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# Targeting Orexin Neurons for Treatment of Obesity is It Feasible in Human Being-A Systematic Review

**Kulvinder Kochar Kaur*, Allahbadia GN and Singh M**

[1]Dr Kulvinder Kaur Centre for Human Reproduction, 721,G.T.B. Nagar, Jalandhar, Punjab, India

[2] Scientific Director, Ex-Rotunda-A Centre for Human reproduction, 672, Kalpak Garden, Perry Cross Road, Near Otter's Club, Bandra, Mumbai, India

[3] Consultant Neurologist, Swami Satyanand Hospital, Near Nawi Kachehri, Baradri, Ladowali road, Jalandhar, Panjab, India

**SUMMARY**

Obesity is increasing at epidemic proportions both in children and adults posing a big public health problem among children as well as adults. With parallel increase in comorbidities like type2 diabetes mellitus (T2DM), metabolic syndrome (MetS) a need arises for developing medical therapies that can maintain long term weight loss. Earlier we have tried to consider multiple options like utilization of drug combinations like Qsymia, Contravene, Liraglutide, thylakoids, probiotics, Combination of glucagon like peptides1 (GLP1) with glucagon etc but nothing has proved to be as efficacious as BS in long term maintenance of weight loss. Earlier we had reviewed the cellular changes related to orexin A and B changes that are isoforms of neuropeptides that get liberated from the lateral hypothalamus (LH). Here we further review the pathophysiology of orexin neurons with regard to their role in neuroinflammation in the central nervous system (CNS) via microglial cell changes and role in spontaneous physical activity (SPA) and sleep physiology commonly termed sleep-wake promoting neuropeptides along with role in reward circuitry and how targeting them might be of help in treating obesity. Possibility is that subtle increases in SPA have been found to improve energy expenditure (EE) and that has been utilized in some workplaces where treadmill like chairs are utilized, restless people who keep sitting and standing do burn calories thus promoting carparks at distance places, no elevators have been thought as some ways by which lethargic individuals refuse to follow exercise might get helped by modulating orexin neurons besides correcting sleep problems coexisting with obesity.

***Corresponding author**

Kulvinder Kaur, Centre for Human Reproduction, India, Fax-91-181-4613422; Tel: 91-181-9501358180, 91-181-4613422, E-mail: kulvinder.dr@gmail.com

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## Introduction

The G protein coupled receptors (GPCR) is the biggest family of the membrane receptors comprising of >800 sequences that get coded by roughly 4% of the genome [1]. These GPCR's sense molecules at the surface of the cell resulting in signal transduction through activating or/inhibiting numerous intracellular signalling paths ending in ultimate cellular actions [2]. First Structural finding of a GPCR was of a bovine rhodopsin done via Palczewski [3]. 1Decade later human GPCR 1st structure that of a β2 adrenergic receptor (βAR) was found by Rasmusen [4]. Ultimately these deeper studies of GPCR landed Leftklowitz and Kolba with the Nobel Prize in chemistry [5]. Also having the name 7transsmembrane (TM) receptors are made up of 7 integral α-helices trans membrane domains (H1-H7) that makes up the extracellular domains (N-terminal domain along with extracellular loops) which are basically responsible for recognizing the ligand and intracellular domains (C-terminal along with intracellular loops) that has the role of controlling the receptor along with signal transduction [6]. An 8th α-helix (H8) that will participate in Gβ/γ binding has been detected via structural evaluation of GPCRs [3]. Ligands that act with GPCRs have markedly separate properties, like light, ions, amines, peptides, proteases, lipids with small along with larger proteins possessing numerous characteristics, hormones, pheromones, neurotransmitters along with odors etc [7]. Once the different ligands bind these GPCRs a structural conformational alteration occurs resulting in activating G proteins (transduction, $GS,Gi/_{o},G_{q/11}G_{12/13}$). Clamp signal pathway via adenylyl cyclase effector and the phosphatidylinositol signal pathway via the phospholipase C effector are the 2 main signal transduction pathways correlated with GPCRs [8]. Simultaneously with its part as a negative controller of the α-subunit , the Gβ/γ that gets dissociated possesses the ability to manipulate the signalling pathway Rhodopsin like control of ion channels, inhibition or activation of adenylyl cyclase, inhibition of phosphatidylinositol-3kinase (PI3K) or the activation of GPCR kinases (βARK) [9]. As per the IUPHAR 6 Groups of GPCRs are identified or classified i) Class A-Rhodopsin like) Class B-Secretin like, iii) Class C-Metabotropic glutamate, iv) Class D-Fungal mating pheromone v) Class E-Cyclic AMP Receptors, vi)Class F-Frizzled/smoothened. This huge family of receptors is expressed broadly right from eukaryotes like yeasts to humans, having necessary

