A Year in Review—Basic Science, Narcolepsy, and Sleep in Neurologic Diseases

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THE PAST YEAR HAS BEEN VERY FRUITFUL FOR SLEEP IN THIS BROAD AND DIVERSE AREA OF RESEARCH. As expected from recent progress in this area, a total of 12 original papers have been published in the area of narcolepsy, ranging from descriptions of the psychological and socioeconomic impact of the disease to new treatments. Following on the pioneer work of Broughton and others1,2 who showed that narcolepsy had socioeconomic costs similar to those of depression or epilepsy, Dodel et al.3 studied the monetary cost to German society of narcolepsy evaluation and treatment and of a narcolepsy disability program. Total annual costs amounted to approximately $12,000 per year, mostly as a result of early retirement. Interestingly, in this population of 75 patients, a significant amount of the cost was due to the appearance of newer more expensive treatments such as modafinil. It is suspected that a similar increase in cost is also occurring in the United States with the recent change in treatment strategies that involve newer drugs such as modafinil, sodium oxybate, and novel antidepressants. The same authors also reported a study assessing attention deficits in narcoleptic patients.4 Surprisingly, they found attention deficits that are difficult to explain solely by sleepiness, suggesting neurobiologic abnormalities in systems other than sleep regulation in hypocretin-deficient patients. In addition to attention deficits, it has also been reported that narcoleptic patients exhibit attenuated emotion-information processing.5 Several articles are also increasing our understanding of the pathophysiology of narcolepsy—either in the context of isolated primary narcolepsy or as a result of a secondary etiology. The study of the hypocretin system in narcolepsy cases was discussed by Kubota et al.6 Martinez-Rodriguez et al.7 and Vankova et al.8 The Kubota et al article was remarkable in that patients very close to disease onset were found to have low hypocretin-1 levels in the cerebrospinal fluid, emphasizing the use of the cerebrospinal fluid test for early diagnosis.9 The other 2 articles documented the presence of hypocretin abnormalities in some cases of excessive daytime sleepiness in association with myotonic dystrophy7 but not in cases of narcolepsy secondary to Niemann-Pick disease, Type C.8 The association of narcolepsy-like sleepiness in myotonic dystrophy is interesting, as the disorder is frequently associated with sleep apnea, potentially confusing the issue of what causes the sleepiness. A similar association of primary excessive daytime sleepiness, hypocretin abnormality, and sleep-disordered breathing has been reported in some cases of Prader-Willi syndrome.9 Clinically, these associations emphasize the importance of considering narcolepsy even if sleep apnea is present because a significant portion of narcoleptic patients develops obesity and has associated sleep apnea. Dominguez-Ortega et al.,10 for example, recently reported a patient with Down syndrome and narcolepsy-cataplexy. Because Down syndrome is commonly associated with sleep apnea,11 this case again emphasized that it is critical to ask about cataplexy and narcolepsy symptoms in all patients with sleepiness.

In the area of isolated narcolepsy, the report by Dauvilliers et al.12 that narcoleptic patients are more often born in March and less often born in September is notable. Similar findings have been reported in Germany,13 raising the possibility that prenatal or early postnatal environmental influences may influence the subsequent development of the disorder. A possible explanation for these phenomena may involve the shaping of the immune system of the fetus during pregnancy or immediately after birth. The finding that narcolepsy is associated with a hypocretin cell loss led Overeem et al.14 to examine whether structural changes in the hypothalamus can be identified in patients with narcolepsy using voxel-based morphometric study of the brain. This area is of great interest because, if successful, it could lead, on a long-term basis, to the development of diagnostic imaging procedures for narcolepsy. Unfortunately, however, no changes were observed, suggesting that the lesion may be too small to be detectable by conventional imaging techniques. Other authors have reported changes in various brain areas using the same technique, raising the possibility that a refinement of the technique may be successful in detecting an abnormality.15,16

The treatment of narcolepsy is also rapidly evolving, as emphasized by 3 reports.17-19 The results of a 12-month open-label trial of sodium oxybate were reported.17 The compound, primarily indicated for the treatment of cataplexy, was found to improve not only cataplexy, but also daytime sleepiness starting at 4 weeks and having a maximal effect at 8 weeks. Effects on cataplexy were even longer to fully manifest and, in most cases, continued to manifest several months after treatment onset. The most commonly reported adverse effects were nausea, headache, dizziness or somnolence, pain, enuresis, and viral infection (only dizziness was significant out of all treatment groups). Nonsignificant decreases in hypnagogic hallucinations and sleep paralysis were also reported starting 1 month after treatment. These results have to be interpreted cautiously because this was not a double-blind study, but the results seem to confirm the clin-
ical impression that indicates that the effect on cataplexy may take several months to fully manifest in patients treated with sodium oxybate. These delays contrast with the immediate effect on disturbed nocturnal sleep.

