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Sleep Disturbances in Alzheimer's and Parkinson's Diseases

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Abstract

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative disorders, and exact a burden on our society greater than cardiovascular disease and cancer combined. While cognitive and motor symptoms are used to define AD and PD, respectively, patients with both disorders exhibit sleep disturbances including insomnia, hypersomnia and excessive daytime napping. The molecular basis of perturbed sleep in AD and PD may involve damage to hypothalamic and brainstem nuclei that control sleep – wake cycles. Perturbations in neurotransmitter and hormone signaling (e.g., serotonin, norepinephrine and melatonin) and the neurotrophic factor BDNF likely contribute to the disease process. Abnormal accumulations of neurotoxic forms of amyloid β-peptide, tau and α-synuclein occur in brain regions involved in the regulation of sleep in AD and PD patients, and are sufficient to cause sleep disturbances in animal models of these neurodegenerative disorders. Disturbed regulation of sleep often occurs early in the course of AD and PD, and may contribute to the cognitive and motor symptoms. Treatments that target signaling pathways that control sleep have been shown to retard the disease process in animal models of AD and PD, suggesting a potential for such interventions in humans at risk for, or in the early stages of these disorders.

Keywords

Alzheimer's disease; Parkinson's disease; sleep; circadian

Introduction

Age-related disruption of the sleep-wake cycle and circadian rhythms are well documented (Brown et al., 2011; Crowley, 2011). However, recent data has shown that neurodegenerative diseases are often associated with sleep disturbances beyond what is observed in normal aging. Alzheimer's disease (AD), characterized by memory loss, is associated with sleep abnormalities including increased sleep time and sleep fragmentation (Vitiello et al., 1990; McCurry et al., 1999). Although the causes of sleep abnormalities in AD are unknown, they often appear after diagnosis and seem to be a by-product of the disease rather than a direct effect of AD pathology in the brain. Parkinson's Disease (PD) is characterized by a host of degenerative motor symptoms including resting tremor, bradykinesia, rigidity, postural instability and freezing. Pathologically, PD brains show loss of dopaminergic neurons in the substantia nigra leading to reduced input in the striatum. In addition, PD patients typically exhibit extensive brainstem pathology and associated autonomic nervous system (ANS) disturbances that often occur before motor signs (Gaig

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and Tolosa, 2009). As in AD, sleep disorders are also well documented in PD; however, unlike AD these often appear years before the hallmark motor dysfunction (Claassen et al., 2010). Further, while sleep behaviors have systematically been ruled out for AD classification and diagnosis, it is possible that some sleep disturbances may be useful for predicting the onset of PD (Bliwise et al., 1989; Vitiello et al., 1990; Schenck et al., 2003; Postuma et al., 2009). It is the goal of this review to outline clinical and experimental studies of sleep disturbances in AD and PD, and to briefly outline potential signaling molecules and brain regions thought to mediate these symptoms.

Alzheimer's Disease

Sleep Disturbances in Alzheimer's Patients

AD patients have been shown to experience alterations in normal sleep patterns that cannot be explained by aging alone. Clinical data demonstrate sleep disturbances such as nighttime sleep fragmentation, decreased slow wave sleep (SWS) and frequent daytime napping in as many as 25–35% of AD patients (McCurry et al., 1999; Moran et al., 2005). In one study of AD patients, 35% were reported to have at least one sleep-related disturbance in the previous week, with increased sleep time and early morning waking being the most common (McCurry et al., 1999). Sleep fragmentation, which can include frequent awakenings and an increase in daytime napping, is the most common sleep disturbance reported in AD patients with an incidence of roughly 30–50% (Vitiello et al., 1990). In addition to these disturbances, the latency to the first episode of REM sleep (REML) is shorter in AD patients (Bliwise et al., 1989). At least one study showed a genetic predisposition to sleep disturbances in AD patients who carried a mutation in the monoamine oxidase A gene, a gene shown to play a role in maintaining circadian rhythm (Craig et al., 2006). In fact, several studies show breakdowns in circadian rhythmicity in AD including an increase in 'sundowning', changes in activity patterns, and fluctuations in normal circadian changes in body temperature (van Someren et al., 1996; Volicer et al., 2001). However, despite the large number of clinical studies that outline sleep disturbance in AD patients, it is clear that these sleep symptoms are not diagnostically useful for determining early stage AD or for use as a biomarker for the disease (Bliwise et al., 1989; Vitiello et al., 1990).

