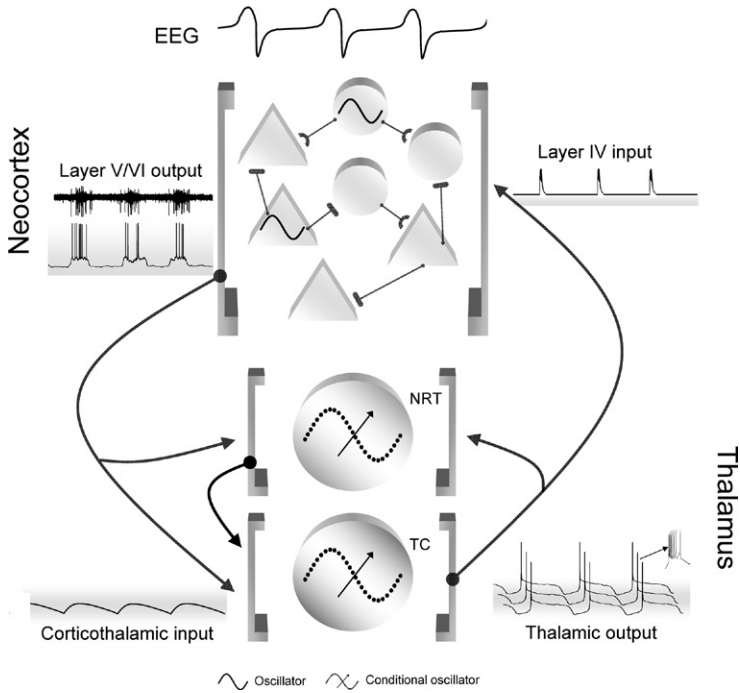

Figure 2.8 ***The interplay of cortical and thalamic oscillators underlies the slow (<1 Hz) sleep rhythm.*** The firing during the UP states of the slow oscillation in layer 5/6 cortical neurons lead to long-lasting corticothalamic EPSPs in TC and NRT neurons. These slow EPSPs bring about the mGluR-induced reduction in I_{Leak}, which is the necessary "condition" for thalamic neurons to exhibit the slow oscillation (for further details, see Crunelli et al., 2005). The LTCP-mediated high-frequency burst that is invariably present at the start of each UP state of the TC neuron slow oscillation leads to highly effective bursts of thalamocortical EPSPs that initiate a new UP state in NRT and layer 4 neurons. The overall UP and DOWN state dynamics of a cortical region, however, are maintained by synaptically generated barrages of excitation and inhibition from other cortical neurons as well as being potentially fine-tuned by inputs from intrinsically oscillating cortical neurons in layers 2/3 and 5. Additional synchronizing inputs (not shown) are provided by short- and long-distance intracortical connections and by intralaminar thalamic afferents that are not restricted to layer 4 (not shown). The symbol ~, without and with a crossing arrow, indicates neurons that function as oscillators or conditional oscillators, respectively (for further details, see Crunelli & Hughes, 2010). *Reproduced with permission from Crunelli & Hughes, 2010.*

that EEG delta waves between 0.5 and 1 Hz in humans and felines and between 0.5 and 2 Hz in rodents may in reality represent the slow sleep oscillation. Indeed, the mechanisms that generate delta waves, particularly in the neocortex, have not been systematically investigated. Moreover,

whereas thalamic delta waves, i.e., the rhythmic occurrence of LTCPs at delta frequency in TC and NRT neurons, can be recorded undisturbed for hours in thalamic slices (see the bottom trace of Fig. 2.1) (Hughes et al., 2002b; Blethyn et al., 2006), they are mostly present in the intact brain only transiently (see Fig. 1 in Steriade, 1993).

CONCLUDING REMARKS

The EEG waves of relaxed wakefulness and NREM sleep, as well as sleep spindles, require the fine dynamic interplay of both intrinsic and synaptic activities across cortical and thalamic territories. The more we understand of these brain rhythms at the cellular, synaptic, and network level the more it becomes manifest that the cortex is built to preferentially generate network-driven rhythms and oscillations whereas thalamic neurons are exquisitely equipped for the expression of highly diverse and powerful, intrinsic oscillations (Fig. 2.1).

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