Experimental treatments of narcolepsy are also being studied. A study by Nishino et al\textsuperscript{18} indicated that intravenous and intracerebroventricular administration of hypocretin-1 are inactive on the symptoms of narcolepsy in hypocretin receptor-2–mutated narcoleptic dogs. A very short-lasting effect was possibly detected after intravenous administration of extremely high doses of hypocretin-1 in a single hypocretin-deficient dog. This study needs to be discussed in the context of a recent report suggesting the therapeutic efficacy of hypocretin after central administration in hypocretin-deficient knockout mouse.\textsuperscript{19} Most likely, brain-penetrant hypocretin-receptor agonists will need to be developed before the potential therapeutic effect of hypocretin replacement therapy can be assessed in humans. Because narcolepsy has been long suggested to be autoimmune in nature, immunotherapy is also being considered as a treatment for narcolepsy. Because most cases of narcolepsy already have extensive hypocretin cell destruction later in the course of the disease, as assessed post-mortem\textsuperscript{20,21} or by measuring hypocretin-1 levels in the cerebrospinal fluid,\textsuperscript{22} most studies in this area are focusing on cases identified as closely as possible to the onset. In this vein, Hecht et al\textsuperscript{23} reported the results of an unsuccessful attempt to prevent further narcolepsy symptoms using prednisone in a case identified 3 months after sleepiness onset but prior to the development of cataplexy. In a parallel study, Lecendreux et al\textsuperscript{24} conducted similar experiments using intravenously administered immunoglobulin and found striking effects in a single case with recent onset. These findings raise the possibility of an antibody rather than cell-mediated autoimmune process and emphasized the need for identifying patients close to the onset of symptoms and pursuing research in this area, since narcolepsy may be reversible close to the onset with the appropriate treatment.

Last year was also notable for a number of basic research articles, many of which pertained to the regulation of rapid eye movement (REM) sleep, the pharmacology of sleep, or both. Murrillo et al\textsuperscript{25} reported on an increased adenosine release in the basal forebrain area after anandamide stimulation of the cannabinoid receptor. The importance of adenosine release in the basal forebrain (but not in other brain regions) in non-REM sleep generation has long been studied since work by Porka-Heiskanen et al in 1997.\textsuperscript{26} A number of other articles have focused on adrenergic mechanisms that regulate sleep. Datta et al\textsuperscript{27} found that microinjections of norepinephrine, serotonin, and adenosine into the pedunculopontine tegmentum, a cholinergic cell group known to be activated during REM sleep, did not suppress REM sleep. These results run contrary to the popular theory that norepinephrine, serotonin, and adenosine suppress REM sleep by direct inhibition of brainstem cholinergic systems, as generally postulated by the reciprocal interaction model. The importance of the adrenergic locus coeruleus in the regulation of sleep, especially REM sleep, should also be revisited in view of results indicating that normal sleep-wake patterns occur in norepinephrine-deficient mice (Hunsley and Palmiter).\textsuperscript{28} Similar results have been reported in dopa-β-hydroxylase-deficient humans who exhibit abnormalities in the autonomic nervous system but have minimal sleep disturbances.\textsuperscript{29} Conditional knockout animals will be essential to test if the lack of sleep abnormalities is secondary to developmental regulation in conventional knock-out animals. In the same vein, 2 articles have highlighted the difficulty in interpreting pharmacologic results and illustrate the relative selectivity of all natural and pharmaceutical agents. In the study of Crochet and Sakai,\textsuperscript{30} dopamine perfusion in the perilocus coeruleus alpha, a brainstem region established by these authors as essential for REM generation, was found to inhibit REM sleep via stimulation of adrenergic α\textsubscript{2} receptors. These results illustrate the fact that even with natural catecholamines, selectivity is not perfect for adrenergic versus dopaminergic receptors. In fact, as an example, dopamine affinity for some α\textsubscript{2} receptor subtypes (especially α\textsubscript{2C}) is very high and higher than the natural affinity of norepinephrine for α\textsubscript{1} receptors. The article by Galoppin et al\textsuperscript{31} on the effect of modafinil on presumed sleep-active ventrolateral preoptic area cells in slices is also interesting in this regard. The mode of action of modafinil is controversial, but we have suggested a low affinity (Ki = 10-6-10-7 M; no affinity for adrenergic reuptake up to 10-4) for the dopamine transporter reuptake site that is compatible with its wake-promoting properties.\textsuperscript{32-34} In this article, an inhibitory effect that is compatible with a weak adrenergic reuptake effect was observed at very high concentrations of modafinil (0.05-0.2 mM).

