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CHAPTER 3

Neurobiology of REM sleep

Pierre-Hervé Luppi, Olivier Clément, Christelle Peyron, and Patrice Fort

Brainstem network generating paradoxical (REM) sleep

Glutamatergic neurons located in the SLD trigger REM sleep

REM sleep characterized by EEG activation and rapid eye movements (REMs) was discovered in 1953 by Aserinsky and Kleitman. It was shown to correlate in humans with dream activity [1,2]. In 1959, Jouvet and Michel discovered in cats that REM sleep is also characterized by a complete disappearance of muscle tone, paradoxically associated with a cortical activation and REMs, and named this state paradoxical sleep (PS) [3,4]. Soon after, they demonstrated that the brainstem is necessary and sufficient to trigger and maintain REM sleep in cats. Using electrolytic and chemical lesions, it was then shown that the dorsal part of the pontis oralis (PnO) and caudalis (PnC) nuclei contains the neurons responsible for REM sleep onset [5]. Furthermore, bilateral injections of a cholinergic agonist, carbachol, into these structures promote REM sleep in cats. The dorsal part, where carbachol injection induces REM sleep with the shortest latencies, was termed the peri-locus coeruleus alpha nucleus (peri-LC α), the pontine inhibitory area (PIA), or the subcoeruleus nucleus (SubC) [6]. In contrast to the data from cats, carbachol iontophoresis into the rat sublateralodorsal tegmental nucleus (SLD), the equivalent of the cat peri-LC α , induces waking (W) with increased muscle activity [7]. Further, in rats, only a few of the numerous c-Fos-labeled cells located in the laterodorsal tegmental

nucleus (Ldt) and SLD after REM sleep hypersomnia were cholinergic [8]. Further, it has been shown that injection of scopolamine, a cholinergic muscarinic antagonist, into the SLD has nearly no effect on REM sleep [9]. In addition, it has been shown that cholinergic neurons of the Ldt and SLD are active during both W and REM sleep and therefore must play a role in cortical activation during both W and REM sleep rather than a specific role in REM sleep genesis [10]. However, it has also been shown that optogenetic activation of Ldt and pedunculopontine (PPTg) cholinergic neurons increases the probability of REM sleep occurrence [11]. Altogether, these results strongly suggest that the pontine cholinergic neurons play a modulatory role in REM sleep genesis and a more central role in cortical activation during both W and REM sleep.

In addition, we have shown that SLD REM sleep-on neurons are not GABAergic. Indeed, the small number of c-Fos-positive neurons expressing a specific marker of GABAergic neurons (glutamate decarboxylase, GAD, the enzyme responsible for synthesis of GABA) in the SLD did not increase in rats displaying an REM sleep rebound compared with control or REM-sleep-deprived animals [12]. In contrast, our results have shown that most of the c-Fos-labeled neurons localized in the SLD after REM sleep hypersomnia express a specific marker of glutamatergic neurons (vesicular glutamate transporter 2, vGlut2) [13] and are therefore glutamatergic. Further, a large number of the REM sleep-on neurons recorded in the SLD have been found to be glutamatergic [10].

A number of results further indicate that SLD REM sleep-on glutamatergic neurons generate muscle atonia via descending medullary projections to GABA/glycinergic neurons. Indeed, it has been shown that the SLD sends direct efferent projections to glycinergic neurons in the ventral (GiV) and alpha (Gia) gigantocellular

nuclei (corresponding to the cat magnocellular reticular nucleus, Mc) and the nucleus raphe magnus (RMg). In addition, glycinergic neurons of the GiV, GiV and RMg express c-Fos after induction of REM sleep by bicuculline (Bic, a GABA_A antagonist) injection in the SLD [7]. Further, glycinergic neurons of these structures project monosynaptically to lumbar spinal motoneurons [14]. These results suggest that GiV, GiV, and RMg glycinergic neurons hyperpolarize motoneurons. It is likely that these neurons are also GABAergic, since a large majority of the c-Fos-labeled neurons localized in these nuclei after 3 hours of REM sleep recovery following 72 hours of REM sleep deprivation express the mRNA of the enzyme responsible for synthesis of GABA (GAD67mRNA) [12]. Further, it has been shown that combined microdialysis of bicuculline, strychnine and phaclofen (a GABA_B antagonist) in the trigeminal nucleus restored muscle tone during REM sleep [15,16]. Altogether, these results indicate that the premotoneurons responsible for muscle atonia of REM sleep are localized in the GiV and co-release GABA and glycine.

