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Neural correlates and potential targets for the contribution of orexin to addiction in cortical and subcortical areas

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Abstract

The orexin (hypocretin) is one of the hypothalamic neuropeptides that plays a critical role in some behaviors including feeding, sleep, arousal, reward processing, and drug addiction. This variety of functions can be described by a united function for orexins in translating states of heightened motivation, for example during physiological requirement states or following exposure to reward opportunities, into planned goal-directed behaviors. An addicted state is characterized by robust activation of orexin neurons from the environment, which triggers downstream circuits to facilitate behavior directed towards obtaining the drug. Two orexin receptors 1 (OX1R) and 2 (OX2R) are widely distributed in the brain. Here, we will introduce and describe the cortical and subcortical brain areas involved in addictive-like behaviors and the impact of orexin on addiction.

Keywords: Orexin, Reward pathway, Addiction, Cortical, Subcortical.

Introduction

Neurons that produce orexin are scattered mediolaterally within the dorsomedial hypothalamus (DMH) and the lateral hypothalamus (LH) (1, 2). LH orexin neurons are more closely associated with reward functions than DMH neurons. These neuropeptides including orexin-A (OXA) and orexin-B (OXB) derive from a common precursor gene in most neurons that are situated merely in the perifornical area (PFA) of the LH (1-3). OXA is a 33 amino acid with two intrachain disulfide bonds which has equal affinity for both receptors (OX1R and OX2R) and a smaller one

OXB is a linear 28 amino acid with higher affinity to OX2R (4-6) (Figure 1). There have been numerous studies on orexin/hypocretin and addiction since 2000, which demonstrate the roles of orexins in drug-seeking and addiction in various cortical and subcortical areas. Previous research has demonstrated that systemic heroin self-administration was alleviated by the administration of opioid antagonists into the lateral hypothalamus (7). Furthermore, a conditioned preference for places is induced by opioid application to the LH (8). Apparently, in the dorsomedial hypothalamus and perifornical area, orexinergic neurons seem to play an important role in the negative reinforcement of withdrawal symptoms (9, 10). In mice lacking orexin, significant decreases in somatic signs of naloxone precipitated morphine withdrawal syndrome were detected (11). OX1R is the main receptor that has a high impact on drug-seeking activities and exhibits an important role in opioid addiction. Many studies have shown that OX1R antagonists can block addiction-related behaviors among different addiction drugs for instance cocaine, nicotine, and alcohol, suggesting that orexin-dependent treatments could serve as the next treatment for drug addiction (12-14). Cocaine or morphine activates orexin neurons of LH that are completely associated with a conditioned preference for environmental contexts. They also showed that blocking OX1R leads to the restoration of extinguished drug-seeking (10). In addition, human investigation shows that drug addicts have raised levels of orexin in their cerebrospinal fluid, which might be linked to greater activation of lateral hypothalamic orexinergic neurons in response to the substance of abuse (15). Furthermore, morphine antinociceptive tolerance is significantly reduced in rats following intracerebroventricular (i.c.v) administration of an OX1R antagonist (16). Further, Harris GC *et al*; 2006,

showed that naloxone-induced withdrawal symptoms of morphine were decreased by systemic inhibition of OX1R via injection of SB-334867 (9). Adaptive changes in chronic morphine treatment may contribute to the development of morphine dependency through the OX1R (17). Evidence of an increase in intracellular calcium concentration by OX1R supports this conclusion (18, 19). G-protein coupled receptor dissociation is involved in the desensitization of mu-opioid receptors due to increased intracellular calcium and calcium-calmodulin-dependent kinases (20). Moreover, morphine antinociceptive tolerance in rats was reduced by i.c.v. injection of selective OX1R antagonist, SB-334867.