part in physiological functions, like homeostasis, hormone secretion, neurotransmission, differentiation of cells, regulation of immunity, metabolism, muscle contraction, vision, smelling, pain etc [10]. With association of role of GPCRs in multiple human physiological along with pathological processes GPCRs have a main role in inflammatory diseases by either escalating and or preventing inflammation [11]. GPCRs can work directly on the immune cells, but further on no immune cells that are existing in particular tissues along with organs [12]. Of the main roles they modulate cell migration, phagocyte activation, degranulation, reactive oxygen species (ROS) generation, increasing vascular endothelial permeability along with inflammatory nociception [11]. Further GPCRs control inflammatory gene expression [13]. Once GPCRs bind to ligand they control transcription factors that are part of inflammatory signalling cascades like Cyclic AMP Response Element Binding (CREB),extracellular signal regulated kinase (ERKs), NFAT, c-Jun, signal transduction and transcription factor3 (STAT3), and nuclear factor kappa activator of light chain activated B kinase (NFκB) of others [11]. Inflammatory diseases like rheumatoid arthritis have GPCR involvement, as does sepsis, irritable bowel disease IBD), Pancreatitis, multiple sclerosis', chronic obstructive pulmonary disease (COPD), renal inflammation, metabolic syndrome (MetS) that is involved with obesity and type 2 diabetes mellitus (T2DM) [14-21]. Crosstalk among the inflammatory workers and GPCRs has made us think of these receptors as having great role in getting targeted for probable treatment options for inflammatory pathologies. Out of the 800 member of this family of GPCRs, orexin receptors is one specific type that, might be a target for therapy of chronic inflammatory pathologies [22]. Here we review the role of orexins and their receptors in obesity, MetS, Sleep disturbances.

## Methods

Thus we conducted a PubMed search for articles utilizing the MeSH terms orexins, orexin receptors, orexins in obesity, MetS, sleep disorders associated with obesity, narcolepsy, lateral hypothalamic stimulation, reward and obesity.

## Results and Discussion

We found a total of 309 articles and further 100 more articles from cross referencing out of which we selected 105 articles for this review. No meta-analysis was done.

**Structure and Physiology of Orexins/Hypocretins:** Orexins/ Hypocretins are made up of 2 neuropeptide hormones[reviewed in 23] made up of 33 and 28mino acids, orexin A (OXA/ Hypocretin1) and (orexin B(OXB/ Hypocretin2) respectively (Fig1). Their encoding occurs by a single precursor polypeptide for both called prepro- Orexin [24]. Initially it was identified in the hypothalamus in 90's, lateral hypothalamic area (LH) neurons project broadly all through CNS, with release of these peptides [25]. Reverse pharmacology isolated them as being the endogenous ligands for 2 orphan GPCR subtypes that were part of class A family, Orexin receptor 1 and 2 (OX1R(Hcrt1) and (OX2R(Hcrt2), respectively [24-25]. (figure1) Phospholipase A2,C and D ,Diacylglycerol lipase ,$Ca^{2+}$,and adenylyl cyclase cascades are the signalling pathways utilized by these Orexin receptors. The main physiological role of orexins remains the control of sleep /wakefulness state [26]. (fig1) One main pathology associated with this function is impaired orexins generation in case of narcolepsy with catalepsy, called type 1 narcolepsy (TIN). Marked impairment of sleep/wakefulness cycles occur in TIN [27]. Thus multiple pharmaceutical labs generated molecules that target orexin receptors, especially antagonists for curing insomnia [28]. Classification of these antagonists is based on their capacity to act on one /both orexin receptors, namely single orexin receptor antagonists (SORAs) and dual orexin receptor antagonists (DORAs). Further sub classification of SORA as per their receptor specificity, SORA1 (like compound 56) and SORA2 (like JNJ-42847922), that use OX1R or OX2R respectively [29]. For the therapy of insomnia, quiet recently suvorexant (MK-4305) got the approval of US food and drug administration (FDA) [30]. Besides their capacity of regulating sleep along with arousal states, orexins control appetite, feeding, gastrointestinal tract (GIT) motility, energy balance, metabolism, blood pressure (BP), neuroendocrine