Sleep Disturbances in Animal Models of AD

Very few studies to date have described sleep disturbances in animal models of AD. Two separate studies documented disturbances in the rapid-eye-movement (REM) phase of sleep in an in vivo genetic mouse model of AD including a reduction in total REMS and REM bouts (Wisor et al., 2005; Zhang et al., 2005). EEG recordings in Tg2576 mice, which overexpress the FAD Swedish hAPP695 mutation gene, revealed reduced REM sleep at 6 and 12, but not 2, months of age (Zhang et al., 2005) implying an age-related reduction in REM sleep in this model. The circadian period was also lengthened in Tg2576 mice compared to controls (Wisor et al., 2005). Further, one study identified a class of cholinergic neurons that are compromised in this model of AD which could indicate that a breakdown of cholinergic signaling is responsible for the age-related reduction in REMS (Zhang et al., 2005). This hypothesis was further strengthened by work that showed that the wake-promoting actions of the acetylcholinesterase inhibitor donepezil were dampened in AD

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mice implying a role for cholinergic transmission in sleep abnormalities in AD. Finally, wheel-running analysis of circadian patterns in the 3xTgAD model of AD showed an increase in activity during what is normally an inactive phase and a decrease in activity during what is normally an active phase compared to controls, implying a breakdown in circadian patterns in this model of AD (Sterniczuk et al., 2010).

Potential Mechanisms of Sleep Disturbance in AD

Alterations in hypocretin signaling—The hypocretins (orexins) are a class of excitatory neurotransmitter hormones that are thought promote wakefulness; narcolepsy is associated with a decrease in hypocretin signaling (Kroeger & Lecea, 2009; Tsunematsu et al., 2011). A recent clinical study showed a 40% reduction in hypocretin-1 positive neurons in post-mortem hypothalami of AD patients compared to controls (Figure 1A) (Fronczek et al., 2011). Further, cerebrospinal fluid levels of hypocretin were also reduced in AD patients compared to controls, further indicating a role for this neurotransmitter in mediating sleep disturbances in AD. In fact, one study measured an inverse correlation between CSF hypocretin levels and wake fragmentation in AD patients (Friedman et al., 2007). Finally, orexinergic signaling has been shown to be responsible for diurnal changes in interstitial Aβ levels, further implying that hypocretin/orexin signaling has an important role in the pathogenesis of AD (Kang et al., 2009).

Disruptions in cholinergic signaling—Cholinergic signaling plays an important role in sleep regulation and many studies outline alterations in cholinergic neurotransmission in AD (German et al., 2003; Berkowitz et al., 1990). Postmortem studies show a loss of cholinergic neurons in the forebrain in dementia, and MRI confirms a decrease in the volume of the basal forebrain cholinergic system in AD (McGeer et al., 1984; Grothe et al., 2011). Transgenic mice overexpressing mutant human amyloid precursor protein (PDAPP) develop AD-like accumulation of amyloid-β, and even prior to the appearance of AD pathology these mice display a loss of cholinergic nerve terminals in the cortex (German et al., 2003). AD patients display lower levels of the ACh-synthesizing enzyme choline acetyltransferase in the brain further implying a loss of cholinergic signaling in AD (Giacobini, 2003). It is possible that cholinergic neurons are more susceptible to the neurotoxic effects of Aβ deposition, as shown using Aβ injections in the rat (Harkany et al., 2000, 2001). Initiation and maintenance of the REM phase of sleep depends on cholinergic signaling; as shown in both experimental and clinical studies (Berkowitz et al., 1990; Wisor et al., 2005). The crucial role of cholinergic neurons in mediating REM sleep and their susceptibility to damage in AD lends credence to the hypothesis that this class of neurons mediates sleep alterations in AD. Donepezil, an acetylcholinesterase inhibitor, is commonly prescribed for AD-type dementia and administration of donepezil increases REM sleep in AD patients, further implying that cholinergic signaling mediates sleep alterations in AD (Moraes-Wdos et al., 2006).

