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Orexin – A Potential Neurotransmitter : A Review

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Abstract: The orexins are recently described hypothalamic neuropeptides. Their discovery was reported by two groups using various techiniques. De et al, identified the Pro-hormone preprohypocretin, and its peptide products namely the orexin-A and orexin B which was also reported simultaneously by sakurai et al who used the technique of Receptor cloning. The findings that cerebrospinal fluid (CSF) Levels of these peptides were abnormal in patients with narcolepsy has stimulated research on the potential role of these peptides in human disease. We represent here an overview of the identification of the neurotransmitter and its receptors, its functions, its projections of the system it's various uses with depression, narcolepsy etc.

Introduction:

"REVERSE PHARMACOLOGY"i.e, the ligand identification using the cell lines that expresses the orphan receptors', which combines with the genetic engineering techniques that has increased our level of understanding the novel signalling systems in the body [1]. Orexin was the first successful example of the factors to which such an approach has been applied [2]. Orexins are newrotransmitters produced in small neuronal populations' within the lateral and peritoneal region of the hypothalamus. It has been derived from a Greek work "OREXINS" meaning appetite. The discovery of orexin is more helpful in regulating the sleep arousal, food intake, wakefulness, feeding behaviours and has exhibited in their action in perilous pathological diseases such as narcolepsy, Alzheimer's, depression, inflammation, etc., They exist in 2 forms which are produced by the charges of preprorexin, ie., Orexin-A with 33 amino acids and orexin-B with 28 amino acids [3]. These are enodogneous peptide ligands for 2 orphan G-protein-coupled receptors found as the human expressed sequence tags. In this outside discusses about the functions, Identification and the uses of orexin and their receptors'.

The Identification of Orexin Peptide:

The orexin neuropeptides were identified by utilizing a subtractive – PCR technique to identify the transcripts that has been expressed specifically in the hypothalamus [4]. A series of CDNA clones were isolated which are exhibited in the hypothalamus but not in the cerebellum and the hippocampus. One of these has been expressed by a bilaterally symmetric structure within the posterior lateral hypothalamus. The CDNA encodes a putative secretary portion of 130 amino acids.

According to its primary sequence, it is predicted that this protein given rise to 2 novel peptide substances that are structurally related to each other. They were named as Orexin-A & Orexin-B [2].

The Orexin Receptors:

So far, two genes for orexin receptors has been identified the phenotypes of OX 1R and OX 2R was

identified in this nice and was found to have sleep state abnormalities, which was indistinguishable from the of prepro-orexin gene-deficient nice. Thus, this observation shows that only two receptors for orexin might exist. There are also other subtypes which are produced from the OX 1R and OX 2R genus by alternative splicing. However 2 alternative c terminus variants of the marine OX 2R, termed M OX2 alpha (443 aa) and M OX2 betoR (460aa) has been observed and reported, but orexin 4 and orexin B did not show any difference in sinding characteristics between the splice variants [5].

Functions of Orexin

The primary role of orexin is the control of sleep and arousal [6, 7]. The orexins has other various multiple functions such as feeding and energy regulation, neuroendocine regulations, cardirovascular system control, GI control, regulation of water balance, the modulation of pain, and the role of behaviour [8]. It has been observed that the orexin-A elevates the metabolic rate and the demonstration that insulin-induced hypoglycaemia activates up to one-third of orexin containing neurons that has led to the suggestion that the orexins are mediators of energy metabolism [9].

Projections of the Orexin System:

The cell bodies that are produced by the orexins are specific to the hypothalmus. These orexins have a widespread anatomical projections within the CNS of the rate with the densest extra-hypothalamic projections to the nor adrenergic locus corellas (LC) and the lesser projections are to the basal ganglia, thalamic regions, the medullar reticular formation and the nucleus of the solitary tract.

There are also lesser minor projections to the cortical regions, anterior and central amygadaliod niche and the olfactory bulb [10, 11, 12].

