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The involvement of noradrenaline in rapid eye movement sleep mentation

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Noradrenaline, one of the main brain monoamines, has powerful central influences on forebrain neurobiological processes which support the mental activities occurring during the sleep–waking cycle. Noradrenergic neurons are activated during waking, decrease their firing rate during slow wave sleep, and become silent during rapid eye movement (REM) sleep. Although a low level of noradrenaline is still maintained during REM sleep because of diffuse extrasynaptic release without rapid withdrawal, the decrease observed during REM sleep contributes to the mentation disturbances that occur during dreaming, which principally resemble symptoms of schizophrenia but seemingly also of attention deficit hyperactivity disorder.

Keywords: paradoxical sleep, catecholamines, dreaming, schizophrenia, ADHD, endophenotype

The nature of human mind activity varies greatly during the sleep–waking cycle. During waking, mental activity is reflective, logically organized, and involves learning processes that lead to memories. During slow wave sleep (SWS), mentation most often comprises "thought-like" content that is seldom visual and that has "a higher degree of correspondence with reality" (p 23; Foulkes, 1962; for ref. see Gottesmann, 2001). This mental content seems to correspond to the secondary process of Freud (1911), which follows the reality principle. As previously underlined by Rechtschaffen et al. (1963), during SWS these "secondary process characteristics. . . are assigned to pre-conscious mentation" (p 546). Recent studies have shown that SWS mental activity reproduces or is the continuation of waking cognitive processes (Nielsen, 2003; Euston et al., 2007; Ji and Wilson, 2007). At the same time, it was shown early on that some dreams occur during SWS (Foulkes, 1962; Tracy and Tracy, 1974; Cavallero et al., 1992; Bosinelli, 1995; Cavallero, 2003), even though it has been emphasized that dreaming can only occur in the presence of certain neurobiological features of the rapid eye movement (REM) dreaming sleep stage (Takeuchi et al., 1999, 2001; Nielsen, 2003).

The mental activity of REM sleep has been "defined as an experience that involves vivid and complex multi-modal imagery, a progression of events and sense of reality" (p 180; Dement, 1965; for ref. see Gottesmann, 2005b); this is once again contrary to SWS mentation, which comprises "background thoughts that occur during the day" (p 180). Today, in fact, it is necessary to distinguish between the mental activity of REM sleep that occurs at sleep onset descending stage I (Sleep Onset REM Sleep: SOREM) and REM sleep occurring after ascending stage II, in more advanced night sleep stages. Even further, within the latter, some authors have distinguished between "active" dreams occurring during the REM bursts and "passive" ones occurring outside of these periods (Dement and Wolpert, 1958; Berger and Oswald, 1962); these studies, however, have not been followed up. It has been underlined by several authors, with the seeming exception of one recent study (Malcolm-Smith et al., 2007), that REM sleep dreaming is most often characterized by threatening content (Manacéine, 1897; Revonsuo, 2003). This is less often the case in SOREM, during which dreams are roughly equivalent in positive and negative content (Foulkes and Vogel, 1965; see Gottesmann, 2005b). Finally, with respect to the psychological quality of REM sleep mentation, it has been long noted by philosophers such as Kant and Schopenhauer, writers such as Alfred Maury, neurophysiopathologists such as Hughlings Jackson, and neuropsychiatrists such as Henri Ey, that numerous similarities exist between dreaming and madness (Gottesmann, 2010b). Today, the properties of dreams, with their hallucinatory perceptions, bizarre imagery, diminished self-reflective awareness, orientational instability, intensification of emotion, and instinctual behaviors (Hobson et al., 2000), are strongly reminiscent of the symptoms of schizophrenia (Gottesmann, 2005a, 2006; Gottesmann and Gottesman, 2007).

While various neurotransmitters [glutamate, gamma aminobutyric acid (GABA), and neuromodulators (acetylcholine, dopamine, serotonin, histamine. . .] also contribute to forebrain functioning, here I will attempt to provide a beginning of an explanation of how noradrenaline (NA) influences the mental activity occurring during REM sleep.