This finding is an opportunity to succinctly re-emphasize the possible role of OX1R on morphine tolerance due to chronic administration of morphine adaptive changes (17). While the OX1R is mainly involved in motivation and reward, the OX2R is contributed to the modulation of the sleep/wake cycle and energy homeostasis. National Institute on Drug Abuse listed orexin-based therapies as a promising treatment goal for drug dependence (21). Therefore, orexin shows many contributions to addiction. To find the neural correlates for the contribution of orexin to addiction, in the present review, we will concentrate on the different roles of orexin in drug addiction in different brain areas.

Ventral tegmental area

The ventral tegmental area (VTA) is a group of neurons positioned near the midline on the floor of the midbrain that included dopaminergic, gamma-aminobutyric acid (GABA)ergic, and glutamatergic neurons. VTA plays the main effect in some procedures including reward and cognition (22), drug-seeking, and natural reward systems of the brain.

VTA is implicated in aversive addictive behaviors, for instance, behavioral sensitization caused by amphetamine or mu-opioid receptor agonists (23). VTA is similarly essential for stress-, cue-, and drug-primed reinstatement in rodents self-administering cocaine (24, 25) or heroin (26, 27). The dopaminergic neurons respond to reward-related stimuli (28) and implicate in the reinforcing activities of abused substances (29, 30). Opiates indirectly raise dopamine transmission by reduction of inhibitory input onto dopamine neurons (31, 32).

It should be noted that LH orexin neurons are the main neurons that send extensive projections to the VTA (33) and play a key role in motivation and reward in response to cocaine (34). Several studies showed that activating orexin receptors in the VTA exhibits a significant impact on the reinstatement of extinguished reward-seeking (33). Harris GC et al; 2005, demonstrated that the activity of these neurons is powerfully linked with cue-reinstated drug and food-seeking behaviors (35). After seven years, Mahler et al; 2012, used orexin for direct intra-VTA injection and showed the reward-seeking behaviors in extinguished rodents in an OX1R-dependent style (36, 37). They also displayed that systemic or intra-VTA injection of an antagonist of OX1R significantly diminished the reinstatement of extinguished seeking behaviors for cocaine, alcohol, or morphine produced by drug-predicting cues or Yohimbine (36, 38). Morphine dependence of the orexin-deficient mice is decreased by the intra-VTA administration of orexin receptor antagonists (11). Moreover, behavioral sensitization to cocaine (39), cocaine self-injection, and cue-induced reinstatement are reduced by the orexin antagonists in the VTA (40). In addition, the activity of VTA dopamine neurons is inhibited by

dynorphin as a component of orexin neurons. Orexin in the VTA simplifies drug-related behaviors by reducing the dynorphin effects (41). Orexin signaling in VTA causes cue-induced demand for cocaine (42). Drug-associated sensory cues augment motivation for drugs and the orexin system contributes to this stimulus-driven motivation (42). The orexin receptors in the VTA are contributed to the sensitization to the expression of morphine-induced preference in rats (43). OX projections to VTA by regulating prefrontal control of dopamine (DA) release may cause motivated behaviors in response to conditioned stimuli (44). Orexin in the VTA exhibits important roles in reward processing and drug abuse in humans, as already established well in rodents (45). OX1R signaling within the VTA is important to regulate cue-induced reinstatement of cocaine-seeking (40). Blockade of VTA OX1R signaling may reduce NAc dopamine in response to drug cue exhibition (40). OXA in the VTA enhanced the motivation to self-administration cocaine (46). Therefore, the OXA may not impact cocaine self-administration when conditions to get cocaine need low effort. Altogether, these data confirm that orexin in the VTA represents a significant contribution to the motivation in response to drugs, cue-induced reinstatement of drug-seeking behaviors, sensitization to the expression of morphine-induced preference, stimulus-driven motivation, and behavioral sensitization to drugs of addiction. VTA is the main target by which orexin signaling modifies reward behaviors (42). Orexin inputs to the VTA seem to display a pivotal role in the regulation of cocaine intake when conditions to get the drug need a high level of motivation (47).

