Orexin 2 Receptor Antagonists from Prefrontal Cortical Circuitry to Rodent Behavioral Screens

Gerard J. Marek, Stephen Chaney and Mark J. Benvenga

Abstract

Orexin is a neuropeptide contained in neurons from several hypothalamic nuclei that project throughout the forebrain analogously to monoamines synthesized by brainstem nuclei. Orexin, like 5-hydroxytryptamine (5-HT), norepinephrine (NE), dopamine (DA), histamine and acetylcholine (ACh) exerts prominent effects on the sleep-wake cycle of all mammals. Activation of the orexin$_2$ receptor appears to induce spontaneous excitatory synaptic currents (EPSCs) on layer V pyramidal neurons due to release of glutamate from thalamocortical terminals similar to activation of 5-HT$_{2A}$ and $\alpha_1$-adrenergic receptors. Layer V pyramidal cells are the major descending output cell in the prefrontal cortex with projections to the thalamus, striatum, amygdala, brainstem and spinal cord. In keeping with salient modulation of prefrontal cortical physiology, orexin$_2$ receptor antagonists exert similar effects to 5-HT$_{2A}$ receptor antagonists in suppressing hallucinogen (e.g., DOI)-induced head twitches and producing antidepressant-like effects on the differential-reinforcement-of-low-rate 72-s (DRL 72-s) schedule of reinforcement. Currently, there is both negative and some preliminary positive evidence that blocking orexin$_2$ receptors may result in antidepressant efficacy in patients with major depressive disorder. Overall, the treatment of mood disorders is an additional potential indication for orexin receptor antagonists beyond simply improving sleep.

Keywords: antidepressant drug screens, excitatory postsynaptic potential currents (EPSCs), DOI-induced head twitches, differential-reinforcement-of-low-rate 72-s (DRL 72-s) behavior, LSN2424100, layer V pyramidal neurons, prefrontal cortex, thalamocortical axons

1. Introduction

Only approximately 50–60% of patients experience an antidepressant response when treated with selective reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) [1–3]. Even those patients that do respond often continue to experience residual symptoms such as insomnia and cognitive dysfunction [4–7]. Thus, novel antidepressant medications are needed that treat a broader expanse of symptoms or are effective in patients that have failed several different classes of antidepressants drugs.

The primary well-documented augmentation treatment for depressed patients already on SSRIs or SNRIs are atypical antipsychotics (aripiprazole, quetiapine,
risperidone or olanzapine) and less so for mirtazapine/mianserin [8–12]. The common pharmacological action shared by these medications is blockade of 5-HT$_{2A}$ receptors [13]. Blockade of 5-HT$_{2A}$ receptors may also be a key pharmacological feature for most tricyclic antidepressant drugs which explain their greater antidepressant efficacy compared to SSRIs [14–17]. However, side effects especially problematic for augmentation of SSRIs/SNRIs with atypical antipsychotic drugs are weight gain and extrapyramidal symptoms. Thus, discovery of a drug targeted on key neurocircuitry modulated by 5-HT$_{2A}$ receptors is one strategy to develop a novel antidepressant medication.

Given that pathophysiology of mood disorders appears to involve the prefrontal cortex and associated macrocircuits, an obvious candidate brain region to provide a context for 5-HT$_{2A}$ receptor blockade at augmenting the effects of SSRIs/SNRIs is the prefrontal cortex [18–21]. In particular, layer V pyramidal neurons can effectively modulate important cortical circuits (including corticothalamic, corticostriatal, cortico-amygdalar and cortico-brainstem) that impact mood, cognition/ executive function, sleep and appetite [22, 23]. One aspect of 5-HT$_{2A}$ receptor function largely restricted to layer V pyramidal cells is increasing the frequency of spontaneous excitatory postsynaptic currents/potentials (EPSC/EPSPs) onto the dendritic branches [24]. This effect appears to be mediated by AMPA receptor stimulation of directly on the layer V pyramidal cells [24, 25]. Lesion studies have suggested that 5-HT$_{2A}$ receptor activation is releasing glutamate from thalamocortical terminals arising from the “non-specific” midline and intralaminar thalamic nuclei [26, 27]. There appear to be hot spots in layer I and layer Va where focal 5-HT-induced release of glutamate sensitive to the sodium channel blocker tetrodotoxin (TTX) occurs, although an amplification of postsynaptic currents, including TTX-sensitive sodium currents [24]. A number of G$_i$/G$_o$-coupled GPCRs (including mGlu$_2$, mGlu$_4$, µ-opioid, adenosine A$_1$ receptors) also suppresses 5-HT- or DOI-induced glutamate release from these terminals [28–33]. Several other G$_q$/G$_11$-coupled GPCRs (α$_1$-adrenergic receptors and mGlu$_5$ receptors) also appear to induce glutamate release onto layer V pyramidal neurons that are suppressed by the sodium channel blocker TTX, µ-opioid agonists, and AMPA receptor antagonists [34, 35]. This rich pharmacological modulation of 5-HT$_{2A}$ receptor-mediated electrophysiological effects on dendritic integration for the principle output neurons in the prefrontal cortex provides heuristic promise for drug discovery efforts with respect to major psychiatric disease, including mood disorders and schizophrenia [36, 37].