CORTICAL NORADRENERGIC FUNCTION

Noradrenergic neurons of the locus coeruleus (LC), the primary source of NA to the forebrain, fire maximally, although at a slow rate, during waking. Their discharges decrease during SWS and then become silent during REM sleep (Hobson et al., 1975; Aston-Jones and Bloom, 1981a; Rasmussen et al., 1986; Takahashi et al., 2010). As a consequence of this progression, both pontine (Shouse et al., 2000) and prefrontal cortex (Léna et al., 2005) release of NA is highest during waking and lowest during REM sleep. This

neuromodulator plays important roles in the control of forebrain function. In certain rare cases of noradrenergic neuron stimulation in the LC, patients described "well being (and) improved clarity of. . . thinking" (p 179; Libet and Gleason, 1994). Moreover, numerous results have shown that NA depletion increases error responses to irrelevant stimuli and decreases responses in attentional tasks (Selden et al., 1990; Milstein et al., 2007); also, increased NA release is concomitant to cognitive improvement through the collection and processing of salient sensory information (Berridge and Waterhouse, 2003). The positive effect of NA on cognitive processes is further evidenced by the observation that attentional processes can be impaired by lesions of the dorsal NA bundle (Leconte and Hennevin, 1981; Tait et al., 2007) or by prefrontal neurotoxic inhibition of dopamine-β-hydroxylase (Milstein et al., 2007; McGaughy et al., 2008), the enzyme that catalyzes the conversion of dopamine to noradrenaline. As described by Arnsten and Pliszka (2011) "in humans, lower activity of dopamine-β-hydroxylase. . . is associated with poor sustained attention (Greene et al., 2009), poor executive function (Kieling et al., 2008), and impulsiveness (Hess et al., 2009)."

There are two modalities of LC neuron activity. First, there is a basic tonic firing pattern, and second, a phasic firing pattern is superimposed onto the tonic firing. The tonic firing increases with vigilance, and its function is presumably to prevent unimportant sensory events from disturbing the perception of threshold and above-threshold stimuli (Berridge and Waterhouse, 2003; Johnson, 2003). In contrast, the phasic discharges are sensitive to novel sensory modifications of sub-threshold intensity, and increases in such discharges precede behavioral changes that can take place during tasks (Bouret and Sara, 2005). "Phasic NA activity serves to interrupt ongoing neural processes when a significant new event is experienced" (p 689; Johnson, 2003; see also Waterhouse et al., 1998). All LC neurons fire together, and only 10% of the neurons are sufficient to maintain normal cortical function (Berridge et al., 1993), because of compensatory NA neuron processes (Chiodo et al., 1983).

Noradrenaline was first shown to primarily inhibit cortical neurons (Krnjevic and Phillis, 1963; Frederickson et al., 1971; Nelson et al., 1973; Foote et al., 1975; Reader et al., 1979; Manunta and Edeline, 1999; Wang et al., 2010), specifically through α_2 receptors. Noradrenaline has an important function in cortex efficiency, as it increases the fidelity of signal detection and transmission in neurons and synapses; it does this by increasing the signal-to-noise ratio of incoming information (Foote et al., 1975; Aston-Jones and Bloom, 1981b; Waterhouse et al., 1990; Warren and Dykes, 1996; Berlucchi, 1997), thereby reducing synaptic noise resulting from parasitic afferents relative to the informative stimulus (Berlucchi, 1997; Berridge and Waterhouse, 2003; for ref. see Gottesmann, 2008).