SLD glutamatergic neurons are inhibited by GABAergic neurons during wake and SWS

A long-lasting REM sleep-like episode can be pharmacologically induced with a short latency in head-restrained unanesthetized rats by iontophoretic applications of bicuculline or gabazine, two GABA_A receptor antagonists, specifically to the SLD. Further, neurons within the SLD specifically active during REM sleep are activated following bicuculline or gabazine iontophoresis [7]. Taken together, these data indicate that the onset of SLD REM sleep-on neurons is mainly due to the removal during REM sleep of a tonic GABAergic tone present during W and slow-wave sleep (SWS). It is likely that such a

strong tonic GABAergic inhibition is necessary to preclude in healthy subjects the occurrence of sleep onset REM sleep (SOREMS) and cataplexy. Combining retrograde tracing with cholera toxin b subunit (CTb) injected in the SLD and GAD immunostaining, we then identified neurons at the origin of the GABAergic innervation. These neurons were localized within the pontine (including the SLD itself) and the dorsal deep mesencephalic reticular nuclei (dDpMe) [17]. Further, the ventrolateral part of the periaqueductal gray (vlPAG) and the dDpMe are the only pontomedullary structures containing a large number of c-Fos-positive neurons expressing GAD67mRNA after 72 hours of REM sleep deprivation [12]. In addition, injection of muscimol in the vlPAG and/or the dDpMe induces a strong increase in REM sleep quantities [12]. These congruent experimental data lead us to propose that GABAergic neurons within the vlPAG and the dDpMe are gating REM sleep during W and SWS by tonically inhibiting REM sleep-on neurons from the SLD.

Role of monoaminergic neurons in the control of REM sleep

A major achievement in the identification of the mechanisms controlling REM sleep was the finding that serotonergic neurons from the raphe nuclei and noradrenergic neurons from the LC cease firing specifically during REM sleep, ie, show a REM sleep-off firing activity, reciprocal to that of REM sleep-on neurons [18]. Later, it was shown that histaminergic neurons from the tuberomammillary nucleus and hypocretinergic neurons from the perifornical hypothalamic area also exhibit REM sleep-off firing activity [19]. These electrophysiological data were the basis for a well-accepted hypothesis suggesting that REM sleep onset is gated by reciprocal inhibitory interactions between REM sleep-on and REM sleep-off monoaminergic neurons [18]. Supporting this neuronal model,

drugs enhancing serotonergic and noradrenergic transmission—monoamine oxidase inhibitors (MAOs) and serotonin and norepinephrine (noradrenaline) reuptake inhibitors (SNRIs)—specifically suppress REM sleep [20]. Further, applications of norepinephrine, epinephrine (adrenaline), or benoxathian (an α_2 adrenergic agonist) to the peri-LC α inhibit REM sleep, but application of serotonin has no effect [21]. It is of note that our data combining a marker of noradrenergic neurons (tyrosine hydroxylase, TH) and c-Fos staining after REM sleep deprivation and recovery suggest that it is unlikely that the LC noradrenergic neurons are involved in the inhibition of REM sleep, particularly during its deprivation. Indeed, the LC noradrenergic neurons do not display c-Fos after 72 hours of REM sleep deprivation. Furthermore, no projection has been observed from the LC to the SLD [17]. Nevertheless, a substantial number of noradrenergic neurons from A1 and A2 cell groups display c-Fos after REM sleep deprivation, indicating that noradrenergic neurons from these medullary cell groups might contribute to REM sleep inhibition [22]. In summary, it is clear that norepinephrine and serotonin inhibit REM sleep, but the targeted neurons remain to be identified. We propose that rather than inhibiting SLD REM sleep-on neurons, norepinephrine and serotonin might inhibit REM sleep by means of a tonic excitation of the dDpMe and vIPAG REM sleep-off GABAergic neurons.