Rostromedial tegmental nucleus

Construction in the midbrain, the rostromedial tegmental nucleus (RMTg), or tail of the VTA, acts as a 'master brake' on the dopamine system (48, 49). It appears that variations of the RMTg action may contribute to the reward-estimation error signal by VTA dopamine neurons (48, 50). This signal is essential to understanding the alterations among anticipated and detected rewards (51). GABAergic projections from the RMTg are disinhibited by acute morphine withdrawal and stimulation of VTA dopaminergic neurons in the rat (52-54). RMTg neurons activation by infusion of amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) significantly decreased ethanol consumption, but RMTg inhibition increased it (55-58). Furthermore, the RMTg is known as a brake of the dopamine system, so it may be implicated in the circuits regulating alcohol addiction through modulating dopamine release in the NAc (59). Intra-VTA injection of suvorexant (orexin receptor antagonist) would reduce the rewarding effect of self-administered cocaine, while intra-RMTg orexin peptide injection would increase the aversive value of self-administered cocaine, thereby suppressing drug-taking. Furthermore, Flanigan ME et al; 2020, discovered that the orexin signaling in GABAergic lateral habenula neurons moderates aggressive behavior in male mice (60). Also, systematic administration of suvorexant successfully lowers motivated cocaine use, and this reduction is linked to decreases in the subjective reward of cocaine self-administered (61). Therefore, orexin in RMTg affects the aversive and aggressive value of drugs probably through the brake of the dopamine system.

Amygdala

In the medial temporal lobe is the amygdala which has 13 subregions, such as the basolateral amygdala (BLA) and the central amygdala (CeA) (62, 63). Studies on humans have demonstrated that the amygdala has a main role in drug-seeking behavior (64, 65). In addition to reinforcing drug-seeking behaviors, the BLA affects reconsolidating drug-related memory (53, 66). Additionally, inhibition of the CeA reduces conditioned place preference (CPP) reinstatement caused by foot shock and morphine with concurrent reduction of Fos protein expression in the VTA and the BNST, but Fos expression in the bed nucleus of the stria terminalis (BNST) was not changed by CeA modulation (67). The orexinergic projections to the amygdala adjust both positive and negative reinforcing features of the drugs of abuse (10). These projections from orexin neurons densely innervate the CeA, thus this area may be one of the main regions for orexin effects on drug-seeking. In addition, hypothalamic orexin neurons have mutual amygdala projections and display a part in resilience and stress-related responses (36, 68). According to prior electrophysiological and behavioral investigations, OXA affects anxiety-like behaviors by altering the spontaneous firing activity of CeA neurons (69). Furthermore, OX1R antagonist reduces fear-potentiated startle responses in rats, which is a model of conditioned fear involving the CeA (70). A further role of OX is the modulation of fear responses. OX neurons send projections to the amygdala which is important in fear learning and fear expression. The central nucleus (CeA) of the amygdala receives the highest density of OX-positive fibers (71). Systemic or intra-CeA injection of OX1R antagonist decreased the expression of conditioned fear. Therefore, the CeA orexinergic pathway can modify conditioned fear via phospholipase C (PLC) and sodium-calcium exchanger activity and that antagonism of

OX1R may be a putative treatment for fear-related disorders (71). Furthermore, the administration of orexin into CeA modifies feeding and gastric motility in rats (72). Since orexin modifies amygdala-dependent threat learning, the orexin system may represent a potential treatment for aversive memories that result in fear and anxiety disorders (73). Blockade of OX1R in the amygdala significantly diminished memory acquisition, decreased anxiety, and reduced sensitized fear in the SB-334867 group. Application of SB-334867 to the amygdala following each fear memory test significantly reduced freezing (74). Furthermore, orexin modifies the hippocampal-dependent memory through the basolateral amygdala (75). It has been shown that intra-CeA administration of SB-334867 reduced cocaine self-administration and stress-induced reinstatement of cocaine-seeking behavior (76). Therefore, it can be concluded that orexin neuron projections to the amygdala display a massive role in the fear responses, anxiety-like behaviors, and stress-related responses associated with addiction.