Noradrenaline acts through the α_1, α_2, and β receptors. Prefrontal α_1 receptor activation impairs cognitive processes, as shown through the administration of agonists to rats (Arnsten et al., 1999) and monkeys (Arnsten and Jentsch, 1997; Mao et al., 1999). In contrast, postsynaptic α_2 receptor activation improves these processes (Steere and Arnsten, 1997; Mao et al., 1999), acting specifically in the prefrontal cortex (Ramos and Arnsten, 2007). This activation is restricted to the NA level (Arnsten and Li, 2005), in the maximal zone of an inverted U-curve (Arnsten and Dudley, 2005). It should be underlined that it is particularly the postsynaptic α_{2a} receptors, whose activation threshold is much lower than that of the α_1 receptors, which are responsible for this improvement in cognitive processes. Indeed, mice with mutations in the α_{2a} subtype show an unusual absence of improved working memory following administration of the α_{2a} receptor-specific agonist guanfacine (Franowicz et al., 1998). At the postsynaptic level, the activation of these receptors reinforces the prefrontal connections between pyramidal cells by blocking potassium channels through the inhibition of cyclic adenosine monophosphate (cAMP), thereby "increasing the efficacy of network inputs, and facilitating prefrontal cortex function" (Arnsten and Pliszka, 2011). Beta receptors, which have the lowest affinity to NA and which activate pyramidal neurons (McCormick et al., 1991), have restricted influence on cognitive processes. Nevertheless, β_1 antagonists infused into the prefrontal cortex or administered systemically improve working memory in rats and monkeys, while β_1–β_2 receptor blocking compounds have no effect. Thus, prefrontal β_1 receptor activation appears to impair cognitive functions (Ramos et al., 2005).

Due to the silencing of the noradrenergic LC neurons during REM sleep, the level of NA in the prefrontal cortex drops from 20.9×10^{-10} M during waking to 9.98×10^{-10} M during this sleep period (Léna et al., 2005). A low level of NA is still maintained because it is diffusely released at the varicosity level (Fuxe et al., 1968; Descarries et al., 1977; Seguela et al., 1990), without rapid enzymatic destruction at the synapse by catecholamine-*O*-methyl transferase (COMT), or reuptake by transporters. However, this low level is insufficient to support normal cortical function. From a neurophysiological standpoint, NA is now well known to induce regular spiking activity in the cortex instead of burst firing (McCormick et al., 1993). However, it has long been established that the pyramidal neurons fire in bursts that are separated by silences of spiking during REM sleep, demonstrating a decrease in inhibitory influences controlling the frequency-limiting process (Evarts, 1964). Thus, the level of NA available during REM sleep is clearly insufficient to regularize pyramidal neuron firing. Since the affinity of NA is highest for the α_{2a} receptors, these are likely the only ones activated during REM sleep to sustain normal prefrontal function. However, because of dorsolateral deactivation (Maquet et al., 1996; Braun et al., 1997; in spite of phasic activation during the eye movement bursts, particularly on the right side (Hong et al., 1995; Kubota et al., 2011 – but interestingly not related to LC phasic discharges; Takahashi et al., 2010, and K. Sakai, Personal Communication 2011) – and the lower levels of dopamine, serotonin, and acetylcholine (see Gottesmann, 2006, 2010a), NA is not sufficient to support normal prefrontal function by itself. In addition, there are reciprocal relations between the LC and the prefrontal cortex, with the latter promoting LC function (Jodo et al., 1998). It can be assumed that, in humans, the prefrontal dorsolateral deactivation that occurs during REM participates in the silencing of the LC, which in turn contributes to the impairment of cortical function. The strong decrease in cortical noradrenaline during REM sleep (Léna et al., 2005) probably also contributes to the abnormalities observed in synchronized gamma rhythms. Indeed, it has been shown that NA, but not serotonergic, reuptake inhibitors favor

gamma rhythms in the septo-hippocampal system (Hajos et al., 2003) and that their intracortical and hippocampal synchronization is impaired during REM sleep (Perez-Garci et al., 2001; Cantero et al., 2004; Massimini et al., 2005; Montgomery et al., 2008), when cortical NA is at its lowest level. Thus, the cortex, and particularly the prefrontal cortex (which is the most phylogenetically recent structure to appear, responsible for the highest integrated processes), is impaired during REM sleep, as evidenced by its deactivation in the dorsolateral area and partly by the decrease in NA release. Simultaneously, the availabilities of dopamine (Léna et al., 2005), serotonin (Cespuglio et al., 1992), and acetylcholine (Marrosu et al., 1995) are also reduced, while the level of glutamate remains unchanged (Gottesmann, 2005a; Léna et al., 2005).