Cholinergic deficits have also been reported to result in impaired attention relatively early in the disease course in the 3xTgAD mouse model of AD (Romberg et al., 2011). When presented with short duration stimuli with unpredictable locations on a touchscreen the 3xTgAD were less accurate in responding to the stimulus and were more likely to make

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perseverative responses that wild-type mice. Performance in the tests of attention was restored to normal in 3xTgAD mice in response to the acetylcholinesterase inhibitor donepezil (Aricept), suggesting that a cholinergic deficit was responsible for the impaired attention in the 3xTgAD mice. The alterations in attention in the 3xTgAD mice appear similar to attentional abnormalities in patients with mild cognitive impairment and AD who often have difficulty in focusing on tasks and are easily distracted (Baddeley et al., 2001; Kim et al., 2007; Saunders and Summers, 2010). A link between disturbed sleep pattern and attentional deficits remains to be established, although it is known that attention is impaired in shift workers (Niu et al., 2011).

Melatonin—Melatonin (N-acetyl-5-methoxytryptamine) is produced in high amounts by cells in the pineal gland in a sleep-related pulsatile manner such that its levels increase shortly before bedtime and decrease in response to the light of daybreak (for review see Hardeland et al., 2011). Ingestion of melatonin can promote sleep and can promote a resetting of the circadian clock. Melatonin is also produced in lower amounts by cells in other brain regions as well as by some cells in peripheral tissues. Receptors for melatonin, which are coupled to G-protein (G_i)-linked receptors that reduce levels of intracellular cyclic adenosine monophosphate. Melatonin receptors are expressed in many different cell types including those of the nervous, cardiovascular, digestive and endocrine systems. AD patients exhibit reduced levels of melatonin receptors in the suprachiasmatic nucleus of the hypothalamus (Wu et al., 2007) and have an altered rhythmicity of melatonin production (Mishima et al., 1999; Skene and Swaab, 2003). These findings suggest a role for perturbed melatonin signaling in the sleep disturbances that are common in AD patients.

It has also been suggested that reduced melatonin signaling contributes to the pathogenesis of AD by promoting the dysfunction and degeneration of neurons in circuits involved in cognition. Several intervention studies in animal models of AD have demonstrated ameliorative effects on disease processes. Matsubara et al. (2003) found that administration of melatonin to APP mutant mice resulted in a reduction in brain levels of Aβ and protein nitration (a marker of oxidative stress) and increased the survival of the mice. Similarly, levels of lipid peroxidation were decreased and levels of glutathione (an endogenous antioxidant) were increased in the brains of APP mutant mice, and this lessening of oxidative stress was associated with reduced expression of proteins involved in apoptosis (programmed cell death) including Bax, Par-4 and caspase-3 (Feng et al., 2006). Olcese et al. (2009) administered melatonin in the drinking water to APP/PS1 double-mutant mice for 5 months and then assessed the behavior of the mice using tests of spatial reference memory and working memory. Whereas the control APP/PS1 mutant mice exhibited severe cognitive impairment, the melatonin-treated AD mice did not. Interestingly, APP mutant mice exhibit heightened anxiety at the end of the dark period (preceding their normal sleep period) which is similar to ‘sundowning’ (increased agitation in the evening) in AD patients (Bedrosian et al., 2011).

Serotonin and Norepinephrine Signaling—Serotonin (5-hydroxytryptamine) and norepinephrine are produced primarily in neurons of the brainstem raphe nucleus and locus coeruleus, respectively; the axons of these serotonergic and noradrenergic neurons innervate

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neurons throughout the cerebral cortex and limbic system (Moore, 1993). Data from pharmacological studies, human and mouse genetics, and clinical investigations have revealed prominent roles for serotonin in the regulation of mood, cognition and sleep (Robbins, 1997; Gingrich, 2002; Myhrer, 2003; McMorris et al., 2006). There is now a large literature describing serotonergic and noradrenergic deficits in AD which manifest as degeneration of neurons in the raphe nucleus and locus coeruleus, and reduced cortical levels of these neurotransmitters (Figure 1A) (Palmer and DeKosky, 1993; Michelsen et al., 2008). A history of depression, a disorder involving both sleep disturbances and reduced serotonin and norepinephrine signaling, is a risk factor for AD (Michelson et al., 2008). It is therefore reasonable to consider the possibility that deficits in one or both of these monoamine neurotransmitter signaling systems occur early in AD, perhaps even prior to cognitive impairment.