Prefrontal cortex

The prefrontal cortex (PFC) in the front part of the frontal lobe involves some cognitive functions (77) and the reinstatement of drug-seeking behavior (78). The medial prefrontal cortex (mPFC) adjusts seeking behavior for most drugs of abuse such as cocaine and ethanol (79, 80). Mu-opioid receptors in the PFC are functionally associated with cocaine craving (81) and alcohol consumption (82).

The mPFC has been proposed as one of the three regions of the brain to impact the behavioral characteristics of ethanol-seeking through a

dopamine-related pathway (83-85). There is a significant interaction between PFC and VTA, as a key node in the control of brain vigilance (86, 87). Some reports have shown that circuits of VTA-mPFC are implicated in morphine reward (88). The orexin-VTA pathway is also thought to show an effect on sleep-wake regulation, according to studies. Injection of orexin-1 into the ventricles stimulates VTA dopamine neurons which project to the PFC and Nucleus accumbens (Nac) shell and can be contributed to the addiction (89). Furthermore, intra-VTA orexin infusion raises PFC dopamine efflux and vigilance (90). Evidence showed that OX1Rs in the mPFC augment the alcohol relapse and promote alcohol intake (91). Orexin neurons in the LH show a vital role in arousal and the execution of mPFC-related higher cognitive functions (92). Injection of OXA into VTA enhances DA release in the prefrontal cortex while SB-334867 diminishes cocaine-induced DA in NAc, showing modulation of VTA DA neurons by orexin inputs (93). Thus, it can be concluded that in mPFC, orexin may involve in ethanol-seeking and drug-seeking behaviors directly or through the dopaminergic pathways.

Nucleus accumbens (NAc)

NAc is a region of the preoptic portion of the hypothalamus in the basal forebrain rostral region (94, 95). Appetitive motivation in drug relapse is mediated by the NAc (96). The NAc has accompanied the acquisition and elicitation of programmed behaviors and heightened opioid susceptibility in addiction. Following persistent abstinence, the pleasurable experience of substance use and environmental cues can trigger relapse and are effective mediators of drug-seeking behavior. Moreover, morphine via

cholinergic and cannabinoid systems can modulate dopaminergic transmission in VTA-NAc circuits (97-102). Moreover, during cocaine cue-induced reinstatement, Fos activated in the NAc afferents to the VTA (103). Repeated injections of cocaine are used to enhance the inhibitory transmission from the NAc inputs onto the VTA GABAergic neurons disinhibiting VTA dopamine neurons (104).

NAc receives heavy orexin projections that exhibit a significant role in drug-seeking like morphine reinstatement (105, 106). According to the evidence, stress-induced drug relapse can be modulated through the effects of the orexinergic system on the NAc. OXA moderates the dopaminergic transmission and enhances dopamine responses in response to psychostimulants in the NAc shell (107). Activation of the NAc shell during withdrawal is required for the OX1R function and may be accomplished by the indirect action of LH orexin neurons (9). It has been shown that orexin reduced postsynaptic N-methyl-D-aspartate (NMDA) currents and improved GABA currents but did not impact glycine-activated conductance in the NAc. Thus, the hypocretin peptides may be inhibitory, possibly through binding to OX1R (108).

Intra-paraventricular injection of OXA augmented DA levels in the NAc (109), showing that this nucleus may be the main relay for the effects of OXA on the mesolimbic DA system and reward-seeking behavior (110). Orexin through activation of OX1R is important for the expression of morphine withdrawal. NAc Shell activation during withdrawal is dependent on OX1R function and is likely mediated by the indirect action of LH orexin neurons (9). It has been demonstrated that SB-334867 reduced dopamine outflow in the NAc shell evoked by acute amphetamine

treatment and that activation of orexin neurons in hypothalamic regions was increased during the expression of amphetamine sensitization (111).
It was proposed that orexins could reveal a central impact on addiction through action on NAc neurons. Therefore, the inhibitory role of orexin in the NAc may be completed through changes in drug relapse and withdrawal behaviors.