Another property of REM sleep is the inhibition of sensory afferents (Williams et al., 1962, 1964), which was first shown through an increased arousal threshold by peripheral stimulation (Dement and Kleitman, 1957; Dement, 1958; for ref. see Gottesmann, 2001). The notion of an involvement of cortical deactivation of primary sensory cortices (Braun et al., 1998) in the inhibition of afferents has been strongly challenged (Hong et al., 2009; Miyauchi et al., 2009). The thalamic transmission process is under the positive influence of postsynaptic α_1 receptors, while α_2 and β receptors mediate inhibition; the facilitating influences follow an inverted U-curve (Devilbiss et al., 2006). During REM sleep, the decrease in noradrenaline levels possibly shifts the curve to the best functional level (Alsene et al., 2011), favoring postsynaptic activation (Sakakura and Iwama, 1965; Iwama et al., 1966; Dagnino et al., 1969; Ghelarducci et al., 1970; Gandolfo et al., 1980). In addition, the decreased NA level observed during REM sleep has both ascending and descending postsynaptic influences on thalamocortical neurons, since in addition to the above described ascending processes, corticothalamic glutamatergic influences (McCormick and Krosigk, 1992; Bonjean et al., 2011) are also disinhibited through NA silencing (Castro-Alamancos and Calcagnotto, 2001). In contrast, vestibular influences (Morrison and Pompeiano, 1966) and the (GABAergic) activation (or disinhibition) of the thalamic reticular nucleus (Hong et al., 2009) inhibit thalamic inputs. Indeed, it has been consistently shown that, particularly during the REM bursts occurring during REM sleep, there is a presynaptic inhibition of thalamic input (Sakakura and Iwama, 1965; Iwama et al., 1966; Dagnino et al., 1969; Ghelarducci et al., 1970; Gandolfo et al., 1980). This presynaptic inhibition can explain the increased sensory and arousal threshold that is present during REM sleep. Moreover, the absence of gamma rhythm resetting by peripheral stimulation during REM sleep (Llinas and Ribary, 1993) is presumably also related to sensory deafferentation. Finally, REM sleep is also characterized by an unexpected shortening of the cortical recovery cycle of responsiveness in both animals (Rossi et al., 1965; Allison, 1968) and humans, as shown by deficits in prepulse inhibition (Kisley et al., 2003). This failure of gate-control processes is certainly at least partly related to cortical NA disinhibition.

To conclude, although some results have supported the notion that the above described waking learning processes are replicated during REM sleep (Smith and Lapp, 1991; Hennevin et al., 1995, 2007; Smith, 1995; Peigneux et al., 2003) despite a strong NA deficit, these conclusions have been strongly disputed (Siegel, 2001; Vertes, 2004; Vertes and Siegel, 2005). Finally, and surprisingly, the rapid evanescence of dreams at arousal could be related to both the precocious recovery of waking NA processes (Gottesmann, 2008) and to the re-establishment associated with the late recovery of dorsolateral prefrontal cortex function (Balkin et al., 2002); both of these processes induce the withdrawal of insufficiently recorded memory traces.

Although the cortex and principally the "prefrontal circuits have the unique ability. . . to guide behavior, thought, and affect" (Ramos and Arnsten, 2007), other forebrain structures are also strongly involved in determining the mental activity associated with REM sleep.