Serotonin-selective reuptake inhibitors (SSRIs) such as paroxetine, sertraline and fluoxetine can improve affective behaviors in patients with AD which may result in improved cognitive function (Chow et al., 2007). Clinical trials of SSRIs in elderly subjects with depression have revealed beneficial effects on cognitive function (Muijsers et al., 2002). Recent studies have demonstrated beneficial effects of long-term treatment, beginning at a presymptomatic stage, on the disease process and cognition in mouse models of AD. For example, Nelson et al. (2007) found that treatment of 3xTgAD mice with paroxetine for 5 months resulted in improved spatial learning ability and reduced anxiety-like behavior, which were associated with reduced levels of Aβ and tau pathologies in the hippocampus. Beneficial effects of the SSRIs fluoxetine (Dong et al., 2004) and citalopram (Cirrito et al., 2011) in mouse models of AD have also been reported. In a small study of cognitively normal human subjects it was found that those that had been treated with SSRIs had significantly less Aβ (measured by PET imaging using an amyloid probe called PIB) compared to those who had not been treated with the antidepressants (Cirrito et al., 2011). The molecular mechanisms by which SSRIs counteract the disease process and improve cognition may include stimulation of BDNF production (Mattson et al., 2004), neurogenesis (Boldrini et al., 2009) and suppression of APP expression (Tucker et al., 2006). Norepinephrine plays an important role in learning and memory by enhancing synaptic plasticity in the hippocampus (Harley, 1991). AD patients exhibit profound loss of noradrenergic innervation of the cerebral cortex and hippocampus (Powers et al., 1988; Weinshenker, 2008). Similarly, aged dogs with cognitive impairment have significantly fewer noradrenergic neurons in their locus coeruleus compared to age-matched cognitively normal dogs (Insua et al., 2010). Selective depletion of norepinephrine in APP mutant mice results in an acceleration of Aβ deposition and inflammation in the cerebral cortex and hippocampus (Heneka et al., 2002; Kalinin et al., 2007). It is not known if deficits in norepinephrine signaling contribute to sleep disturbances and cognitive impairment in AD. However, given the evidence that norepinephrine stimulates BDNF production and neurogenesis, and can enhance cognitive function, trials of agents that enhance noradrenergic signaling in AD patients are warranted.

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Parkinson's Disease

Clinical Studies of Sleep Disturbance in PD

A plethora of clinical studies confirm that a host of sleep disturbances are associated with PD and these may appear decades before the appearance of the traditional motor symptoms of PD (Eisensehr et al., 2003; Comella 2003; Maria et al., 2003; Dauvilliers 2007; Claassen et al., 2010). Sleep disturbance is among the most common non-motor symptoms of PD with an incidence in the range of 60–98% of PD patients. It is often the cause of major discomfort in patients (Lees et al., 1988; Tandberg et al., 1998; Comella 2007).

The most common sleep complaint in PD patients is frequent nocturnal awakenings and sleep fragmentation (Factor et al., 1990; Tandberg 1998; Comella 2003). PD patients complain of frequent awakenings which, if prolonged, can result in an overall reduction in sleep time eventually causing excessive daytime sleepiness.

REM sleep behavior disorder (RBD), characterized by dream enactment accompanied by excessive motor activity, is associated with PD with roughly a third of PD patients displaying this sleep disorder (Gagnon et al., 2002). RBD is observed in other α-synucleinopathies beyond just PD, including multiple system atrophy and dementia with Lewy bodies (Comella 2003; Boeve et al., 2007; Postuma et al., 2009). Recent studies have shown that RBD can appear prior to the motor symptoms associated with PD and other α-synucleinopathies. In fact, at least one study showed that at a mean follow up of 10 years 65% of patients who present with RBD go on to develop a neurodegenerative disease (Schenck et al., 2003). Although a second study found a lower percentage at a 12 year follow up (52.4%), that study found that a majority of RBD patients developing neurodegenerative diseases presented with α-synucleinopathies (Postuma et al., 2009).

