



OREXIN: A TREATMENT FOR NARCOLEPSY?

by Regina Patrick RPSGT

Orexins are neuroexcitatory peptides that are secreted by special neurons in the hypothalamus. Peptides were initially studied for their role in appetite. Scientists later found that peptides also played a role in sleep and wake. In people with narcolepsy, orexin-secreting neurons (i.e., orexinergic neurons) are inexplicably and progressively destroyed, possibly as the result of an autoimmune reaction. The destruction of orexinergic neurons reduces the amount of orexin in the brain. It is thought that low brain levels of orexin is responsible for the problems with wakefulness and sleep experienced by narcoleptics. The neuronal loss is permanent but scientists are working to determine whether restoring orexin levels in the brain

Scientists are working to determine whether restoring orexin levels in the brain could reverse narcolepsy

could reverse symptoms in narcolepsy. A recent primate study indicates that the answer to this may be yes.

In 1998, two teams of researchers independently discovered two peptides that appeared to increase

appetite. One team of researchers, headed by Takeshi Sakurai, named the peptides orexin-A and orexin-B (from the Latin word, orexis, meaning “appetite”). The second team of researchers, headed by Luis de Lecea, named the peptides hypocretin-1 and hypocretin-2. The “hypo-” in their term is derived from hypothalamus, the brain structure that produces the peptides, and “-cretin” since the peptides belong to a family of molecules called incretins that stimulate the release of insulin after a meal. Later research proved that hypocretin-1 and orexin-A were the same molecule and hypocretin-2 and orexin-B were the same molecule. Both terms continue to be used today.

Subsequent investigations into the neural pathways of orexinergic neurons found that they project into brainstem areas such as the locus ceruleus, raphe nuclei, and reticular formation that control various aspects of rapid eye movement (REM) sleep and wake. The orexins may play a role in narcolepsy through these projections.

Narcolepsy is a hypersomnia disorder. That is, it is a disorder characterized by excessive daytime sleepiness and/or recurrent episodes of uncontrollable but brief periods of sleep. Additionally, a person with narcolepsy may have cataplexy, sleep paralysis, and/or hypnagogic hallucinations. Cataplexy is the sudden temporary loss of tone in all or a few skeletal muscles when a person experiences heightened emotion (e.g., mirth, anger, etc.). If all skeletal muscles become weak, a person will fall to the floor apparently unconscious; however, the person does remain aware of what is going on around him/her but is unable to move. Sleep

paralysis is a temporary inability to move one’s skeletal muscles during the transition between wake and sleep. A hypnagogic hallucination is vivid imagery that occurs with the onset of sleep that is hard to distinguish from reality. Cataplexy, sleep paralysis, and hypnagogic hallucinations are thought to be the result of REM sleep phenomena (e.g., low muscle tone, dreaming) manifesting during wake. Although all narcoleptics struggle with hypersomnia, not all have cataplexy, sleep paralysis, and hypnagogic hallucinations.

Both orexin-A and orexin-B in animal studies have been shown to increase attention and alertness. One difference between the molecules is that orexin-A (a 33 amino acid residue molecule) can cross the blood-brain barrier but orexin-B (a 28 amino acid residue molecule) can not. Additionally, orexin-B is quickly degraded when it is injected intravenously into a subject. Therefore, orexin-A is more commonly used to study the effect of this class of peptides in the brain.

Most recently, Sam A. Deadwyler et al. in 2007 reported their experience with using orexin-A to improve memory and performance in sleep-deprived rhesus monkeys undergoing a delayed match-to-sample (DMS) task. The monkeys were sleep deprived for 30 – 36 hours. Since research in other animal studies had indicated that the intranasal delivery of orexin has a greater effect than intravenous delivery, the researchers compared the effects of intravenous vs. intranasal administration of orexin-A on memory and performance in the monkeys.