GABAergic neurons are responsible for the inactivation of monoaminergic neurons during REM sleep

The application of bicuculline to monoaminergic neurons during SWS or REM sleep induces a tonic firing in both types of neurons [23,24]. These results indicate the existence of a tonic GABA input to the LC and DRN that is active during sleep and strongly suggest that an increased GABA release is responsible for the REM sleep-

selective inactivation of monoaminergic neurons. By combining retrograde tracing with CTb and GAD immunohistochemistry in rats, we found that the LC and DRN receive GABAergic inputs from neurons located in a large number of distant regions from the forebrain to medulla [24]. Two brainstem areas contained numerous GABAergic neurons projecting both to the DRN and LC, and were thus candidates for mediating the REM sleep-related inhibition of monoaminergic neurons: the vIPAG and the dorsal paragigantocellular nucleus (DPGi) [24]. We then demonstrated by using c-Fos that both nuclei contain numerous LC-projecting neurons selectively activated during REM sleep rebound following REM sleep deprivation [25]. Since the DPGi has not previously been considered in sleep mechanisms, we studied the firing activity of the DPGi neurons across the sleep–wake cycle in head-restrained rats [26]. In full agreement with our functional data using c-Fos, we found that the DPGi contains numerous REM sleep-on neurons that are silent during W and SWS and fire tonically during REM sleep. The REM sleep-on neurons start discharging approximately 15 s before REM sleep onset and become silent around 10 s before EEG signs of arousal. Taken together, these data highly suggest that the DPGi contains the neurons responsible for the inactivation of LC noradrenergic neurons during REM sleep [26]. A contribution from the vIPAG to this inhibitory mechanism is also likely. Indeed, an increase in c-Fos/GAD immunoreactive neurons has been reported in the vIPAG after a REM sleep rebound induced by deprivation in rats [12]. In summary, a large body of data indicates that GABAergic REM sleep-on neurons localized in the vIPAG and the DPGi hyperpolarize monoaminergic neurons during REM sleep.

Role of the hypothalamus in REM sleep control

Surprisingly, a very large number of c-Fos-positive cells were observed in the posterior hypothalamus (PH), including the zona incerta (ZI), the perifornical area (PeF), and the lateral hypothalamic area (LH), after REM sleep hypersomnia [27]. By using double-immunostaining, it has been further shown that around 75% of PH cells labeled for c-Fos after REM sleep rebound express GAD67mRNA and are therefore GABAergic [28]. One-third of these GABAergic neurons were also immunoreactive for two neuropeptides, melanin-concentrating hormone (MCH) [27] and nesfatin [29]. In support of these data, it has been shown in head-restrained rats that MCH neurons fire exclusively during REM sleep [30]. Rats receiving intracerebroventricular (icv) administration of MCH showed a strong dose-dependent increase in quantities of REM sleep and, to a minor extent, SWS [27]. Such a sleep increase has been obtained using chronic (24-hour) optogenetic activation of MCH neurons [31]. Finally, it was shown that optogenetic activation of MCH neurons specifically at the onset of SWS epoch did not increase SWS duration but increased the probability of SWS-to-REM sleep transitions. More importantly, optogenetic stimulation of MCH neurons at the REM sleep onset significantly prolonged the duration of REM sleep episodes [32]. In agreement with our results showing that MCH neurons constitute only one-third of the GABAergic neurons activated during REM sleep hypersomnia, it has been shown that a large population of GABAergic neurons not expressing MCH localized in the LH area also discharge maximally during REM sleep [33]. Since these neurons anticipate REM sleep onset, they could play a role in triggering REM sleep.

To determine the function of the LH MCH⁺/GABA⁺ and MCH⁻/GABA⁺ neurons in REM sleep control, either all LH neurons were inactivated with muscimol (a GABA_A

agonist) or only those bearing α_2 -adrenergic receptors were inactivated using clonidine. It was found that muscimol and to a lesser degree clonidine bilateral injections in the LH induced an inhibition of REM sleep with or without an increase in SWS quantities, respectively. It has been further shown that after muscimol injection in the LH, the vIPAG/dDpMe region contains a large number of c-Fos/GAD67⁺ and of c-Fos/CTb⁺ neurons in animals with a CTb injection in the SLD. Our results indicate that the activation of REM sleep-on MCH/GABAergic neurons localized in the LH is a necessary step for REM sleep to occur. They further suggest that MCH/GABAergic REM sleep-on neurons localized in the LH control REM sleep onset and maintenance by means of a direct inhibitory projection to vIPAG/dDpMe REM sleep-off GABAergic neurons. On the basis of our results, it can be proposed that MCH/GABAergic neurons of the LH constitute a “master” generator of REM sleep that controls a “slave” generator located in the brainstem. To reconcile the Jouvet hypothesis (ie, that the brainstem is necessary and sufficient to generate a state characterized by muscle atonia and REM [5]) with our results, it can therefore be proposed that after removal of the forebrain, the brainstem generator is sufficient to induce a state with muscle atonia and REM by means of a reorganization of the brainstem systems generating REM sleep. However, the brainstem generator would be under control of the LH generator in intact animals.