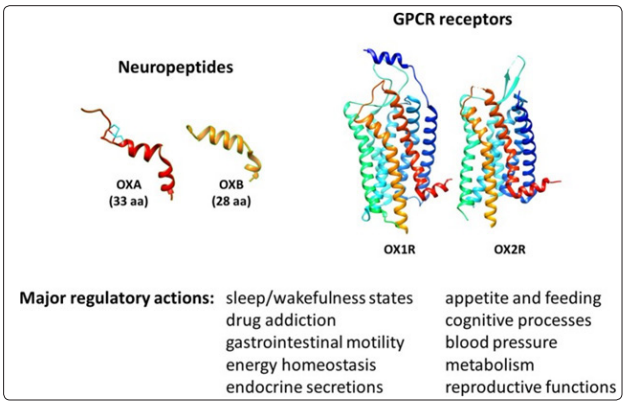


**Figure 1:** Orexin

Expression in peripheral tissues have been evaluated utilizing immunohistochemistry and reverse transcription-polymerase chain reaction (RT-PCR) methods that isolated especially the prepro- Orexin precursor. Inspire of marked differences in the expression amounts, Orexins have been isolated from adrenal glands, adipose tissue (AT) [40]. Kidney [41]. Colon [42]. Pancreas and reproductive organs that has testis also [43]. And prostate [44]. Similarly orexin receptors get expressed in peripheral tissues that includes the GIT, adrenal glands, endocrine pancreas, reproductive organs and adipose tissue (AT) [39-45]. In such tissues paracrine action can occur. Actually healthy people have very low circulating orexin amounts (range2-45pm, that is 1000 fold < than $IC_{50}$ of receptors) [46]. Though the exact place from where orexins in disease is unknown abnormal expression orexin receptors in particular human diseases has been shown and might help in getting novel therapeutic targets. Presence of bidirectional crosstalk among the nervous system (NS) and immune systems has been shown in last 10-20yrs. Thus effect of delivering exogenous orexins in the central nervous system (CNS) (neuroprotection) and immune (anti-inflammatory action) systems in physiological along with pathophysiological problems like neuroinflammation, systemic inflammation.

## Neuroinflammation and Orexins

The interaction among neurons, microglia, and glial cells within the CNS is really dynamic and responds to the markedly variations in the surrounding stimuli. Like in answer to injury ,infection or disease ,the cell microenvironment of the CNS manufacture inflammatory mediators that are cytokines ,chemokine's ,adhesion molecules ,prostaglandins ,and free radicals .These mediators help in recruiting more immune cells in addition to the action of astrocytes and microglia. Especially in case of healthy brain, microglia, resident macrophage-type immune cells of the CNS which share many properties with macrophage are key for maintaining health of the neurons (implying helping in generation and removal of synapses) by preservation of a good CNS surroundings. Actually, microglial cells have the ability of producing proper responses (implying inflammatory and activated a Vis anti-inflammatory and resting) as per the kind of stimuli.

Hence there are benefits of immune reaction of the CNS, that needs to be regulated strictly for effective recuperation of physiological homeostasis, but if there is prolonged neuroinflammation, that is usually associated with a microglia that has a chronic inflammatory phenotype which can provoke harmful effects on the CNS, implying continuous neuronal loss. Hence neuroinflammation is the critical procedure aiding in the continuation and exaggeration of neurodegenerative and/or inflammatory conditions of the CNS. This theory got bigger proof with the discovery of orexins causing both neuroprotection along with immune modulatory activity ,and thus be seen as group of biological substances having a great property of treating immunemediated CNS problems like narcolepsy, metabolic problems, Alzheimer's disease, and multiple sclerosis. A large amount of proof is there regarding innovative role of orexin and its receptor system in the immune along with MS. OXA, demonstrates through ctivation of receptors, neuroprotection and immune modulatory activity and hence delivery of this might be of help in the diseases discussed.