Many authors are refocusing their efforts from the study of the brainstem to the study of structures in the forebrain. Using FOS as a marker for neuronal activation, Torterolo et al\textsuperscript{35} suggested a primary activation of the hypocretinergic hypothalamic system during wakefulness in association with locomotor activity in rats. The role of locomotion in activating hypocretin systems is debated and has been discussed in various animal species by Wu et al, Zeitzer et al, and Zhang et al.\textsuperscript{36-38} Simon-Arceo et al\textsuperscript{39} further explored the role of the amygdala in the regulation of sleep. The authors found increases in REM sleep, pontogeniculooccipital waves, and, in some instances, slow-wave sleep after vasoactive intestinal peptide injections in this structure. Imaging studies in humans have shown activation of amygdala and other limbic structures during REM sleep.\textsuperscript{40,41} Recent pharmacology work of Sanford and Morrison\textsuperscript{42} also indicated the functional importance through microinjection studies in this structure. Interestingly, de Andres et al\textsuperscript{43} also found that REM-sleep rebound after deprivations does not occur in decerebrate cats, demonstrating important influences of the descending forebrain on brainstem structures involved in the generation of REM sleep. A recent study\textsuperscript{44} also showed that fear conditioning can influence subsequent REM sleep in a mouse strain in a dependent fashion, suggesting genetic influences.

The effect of vagus nerve stimulation on sleep stages in animals and refractory epilepsy in humans has been long documented. Effects on refractory depression and breathing during sleep apnea have also been found. Building on a recent finding by Malow et al\textsuperscript{45} indicating improvement in subjective (Epworth Sleepiness Scale) and objective (Multiple Sleep Latency Test) sleepiness in subjects treated with vagus nerve stimulation, independent of seizure response, Rizzo et al\textsuperscript{46} also found decreased napping and increased alertness in 10 patients with refractory epilepsy who were treated with vagus nerve stimulation. In this study, decreasing effects on REM sleep were also noted during nocturnal sleep, a finding that has not always been found in other studies. Overall, these studies indicate that vagus nerve stimulation can improve sleepiness in patients with epilepsy and
may have other effects on sleep and breathing during sleep, most likely via brainstem influences.

Neurodegenerative diseases such as Alzheimer disease are frequently associated with sleep disorders, including for example, electroencephalogram slowing47 and sleep apnea.48 Based on the observation of cholinergic cell-body loss in the basal forebrain in patients with Alzheimer disease, acetylcholine esterase inhibitors are frequently prescribed and have been shown to improve behavioral disturbances. In a recent double-blind, placebo-controlled study comparing placebo and galantamine, Markowitz et al49 evaluated the effects of this drug on the sleep symptoms of patients with mild to moderate Alzheimer disease. No significant positive or negative drug effects were found using the Pittsburg Sleep Quality Index and observations by bed partners of sleep apnea-like symptoms.

Sleep disturbances are also increasingly recognized as common and clinically significant in patients with treated and untreated Parkinson disease. Marinus et al50 developed a short 10-item scale, the SCOPA Sleep Scale, and validated the scale in 104 controls and 143 patients with Parkinson disease. Large differences were found, and some aspects of the scale were found to correlate well with the widely used Pittsburg Sleep Quality Index and the Epworth Sleepiness Scale. The SCOPA scale addresses both nocturnal sleep disturbances and daytime sleepiness and could be used for various other neurologic disorders. REM-sleep abnormalities, most notably REM behavior disorder, are increasingly recognized as an integral feature of Parkinson disease and other synucleinopathies, sometimes preceding the onset of Parkinson disease by many years.51 In the paper by Eisensehr et al,52 positron emission tomography imaging studies of the dopamine transporter and dopamine D2 receptors were conducted in 8 subjects with idiopathic subclinical REM behavior disorder, 8 subjects with idiopathic clinically manifest REM behavior disorder, 11 controls, and 8 subjects with Parkinson disease. A surprising progressive loss of dopamine transporters was observed from subclinical to clinical REM behavior disorder and then manifest Parkinson disease. Muscle activity lasting persistently longer than 0.5 seconds was associated with reduction in striatal transporter binding. Postsynaptic D2 receptor binding was unchanged. These results add further credence to the suggestion that even subclinical REM behavior disorder is pathophysiological related to Lewy body diseases such as Parkinson disease.

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