In addition to the descending pathway to the REM sleep-off GABAergic neurons, the MCH/GABAergic REM sleep-on neurons might also promote REM sleep by means of other pathways to the histaminergic neurons, the monoaminergic REM sleep-off neurons and the hypocretinergic neurons [7,32]. Indeed, Jégo et al [32] have shown that optogenetic activation of MCH neurons inhibit other postsynaptic targets, such as

histaminergic cells in the TMN and the medial septum, through activation of the GABA_A receptor.

The mechanisms at the origin of the activation of the MCH/GABAergic neurons of the LH at the entrance to REM sleep remain to be identified. A large number of studies indicate that MCH neurons also play a key role in metabolic control [34]. Therefore, the activation of these neurons at the onset of and during REM sleep could be influenced by the metabolic state. In addition, it is likely that yet undiscovered endogenous cellular or molecular clock-like mechanisms may play a role in their activation.

The cessation of activity of the MCH/GABAergic REM sleep-on neurons and, more widely, of all the REM sleep-on neurons at the end of REM sleep episodes may be due to a different mechanism than the entrance into the state, possibly the reactivation of the arousal circuits, which are known to silence MCH neurons in vitro [35]. Indeed, animals enter REM sleep slowly from SWS, whereas they exit it abruptly by a microarousal. This indicates that the end of REM sleep episodes is induced by the activation of the wake systems like the monoaminergic, hypocretinergic, or histaminergic neurons. However, the precise mechanisms responsible for their activation remain to be identified.

A network model for REM sleep onset and maintenance

As described above, most of the populations of neurons responsible for REM sleep control were identified by means of c-Fos labeling induced by REM sleep deprivation and REM sleep hypersomnia. In the future, it will be important to employ additional experimental approaches to fully determine the role of these neurons, including tract-tracing, single-unit recordings, and inactivations and activations by genetic or

pharmacological tools. Furthermore, several regions that contain a large number of c-Fos-labeled neurons require additional studies, including the lateral paraventricular nucleus, the lateral parabrachial nucleus, the nucleus raphe obscurus, and the dorsal PAG [8].

The observation that REM sleep episodes in the rat start from SWS after a relatively long intermediate state during which the EEG displays a mix of spindles and theta activity, and then terminate abruptly by a short microarousal, deserves further attention. These findings suggest that different mechanisms are responsible for the entrance to and exit from REM sleep. Altogether, these characteristics, as well as our current knowledge of the neuronal network, lead us to propose an updated model of the mechanisms controlling REM sleep onset and maintenance.

REM sleep onset would be due to the activation of glutamatergic REM sleep-on neurons in the SLD (Fig. 3.2). . During W and SWS, the activity of these REM sleep-on neurons would be inhibited by a tonic inhibitory GABAergic tone originating from REM sleep-off neurons localized in the vlPAG and the dDpMe (Fig. 3.2).. These REM sleep-off neurons would be activated during W by the Hcrt and the aminergic neurons. The onset of REM sleep would be due to the activation by intrinsic “clock-like” mechanisms of REM sleep-on MCH/GABAergic hypothalamic neurons and REM sleep-on GABAergic neurons localized in the DPGi and vlPAG. These neurons would inactivate the REM sleep-off GABAergic neurons and the aminergic and Hcrt waking neurons. The disinhibited ascending SLD REM sleep-on neurons would in turn induce cortical activation via their projections to intralaminar thalamic relay neurons in collaboration with W/REM sleep-on cholinergic and glutamatergic neurons from the laterodorsal (Ldt)

and pedunculopontine (PPT), mesencephalic, and pontine reticular nuclei and the basal forebrain. Descending REM sleep-on SLD neurons would induce muscle atonia via their excitatory projections to glycinergic neurons localized in the GiV and GiV reticular nuclei and the nucleus raphe magnus (RMg) (Fig. 3.2). The exit from REM sleep would be due to the activation of waking systems. The waking systems would inhibit the hypothalamic MCH/GABAergic and the brainstem GABAergic REM sleep-on neurons.