THE FIRST NEXT MAJOR STRUCTURE INVOLVED IN MENTATION IS THE NUCLEUS ACCUMBENS

Dysfunction of this limbic structure is responsible for mental disturbances such as hallucinations and delusion. For decades, the main neuromodulator involved in its function was thought to be dopamine (MacKay et al., 1982). However, it is now known that the nucleus accumbens is subjected to strong glutamatergic influences originating from the prefrontal cortex (Brake et al., 2000; Jackson et al., 2001), hippocampus (Lipska et al., 1993), and amygdala (Floresco et al., 1998). This structure also has NA afferents mainly originating in the medulla oblongata A_1 and A_2 nuclei, and secondarily from the LC (Delfs et al., 1998). These influences are now considered to be important, since the NA concentration in the nucleus accumbens is as high as that of dopamine (Tong et al., 2006) and varies in parallel with the level of glutamate (Swanson and Schoepp, 2003; Léna et al., 2005).

Accumbal NA release is controlled by presynaptic α_2 autoreceptors, the sensitivity of which varies with the NA concentration at the synapse (Aono et al., 2007; Verhelj and Cools, 2009a). Alpha-2 receptor agonists promote dopamine release by inhibiting NA release (Pothos et al., 1991), and postsynaptic α_2 receptors (heteroreceptors) inhibit dopamine release (Verhelj and Cools, 2009b). In some cases, β receptor activation favors dopamine release (Misoguchi et al., 2008; Verhelj and Cools, 2009b). However, the activation thresholds of the different NA receptors (again, $\alpha_2 < \alpha_1 < \beta$ favor NA-mediated inhibition of dopamine release; as evidence of this, dopamine release is only increased after massive NA concentrations are attained by inhibition of reuptake (Misoguchi et al., 2008). Finally, noradrenaline also controls dopamine availability, as there is dopamine uptake at NA terminals (Carboni and Silvagni, 2004).

During REM sleep, the activation of the nucleus accumbens is evidenced by the presence of even more active neuron firing than occurs during waking (Callaway and Henriksen, 1992). The concentration of NA is minimal during this sleep stage (Léna et al., 2005). Although the A_1 and A_2 medulla oblongata nuclei have not been recorded during the sleep–waking cycle, they seem to be inhibited during REM sleep-like the LC; as confirmation of this, the firing of another low brainstem NA nucleus, A_5, also becomes silent during REM sleep (Fenik et al., 2002). Because of the above described different influences that NA has on the regulation of dopamine, the near absence of NA is presumably, at least in part, responsible for the maximal dopamine release that takes place during REM sleep (Léna et al., 2005), and could explain the abnormal mental activity of dreaming, with its hallucinations and delusions

characteristic of high accumbal levels of dopamine (MacKay et al., 1982).

In contrast to aspartate, glutamate release also decreases during REM sleep (Léna et al., 2005). This could be related to the prefrontal dorsolateral deactivation (Maquet et al., 1996; Braun et al., 1997), but could also partly result from hippocampal dysfunction. Indeed, although the same theta rhythm is present during REM sleep (Cadilhac et al., 1961; Michel et al., 1961) as during active waking (Jung and Kornmüller, 1938; Green and Arduini, 1954), hippocampal function should be different, particularly because of the noradrenergic (Segal, 1974; Segal and Bloom, 1976) and serotonergic (Segal, 1981, 1990) silence observed during REM sleep. For example, a nearly continuous hippocampal theta rhythm is observed not only in "cerveau isolé" transected cats (Tokizane, 1965; Olmstead and Villablanca, 1977) and rats (Gottesmann et al., 1980), but also in transections injuring the posterior hypothalamus (Glin et al., 1991). Thus, hippocampal electrophysiological field activity is not a faithful criteria of the functional state of this structure (Gottesmann, 2000) or of the level of glutamate released during REM sleep.