Sleep Disturbances in Animal Models of PD

Sleep disturbances in early and confirmed PD are well documented and widely accepted. However, despite the range of clinical data on sleep disorders and the great number of animal models of PD, few studies to date describe clinically relevant sleep abnormalities.

One of the most common animals of PD employs neurotoxin injections to eliminate dopaminergic transmission, with the most widely used toxin for this purpose being 1-methyl-4-phenyl-1,2,3,6-tetrahydropuridine (MPTP). Injection of MPTP induces motor dysfunction and a loss of dopaminergic neurons in mice and monkeys, thus mimicking pathology and behavior of PD (Burns et al., 1983). In addition, a range of animal models show alterations in sleep patterns following MPTP injection. EEG indicates that rhesus monkeys demonstrate deregulation of REM sleep following MPTP injection and this sleep abnormality precedes the appearance of motor dysfunction (Barraud et al., 2009). Similarly, MPTP injection disrupts normal muscle atonia during paradoxical sleep in the marmoset, reminiscent of RBD (Verhave et al., 2011). Paradoxical sleep is also reduced in the mouse, rat and cat following MPTP injection (Pungor et al., 1990; Lima et al., 2007; Laloux et al., 2008a; McDowell et al., 2010). This effect appears to extend to other, less common neurotoxins; ingestion of the environmental toxin cycad causes hypersomnolescence as evidenced on EEG in rats (McDowell et al., 2010).

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MPTP-induced PD demonstrates both the primary motor symptoms of the disease as well as the non-motor symptoms of perturbed sleep, as described above. However, these models lack full clinical relevance due to the severity of the insult as well as the lack of progression of dysfunction. For this reason, many researchers use α-synuclein overexpressing animal models of PD which exhibit slower progression of dopaminergic neuron dysfunction and associated motor symptoms (Kudo et al., 2011). While α-synuclein accumulation is considered a hallmark of PD, much less is known regarding the effect of α-synuclein accumulation on sleep. Recently, Kudo et al. used wheel running patterns to evaluate circadian patterns in a transgenic mouse overexpressing α-synuclein. They observed lower nighttime activity and fragmented wheel running activity in the α-synuclein overexpressing mice compared to wild-type controls (Kudo et al., 2011). Consistent with these alterations in sleep behaviors, the authors observed reduced neuronal firing in the superchiasmatic nucleus. Although this paper is the first of its kind to outline sleep patterns in a α-synuclein based mouse model of PD, at least one other genetic model of PD demonstrates sleep alterations. Mice with a reduction in expression of the vesicular monoamine transporter 2 (VMAT-2) display increased oxidative stress, loss of dopaminergic terminals, cell loss in the substantia nigra and accumulation of α-synuclein making this model relevant to PD (Taylor et al., 2009). In addition to the hallmark PD pathologies, VMAT-2 deficient mice display dampened circadian rhythms and reduced latency to sleep, further lending clinical relevance to this mouse model of PD (Taylor et al., 2009).