<Insert Fig. 3.1 and 3.2>

Dysfunctions of the network that are responsible for REM sleep behavior disorder

REM sleep behavior disorder (RBD) is characterized by the acting out of dreams that are vivid, intense, and violent. Dream-enacting behaviors include talking, yelling, punching, kicking, sitting, jumping from bed, arm flailing, and grabbing. The person may be awakened or may wake up spontaneously during the acting and vividly recall the dream that corresponds to the physical activity. RBD is usually seen in middle-aged to elderly men. The disorder may occur in association with various degenerative neurological conditions such as Parkinson disease (PD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB) [36].

Several studies indicate that it is unlikely that RBD is due to a dysfunction of the dopaminergic nigrostriatal system. The strongest arguments are that RBD does not occur in about half of PD patients and that the use of dopaminergic agents usually does not improve RBD. In neurodegenerative diseases, where RBD is frequent, neuronal cell loss has been observed in the brainstem structures modulating REM sleep, such as the locus subcoeruleus, the pedunculopontine nucleus, and the gigantocellular reticular nucleus,

and also in their rostral afferents, especially the amygdala [36]. In cats and rats, electrolytic and neurochemical lesions limited to the SLD eliminate the tonic muscle atonia and induce phasic muscle activity during REM sleep. The phasic events include large limb twitches, locomotion, fear, and attack and defensive behaviors [37]. Notably, larger lesions induce a decrease in the total quantities of REM sleep [5], whereas RBD patients display normal quantities of REM sleep. Selective experimental lesions in the ventromedial medullary reticular nuclei have been also reported to induce a decrease of atonia during REM sleep with an increase of phasic events [38]. On the basis of these and our own experimental data, we propose that RBD in patients without atonia during REM sleep could be due to a lesion of a subpopulation of REM sleep-on glutamatergic neurons of the SLD responsible for inducing muscle atonia via their descending projections to the premotor GABA/glycinergic neurons of the GiV. This implies that REM sleep-on neurons of the SLD are divided into at least two subpopulations: one descending and responsible for muscle atonia, and the other inducing the state of REM sleep itself and EEG activation (Fig. 3.3). Data obtained in cats supports the existence of these two populations of SLD REM sleep-on cells (see above), but they have not been identified in rats. If these two populations exist, it remains to be discovered why only the descending SLD neurons would be destroyed in RBD patients. In any case, RBD patients should not have a large lesion of the SLD and surrounding nuclei, since they do not display a decrease in total REM sleep amount. Another possibility is that SLD neurons are intact and the premotor GABA/glycinergic neurons of the GiV are damaged. This better fits with the fact that only the atonia is lost in RBD, and not the state of REM sleep per se (Fig. 3.3).

The RBD reported in narcoleptic patients is likely due to the absence of hypocretin, although it cannot be completely ruled out that the SLD–GiV atonia pathway is lesioned in these patients. One possibility is that, under normal conditions, Hcrt neurons excite the SLD–GiV atonia pathway during REM sleep, in particular during the muscle twitches induced by a phasic glutamatergic excitation of the motoneurons (Fig. 3.4). Two results support this hypothesis. First, although Hcrt neurons are mainly active during active waking, they display bursts of activity during the twitches of REM sleep [19]. Second, application of hypocretin in the SLD region induces REM sleep with atonia [39].

<Insert Fig. 3.3 and 3.4>

Dysfunctions of the network that are responsible for cataplexy in narcoleptic patients

