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NARCOLEPSY - CURRENT TREATMENT AND UPCOMING GABA DIRECTED TREATMENT - A REVIEW

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ABSTRACT

Narcolepsy is a chronic disorder involving permanent loss of brain's ability to regulate sleep-wake cycles resulting in excessive daytime sleep. It can occur in any age but first noticed in teenagers. Narcolepsy cannot be complete cured but symptoms can be controlled using CNS stimulants, antidepressants, gamma hydroxy butyrate, etc. Several researches are still being carried out to develop further treatments options targeted towards neurotransmitters. Out of these neurotransmitters, GABA plays an important role in regulation of sleep. In this paper, we will review briefly about current treatment procedures and ongoing research on other medications mainly focusing on GABA directed treatment for narcolepsy.

INTRODUCTION

Sleep is one of the important things to keep the body healthy. Impairment in sleep leads to various health problems and causes change in natural ability of the body to heal itself. Decrease in sleeping time from 8 hours to 4 hours for even less than a week leads to advanced ageing, diabetes, hypertension, obesity and memory loss.

Narcolepsy is a chronic disorder involving permanent loss of brain's ability to regulate sleep-wake cycles resulting in excessive day time sleep[1],[2]. Narcolepsy can occur in both males and females of any age. Symptoms are first noticed in teenagers and young adults. Certain variations in human leukocyte antigen (HLA) complex were thought to increase the risk of auto-immune response to hypocretin or orexin protein producing neurons in brain resulting in narcolepsy.[3] Complications of narcolepsy include cardiovascular disorders, migraine and

Parkinson disorder. Three tests that are commonly used in diagnosis of narcolepsy are polysomnogram, multiple sleep latency test (MSLT) and Epworth sleepiness scale.[4],[5]

CURRENT TREATMENT

Narcolepsy can only helped, but cannot be completely cured. The time required to achieve control of symptoms may take several months or longer. Common medications used to treat narcolepsy symptoms include:

- **Central nervous system stimulants:** CNS stimulants are the mainstay of drug treatment for narcolepsy. These include modafinil, armodafinil, methylphenidate, amphetamine, dextroamphetamine, etc. used to promote wakefulness and alertness.
- **Sodium oxybate :** Sodium oxybate also known as GHB (Gamma Hydroxy Butyrate) , is considered safe for treating narcolepsy to promote sound sleep, diminish daytime sleepiness, and reduce incidences of cataplexy. It is the only drug approved by FDA for cataplexy.
- **Antidepressants:** Selective serotonin reuptake inhibitors (SSRIs) used to treat depression may also be used to suppress REM sleep, and alleviate symptoms of cataplexy, hallucinations, and sleep paralysis. These include fluoxetine, sertraline, atomoxetine , clomipramine, imipramine, protryptiline, desipramine, viloxazine and newer antidepressants such as venlafaxine.

TREATMENT IN PEDIATRIC PATIENTS

For children younger than 7 years who have narcolepsy, pemoline was previously considered the initial drug of choice. However, the FDA(Food and Drug Administration) concluded that the overall risk of liver toxicity from Pemoline outweighed the benefits. Currently, no FDA-approved pharmacotherapy is available for children with narcolepsy. However, the medications used to treat narcolepsy in adults have been used off-label in the pediatric population with positive results. In particular, methylphenidate and modafinil have been proved effective for patients of 6-15 years old.[6],[7],[8]

LIFE STYLE MODIFICATIONS

"Prevention is better than cure". On this code, the steps to be followed to prevent narcolepsy and its complications are:

- ❖ Go to bed at same time every night and wake up at same time every morning.
- ❖ Go to bed in a cold and dark room.

- Don't go to bed empty stomach or full stomach. Avoid high carbohydrate diet before going to bed.
- Avoid electronic devices about one hour before going to bed.
- Expose more to sunlight during day time.
- Avoid alcohol and caffeine.
- Adequate water intake
- Regular exercise.
- Safety precautions during driving.[9]

ONGOING RESEARCH ON SOME MEDICATIONS

Neurotransmitters play a major role in regulating CNS functions and sleep. Researchers now a days are targeting various neurotransmitters in brain for narcolepsy treatment. These are:

Histamine-directed medications

Based on the role of histamine in keeping people awake medications that act on histamine are under development for the treatment of excessive sleepiness. It remains to be seen whether these H_3 antagonists (e.g. pitolisant) will be particularly useful as wake-promoting agents.

GABA-directed medications

Due to the possible role of hyper-active GABA receptors in the primary hypersomnia , medications that could counteract this activity are being studied to test their potential to improve sleepiness. These currently include clarithromycin and flumazenil.[10],[11]

Hypocretin agonists

Hypocretin-1 (also called orexin) has been shown to be strongly wake-promoting in animal models, but it unfortunately does not cross the blood brain barrier. Therefore, companies have developed hypocretin receptor antagonists, like suvorexant, for the treatment of insomnia.