**Neuroprotective Activity of Orexins**

Recently it has been shown that the hypothalamic neuropeptide OXA might have an essential part in neuroprotection, partly by decreasing apoptosis and inflammation [37-47]. Thus using orexin/ataxin mice that is a transgenic mouse model of Neurodegeneration, loss of orexin has been related to Neurodegeneration, with memory and cognitive deficiencies and neuroinflammation [48]. Corroborating, a part of endogenous orexin in Neurodegenerative/inflammatory brain condition, expression of orexin was observed to be escalated in lesioned CNS parts in murine controlled cortical impact (CCI) and transient common carotid artery occlusion (tCCAO), models of brain injury caused by trauma and cerebral ischemia respectively [49-50]. The cellular positioning of orexin receptors was probed further with immunofluorescence. Though expression of orexin receptors is understood to be neuronal in brain tissue that is healthy, its expression by glial cells was also documented in these models .Like OX1R was observed to be up regulated in microglia following CCI [49]. Further astrocytes and oligodendrocytes also expressed OX1R after tCCAO [50]. Despite no proof in human pathology, these works might point a probable role of orexin besides being in neurons, is also there on glial cells. There are documentations that neuroprotection stimulated by orexin could depend on microglial manipulation [47-51]. These microglia serve as a sentry which has the ability to respond to endogenous signalling effectively for starting adequate neuroinflammatory reactions via dynamic transition among the neurotoxic proinflammatory (M1) and neuroprotective (M2) phenotypes. Like after cerebral ischemia, microglia might take up 2 phenotypes; 1stly an activated neuroprotective M2 phenotype along with decrease in O2 amounts and the shift to a proinflammatory (M1 phenotype, initiating cell death [52]. Although inflammation is an essential normal immune response, chronic M1 proinflammatory activity might be damaging and adds to future neuronal malfunction and injury [53]. Various proofs are showing how orexins and orexin receptors have role in this .In fact, in vivo OXA displayed marked neuroprotective roles in various models of rodent cerebral ischemia, decrease size of infarct [47].Various in vitro experiments displayed that OXA helps in survival of neurons and their protection from death induced by oxidative and hypoxic stress. Like OXA and OXB had the capacity of avoiding cobalt induced stress damage in primary rat cortical neurons [54].With the utilization of SH-SY5Y human neuroblastoma cell line, which is an in vitro cellular model of dopaminergic neurons in relation to Parkinsonism, other workers have demonstrated that orexins initiate neuroprotective roles meaning antiapoptotic and antioxidant actions (getting regulated by PKC and PI3K signalling pathways) from MPP (+) and 6hydroxy dopamine (OHDA)-stimulated neurotoxicity [55]. Following in vitro observations have importance in the pathogenesis of multiple sclerosis (MS). Collected proof indicates that oxidative stress, in part minimum attributes to MS pathophysiology in the form of demyelination, axonal damage and neuronal death. Microarray evaluation of neuronal differentiated SH-SY5Y cells with OXA application showed up regulation of somatisation receptors vasoactive intestinal peptide(VIP), endothelin-1 (EDN1) and members of the NF-κB pathway, all of which aid in being neuroprotective [56].

**Immunoregulatory Properties of Orexins**

Besides actions on CNS, various workers have demonstrated that OXA can work in vivo as an anti-inflammatory neuropeptide, which gives more weightage to the therapeutic efficacy of orexin in Neurodegenerative and/or inflammatory conditions. In a rat model of ischemia-reperfusion-created gastric injury, OXA infusion i)surprisingly decreased gastric injury unimaginably by reducing the formation of reactive oxygen species (ROS) and ii) diminishing myeloperoxidase action in gastric tissue, which points to a reduction in polymorph nuclear infiltration and /or action [57]. Another researchers subsequently in a murine focal cerebral ischemia model showed that the degree of brain damage was abrogated via the endogenous orexin system, i.e. an action correlated with decreased inflammation (reduction of IL-6 and TNF-α amounts) [58]. Currently peripheral delivery of orexin diminished the amounts of proinflammatory mediators (cytokines and chemokines) and helped in mice survival in lipopolysaccharide (LPS) stimulated endotoxin shock model [59]. Further LPS exposure led to down regulation of orexin signalling, that corroborates, a role of orexin at the time of an inflammatory action [60]. Notably this study showed that peripheral delivery of orexin A could cross the blood brain barrier (BBB) in the time of endotoxic shock problem acting directly in decreasing inflammation in the CNS. Hence a strong proof that the orexinergic system can deliver benefits in immunoregulatory actions besides in inflammatory in case of immune –driven Neurodegenerative conditions is there. Although results are little as far as the orexinergic receptors in immune cells, it was found that OX1R and OX2R receptors get expressed in murine central along with peripheral immune cell tissue and especially in sorted T ($CD4^+$and $CD8^+$) and myeloid ($CD11b^+$) cells [61]. Further the same group presented that OX1R were expressed in murine colonic lamina propria immune cells [62]. What are the cellular along with molecular explanations of anti-inflammatory effects of OXA is not well evaluated, and mainly in vitro studies have been done. A direct action of orexinergic signalling on microglial cells lines has been demonstrated [47-51]. Normally the heavy proinflammatory agonist LPS enhances TNF-α generation in microglial cell line BV2 along with OX1Rexpression.Treatment of BV2 cells with OXA before LPS exposure caused a drop in TNF-α as demonstrated by Xiong, et al. [47]. Though this might point to effect on innate immune cell ways, problem is this is in vitro work. More work is needed to show how these results might explain the mechanism of orexin immunoregulatory characteristics in vivo.

