The discovery of hypocretin (Hcrt or orexin) cell loss [1] and Hcrt depletion [2,3] has revolutionized our understanding of human narcolepsy. It has opened the possibility of treatment of narcoleptics with Hcrt [4] or Hcrt agonists. It has also provided a neurochemical test for narcolepsy in the measurement of Hcrt in the cerebrospinal fluid [5]. Further diagnostic progress based on this discovery could include in vivo brain imaging for the lost cells and even a blood test for narcolepsy. However, initial attempts at a blood test have not produced consistent results or proof that what is being assayed is really Hcrt and linked to central Hcrt level [6–9].

It has recently become apparent that while a Hcrt deficiency is characteristic of narcolepsy with cataplexy, not all narcoleptics with cataplexy share the Hcrt deficiency [5]. Furthermore, since narcolepsy without cataplexy, as defined by accepted nosology, is often accompanied by normal cerebrospinal Hcrt levels as others have reported [10], and as Bassetti et al. emphasize in this issue [11], the practical clinical value of the cerebrospinal fluid test is unclear, since it is sleepiness without cataplexy that presents a diagnostic challenge. In narcolepsy without cataplexy, the presence or absence of Hcrt has not yet been shown to correlate with any other readily measured symptom, or with the intensity of sleepiness. Narcoleptics without cataplexy have long been known to have similar human leucocyte antigen (HLA) linkage, non-cataplexy symptoms and drug responses to those with cataplexy.

A more fundamental issue illustrated in the article by Bassetti et al. [11] and in other recent work that they cite is the extent to which hypersomnolent symptoms in general are accompanied by a Hcrt deficiency. Given the lack of a consistent link between Hcrt deficiency and narcolepsy without cataplexy, it is not surprising that a marked Hcrt deficiency is not characteristic of hypersomnolence. The enthusiasm generated by Hcrt’s key role in narcolepsy should not lead us to label it the ‘waking chemical’. Multiple systems are involved in generating sleep and wakefulness, and multiple pathologies will probably be shown to underlie hypersomnolent syndromes. Moreover, researchers should be aware that Hcrt levels are not simple ‘trait’ variables that are characteristic of an individual. Rather, behavior occurring prior to collection can have a major effect on Hcrt levels. Our recent work in normal cats [12] and dogs [13] showed a near doubling of cerebrospinal fluid Hcrt levels after as little as 2 h of exercise. Much of the reported variability in Hcrt levels may be due to behavior occurring prior to cerebrospinal fluid draws, although clearly this cannot account for the dramatic reduction in Hcrt in narcoleptics with cataplexy, correlated with their loss of Hcrt containing neurons.

The Hcrt discoveries have given us a powerful analytic tool for understanding narcolepsy and distinguishing it from other hypersomnolent syndromes. Measurement of other neurotransmitters and their metabolites, HLA status and other genetic markers will undoubtedly lead to the identification of multiple hypersomnolent syndromes and perhaps even the subdivision of narcolepsy into several diagnostic categories.

References


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