For the DMS task, the monkey would move a cursor to a target in the center of a computer screen. On hitting the target, a sample image would come onto the computer screen. (The sample image was clip art images of faces, people, photographs, cartoons, animals, toys, colors, etc.) The monkey would then place the cursor onto the sample image. This triggered the screen to go blank for 1 to 90 seconds (i.e., the delay interval). After the delay interval, a group of two to eight images came on the screen. Only one image (called the match image) was identical to the sample image with the other one to seven images being the distracter images. If the monkey placed the cursor on the match image, it was rewarded with a fruit drink. Each monkey performed the DMS task under six conditions: 1) alert and administered a saline solution (i.e., the baseline alert condition); 2) alert and administered intravenous orexin-A; 3) alert and administered intranasal orexin-A; 4) sleep-deprived and administered a saline solution (i.e., the baseline sleep-deprived condition); 5) sleep-deprived and administered intravenous orexin-A; and 6) sleep-deprived and administered intranasal orexin-A.

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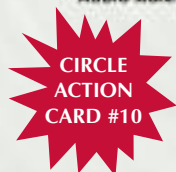
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For intranasal administration, the researchers placed an orexin-A solution in an atomizer. The atomizer sprayed the orexin solution in a mist about 5 – 10 centimeters (2 – 4 inches) from an animal's nostrils. Intravenous administration of orexin was done 10 minutes before testing and intranasal administration, 5 – 10 minutes before testing.

Deadwyler et al. found, as expected, that the monkeys performed worse overall on the DMS task during their baseline sleep-deprived condition (approximately 65% correct answers) than they had during their baseline alert condition (approximately 78% correct answers). When the sleep-deprived monkeys were given intravenous orexin-A, they got a approximately 75–78% of the answers correct. But when they were given intranasal orexin-A, they got approximately 80% of the answers correct.

The researchers were surprised to find that when fully alert monkeys are given orexin-A, they perform no better or slightly worse on the DMS task – approximately 81% correct answers with intranasal administration and 75% correct answers with intravenous administration – than at their baseline alert condition (approximately 78% correct). They surmise that the activation of the orexin receptor 1 by orexin-A may differ during wake

and sleep deprivation. This in turn may negatively affect the ability of orexin-A to enhance memory and performance in alert monkeys. Nevertheless, the researchers concluded that orexin-A can increase attention and alertness in sleep-deprived monkeys.

Further supporting their conclusion, the researchers took baseline positron emission tomography (PET) scans of the monkeys' brain activity before and after sleep deprivation with no orexin treatment. They compared these scans with PET brain scans taken during sleep deprivation with intravenous orexin-A and with intranasal orexin-A.

In a PET scan, a radioactive form of glucose, fluorodeoxyglucose, is tracked as it is utilized in a body tissue. The greater the activity in the tissue, the greater the amount of glucose utilized by the tissue, and therefore the greater the amount of radioactivity in the tissue. They found that areas most affected by sleep-deprivation – the thalamus, dorsolateral prefrontal cortex, and the medial temporal lobe – had decreased glucose uptake during the sleep-deprived state. Intravenous orexin-A restored activity to those areas but intranasal orexin-A restored the activity to a greater degree.

Current treatments for narcolepsy consist primarily of stimulant drugs to maintain wakefulness and antidepressants and other drugs (e.g., sodium oxybate) to combat cataplexy, hypnagogic hallucinations, and sleep paralysis. However, drug therapy only offers incomplete relief for many people with narcolepsy since residual sleepiness or episodes of cataplexy may remain and continue to negatively impact work, socialization, or one's safety to self or others. Additionally, treatment side effects (e.g., addiction to stimulant drugs) may be problematic.

That orexinergic neurons are progressively destroyed in people with narcolepsy suggests that replacing orexin may relieve symptoms more effectively than current treatments. However, orexin replacement has not been easily transformed into a treatment since the peptides (particularly orexin-B) do not easily pass the blood-brain barrier when administered intravenously. Development of an orexin nasal spray may offer a new avenue in treating narcolepsy. More studies are needed to determine if orexin-A treatment can be as effective in humans as it is in primates. If proven effective, subsequent studies will be needed to determine the safety of orexin-A treatment, the therapeutic dosage, and for whom the treatment is and is not beneficial.

The Deadwyler study was the first to demonstrate that administration of orexin improves performance and memory in sleep-deprived primate subjects. If orexins are proven to have the same results in humans, this could be a big step in bringing an effective treatment to many people struggling with narcolepsy.

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