**HFD Induced Obesity**

With the finding that orexin controls appetite, in addition to energy balance and metabolism and ii)OXA shows marked neuroprotective action like by ameliorating oxidative stress related cell death, other workers wanted to find the mechanism by which these versatile orexin- microglia interaction may

tamper with the brain health to stimulate obesity via HFD in saturated Fatty Acids (SFA)-(like palmitic acid [PA], C16.0 ) exposure [51]. Chronic consumption of diet rich in PA helps in neurodegeneration, partially by early occurrence of enhanced oxidative stress ,excessive ROS production, insulin resistance (IR), along with hippocampal neuroinflammation (meaning circulating proinflammatory cytokine liberation by microglial cells) [48-69]. Moreover >ROS causes deranged hypothalamic gene expression profiles related to obesity etiopathogenesis that means down regulation of the neuronal ant apoptotic protein Bcl-2 (B cell lymphoma 2), and up regulation of the pro apoptotic protein Bax (B cell lymphoma 2 associated X protein) [70]. Utilizing the immortalized murine BV2 microglial cell line, PA therapy I) increases OX1R gene expression but not that of OX2R and effects a switch of BV2 microglial cell line to a proinflammatory M1 State [51]. Simultaneously other groups showed that PA diet stimulates microglia to a proinflammatory M1 phenotypes, helping in liberation of proinflammatory cytokines like TNF-α and IL-6, either via NF κB pathway or a toll like receptor(TLR4) pathway [51-71]. Moreover, activation of microglia by saturated fatty acids (SFA) through TLR4 aids in neuronal cell death [71]. But OXA, blocked the deleterious effects of PA. Orexin actually has an ability of stimulating a neuroprotective anti-inflammatory M2 like microglial phenotype instead of the PA stimulated neurodamaging proinflammatory microglial M1 phenotypes. Escalated expression of the M2 like microglial phenotype that were identified by the microglial marker arginase1, inhibited the generation of proinflammatory cytokines like TNF-α, IL-6, and inducible nitric oxide synthase (iNOS) mediators [51].

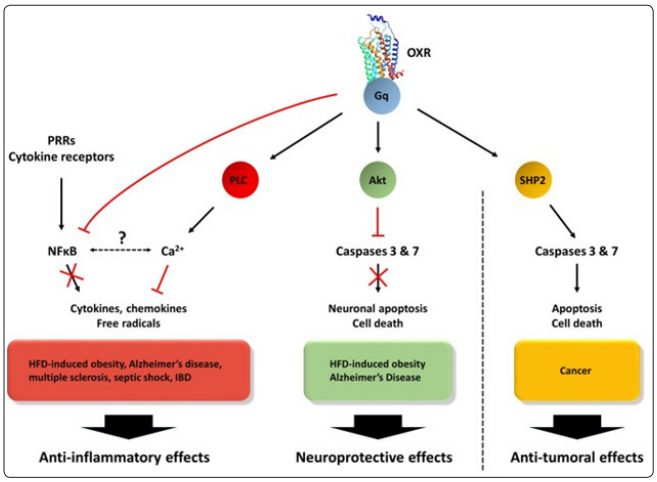


**Figure 2**

Courtesy ref no-95-Orexins/OXR system-modulated signalling pathways involved in anti-inflammatory, neuroprotective and antitumoral effects. The orexin/receptors system may trigger: (1) antiinflammatory functions through the inhibition of NFκB and the activation of PLC/$Ca^{2+}$ pathways, (2) in the CNS, neuroprotective actions via the inhibition of caspases 3/7 by Akt pathway and (3) in the context of cancer, anti-tumoral effects through the activation of caspases 3/7 by SHP2 signaling pathway

Moreover with the help of immortalized murine hypothalamic neuronal cell line (called m Hypo A-1/2) protection of hypothalamic neurons by OXA from PA stimulated hypothalamic microglial impaired function, was demonstrated by Duffy et al [72]. This benefit had an association with I) reduced caspase 3/7 apoptosis ,stability of Bcl-2 gene expression ,and further Bax /Bcl- 2 gene expression ratio ii) prevention of ROS generation and iii) a conversion of PA stimulated changes in intracellular metabolism, basal /maximum respiration, ATP generation along with reserve capacity [72]. With these results it gets corroborated that Orexin effectively can block the effects of PA and might work as a strong immune controller of M1/ M2 phenotype microglia, diminishing proinflammatory cytokines and enhancing anti-inflammatory cytokines for achieving a neuronal microenvironment that is of benefit.