Narcolepsy–cataplexy is characterized by two major symptoms, excessive daytime sleepiness (EDS) and cataplexy, and two auxiliary symptoms, hypnagogic hallucinations and sleep paralysis. EDS occurs daily and is characterized by sleep episodes with a premature onset of REM sleep. A sudden decrease in muscle tone triggered by emotional factors, most often positive, characterizes cataplexy. It can affect all striated muscles or can be limited to facial muscles or to the upper or lower limbs. The monosynaptic H-reflex is suppressed, as during REM sleep. Patients remain fully conscious during cataplexy [40]. All these symptoms suggest that REM sleep is disinhibited in narcoleptic patients. It has been shown that disruption of the type 2 hypocretin receptor induces narcolepsy in dogs and mice [41,42]. No mutation has been found in human narcoleptics [43]. Instead, a marked reduction in the quantities of the peptide Hcrt 1 was found in their

cerebrospinal fluid and a disappearance of Hcrt staining was observed in the hypothalamus of post-mortem brain tissues [43]. It is notable that Hcrt neurons are specifically active during W and increase their activity during muscle activation [19]. They are silent during SWS or REM sleep, except during phasic twitches, when they can fire in bursts. It is of interest that they start to fire several seconds before the onset of W at the end of REM sleep episodes [33]. Hcrt neurons, like aminergic neurons, send projections throughout the brain, from the olfactory bulb, cerebral cortex, and thalamus to the brainstem and the spinal cord [44]. It is therefore difficult to determine, solely on the basis of the projections of the Hcrt neurons, which missing pathway(s) are responsible for the four symptoms of narcolepsy. It has been proposed that the absence of dense Hcrt projections to the histaminergic and noradrenergic LC neurons might be responsible for narcolepsy symptoms. Indeed, icv administration or local injection of Hcrt in the noradrenergic LC or the histaminergic TMN neurons induces W and inhibits REM sleep [45,46]. Further, administration of selective norepinephrine reuptake inhibitors and α_1 -adrenergic agonists specifically suppress cataplexy [40]. Besides, the absence of the hypocretin input on serotonin neurons could also play a role, since serotonin reuptake inhibitors are effective in treating cataplexy, at least in humans [40]. Strongly supporting this hypothesis, it has been shown that targeted restoration of orexin receptor expression in the dorsal raphe (DR) and in the locus coeruleus (LC) of mice lacking orexin receptors inhibited cataplexy-like episodes and pathological fragmentation of wakefulness (ie, sleepiness), respectively [47]. Finally, a missing hypocretin projection to GABAergic REM sleep-off neurons might be implicated, since the most recent treatment for cataplexy, namely γ -hydroxybutyrate (GHB), may act through increased GABA_B

transmission [48]. This is an attractive hypothesis in view of our finding that GABAergic REM sleep-off neurons localized in the vIPAG/dDpMe region gate the onset of REM sleep by means of their tonic inhibition of the SLD neurons during W and SWS. Further, we have found that inactivating neurons in the vIPAG/dDpMe region by means of muscimol induces not only an increase in REM sleep quantities but also an increase in SOREMS [12]. It thus can be hypothesized that during emotions in healthy subjects, there is a phasic increase in hypocretin release on GABAergic REM sleep-off neurons. Since the hypocretinergic neurons also project to aminergic neurons, they would excite these neurons, which in turn would reinforce the activation of the GABAergic REM sleep-off neurons via direct projections (Fig. 3.1). The phasic increase in inhibition by GABAergic REM sleep-off neurons would counterbalance an increased glutamatergic excitation of SLD neurons arising in the central amygdala (Fig. 3.5). We have indeed demonstrated that non-GABAergic neurons of the central amygdala project to the SLD [17]. Further, neurons increasing their activity during W and/or REM sleep or prior to and during cataplexy were recorded in the central amygdala [49]. Further, bilateral, excitotoxic lesions of the amygdala markedly reduced cataplexy in orexin knockout mice [50]. In short, cataplexy could be due to a phasic activation of SLD neurons by central amygdala neurons, normally counterbalanced by an increased phasic GABAergic inhibition from vIPAG/dDpMe neurons. Notably, our hypothesis implies that the projection from central amygdala neurons specific to the REM sleep-on SLD neurons is responsible for muscle atonia projecting to GABA/glycinergic premotoneurons and not to those responsible for REM sleep itself or the EEG activation. Indeed, in such a case, a full REM sleep episode would be induced. Cataplexy would be inhibited in narcoleptic

patients treated with SNRIs or α_1 -adrenergic agonists by means of an increased excitation of the GABAergic REM sleep-off neurons. EDS, sleep paralysis, and hypnagogic hallucinations suggest that the Hcrt neurons might inhibit and delay the onset of REM sleep and strongly contribute to the abrupt cessation of REM sleep episodes, in line with the increase in their firing before the end of a REM sleep episode [30]. In their absence, the onset of REM sleep could occur more quickly and the end of REM sleep might take more time, leading to hypnagogic hallucinations and sleep paralysis, respectively. The inhibition of REM sleep by hypocretineric neurons would be directly by means of excitation of the REM sleep-off GABAergic and aminergic neurons.