THE SECOND STRUCTURE I WILL ADDRESS HERE IS THE AMYGDALA

The amygdala is the main central structure involved in encoding emotional information and promoting avoidance learning storage (Ferry et al., 1999). Its afferents bring affectively charged information from the environment, and the amygdala triggers appropriate emotional responses. Several nuclei have a predominant function, and the output of the amygdala is primarily influenced by NA, as 54% of pyramidal neurons respond to NA whereas only nearly 3% respond to dopamine (Miyajima et al., 2010). First, the basolateral complex is considered one functional unit, since the basalis and lateral nuclei react similarly to NA, being inhibited in 64 and 74% of cases, respectively (Buffalari and Grace, 2007). The basolateral complex is reciprocally related to the LC, with each structure activating the other. However, the amygdala also receives afferents from the medulla oblongata NA A_1 and A_2 nuclei. The centralis nucleus seems to be under the inhibitory control of the basolateral complex, and its efferents on the one hand are directed to the LC, also activating A_2 and adrenergic C_2 nuclei (Wallace et al., 1992; Bouret et al., 2003; the latter controlling LC functioning), and on the other hand promote hypothalamic vegetative influences supporting behavioral characteristics of stress (Cecchi et al., 2002; Buffalari and Grace, 2007). It is noteworthy that, in the same way, dorsal raphe nucleus afferents to the centralis nucleus inhibit the neurons (Jha et al., 2005), leading to a complementary disinhibition of glutamate output during REM sleep (Grace, 2000; Tran and Keele, 2011), and as a consequence of this, a reinforced affective load of mentation.

Both stimulation of the LC and stress increase the release of NA in the basolateral area (Buffalari and Grace, 2007), and NA deficits impair the consolidation of avoidance reactions and suppress c-Fos expression in the amygdala (Radwanska et al., 2010). Noradrenaline infusion into the basolateral area inhibits the majority of pyramidal neurons by activating GABAergic interneurons (Kaneko et al., 2008) via the activation of α_1 receptors (Lazzaro et al., 2010). Emotional memory consolidation by NA has been confirmed in humans, since clonidine (an α_2 receptor agonist) inhibits this process (Groch et al., 2011), while reboxetine (a reuptake inhibitor) promotes it (Gais et al., 2011). Moreover, the α_2 receptor antagonist idazoxan infused into the basolateral amygdala enhances avoidance memory consolidation (Ferry and McGaugh, 2008). Finally, while NA and β-agonists favor avoidance memory consolidation while requiring α_1 receptor activation in a first step (Ferry et al., 1999), magnetic resonance imaging (MRI) has shown that activation of the amygdala by emotional pictures, or verbal stimuli can be decreased by blockade of the β receptor (Strange and Dolan, 2004; Stegeren van et al., 2005); consistent with this, β antagonists are used as anxiolytics (Hurlemann et al., 2010).

The amygdala is activated during REM sleep, as was first shown by neuron recordings. There are units firing at a higher rate than during SWS (similar to the rate observed during waking; Reich et al., 1983; Zhang et al., 1986; Gulyani et al., 2002), as well as REM sleep-on specific neurons, which fire at high or low rates and which are disinhibited because of, at least in part, NA silence. Indeed, as both LC stimulation and footshocks inhibit neurons of the amygdala (Chen and Sara, 2007), the silence or near silence of LC neurons during REM sleep should also disinhibit the amygdala. Indeed, NA is strongly reduced in the amygdala during REM sleep [by from 61 (Park, 2002) to 85% (Shouse et al., 2000) as compared to waking]. In addition, tomographic studies have also shown that the amygdala is activated during REM sleep (Maquet and Franck, 1997).

Since glutamate release is decreased in the nucleus accumbens during REM sleep, very probably as a result of prefrontal and hippocampal dysfunction, the remaining accumbal glutamate could mainly be a product of the (NA-mediated) disinhibition of the amygdala (Grace, 2000). The NA deficit present during REM sleep, like experimental deficits induced during waking, could impair amygdala (Strange and Dolan, 2004) and hippocampal-based (Kukolja et al., 2011) emotional encoding, and retrieval of mental processes (Murchison et al., 2011); this is the case even though an often excessive emotional activity is operative during REM sleep, explaining affectively loaded dreams. Moreover, glutamate release by the activation of the amygdala could participate in the increase in dopamine in the nucleus accumbens (Floresco et al., 1998), promoting hallucinations, and delusions during dreaming. As seen above, the nature of the emotional load during SOREM and REM sleep dreams appears to be different. Certainly partly due to NA influence, this distinction is probably related to differences in glutamate output in the amygdala. In this structure, NA seems to be more involved in the affective quality of mental activity than in the encoding of dreams, since SOREM dreams are not known to be better retrieved than REM sleep dreams.