In humans the cell bodies that are produced by localization of orexin are restricted to the dorsolateral hypothalamus with extensive dense projections to the clocks corellas (LC) dorsal raphe nuclei, susprachiasmatic, amygdale, basal for brain, cholinergic brain system and spinal cord [13, 14]

Potential uses of Orexin:

Orexin and Depression

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest one reasons for the cause of depression is low levels of serotonin and noradrenalin in parts of the brain. In recent times the locus has shifted towards neuropathies. On the theoretical grounds, orexins may be linked to depression and offer a therapeutic path to treatment of depression, but there is very less understanding of how things work at molecular level and there are currently no viable depression treatments based on the orexin circuit at this time [15].

Orexin and Aging

Aging is a process of becoming old. Recent studies have show that orexin levels do not change with age in the brains, in people with narcolepsy. Thus age related sleep disorders do not appear to be a function of orexin levels.

But experiments on rats have shown changes in the hypothalamus of orexin neurons which may cause age – related dysfunctions in arousal, learning and memory. The elderly rates show no response to external administration of orexin as much as younger rates do [15].

Alzheimer's Disease:

Alzheimer's disease (AD) is a current and (growing) burgeoning public health problem that really has (minimally) scarce effective therapies. Interestingly, sleep disorders are multifaceted and represent an early component of AD. The severity of sleep disruption appears to (parallel) be juxtaposed with the severity of dementia.

Moreover, phase delay and increased nocturnal activity seem to (differentiate) distinguish patients with Alzheimer's disease from patients with other types of dementia. The numerous studies that have shown an attired circadian rest-activity in Alzheimer's disease seem to indicate that sleep regulation may be related to the neurobiology of Alzheimer's disease. It is know that accumulation of intercellular new fibrillary tangles of tab proteins and extracellular B- amyloidal (Alzheimer's disease) plaques play a (central) pivotal rate in the pathogenesis of Alzheimer's disease. Some authors using in vivo microdialys is in mice (showed) suggested a correlation b/w inferential AB amount and wakefulness or orexin infusion.

The infusion of a dual orexin receptors antagoinst was associated with a decrease of initial fluid AB amount. These finding suggest that chronic sleep deprivation can play a role in the pathogenesis of AD. However patients with narcolepsy – cataplexy orexin lasing are (not protected against) not immune to AD [16].

Post Stroke Inflammation, Cognitive Decdie Depression

These features that appear after a stroke. The importance of three emerging roles of orexins after a stroke are 1, orexin controls inflammation by regulating immune mediators such as pro-inflammatory cytokines after stroke ; 2 orexin improves memory by modulating other neurotransmitters, and promoting hippocampus never genesis, and protecting the neuronal damage against post stroke induced oxidative stress and ;3 orexin mitigates depression by accelerating neurotrophic factor secretion and by promoting long term potentiating through calcium, influx's increase [17].

Narcolepsy:

Narcolepsy is a chronic sleep disorder, characterized by excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, and sleep paralysis. The major pathophysiology of human narcolepsy has been recently identified based upon the discovery of narcolepsy genes in animals; the genes involved in the pathology of the orexin ligand and its receptor. Mutations in hypocretin-related genes are rare in humans, but hypocretin-ligand deficiency is found in a large majority of narcolepsy with cataplexy [18].

Hypocretin in Neurological and Psychiatric Disorders

The role of orexin in other neurological illnesses is to be established. A study [19] has been found that CSF orexin levels does not differ significantly between two groups, one with neuroimmunological disease and the other with the non-neuroimmunological disease, and normal controls. The dense orexin projections to the noradrenergic, serotonin, dopaminergic, cholinergic, and GABA/glutamate areas of the brain suggest a possible role in psychiatric and neuropsychiatric disorders [20, 21]. The orexin system may be considered as an important one in disorders such as depression and bipolar affective disorder. More recently, emphasis has shifted to the possible roles of neuropeptides in the aetiology and treatment of depression [22, 23, 24, 25, 26, 27]. Involvement of the hypocretin system in depression is suggested on neuroanatomical and pharmacological grounds. The only substance known to interconnect all the relevant areas of the brain implicated in the neurobiology of depression is orexin and the excitatory innervation of the LC and dorsal raphe region, the stimulation of dopamine and acetylcholine and the prohistaminergic actions all point to an antidepressant effect. These therapeutic possibilities remain to be clarified by appropriate studies.

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