<Insert Fig. 3.5>

Acknowledgments

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Fig. 3.1

State of the network responsible for REM sleep during wake and at the end of a REM sleep episode. During wake, REM sleep-off GABAergic neurons located in the vIPAG and dDpMe tonically inhibit SLD glutamatergic neurons. These REM sleep-off GABAergic neurons are excited by monoaminergic and hypocretin inputs. Wake-on neurons activate the cortex either directly or by means of a relay in the intralaminar thalamic nuclei. Direct pathways from the noradrenergic and serotonergic neurons to the cortex contributing to wake are not shown here for clarity. 5HT: serotonin; Ach: acetylcholine; BF: basal forebrain, DPGi: dorsal paragigantocellular reticular nucleus; dDpMe: dorsal deep mesencephalic reticular nucleus; DRN: dorsal raphe nucleus; GiV: ventral gigantocellular reticular nucleus; Glu: glutamate; Gly: glycine; Hcrt: hypocretin (orexin)-containing neurons; His: histamine; LC: locus coeruleus; Ldt: laterodorsal

tegmental nucleus; LPGi: lateral paragigantocellular reticular nucleus; MCH: melanin-concentrating hormone; PH: posterior hypothalamus; PPT: pedunculopontine nucleus; vIPAG: ventrolateral periaqueductal gray; VLPO: ventrolateral preoptic nucleus; SCN: suprachiasmatic nucleus; SLD: sublaterodorsal nucleus.

Fig. 3.2

State of the REM sleep-generating network during a REM sleep episode. The onset and maintenance of REM sleep is due to the intrinsic “clock-like” activation of GABAergic neurons localized in the posterior hypothalamus (some of them also containing MCH), the vIPAG/dDpMe, and the DPGi. These neurons inhibit all W neurons and the REM sleep-off GABAergic neurons of the vIPAG and dDpMe. SLD glutamatergic neurons are disinhibited and start to generate muscle atonia and cortical activation by means of their descending and ascending projections, respectively. They excite glycinergic/GABAergic neurons of the GiV, which in turn hyperpolarize spinal and cranial motoneurons.

Fig. 3.3

State of the network responsible for REM sleep during idiopathic RBD. In idiopathic RBD patients, the descending but not the ascending SLD glutamatergic neurons have degenerated. Another possibility is that only the GiV glycinergic/GABAergic neurons have degenerated. Movements are induced during REM sleep by direct or indirect glutamatergic projections from the motor cortex to spinal and cranial motoneurons.

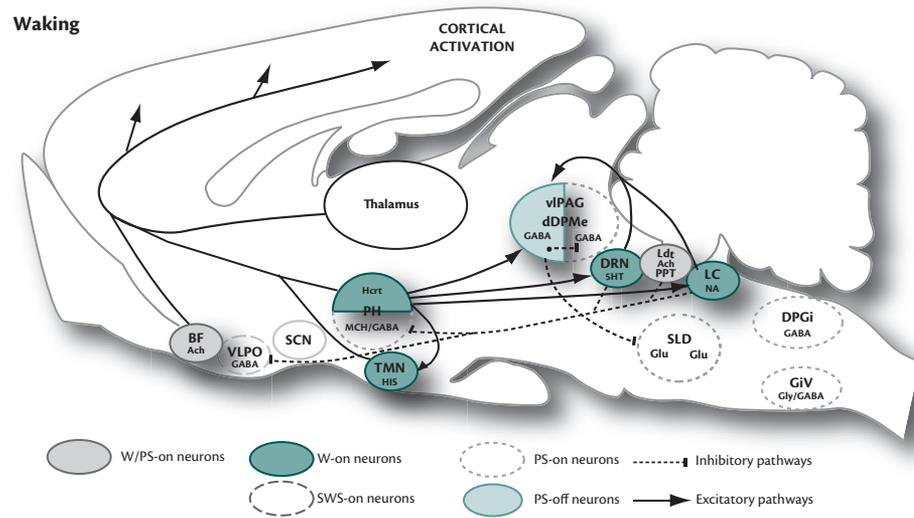
Fig. 3.4

State of the network responsible for REM sleep during RBD in narcoleptic patients. In narcolepsy, the network responsible for muscle atonia is intact. Phasic movements during REM sleep are induced by a phasic activation of motoneurons due to the absence of an