A complementary neurobiological alternative to explain the rapid evanescence of dreams upon awakening (Gottesmann, 2006, 2008) could be the usually rapid reappearance of NA in the few seconds prior to behavioral arousal (Aston-Jones and Bloom, 1981a; Takahashi et al., 2010). This precocious restoration of some forebrain waking processes, with a highly probable re-establishment of intracortical (Perez-Garci et al., 2001; Corsi-Cabrera et al., 2003), intra-hippocampal (Montgomery et al., 2008), and hippocampo-cortical (Cantero et al., 2004) relations, could erase previous fragile memory traces (Gottesmann, 2008). This possible NA-mediated

basis for forgetting upon exit from REM sleep could be reinforced by the later recovery of function in the prefrontal cortex (Balkin et al., 2002), the brain area involved in long-term memory storage.

DISCUSSION

As recalled above, the forebrain is an interdependent ensemble of structures which are subjected to numerous neurotransmitters and neuromodulators acting simultaneously at different types of receptors situated presynaptically, postsynaptically, or both; further, several types of receptors, noradrenergic in the present case, can be localized on the same target neurons with distinct activation thresholds. Moreover, a single structure, here the LC, can project to and differently influence several forebrain areas: the LC maximally influences the somatosensory cortex when tonically firing at 0.5 Hz, whereas in the thalamic ventroposterior medial nucleus the highest sensitivity occurs at 1 Hz stimulation. Moreover, such LC firing inhibits the somatosensory cortex neurons in 63% of cases, whereas it activates the thalamic neurons in 65% of cases (Devilbiss and Waterhouse, 2004). Thus, interpreting the neurochemical basis of mental activities requires caution, all the more so since 31% of somatosensory cortex neurons are activated by NA.

Although today this notion has been partly questioned (Domhoff, 2007), the main characteristic of REM sleep mentation is its similarity to symptoms of schizophrenia (Gottesmann, 1999, 2005a, 2006); indeed, 11 published neurobiological properties of REM sleep (Gottesmann, 2007, 2010a) represent powerful potential endophenotypes (Gottesman and Gould, 2003) of this disease (Gottesmann and Gottesman, 2007; Gottesmann, 2010a). It is noteworthy that although some neurobiological criteria of REM sleep are also encountered in syndromes like depression and bipolar psychotic disorders, we have now identified fourteen strong similarities with schizophrenia. As confirmation of this, NA reuptake inhibiting factors are included in antipsychotic formulations (Friedman et al., 1999; Linner et al., 2002) because of the deficit of this neuromodulator in schizophrenia, although this is also the case in other conditions, particularly depression.

Moreover, NA promotes prefrontal attentional processes, and although its decrease cannot be expected to single-handedly account for dorsolateral prefrontal deactivation – which also occurs in schizophrenia, particularly when cognitive performances are impaired (Buschbaum et al., 1982; Weinberger et al., 1986; Berman et al., 1993; Fletcher et al., 1998) – the NA deficit seen in both states seems at least to be responsible for the anarchic firing of cortical pyramidal neurons (Evarts, 1964; McCormick et al., 1991). This reduced efficiency of cognitive processes during REM sleep and in schizophrenia is certainly related to the decrease in the signal/noise ratio of neuron activity. In the same way, NA favors gamma rhythm activity. The lowered NA level in both states could explain the corresponding cerebral disconnections, as shown by the disappearance of coupled gamma activity during REM sleep (see above) as well as the dysfunction in this rhythm in schizophrenia (Uhlaas and Singer, 2010), a complementary index of impaired intracerebral relations (Young et al., 1998; Meyer-Lindenberg et al., 2001, 2005; Peled et al., 2001; Kubicki et al., 2008). Moreover, in the nucleus accumbens, which is involved in the hallucinations and delusions observed in both states, the decrease in NA is, at least in part, responsible for the increased level of dopamine (Pothos et al., 1991); this occurs by disinhibition of release and loss of uptake in NA terminals (Carboni and Silvagni, 2004). Finally, in the amygdala, the lower level of NA during REM sleep disinhibits the pyramidal neurons, allowing the activated structure (see above) to excessively manifest itself, particularly by glutamate release in the nucleus accumbens; this results from deficits in prefrontal and hippocampal afferents (Grace, 2000) and promotes the threatened mental activity often encountered during dreaming and in schizophrenia.