**Sleep and Orexins/Hypocretins**

At present >78 million adults and additionally 13 million children in US are obese, and so many million further overweight [73]. Besides marked correlation with multiple other health comorbidities, obesity is recognized as being a risk for excessive daytime sleepiness (EDS) along with quality of sleep being bad, that results in poor quality of life [74]. Obstructive sleep apnea (OSA) is a proper causative factor for both EDS and bad quality of sleep, particularly in obese subjects, but escalating proof points that EDS continues in obese persons who had no OSA or those properly had therapy of OSA [74-75]. Moreover loss of weight in obese subjects (having OSA or not) has a great effect on EDS and night time sleep quality getting markedly better. Particularly, obese subjects having had the examination for sleepiness prior to and following bariatric surgery (BS) display that a surprising reliance in EDS following 1mth, despite them being obese still [74-76]. Hence daytime tiredness and sleepiness get better with loss of weight, but what are the factors behind this is unclear that are initiating this problem. Probable ways of explaining this are i) negative energy balance (implying imbalance of the calories causing loss of weight) andii) decreased body mass/adiposity (implying direct association of body weight and /or fat and wake problems). Saying in other way, is it possible that an obese person who is in negative energy balance get improved or bad sleep quality and EDS as compared to a lean person relatively in positive energy balance?. If energy balance (and not only obesity by itself) is actually contributing initially to the sleep /wake problems, innovative ways for improving sleep quality in obese along with nonobese subjects might be found. If energy balance (and not only obesity by itself) is actually contributing initially positive energy balance to the sleep /wake problems, innovative ways for improving sleep quality in obese along with nonobese subjects might be found. Human sleep phenotype (i.e. fragmented sleep and EDS) in the absence of any OSA can be recaptured in animal models [77]. Obesity occurs in transgenic mice having lepton signalling abnormalities and display > total sleep time and are incapable of maintaining wakefulness [78]. Feeding non transgenic mice chronically high fat diet (HFD) =>diet induced obesity (DIO) that markedly decreases wakefulness in both rats as well as mice in association with the level of weight gain [79]. Also chronic feeding mice having DIO, a lactogenic diet corrects both body weight and sleep problems [79]. But it is not known if weight, adiposity, diet and /or energy balance affect sleep /wake action within these animal models. To start getting insight into the relative part of weight/ adiposity along with diet and energy balance Peron et al formed an innovative feeding method with the use of 2 diets, i.e. regular chow (RC) and HFD 45% Kcal from fat). Measurement of sleep / wake patterns at baseline (when all animals ate RC),following 8wks on either diet (week 8:RC or HFD), and ultimately a 1week (wk.) shift to the alternate diet (Week 9:RC-→HFD or HFD--→TRC) or an extra week under the same diet(week9 RC--→RC or HFD--→HFD), At the final point of time and sleep wake fragmentation in the dark phase, the 2 earlier groups (known as ‘’diet interchange’ ’paradigm) had same weights ,but separate energy balance. Thus a posit that animals in positive energy balance (weight gain) would probably get >total sleep time along with sleep wake fragmentation in the dark phase (i.e. EDS) as compared to the mice in negative

energy balance (weight loss). Finally, to find the part of the sleep /wake regulation get disturbed, they evaluated in what way acute along with chronic diet changes change sleep homeostasis after forcible wakefulness. Thus they used C57BL/6J mice given the diet described in the above way. Sleep recordings were done at week 0 (baseline), week 8 (prediet switch), the week 9(post diet switch) for all groups .Sleep homeostasis was checked at week 8 and week 9. They did a quantification of changes in total wake, no rapid eye movement (NREM), and, rapid eye movement (REM), besides the differences in bout fragmentation /consolidation. At week 9, the 2 diet shift groups had similar body weight. But animals shifted to HFD (hence gaining weight) displayed reduced wake time ,>NREM sleep time ,and further deterioration of sleep wake fragmentation as compared to mice shifted to RC (that were in weight loss ).These changes were caused by significant sleep /wake alterations initiated by acute dietary shifts(wk8-→wk. 9). Sleep homeostasis, as checked by delta power increase after sleep deprivation, was unaffected by their feeding method. Thus concluding that acute dietary shifts are enough to change sleep and wakefulness without any body weight dependence and with no changes on Sleep homeostasis [80].