Potential Mechanisms of Sleep Disturbance in PD

Dopaminergic Signaling—The exact mechanisms by which sleep behaviors are disrupted in PD are not entirely known, however, unlike AD, it appears that sleep alterations are directly related to the disease pathology. As outlined above, administration of toxins that target dopaminergic neurons result in sleep abnormalities in a range of animal models (Barraud et al., 2009; Verhave et al., 2011; Lima et al., 2007; Pungor et al., 1990; McDowell et al., 2010; Laloux et al., 2008a). In fact, administration of MPTP directly to the substantia nigra results in a decrease in REM sleep and a decrease in sleep latency (Lima et al., 2007). Further, both PD and schizophrenia are associated with sleep disorders although PD is related to a lack of dopamine and schizophrenia is related to an increase (Sarkar et al., 2010). It is possible that destruction of dopaminergic signaling in PD causes a breakdown in the control of wakefulness leading to increased excessive daytime sleepiness. In other words, a decrease in dopamine in PD could potentially be responsible for excessive daytime napping due to the arousal-related role of dopamine. Dopamine has been shown to promote wakefulness in variety of animal models including drosophila and mice (Andretic 2005; Qu et al., 2010). L-DOPA, the dopamine precursor that passes through the blood-brain barrier, activates histaminergic neurons in the hypothalamus which promote wakefulness (Figures 1A & 1B) (Yanovsky 2011). Dopamine receptor agonists promote wakefulness (Isaac & Berridge 2003). Conversely, dopaminergic signaling has also been demonstrated to be associated with sleepiness and the sleep state. An increase in dopamine release is observed during the REM phase of sleep in the cortex, nucleus accumbens and midbrain (Lena et al., 2005; Maloney 2002). Additionally, using EEG readings in the midbrain, Dahan et al., observed a pattern of burst firing of dopaminergic neurons during the REM phase; a phenomenon associated with a synaptic release of dopamine (Dahan et al., 2007; Monti &

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Monti 2007). Further evidence for a role of dopamine in mediating sleep lies in the increase in dopamine measured in the forebrain after sleep deprivation, which could perhaps indicate a compensatory mechanism designed to promote rebound sleep (Zant et al., 2011).

There are several possible explanations for this apparent discrepancy. It is possible that different dopamine receptors mediate wakefulness and sleep. In an EEG study of D_2R knockout mice, periods of wakefulness were reduced compared to wild-type controls (Qu et al., 2010). It is also possible that dopamine acts to mediate both wakefulness and sleep depending on the concentration of the neurotransmitter. Dopamine demonstrates this 'U' shape effect for several physiological phenomena (Monte-Silva et al., 2009; Seamans and Yang, 2004). For example, either insufficient or excessive dopamine impairs cognitive functions (Cai and Arnsten, 1997; Seamans and Yang, 2004). Finally, it should be noted that both of these explanations may suffice; differing concentrations of dopamine may activate different classes of receptors based on receptor affinity.

Brainstem accumulation of α-synuclein—A second hypothesis for the etiology of sleep disorders in PD is that it is caused by accumulation of α-synuclein in the brainstem. As mentioned above, RBD is common in PD and can precede the appearance of α-synucleinopathies by many years. Although the pathology of RBD is unknown, some theories include degeneration of lower brainstem nuclei; there is evidence of postganglionic sympathetic denervation and cardiac autonomic dysfunction in RBD (Miyamoto et al., 2006; Mitra & Chaudhuri, 2009; Postuma et al., 2010). Further, ample evidence exists for the presence of PD pathology, including α-synuclein accumulations and Lewy bodies, in the brainstem of PD patients. The areas of the brainstem involved in the regulation of sleep, wakefulness and arousal are the pendunculopontine nucleus, the laterodorsal tegmental nucleus, the locus coeruleus, and the dorsal raphe and all of these regions show lesions at an early stage of the disease prior to the onset of motor symptoms (Hirsch et al., 1987; Hobson & Pace-Schott, 2002; Pace-Schott & Hobson, 2002; Turner, 2002; Braak et al., 2003; Grinberg et al., 2010). Thus, brainstem pathology appears early in the disease state similar to the early appearance of sleep alterations relative to motor symptoms, which implies a role for the brainstem in mediating sleep disturbances in PD.

Hypocretin Signaling—In PD patients, the hypothalamus, which regulates sleep and metabolism, shows evidence of the presence of Lewy bodies, potentially indicating that PD pathology in the brain directly influences sleep patterns (Fronczek et al., 2007; Kremer & Bots, 1993). The hypocretins (orexins) are a class of excitatory neurotransmitter hormones that are thought promote wakefulness (Tsunematsu et al., 2011). Narcolepsy is associated with a decrease in hypocretin signaling (Kroeger & Lecea, 2009). There is evidence of a loss of hypocretin positive cells in the hypothalamus in PD patients implying a role for hypocretin signaling in sleep disturbances in PD. Hypocretin-positive cells are also decreased in the cortex as well, and CSF hypocretin levels are also decreased in PD patients compared to controls (Fronczek et al., 2007; Lessig et al., 2010). Further, at least one study showed an increase in the loss of hypocretin cells with PD progression; hypocretin cell loss in stage 1 was only 23% but reached 65% by stage 5 (Thannickal et al., 2007).

