Narcolepsy: The Tip of an Iceberg of Neurological Dysfunction

Moshe Turner

ABSTRACT

Here, we demonstrate that a significant reduction in or total silencing of signaling by orexin neurons produces numerous systemic effects of which the symptoms of narcolepsy constitute only a small subset. We then suggest that this broad range of symptoms, having a single cause, be characterized, named, and entered into the taxonomy of diseases as a systemic neurological disorder. We opine that doing so would help to bring clinicians to a better awareness of the many physiological and behavioral manifestations of absent or significantly diminished orexinergic signaling, helping to improve the interactions they have with narcoleptic patients and the quality of the care they provide to them.

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INTRODUCTION

Narcolepsy is classified as a central disorder of hypersomnolence in both the ICSD-3 (1), and the DSM-5 (2). People with narcolepsy have difficulty maintaining the waking state (3, 4, 5, 6), a function primarily of a small number of hypothalamic cells called both orexin, and hypocretin neurons (7, 8). Regardless of the still uncertain etiology of the disorder (9), abundant research has shown that the symptoms of narcolepsy result from the nearly complete loss or significant disabling of orexinergic signaling, manifesting as type 1 narcolepsy, with cataplexy, and type 2, without cataplexy (10, 11, 12).

Orexin neurons do more than stabilize arousal, and the pentad (formerly tetrad) of narcolepsy symptoms (13) comprise only the more visible or easily identifiable tip of the iceberg of dysregulation caused by disrupted orexinergic signaling. Orexin neurons integrate afferent limbic and autonomic signals (14, 15, 16, 17) and efferently direct fast physiological and behavioral responses to changing conditions. They regulate or modulate: locomotion and spontaneous physical activity (18, 19), mood and emotion (20, 21, 22), reward-seeking/addictive behavior (23, 24, 25, 26, 27), autonomic response to allostatic challenges (28,29), appetitive behaviors (food seeking and satiety) (30, 31, 32, 33, 34, 35), gastrointestinal function (36,37), nociception (38, 39), sex drive (40, 41), the micturition reflex (42), thermoregulation/ thermogenesis (43, 44), energy storage and expenditure (45, 46, 47, 48, 49), fear learning (50, 51, 52, 53), executive function and cognitive flexibility (54, 55, 56), memory formation (57), decision making (58, 59), olfaction (60) and other functions. They do this by signaling with the orexin peptides in conjunction with several other excitatory and inhibitory transmitters also expressed on orexin neurons (61, 62, 63).

Reading an ever-changing score, so to speak, orexin neurons direct the members of the neural orchestra (64,65,66) to play their parts on time and in key . Without this direction the music becomes discordant. Some members might try to play the piece on their own; for example, histamine neurons in the tuberomammillary nucleus of the posterior basal hypothalamus can assist with wakefulness (67, 68). Others might

elect to play an entirely different tune. The result is disharmony that increases over time. While the specific symptoms of narcolepsy are not progressive, the cumulative effects of consistently poor nighttime sleep and the systemic effects of the sustained loss of orexinergic signaling over time eventually manifest as problems such as hypertension, obesity, diabetes, depressive behaviors, etc. (69, 70, 71, 72, 73, 74).

That's a lot to unpack from a box labeled "sleep disorder". As demonstrated above, the symptoms of narcolepsy are only a subset of symptoms that belong to a much wider, encompassing disorder of disrupted orexinergic signaling. That larger disorder is neither named nor characterized in the taxonomy of diseases.

Regardless of how we got here, it is necessary to ask if it is wise or appropriate to allow the situation to persist. Should a disorder which causes such extensive physiological and behavioral dysfunction to remain classified as a hypersomnia? As mentioned in a previous article (75), general care providers and most specialists not working specifically in sleep medicine can go for a long time without coming across a narcoleptic patient. They are generally not trained to recognize narcolepsy at all, let alone to consider the interconnected nature of the many discrete physiological dysfunctions that defective orexinergic signaling gives rise to. Misclassifying a systemic disorder as a hypersomnia contributes to a lack of awareness that keeps it off the minds of most clinicians. That lack of awareness can cause difficulties to develop in the interactions between clinicians and narcoleptic patients.

Consider what might happen when even a person with an existing diagnosis of narcolepsy appears in a clinical setting presenting with one or more of these other symptoms not obviously related to narcolepsy. Sometimes such a patient will present with a baffling grab bag of apparently disconnected complaints. When that happens (and it does) the clinician could easily be forgiven for rendering a diagnosis of dysautonomia (76), or for simply finding the patient to be a bit hysterical, or depressed. Having a disorder of disturbed orexinergic signaling in the literature would help to bring clinicians to a greater awareness of its systemic effects beyond narcolepsy. That would surely help to improve the interactions that people with narcolepsy have with clinicians and the quality of the care they receive.

"Narcolepsy" has served well as a name for a sleep disorder since it was named by the French physician Jean-Baptiste-Edouard Gélineau in 1880 (77), and it still does. It is not necessary to undo over a century's worth of association of its symptoms with that name. However, now that the group of symptoms which constitute narcolepsy are known to be part of an encompassing disorder, that encompassing disorder should be named and entered into the literature as a distinct entity.

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