Getting Good action levels in a healthy way all over the day might cause marked effect on both social along with medical costs of obesity [81]. Especially in those subjects who cannot or don't want to perform exercise that is maintained. The neuropeptide orexin or hypocrite seems to be a good target from point of achieving treatment along with sustaining healthy body weight a variety of physiological functions that are closely interlinked to body weight, especially spontaneous physical activity (SPA) along with intake of calories [82-84]. Both animals and humans who have deficiency in orexin display decreased physical activity and increased obesity rates [82-86]. Once orexin tone is exaggerated in animals, by intracranial peptide infusions or stimulation of activity of orexin neurons an enhancement of SPA along with burning of calories takes place [84-88]. Daily giving orexin for 10days, orexin has a protective action regarding weight gain at the time of HFD intake [86-89]. Although these results are encouraging, detailed part in physical activity along with energy expenditure (EE) in protection from adiposity remains unknown and particular role of orexin neurons action in obesogenic circumstances is not clear currently. Production of orexin takes place in neurons that are situated in the LH, a part which is a markedly heterogenous brain area having mixed cell aggregates, complicated connectivity processes and functions [31-88]. That has perifornical and dorsomedial parts of the hypothalamus included [25-90]. Along with in peripheral tissue [41]. Evaluation of orexin neurons action in vivo is difficulty in view of being unable to regulate neural action in a cell -type based manner. With the advances in genetics along with pharmacology from a technical point of view least invasive neuromodulator having cellular along with anatomic selectivity is possible. Neuromodulator in a pharmacosynthetic /chemo genic way, Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) lead to constant change in neuronal action that remains for minutes to hours. Dependence of DREADDs is on the basis of modification of GPCR's that have been manipulated to give up their binding capacity for their ligand that is biological and acquire marked activation occurring by a synthetic Designer drug. Here the Designer drug utilized was Clozapine N-Oxide (CNO), believed usually to be inactive physiologically in the case of rodents [91]. Notably with DREADDs, within subject evaluation protocols got managed, that is the method liked in studies that examine dependent variables although; person to person variability is seen like for SPA [86-89]. In this study for targeting cells and anatomical locations stereotactic injection of a virus that contained the DREADD construct, that was encoded in an inverted reading frame and surrounded by lox-p recombination sites was utilized. In the LH orexin cells are believed to project a medial to lateral functional gradient, like the neurons in the medial area have > concern in circadian and arousal responses ,as compared to lateral parts that have biggest correlation with physical activity. For concentration on an orexin neuron group considered to be crucial for physical activity, virus was injected in the caudal lateral LH of mice that had been manipulated to express the DNA-recombinase, Care, driven by the orexin promoter. The reason why Gq-coupled DREADD, hM3Dq, was selected was in view of its capacity for generating burst like firing just like the maintained cellular activity seen at the time of neuropeptide release [84]. Further follow up evaluation that was complimentary utilized the Gi- coupled DREADD, hM4Di, to obtain neuronal silencing for a long time. Systemically delivered Designer drug, CNO, caused selective activation (hM3DQq) or inhibition (hM4Di) DREADD expressing neurons in caudal lateral LH. Thus DREADDs that caused selective activation of orexin neurons in mouse LH for measuring SPA were utilized. For achieving DREADDs targeting AAV vectors were injected stereotaxic ally into caudal LH of heterozygous orexin- Cre or C57BL/6J miceby Zink et al. In 1 particular set of studies, orexin neurons excitation was evaluated (virus: AAV2-EF1a-DIO- hM3Dq-mCheryl) and examination sessions started 15 min before dark cycle started. CNO (1 or 5mg/kg) or saline was intraperitoneally injected and then time taken while movement in open field chambers got measured for 2 hrs. Different mouse cohort studies were conducted in the form of follow up where quantification of SPA simultaneous with EE alteration along with chow intake with the use of indirect calorimetry chambers (Sable System™). After mice got acclimatized, evaluation sessions (saline and /or CNO) was carried over a 1week time period, with injections delivered on daily basis. Alterations in SPA, EE, chow intake, faecal boli, and body composition (EchoMRI™) were recorded. More mice cohorts received HFD and got an injection of CNO/day for 10days for checking the ability of orexin activation for helping in DIO prevention. Activation of orexin caused an enhanced SPA in both male and female mice that was correlated with escalation of EE in the absence of any differences in chow intake. In relation to HFD Activation of orexin resulted in significant amelioration of gain in weight and adiposity. A reduction in SPA occurred on the utilization of DREADDs for inhibition of orexin action. Thus these findings showed that orexin neurons have a key part in modulating physical activity and pointed to an innovative target for the treatment of obesity [92]. Aging has an effect on multiple physiological conditions like behaviour. Of these lots of processes get controlled, minimum by hypothalamic orexin neurons, with decrease of orexin tone might result from aging. Thus Stanojlovic et al. ,posited that DREADD stimulation of orexin neuronal activity might abrogate the aging action on metabolic and behavioural changes in young as well as middle aged mice .To get DREADD targeting stereotaxically injection AAV vectors(AAV2-HSyn-DIO- hM3Dq ($G_q$) (-mCheryl) into the LH of 5 and 12 maths old orexin-Cre female mice and was ensured by immunohistochemistry ( IHC) evaluation of OXA and cherry expression .Following recovery ,animals underwent a number of behavioural tests like elevated plus maze (EPM),open field (OFT), and novel object recognition tests(NORT) to test the action of aging on anxiety like behaviour, routine locomotion and working memory. They utilized a comprehensive laboratory animal monitoring system (CLAMS) for measurement of SPA and EE. The data pointed that orexin neuronal activation ameliorates the aging stimulated decrease in anxiety like behaviour in middle aged mice ($p<0.005$) and enhances locomotion in young as well

as middle aged mice ($p<0.005$.Also orexin neuronal activation enhances SPA ($p<0.01$) and EE ($p<0.005$) in middle aged mice, bringing the amounts back to that seen in young mice. Thus data from this experiment isolated orexin neurons as potential targets for curing age –associated dysfunction in cognitive and anxiety –associated behaviour, and energy balance [93].