Another possible relationship between dreaming and schizophrenia has been shown by responsiveness studies, which have demonstrated the presence of a cortical disinhibition in animals and humans that takes place during REM sleep and which could be consecutive to an NA decrease; the same disinhibition has been observed in schizophrenia by a deficit in prepulse inhibition (Kisley et al., 2003). The thalamic sensory deafferentation that occurs during REM sleep due to presynaptic inhibition of afferents, could contribute both to this sleep stage and to schizophrenic hallucinations (Behrendt and Young, 2005). The involvement of NA in thalamic transmission processes could also be hypothesized based on the difference in the sensory arousal threshold during SOREM, when it is low (Dement and Kleitman, 1957; and personal observations) while the NA level is very probably close to the waking level, and during REM sleep, when the threshold is high (see above) while NA is very low. However, mismatch negativity, an index of a kind of sensory detection, can be observed not during SWS but during SOREM (Nittono et al., 2001) and REM sleep (Sculthorpe et al., 2009), revealing a similar "pre-conscious level of processing" (Sculthorpe et al., 2009), or a kind of "protoconsciousness" (Hobson, 2009).

Finally, it is possible that the muscular atonia present during REM sleep (Jouvet and Michel, 1959; Berger, 1961; Michel et al., 1961), which is induced by lower brainstem processes (Jouvet and Mounier, 1960; Jouvet and Delorme, 1965; Henley and Morrison, 1974), conceals some symptoms of attention deficit hyperactivity disorder (ADHD), which is also related to an NA deficit (Arnsten and Dudley, 2005; Arnsten and Pliszka, 2011; Gronier, 2011). Indeed, the "vivid" mentation of REM sleep (Reeves et al., 2001), the classical jumping from one subject to another, the emotional instability, and the impulsivity, attention, and memory consolidation deficits (Prehn-Kristensen et al., 2011) are also encountered in ADHD. In both states, there is an impairment of inhibitory control processes regulating mentation and behavior, i.e., a kind of "say no" (Aston-Jones and Gold, 2009) ability deficit, which is partly related to right inferior frontal (Aston-Jones and Gold, 2009) and left dorsolateral prefrontal dysfunction (Burgess et al., 2010); both of these are concomitant to the NA decrease. While Methylphenidate, a dopamine/NA reuptake inhibitor, improves ADHD by activating prefrontal dopamine D_1 as well as NAα_{2a} receptors (Gronier, 2011) (the latter at least partly located on GABAergic interneurons: Wang et al., 2011), the more specific α_{2a}, agonist guanfacine, while also acting on postsynaptic α_{2a} receptors in the dorsolateral prefrontal cortex (Arnsten, 2011), also improves patients with ADHD (Scahill et al., 2001; Biederman et al., 2008; Kollins et al., 2011).

Thus, partly related to the NA deficit, the dorsolateral prefrontal deactivation occurring during REM sleep, together with consecutive or simultaneous amygdala, and nucleus accumbens

disinhibition, could provide the basis for the emotional and psychotic-like – and most often not definitively stored – dreaming activity that takes place during this sleep phase. At the same time, similar prefrontal deficits and correlative activation and disinhibition of other main cortical areas could explain the usually lively, unstable, and disorganized mental content of dreams, which is also observed in ADHD: "deficits in prefrontal cortex function are evident in most neuropsychiatric disorders" (Ramos and Arnsten, 2007).

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