Locus coeruleus (LC)

The locus coeruleus (LC) nucleus, bilaterally situated near the fourth ventricle, is the core noradrenergic assembly comprising neurons that have a high density of μ-opioid receptors (MORs). Furthermore, LC neurons experience substantial tolerance resulting from continuing opiate exposure (112-114). Earlier studies demonstrated the development of receptor desensitization by opioids in LC neurons (115-118). LC participates in the expression of somatic signs of opiate withdrawal syndrome. Behavioral responses to opioid withdrawal are mimicked by the electrical stimulation of LC neurons (119).
In LC neurons, the expression of OX1R is high (120, 121) and LC collects extensive orexinergic efferents (122). Naloxone-elicited neuronal activity in the LC is suppressed by SB-334867 (selective orexin-1 receptor antagonist) administration before each morphine injection. Our previous study revealed that blockade of OX1R is contributed to the development of morphine dependency through reduction of the cAMP response element-binding protein (CREB) and Phospholipase C β3 (PLCβ3) levels in the LC of morphine-dependent rats (123). Furthermore, OX1R inhibition significantly reduced the augmentation of cAMP levels by the naloxone treatment in the LC neurons of morphine-dependent animals

(124). Orexin-A through activation of OX1R and a protein kinase C (PKC)-dependent mechanism promotes met-enkephalin-induced opioid receptor desensitization in rat locus coeruleus neurons (125). Moreover, morphine-induced analgesia can be inhibited by the long-term application of orexin into the thalamic paraventricular nucleus (126). Remarkably, both orexinergic and opioidergic systems affect through G-protein mediated signaling pathways. Orexin receptors through activation of OX1Rs and Gq-mediated pathway activate phospholipase C that promoting the synthesis of diacylglycerol (DAG). Then, DAG activates PKC leading to phosphorylation of μ-opioid receptors (125). It seems that orexins could play a pivotal role in modulating inhibitory and excitatory neurotransmitter systems and hence modulate LC neuronal responses during opiate withdrawal.

Nucleus Paragigantocellularis (PGi)

PGi is located in the rostral ventral medulla of the brain. It is a central brain area implicated in regulating cardiovascular and respiratory functions in response to sympathetic stimulation. In addition to sending collateral projections to the LC, PGi also links to the nucleus of the solitary tract (NTS). Furthermore, PGi neurons are widely distributed across parts of the brain that are essential for regulating nociception and autonomic function (127). The NAc, VTA, and LC are involved in reward production and addiction, primarily by receiving the lateral paragigantocellularis nucleus glutamatergic afferents (128, 129).

The elimination of naloxone-precipitated morphine induces increased expression of c-Fos in the dorsomedial hypothalamus and perifornical area

orexinergic neurons (9). Additionally, during naloxone-precipitated morphine withdrawal, these neurons are activated (11). OX1R antagonism in PGi reduces naloxone precipitated morphine withdrawal symptoms in rats (130). In lateral Paragigantocellularis (LPGi), ORXA-induced antinociception is mainly mediated through the OX1R which might play a potential effect on processing the pain information associated with descending pain modulation (131). A decrease in the symptoms of withdrawal precipitated by naloxone is associated with the systemic and central administering of the OX1R antagonist SB-334867 (132). Moreover, in the LC nucleus, blocking of OX1R was observed to decrease the production of dependence on morphine (133). Further studies showed that inhibited OX1R in the LPGi nucleus greatly decreases the progression of behavioral symptoms and morphine dependence by injecting naloxone in morphine-dependent rodents (127, 134). Thus, LPGi is the essential region where OX1Rs are more densely distributed in this area and involved in the progression of morphine dependence. It seems that orexin in PGi of addicted animals is involved in the decrement of morphine dependency and withdrawal syndrome.

