OREXIN MODULATORS ARE CRITICAL FOR TREATING INSOMNIA

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Human sleep is a circadian based oscillation between rapid eye movement sleep (REM or dream sleep) and non-rapid eye movement sleep (NREMS). A typical period begins with NREMS, cycling through a series of stages (from 1 to 4). Normal sleep "architecture" consists of a preponderance of NREMS, especially Stages 3 and 4 early in the sleep period, with a shift to an increasing proportion of time spent in REMS as the sleep period progresses. Stages 3 and 4 are collectively known as slow wave sleep (SWS), based on sleep EEG (polysomnography or PSG) wave characteristics (high voltage, low frequency, <4 Hz). The thalamus is considered a key site for the generation of the synchronized slow wave activity (SWA).

Primary insomnia is a disorder in which individuals suffer from pronounced and sustained difficulty in initiating or maintaining sleep, and with the complaint that their sleep is often "non-restorative". Insomniacs experience significant difficulty in occupational, social, or other areas of functioning; and they may nap frequently during the day or experience excessive sleepiness. A DSM-IV-TR diagnosis of primary insomnia requires that the individual suffer from these symptoms for at least a month, and the symptoms should not stem from another primary sleep disorder, another psychiatric problem, or a medical illness. The pathophysiology of primary insomnia is unknown, but efficacy assessment of novel hypnotic agents in patients with this condition is standard as it represents a "pure" sleep disorder, in principle that is not due to ongoing medical or psychiatric problems.

The orexin signaling pathway includes two ligand peptides, Orexin A and B, formed from the orexin pre-propeptide, which is selectively expressed in a subset of neurons whose cell bodies reside within the lateral hypothalamus. Among the several functions of the hypothalamus, the control of the circadian and circannual rhythms is of notice. From the hypothalamus, orexinergic neurons project widely throughout the brain and activate neural centers such as locus coeruleus and tuberomammillary nucleus. These neural centers mediate wakefulness. Down regulation of central orexin activity has been conclusively linked to narcolepsy and abrupt sleep onset. As predicted by these proarousal effects of orexin, preliminary results in human subjects (both externally and within our program) suggest that orexin antagonism seems to increase sleep, including improving sleep in patients with insomnia.

Pharmacological treatment of insomnia in the United States and Europe is currently dominated by benzodiazepines (BZD), non-BZD hypnotics acting at the benzodiazepine site (e.g., zolpidem, zaleplon), and sedating antidepressants such as trazodone. The benzodiazepines have a number of properties and side effects that have limited their use: next-day sedation, memory disturbances, hallucinations (e.g., triazolam), rebound insomnia (especially the short half-life agents), and physical and psychological dependence. BZDs treat insomnia by lengthening the period of stage two sleep, but at the expense of shortening periods of deeper sleep and REM sleep. Newer non-BZD treatments are GABA-A alpha 1 selective modulators that act at the BZD binding site. Although these newer agents are claimed to exhibit little or no tolerance and risk for dependency, recent observations suggest that subjects with psychiatric disorders, and especially subjects with a history of substance abuse, may be at specific risk of developing substance abuse with zolpidem and zopiclone. Next-day negative cognitive effects (Digit Symbol Substitution Test) in the elderly are cited in the zolpidem label. In part because of the potential risk for abuse and dependency in BZD and BZD-like compounds, all hypnotics currently marketed in the United States are scheduled compounds. Prescriber concern for abuse potential is in part the driver for off-label use of sedating antidepressants such as trazodone. Trazodone, however, is itself associated with significant side effects including daytime somnolence, orthostatic hypotension, dizziness, priapism, and perhaps tolerance in depressed patients.

After four decades of insomnia therapy dominated by BZD and BZD-like hypnotics, recent identification of orexin antagonists that target pathways directly linked to the circadian biology, offers promise for future therapies that overcome the limitations and disadvantages of those affecting the GABA-A receptor system. These uniquely focused approaches may present new opportunities outside of traditional efficacy on sleep induction and maintenance as well. For example, based on a growing body of evidence that sleep enhances cognitive function through its role in memory consolidation, the appealing possibility exists that future therapies directed at novel targets could enhance next-day performance.

The efficacy of orexin antagonists seems to be in line with the efficacy of currently available products. Focusing on the efficacy alone provides an incomplete picture. We take the position that orexin antagonists will address the core of the pathophysiology of insomnia, by inducing a more physiological sleep and without the long term consequences of sedative medications.