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Future Directions

The functional and structural integrity of neuronal circuits that play critical roles in the regulation of sleep is compromised in AD and PD. One clue to understanding why this is so comes from evidence that several of the major risk factors for sleep disorders are also risk factors for AD and PD including old age (Thal et al., 2004; Crowley, 2011), depression (Franzen and Buysse, 2008), obesity/diabetes (Tasali et al., 2009; Riederer et al., 2011) and a sedentary lifestyle (Santos et al., 2007; Lang-Asschenfeldt and Kojda, 2008). Elucidating the mechanism(s) that explains these shared risk factors should identify convergence points in the pathogenesis of age-related sleep disorders and AD and PD. One possibility is that neurons that regulate sleep are vulnerable because they are rendered unable to cope with the cellular stresses that occur in aging and neurodegenerative disorders (Figure 1B). Indeed, old age, excessive energy intake and lack of exercise all impair the ability of neurons to respond adaptively to stress resulting in increased oxidative stress and accumulation of damaged/misfolded/aggregated proteins (Figure 2) (Chen and Russo-Neustadt, 2007; Stranahan et al., 2009; Arumugam et al., 2010; Martin et al., 2010). Consistent with this notion, noradrenergic and orexinergic neurons in sleep circuits of aged animals exhibit reduced responsiveness to wakefulness and an aberrant endoplasmic reticulum stress response (Naidoo et al., 2011). A better understanding of the cellular and molecular mechanisms shared in age-related sleep disorders and AD and PD may lead to novel interventions for the prevention and treatment of all of these disorders.

Two environmental factors that may reduce the risks of sleep disorders, AD and PD are regular exercise and moderation in dietary energy intake (Sherrill et al., 1998; Luchsinger et al., 2002; Baker et al., 2010; Ahlskog, 2011). Both exercise and dietary energy restriction have been shown to counteract the disease process at the molecular and cellular levels in animal models of AD (Adlard et al., 2005; Wang et al., 2005; Halagappa et al., 2007; Parachikova et al., 2008) and PD (Duan and Mattson, 1999; Maswood et al., 2004; Zigmond et al., 2009; Lau et al., 2011). Both exercise and energy restriction enhance neurotrophic factor signaling and up-regulate mechanisms that protect against the aberrant accumulation of self-aggregating proteins including Aβ and α-synuclein (Walker et al., 2006; Irvine et al., 2008). Elucidation of the mechanisms by which exercise and energy restriction counteract the age-related sleep disorders and neurodegenerative disorders should be a major goal of future research.

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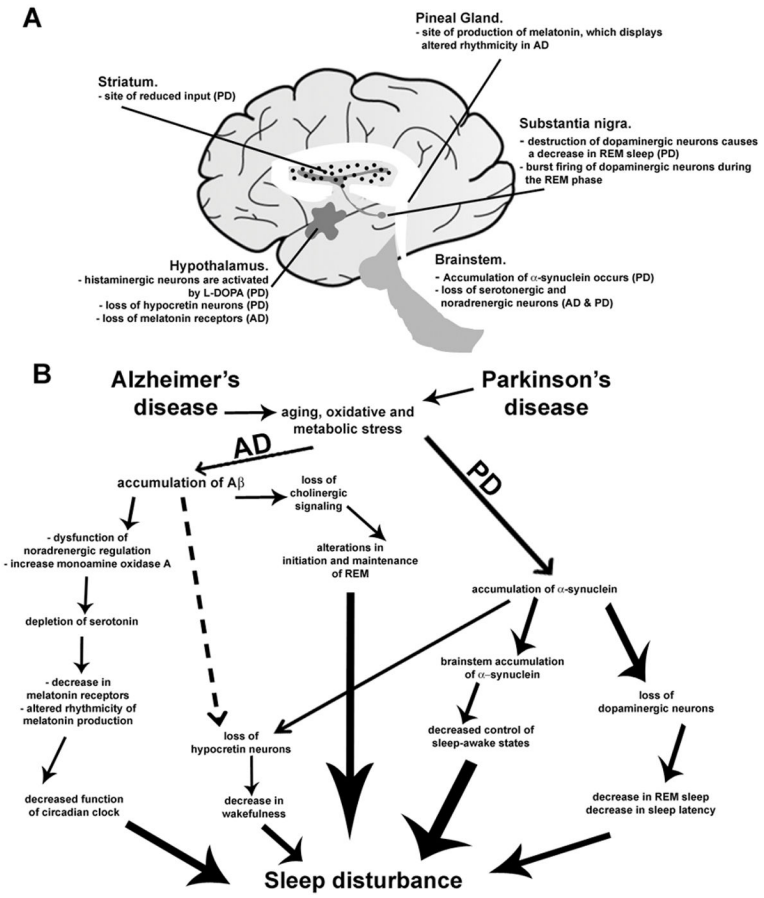