Ventral Pallidum (VP)

Rewarding stimuli and motivated behavior are the functions of the ventral Pallidum (VP) (135). VP GABA neurons are a great source of inhibitory input to the VTA (136). Population activity in the VTA dopamine neurons is related to the inhibition of the VP (137). VP involves in behaviors of drug dependence. Opiates inhibit ventral Pallidum neurons projecting onto dopamine neurons (138). Moreover, VP lesions inhibit morphine self-administration (139). VP is one of several forebrain targets of the LH

orexin neurons. LH orexin neurons project to a wide variety of forebrain targets, including the ventral pallidum (VP). The posterior half of the VP is particularly densely populated with orexin inputs (140). Consequently, OX1R and OX2R are expressed in VP neurons (141), sending mutual output to the LH (142). The results of studies indicate that OX1R is highly concentrated in VP (143), showing that the reward behavior may be modulated by this region. OX1R signaling in VP is a crucial target in opioid addiction. Inactivation of VP reduces heroin consumption in reinforcement (144) and morphine conditioned place preference expression (145). Remifentanil demand and seeking are reduced by the systemic administration of the selective OX1R antagonist. Inactivation of VP diminishes willingness to get the sweetness of reward (146). Therefore, effort-related choice behavior is regulated by the VP. The reward's hedonic properties are mediated by the VP. Orexin signaling and reward's hedonic properties are increased for sucrose by the intra-VP microinjections of orexin-A (147). Furthermore, the orexin system mediates the hedonic features of natural versus drug reward. This indicated that the hedonic hotspot of the posterior VP may also contribute to the orexin-induced enhancement of food's hedonic impact (148, 149). Extinguished remifentanil seeking is reduced by the intra-VP administration of SB-334867. However, reinstatement behavior happens through a greater reward network where the VP is a part of it (150). Thus, this behavior is encouraged by the OX1R signaling at other locations (151, 152). Furthermore, intra-VP administration of SB-334867 reduced reinstatement behavior in highly motivated animals. This data suggested the therapeutic effects of OX1R antagonists in highly motivated animals. Therefore, in an addiction state, orexin in VP may involve some types of

affective psychopathology and mood disorders. OX1R activation in VP alters motivation for the opioid remifentanil. Orexin fibers densely innervate VP and regulate opioid reward. Intra-VP microinjections of the OX1R antagonist SB-334867 reduced motivation (enhanced demand elasticity) for remifentanil without changing remifentanil consumption at low effort. Demand elasticity demonstrates the degree of cue-induced remifentanil seeking that was reduced by SB-334867 into VP without alteration of extinction responding (153). Highly motivated rats exhibited higher attenuation of reinstatement behavior by SB-334867. Together, these discoveries display a discerning role for VP OX1R signaling in motivation for the opioid remifentanil. It can be concluded that orexin in VP increases the reward's hedonic properties, motivation, and drug-seeking behaviors.

Bed Nucleus of the Stria Terminalis (BNST)

BNST is a brain region involved in anxiety, fear (122, 127, 154-158), stress, and reward functions (128, 129). It has an important role in stress-induced reinstatement of drug-seeking (24, 139, 143). Electrophysiological studies showed that chronic morphine selectively increases the excitatory postsynaptic currents (EPSC) mediated by AMPA in VTA projecting BNST neurons (159). BNST send GABAergic and glutamatergic projections to VTA (160-163). BNST–VTA pathway is involved in the cocaine locomotors-activating effects (164) and the expression of cocaine CPP (165). Moreover, neuropeptide S (NPS)-containing axons reside proximal to OXA positive neurons in the hypothalamus, and an enormous number of these neurons express NPS

