

## **ARE OREXIN MODULATORS ARE CRITICAL FOR TREATING INSOMNIA? NO**

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Orexin: Orexin or Hypocretin-1 is a peptide produced in the hypothalamus, which has been recently identified to be involved in the regulation of arousal, energy metabolism and nociception.

Hypocretine-1 deficiency is associated with narcolepsy with cataplexy.

We know now that insomnia and chronic sleep loss can lead to obesity.

It is hypothesised that hypocretine-1 is involved in this process, since it both regulates sleep as well as metabolism.

Since 2007 we know that hypocretine-1 is functioning as stabilizer of the so-called "Flip-Flop switch" that switches sharply between sleep and wake. It is also involved in the sharp shift from NonRem to Remsleep and back.

It has been postulated that suppression of hypocretine-1, its producing neurons or receptors, could influence sleep, specifically could cure insomnia.

Trials are underway in the US to measure the effects and side effects of Almoreant, an oral dual orexin receptor antagonist. This substance decreases alertness and increases sleep in rats, dogs and humans. Until the present no cataplexy has been detected as a side effect, however data are limited.

Insomnia: Insomnia however is not only mediated through the hypocretin-1 system. Insomnia is more often caused by stimulation of our sensory systems mostly the visual and auditory systems. Light from smartphones, PDA's and PC's stimulate alertness through the supra chiasmatic circadian clock system, which in its turn suppresses the release of melatonin, the sleep hormone. Light is delaying the circadian clock and prolongs wake periods. The alarm clock in the morning is fixed on an early waking time, which results in loss of sleep time. When these smartphones, PDA's and PC's are used for social media, messaging and surfing on internet, also the content of the messages can will delay sleep and cause awakenings which also result in insomnia.

Loss of sleep causes metabolic changes resulting in immune deficiency, obesity, mental decline, higher irritability and sleepiness, tired persons and finally can cause depression. Most insomnia's are the result of above secondary causes, which are in fact the result of our 24/7 society and stress.

Primary insomnia is a rare diagnosis, most probably genetically caused.

Most insomnia's are caused by above circadian clock changes and psycho physiological factors. They do not involve a primary imbalance in sleep hormones.

These types of secondary insomnias should not be treated with hormones that will influence sleep homeostasis.

Therefore a Hypocretine-1 antagonists are not critical and are not the first choice of treatment for most of the insomnias, since they do not target the cause of the problem and most probably will lead to side effects. Better and cheaper treatments are available in the form of sleep hygiene and cognitive behavioural therapy. Time permitting also the relationship between orexins, sleep and headache will be discussed.