Figure 1.

Potential mechanisms underlying sleep disorders in Alzheimer's and Parkinson's diseases. (A) Brain regions involved in regulating sleep are susceptible to disease pathology in both AD and PD. (B) Sequences of events that may lead to sleep disturbances in neurodegenerative diseases. It is noteworthy that although accumulation of Aβ or α-synuclein may occur prior to the onset of sleep disturbances, it is often the case, particularly in PD, that sleep symptoms appear well before the hallmark deficits of the disease (motor dysfunction, in the case of PD).

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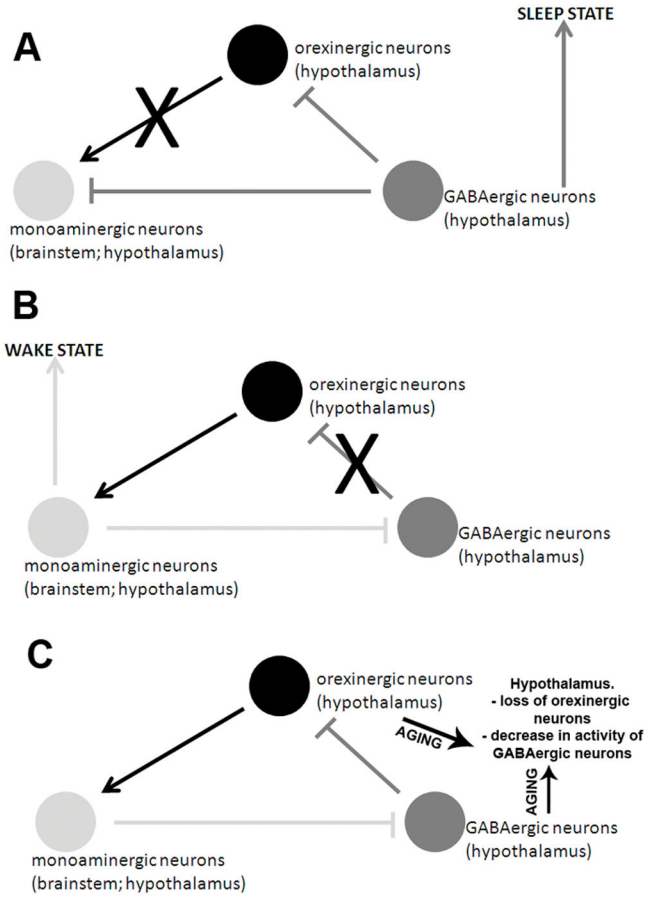

Figure 2.

Mechanisms by which aging may disrupt the function of neural circuits that regulate sleep – wake cycles. (A) During the sleep state, γ-aminobutyric acid, or GABA, inhibits neurons in both the brainstem and the hypothalamus. During the 'wake' state (B), GABAergic neurons in the hypothalamus are inhibited by monoaminergic neurons in the brainstem and hypothalamus. In aging, (C), the hypothalamus experiences both a loss of hypocretin/ orexinergic neurons and also a decrease in GABAergic signaling thus disrupting the sleep-wake cycle.