receptors, implying a direct connection between the two systems. Retrograde tracing investigations revealed that unilateral intra-paraventricular nucleus or intra-BNST red fluorobead injection tagged OXA somata on both sides, indicating that NPS recruits two different neuronal pathways. Intra-BNST or paraventricular nucleus (PVN) injection of OXA comparably increased alcohol desire as hypothalamic NPS injection, albeit to a lower extent. This result showed that BNST is implicated in OXA neurocircuitry regulating the enhancement of cue-induced reinstatement by NPS (166). In BNST, OXA induces membrane depolarization and action potentials that may lead to anxiety. The OXA-induced anxiety in the BNST depends on the activity of NMDA receptors (167). BNST to LH pathways induces divergent emotional states (168). It seems that the role of orexin in BNST is mostly through effects on the emotional states and also the desire for drugs of abuse. OXA causes anxiety-like behavior via glutamatergic receptors in the BNST. The anxiogenic effects of OXA in the BNST also seem to be depending on NMDA-type glutamate receptor activity. Prior injection of the NMDA antagonist in the BNST inhibited the anxiety-inducing effects of OXA. Injections of AMPA antagonists into the BNST before OXA resulted in only a limited reduction of anxiety-like behaviors (167). In the passive avoidance tests, OXA diminished the retention time to enter the darkroom, representing its inhibitory effect on avoidance learning. The blockade of avoidance learning is presumed to be a result of the anxiolytic effect of OXA (169). SB-334867 reduced the somatic symptoms of withdrawal and diminished morphine withdrawal-induced c-Fos expression in the BNST. These results represent a critical role of OXA signaling, through OX1R, in the activation of the brain stress system in the BNST to morphine

withdrawal and show the involvement of orexinergic subpopulations in this action (170).

Pedunculopontine Tegmental Nucleus and Laterodorsal Tegmental Nucleus

Pedonculopontine tegmentum (PPT) and laterodorsal Tegmental Nucleus (LDT) are part of the mesopontine tegmentum that is modulating arousal and reward-driven behaviors (171-175). A bunch of research showed that drug-dependent behaviors relate to the LDT. Particularly, local pharmacological manipulations demonstrated that the acquisition and expression of cocaine CPP facilitated by the LDT and it also participates in the cocaine-primed reinstatement of drug-seeking (176, 177). In addition, drug-dependent behaviors are associated with the PPT (178), and the cocaine-primed reinstatement of drug-seeking is reduced through the PPT inactivation (177) . Morphine CPP and heroin self-administration are reduced by the PPT lesions (179, 180). It has been shown that two Gq protein-coupled receptors mediate orexin peptide effects (181) that are manifested within the LDT (120, 143, 182). In vivo, extracellular recordings from mouse brainstem slices indicated that orexin induced extended firing of LDT neurons (183). The non-cholinergic and cholinergic LDT neurons mediate this excitation (184, 185). Numerous brain areas express OX1R such as the LDT and PPT (120, 143, 186). Vesicular acetylcholine transporter (VAChT)-positive cholinergic neurons in the PPT and LDT manifested OX1R but not OX2R mRNA (187). Based on these findings, it seems likely that orexins and their receptors have a wide variety of regulatory roles within the cholinergic and monoaminergic

systems. Moreover, it is reported that emotional stimuli increased the release of orexins in the PPT, which inhibit cholinergic neurons indirectly, preventing muscle atonia.

Dorsal Raphe

Dorsal raphe (DR) is the main source of serotonin in the brain, containing GABAergic (188), glutamatergic (189), and dopaminergic neurons (190), and this region is mainly examined in the controlling affective state (191). Projection of dorsal raphe serotonin neurons to the VTA influences drug-related behavior (192). Furthermore, instrumental behavior is reinforced by the selective activation of the non-serotonergic DR neurons projecting to the VTA being enough to elicit CPP (193, 194). However, there is a weak reinforcement of the activation of serotonergic DR neurons projecting to the VTA (194). Also, DR receives the most extreme orexinergic innervation. As mentioned above, similar to heterogeneous structures, DR has different cell types including serotonergic, GABAergic, and glutamatergic neurons (195).

