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Autonomic Alterations in Narcolepsy—Contrasting Results in Mice and Men

Commentary on Sorensen et al. Attenuated heart rate response is associated with hypocretin deficiency in patients with narcolepsy. SLEEP 2013;36:91-98.

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In the current issue of *SLEEP*, Sorensen and colleagues[1] show a reduced heart rate response to arousals and leg movements in narcolepsy patients who lack hypocretin-1. This attenuated heart rate increase was independent of the occurrence of cataplexy and other factors such as age, gender, disease duration, and BMI. The authors conclude that the hypocretin system plays an important role in autonomic regulation during sleep.

Since the discovery of the hypocretin system and its relationship to narcolepsy with cataplexy, it has proven difficult to gain insight into the exact effects of the hypocretins (or lack thereof) on the autonomic nervous system. At first, animal studies provided results that were in line with what were thought to be the most logical effect of the hypocretins. Administration of hypocretin or stimulation of hypocretin secreting neurons led to an increase in sympathetic output parameters such as increased heart rate, blood pressure, and body temperature.[2] Conversely, lower heart rate and blood pressure during wakefulness were found in hypocretin neuron-ablated rats and hypocretin deficient mice.[3-6] This nicely fit with the theory that a lowered sympathetic tone would be a logical corollary of hypocretin deficiency. This, in turn, could explain a lowered metabolic rate and the obesity that is characteristic of narcolepsy. However, in reality it was not this simple.

Sleep studies in transgenic and knock out mice yielded different results. During sleep, an increase in blood pressure was reported.[6,7] Also in contrast to the previous experimental models, various human studies gave the suggestion of sympathetic activation: heart rate was found to increased both during wake[8,9] and sleep,[9] and the physiological sleep-related blood pressure decline appeared to be blunted in narcolepsy patients.[9,10] It was hypothesized that these sympathetic changes were explained by the continuous fight against sleep or to a loss of state boundary control with frequent shifts between different vigilance and sleep states. Alternatively, a changed sympathetic tone might also truly be a direct consequence of hypocretin deficiency itself. The mechanisms are however still unknown. Attempts to dissect the contribution of the sympathetic and parasympathetic system to the heart rate changes have yielded contradicting results. The sympathovagal balance during wakefulness was reported to be increased,[11] decreased,[8] or normal.[12] The complexity of the matter may perhaps be reflected in the fact that in rodents, hypocretin neurons innervate both parasympathetic as sympathetic regions of the autonomic nervous system.[13]

Sorenson et al.[1] provide a new piece of the unsolved autonomic puzzle in a large group of narcolepsy patients with known hypocretin status. The expected increase in heart rate following an arousal or leg movement during sleep was chosen as a parameter of autonomic function. Furthermore, results were analyzed taking into account different sleep stages, including REM sleep. Assessing autonomic function was thus not hampered by the unknown influences of fighting sleepiness and frequent shifts between states. They found that narcolepsy patients showed a decreased heart rate response to arousal compared to healthy controls in both stage 2 sleep and REM sleep. The results are in line with a smaller study, demonstrating an impaired heart rate response to periodic leg movements in patients with narcolepsy without known hypocretin status.[14] Sorenson et al. also found that heart rate response associated with arousals was lower in hypocretin deficient subjects compared to narcolepsy patients with normal hypocretin levels.[1] The authors concluded that hypocretin deficiency is the primary predictor of this dysfunction.

We believe that an alternative explanation for the results of Sorenson et al. could be that the heart rate changes are the consequence of the altered sleep architecture, since other factors affecting sleep-related heart rate changes such as length of sleep stages were not taken into account. After all, do we know how long the autonomic nervous system takes to adjust to a sleep state change? Could the attenuated heart rate response in narcolepsy point to decreased sympathetic signaling? Interestingly, in their study, Sorenson et al. mention that hypocretin-deficient narcolepsy patients already had an elevated heart rate at baseline although this data is not directly shown. Accordingly, an elevated baseline heart rate during sleep in hypocretin-deficient subjects was also described by Grimaldi et al.[9] in a recent paper. In this elegant small study, it appeared that despite the elevated heart rate, day-night and state-dependent heart rate modulations were intact. Thus, while the attenuated heart rate response to leg movements[1,14] or arousals[1] in narcolepsy may point towards a decreased sympathetic tone, the constantly elevated heart rate[9] and the blunted overnight blood pressure decline[9,10] may favor the opposite. Thus, the direction of the autonomic changes in narcolepsy, either suggesting a sympathetic increase or decrease, seem to reverse in the sleep-wake cycle with notable contrasts in the presence or absence of arousing stimuli.

What is the clinical importance of these autonomic changes? Alterations in heart rate and blood pressure regulation could

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influence the cardiovascular risk profile. The "non-dipping" blood pressure profile in narcoleptic patients, as reported by Grimaldi et al.[9] and Dauvilliers et al.[10] has been associated with an increased mortality. However, despite also being more obese, a higher incidence of cardiovascular events has not been reported thus far in narcolepsy. To fully understand the autonomic consequences of narcolepsy and its possible relation to cardiovascular risk, further research is needed. New cardiovascular studies using state-dependent analysis may prove fruitful to further dissect the direct effects of the hypocretin deficiency and the associated altered sleep/wake regulation. Moreover, epidemiological studies could help to clarify whether the complex autonomic changes are of clinical importance.

CITATION

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.

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