L-carnitine

Abnormally low levels of acylcarnitine have been observed in people with narcolepsy. These low levels have been associated with primary hypersomnia in general in mouse studies. Administration of acetyl-L-carnitine was shown to improve these symptoms in mice. A subsequent human trial found that narcolepsy patients given L-carnitine spent less total time in daytime sleep than patients who were given placebo.[12]

RESEARCH ON GABA DIRECTED TREATMENT

Even though different neurotransmitters are analyzed in brain, the role of GABA is yet to be discussed more. This is because they play a major role in CNS depression and sleep cycle.

GABA RECEPTORS

The **GABA receptors** are a class of receptors that respond to the neurotransmitter gamma-amino butyric acid (GABA), the chief inhibitory compound in the mature vertebrate central nervous system. There are two classes of GABA receptors: $GABA_A$ and $GABA_B$.

1. $GABA_A$ receptors are ligand-gated ion channels
2. $GABA_B$ receptors are G protein-coupled receptors.

$GABA_A$ RECEPTORS

GABA receptors are members of family of Cys-loop ligand-gated ion channels. In ionotropic $GABA_A$ receptors, binding of GABA molecules to their binding sites in the extracellular part of the receptor triggers opening of a chloride ion-selective pore. The increased chloride conductance drives the membrane potential towards the reversal potential of the chloride ion, thus inhibiting the firing of new action potentials. This mechanism is responsible for the sedative effects of $GABA_A$ allosteric agonists.[13]

$GABA_B$ RECEPTORS

GABAB receptors are G-protein coupled receptors (GPCR) that associate with a subset of G-proteins, that in turn regulate specific ion channels and trigger cAMP cascades. GABAB receptors comprise a macromolecular signaling hetero complex, critical for efficient targeting and function of the receptors. The regulation of this complex of GABAB receptors in the brain may provide opportunities for new ways to regulate GABA-dependent inhibition in normal and diseased states of the nervous system[14]

ROLE OF GABA RECEPTORS IN SLEEP

GABA is the main inhibitory neurotransmitter of the CNS. It is well established that activation of GABAA receptors favors sleep. Three generations of hypnotics are based on these GABAA receptor-mediated inhibitory processes. The first and second generation of hypnotics (barbiturates and benzodiazepines respectively) decrease waking, increase slow-wave sleep and enhance the intermediate stage situated between slow-wave sleep and paradoxical sleep. The third generation of hypnotics (imidazopyridines and cyclopyrrolones) act similarly on waking and slow-wave sleep but the slight decrease of paradoxical sleep

during the first hours does not result from an increase of the intermediate stage. It has been shown that GABAB receptor antagonists increase brain-activated behavioral states (waking and paradoxical sleep: dreaming stage). Recently, a specific $GABA_C$ receptor antagonist was synthesized and found to increase waking at the expense of slow-wave sleep and paradoxical sleep.[13],[14]

UPCOMING GABA DIRECTED TREATMENT FOR NARCOLEPSY

The following are the treatment options which are directed towards GABA neurotransmitter on which the research is going on for treatment of narcolepsy:

FLUMAZENIL

Flumazenil is the only GABA receptor antagonist. It is currently available as an intravenous formulation. Researchers consider it to be a promising medication in the treatment of primary hypersomnia. The research showed that flumazenil provides relief for most patients whose CSF contains the unknown "somnogen" that enhances the function of GABA receptors, making them more susceptible to the sleep-inducing effect of GABA.. Previous studies have shown that flumazenil increases vigilance in patients with sleep deprivation, idiopathic recurrent stupor and hepatic encephalopathy. However, the drug's side effects include anxiety and seizures. These adverse events together with the short-lived activity of the drug have reduced its development for treating sleep disorders.[10]

CLARITHROMYCIN

In a test tube model, clarithromycin (an antibiotic approved by the FDA for the treatment of infections) was found to return the function of the GABA system to normal in patients with primary hypersomnia. In order to further determine whether clarithromycin is truly beneficial for the treatment of narcolepsy and idiopathic hypersomnia, a small, double-blind, randomized, controlled clinical trial was conducted which showed that clarithromycin improved subjective sleepiness in GABA-related hypersomnia. However, researches are being carried out for its further commercial use. It is important to note that the positive effect of clarithromycin is secondary to a benzodiazepine antagonist-like effect. [11],[15]

BACLOFEN

Researchers found that a form of Baclofen, a drug used to treat muscle spasticity, works better at treating narcolepsy than the best drug currently available when tested in mice.

The research team found that R-baclofen promoted sleep time and longer bouts of wakefulness during the appropriate times for mice and also suppressed cataplexy. GHB modestly reduced cataplexy and increased sleep intensity, but did not improve other symptoms of narcolepsy to the extent that R-baclofen did. The next step would be to perform a study in narcoleptic patients to determine its potential for treatment of human narcolepsy.[16]

CONCLUSION

Narcolepsy is a sleep disorder which can affect psychological, social and developmental activities. The available current treatment can not completely cure the disease So, many researches are being carried out for developing treatment options with more therapeutic outcomes.. The current research on going on GABA directed treatment for narcolepsy is still in clinical trial level. Current researches are also focusing on preventing the loss of hypocretin producing neurons. Future research may also investigate the restoration of hypocretin signaling with agonists or gene therapy.

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