The orexinergic neurons of LH have a projection to serotonergic neurons in DR which play roles in spatial memory. Previous studies reported that OXA significantly stimulates serotonin-containing neurons. Furthermore, serotonin acts on 5-HT1B and 5-HT2C receptors in the hypothalamus and decreases the intake of food, especially carbohydrate intake. The OXA-mediated LH–raphe link may be one part of a negative feedback loop that regulates food intake (196). Orexin through inward sodium current depolarizes DR neurons. Orexin increases the Ca2+ transients in

serotonergic DR neurons (197). It appears that orexin peptides function as neuromodulators in the DR. Orexin A excites serotonergic neurons in the dorsal raphe nucleus of the rat (198). The excitatory effect of orexin-A on serotonergic neurons of dorsal raphe is through synaptic communication by OX1R (199). Furthermore, orexin controls serotonin neurons in the dorsal raphe nucleus by excitatory direct and inhibitory indirect effects (200).

Mesocorticolimbic dopamine reward pathway

As a primary system, the mesocorticolimbic DA system has a pivotal role in motivation, reward, learning, memory, and movement (201). Orexinergic neurons have broad projections with midbrain DA neurons of the VTA and the mesocorticolimbic target regions NAc, mPFC, and amygdala (33, 202). Drug reward research is centered in these regions (203). Despite the very high levels of reactions between orexinergic neurons and mesocorticolimbic neurons in various brain regions, most of the work is done by the VTA (204). According to the Microdialysis studies, extracellular DA levels in the NAc are increased by abusing drugs and neuroadaptations due to addiction Observed in this system. VTA has a high density of orexin receptors on both DA-containing and GABA-containing neurons. The LH projections of the orexin are located in the VTA. VTA includes a large number of the orexin-containing dense core vesicles suggesting non-synaptic effects. Through a direct postsynaptic effect, DA and non-DA neurons are activated by the orexin which exerts an excitatory action in the VTA. DA neurons placed in the caudomedial portion of the VTA can express enhanced Fos in response to intra-VTA orexin. Moreover, DA can be augmented at the NAc shell level, but not at

the NAc core level and the mPFC. NMDA receptor-mediated postsynaptic currents can be instigated by the intra-VTA orexin showing the importance of orexin in long–term neural plasticity. Reverse effects compared to VTA are seen in NAc. Activation of orexin receptors in the NAc leads to depolarization of NAc shell neurons via OX1R (205). OX1R is the principal receptor in the NAc that is responsible for orexin's actions although both receptors are expressed in this region.

Conclusion

The orexin regulates various central nervous system processes related to feeding, sleep, arousal, reward processing, and drug addiction via wide-ranging projections, its complex circuits with other neuron types, and the diffused distribution of orexin receptors. When orexin-containing neurons are injured or lost, the related neurons and orexin-containing neurons become imbalanced. Following the disruption of the neurotransmitter systems, signs of neurological disease develop. Currently, promoting the activity of orexin-containing neurons selectively or blocking the action of the orexin receptor using a receptor antagonist is a successful approach for neurological diseases involving the orexin/receptor system. Hence, due to its widespread innervation in reward brain regions, orexin has a key role in addictive-like behaviors. However, further research is needed to fully comprehend the involvement of this neuropeptide system in these behavioral processes.

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Legend

Figure 1: The structures of the orexin-A (OXA) and orexin-B (OXB). OXA and OXB neuropeptides derive from a common precursor gene. OXA is a 33 amino acid with two intrachain disulfide bonds which has equal affinity for both receptors (OX1R and OX2R) and a smaller one OXB is a linear 28 amino acid with higher affinity to OX2R.