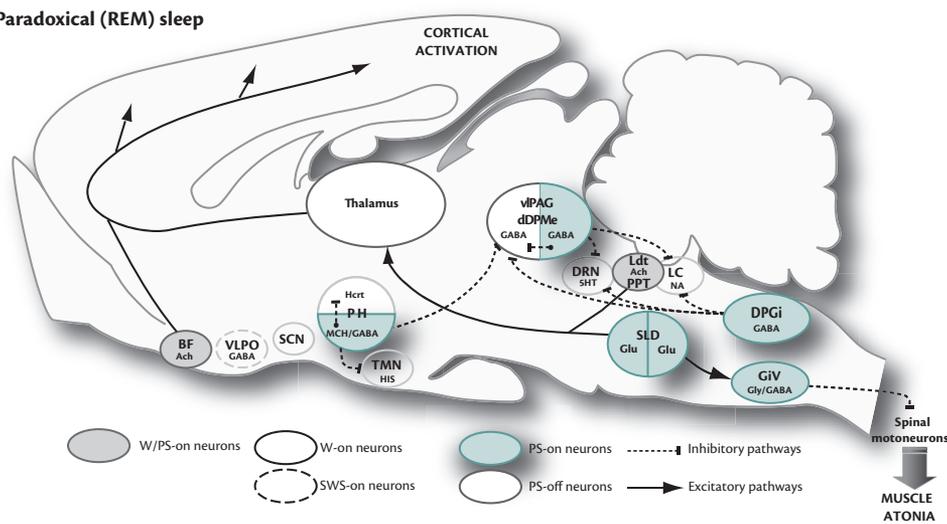
excitatory projection of the Hcrt neurons specifically to the descending SLD REM sleep-on neurons.

Fig. 3.5

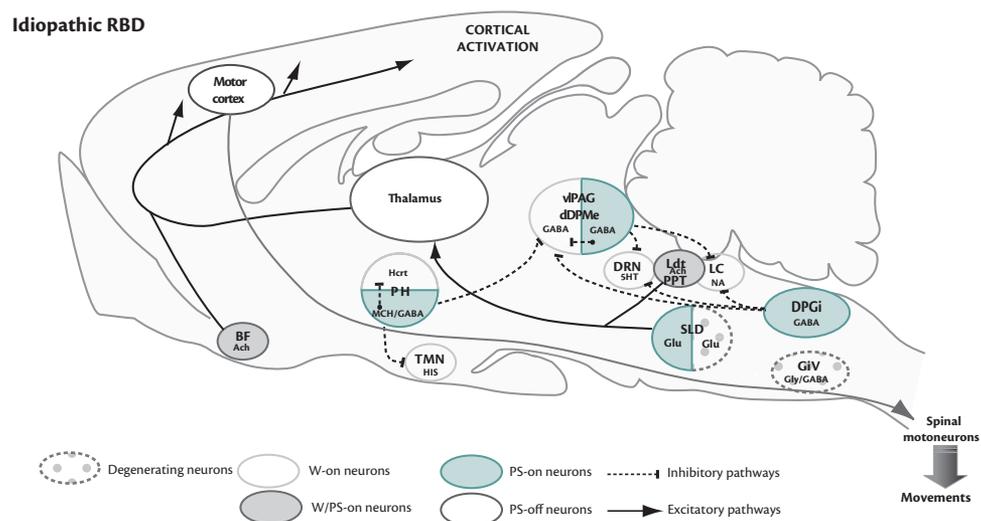
State of the network responsible for REM sleep during cataplexy. Cataplexy is induced by activation of a glutamatergic pathway from the emotionally driven central amygdala (ACE) to the descending SLD glutamatergic neurons. In healthy subjects, the hypocretin neurons would be excited. They would excite GABAergic REM sleep-off neurons located in the vIPAG/dDpMe and thereby increase the inhibition of SLD glutamatergic neurons and counteract the excitation coming from the central amygdala.



Paradoxical (REM) sleep



Idiopathic RBD



RBD in narcoleptics