**SPA & Orexins/Hypocretins**

Further Kotz et al, reviewed regarding role of SPA being an activity that is not stimulated by any goal that gives rewards like in case of food seeking behaviours .Usually it is appreciated that SPA is only fidgeting, by that is a poor understanding, as that type of behaviour might be related to particular types within neurodegenerative diseases along with separate movement conditions. Rather SPA needs to be considered as PA behaviour which occurs by a nonconscious drive for a motion. Like restlessness that might have fidgeting along with gestures, recurrent sit and stand movement, with maximum time spent standing and in motion. Any time of PA leads to EE, and thus preventing weight increase and diminish increased adiposity. Thus Kotz all using human along with animal research regarding use of SPA in decreasing weight acquisition, positing that neuromodulators can be targeted for this and further work needed in this field [94]. Further Couvineau et al. Detailed the treatment of narcolepsy on the basis of neuroprotective and anti-inflammatory actions of orexin [95].

**Other Neurons of LH**

But contrary to above till now we thought that Hypocretin (Orexin) Neurons were the only initiating Neuronal condensations in the LH but subpopulations constituting inhibitory areas in this region and glutamatergic Neurons in the adjacent submammilary nucleus (SuM) have been shown to initiate wakefulness Thus Heists et al., conducted a chemogenic excitation of LH Neurons in case of mice and found enhanced wakefulness which extended for >4h without any abnormal behaviour or EEG abnormalities. This escalated wakefulness was same whether dual orexin receptor blocker almorexant (ALM) was present or absent. Evaluating the hM3Dq transfection along with cFos expression in LH inhibitory neurons and in the SuM did not establish enhanced wakefulness was secondary to these wake – promoting areas, though one can't completely rule out that proposition. For analysing the association to the Hypocretin system they again did the study on Orexin-tTA mice with or without diet doxycycline (DOX), that helped them to modulate the Hypocretin neuron %age which expressed hM3Dq.In case of DOX –fed mice, 18% of Hypocretin neuron in addition to other LH neurons expressed hM3Dq, with these mice demonstrating a marked rise in wake following hM3Dq activation even when ALM was present. In mice that were shifted to NC, 62% of Hypocretin neurons expressed hM3Dq in addition to other LH cells .Thus chemogenic excitation producing even >maintained arousal that could be decreased to earlier amounts by ALM therapy. In all these data suggested that an LH Neurons which helps wakefulness via an Hypocretin-independent pathway which might act together with the Hypocretin system for extending arousal [96].

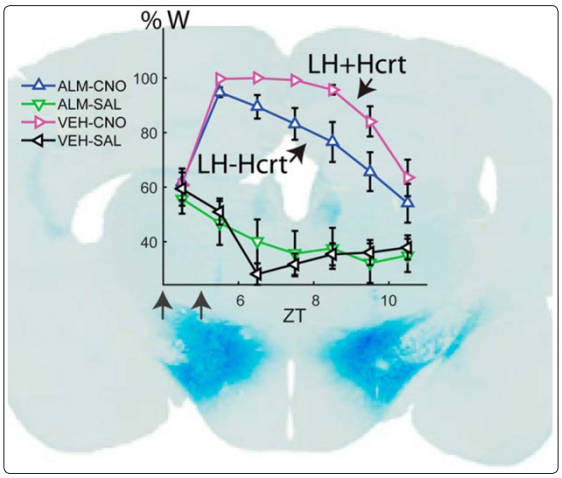


**Figure 3**

**Conclusions**

Thus we have been trying to find a medical therapy for treating obesity where we have tried several options like use of Qsymia (topiramate, phentermine), Contrave (naltrexone, bupropion), liraglutide, glucagon like peptide 1 (GLP1) with glucagon, thy lakoids, although till now we don't have any medical therapy by which long term weight loss can be maintained other than bariatric surgery (BS) [97-104]. that has the disadvantage of cost along with side effects. Hence here we have tried to review the role of orexins in obesity and how by targeting them especially in HFD induced obesity might be of help especially as there may be certain gene mutations working like in FTO allele ANKR (reviewed in ref and by orexin neuronal manipulation it might help in increasing SPA, shift to M2 like response in the microglia having the anti-inflammatory action along with the projections of LH being in all areas of brain including the reward promoting orbitofrontal cortex (OFC), ventral tegmental area (VTA), nucleus accumbens (NAc) it may help in treating the addiction like effects of high triglycerides and carbohydrates found in obesity along with improve the associated sleep problems [102].

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