The increase in spontaneous EPSC/EPSPs upon layer V pyramidal cells induced by 5-HT$_{2A}$ receptor activation may be associated with other electrophysiological, biochemical and behavioral effects involving the medial prefrontal cortex (mPFC). On an electrophysiological level, electrical stimulation of the white matter below the cortex appears to result in an induction of “late” EPSC/EPSPs during washout after application of 5-HT or when the phenethylamine hallucinogen DOI is bath-applied to the cortical slice [38]. These late EPSCs are also suppressed by a range of neurotransmitter receptors that suppress spontaneous 5-HT-induced EPSCs such as agonists for mGlu$_2$, µ-opioid, and adenosine A$_1$ receptors [30, 32]. There are also some differences between these two electrophysiological responses as NMDA receptor stimulation appears important for the electrical stimulation/DOI-evoked responses unlike the spontaneous 5-HT-induced EPSC/EPSPs [39].

Secondly, systemic DOI administration also induces a range of immediate-early gene-like signals in the prefrontal cortex/neocortex that are also suppressed by activation of mGlu$_2$ autoreceptors and appear dependent on glutamate release from thalamocortical terminals [40–45]. This effect of prefrontal cortical 5-HT$_{2A}$ receptor activation is relatively sparsely studied compared to the electrophysiological or behavioral sequelae.
Third, either systemic administration or local prefrontal cortical administration of agonists for 5-HT$_{2A}$ receptors induces a robust increase in the frequency of head twitches (a behavior infrequently observed under baseline condition) [46, 47]. Agonists or positive allosteric modulators of mGlu$_2$, mGlu$_4$, μ-opioid, adenosine A$_1$ receptors also suppress DOI-induced head twitches [28, 31, 48–52]. Naturally, these head twitches induced by direct 5-HT$_{2A}$ receptor agonists are also suppressed by a number of antidepressant drugs that potently block 5-HT$_{2A}$ receptors or down-regulate 5-HT$_{2A}$ receptors such as mirtazapine [53], mianserin [54–57], trazodone [55, 58–60], nefazodone [58, 61] and tricyclic antidepressants [55, 57, 62–68] Some of the tricyclic antidepressants are active only with chronic daily administration. While the antidepressant and monoamine oxidase inhibitor (MAOI) tranylcypromine does not directly bind to 5-HT$_{2A}$ receptors, chronic daily administration of this antidepressant has been found to suppress 5-methoxy-N,N-dimethyltryptamine-induced head twitches under conditions associated with a down-regulation of 5-HT$_{2A}$ receptors [63]. The clinical lore regarding μ-opioid receptor agonists and potential antidepressant action is intriguing in light of effects for this class of drugs on DOI-induced head twitches have been discussed elsewhere [36].

Finally, an argument was advanced recently that the basis for detecting antidepressant-like drug effects on the operant differential-reinforcement-of-low-rate 72-s (DRL 72-s) schedule may be related to the biology of a range of neurotransmitter systems that interact with the 5-HT$_{2A}$ receptor in the prefrontal cortex to modulate motor impulsivity [69, 70]. As expected from the similar effects of 5-HT$_{2A}$ receptor antagonists compared to mGlu$_2$ receptor positive allosteric modulators (PAMs) and also to adenosine A$_1$ receptor agonists for the prefrontal electrophysiology discussed above, 5-HT$_{2A}$ receptor antagonists, mGlu$_2$ receptor PAMs and adenosine A$_1$ receptor agonists all test similar to known antidepressant drugs in rats performing under the DRL 72-s schedule [51, 71–77].

The underlying thesis of this chapter is that understanding how other neurotransmitter systems interact with 5-HT$_{2A}$ receptors in the medial prefrontal cortex on an electrophysiological, biochemical and behavioral scale may help discover novel antidepressant drugs. Orexin (OX) receptor agonists/antagonists appear to be one such neurotransmitter system that interacts with critical biological aspects of 5-HT$_{2A}$ receptor activation/blockade in thalamocortical pathways influencing the principle output (layer V pyramidal cells) of the prefrontal cortex in a manner suggesting that OX$_2$ receptor antagonists are putative antidepressant medications.

2. Orexin-2 receptor blockade and putative antidepressant action

The orexins are two peptide neurotransmitters produced in several nuclei within the lateral hypothalamus which are intimately involved in arousal and reward [78]. The name “orexin” was originally coined from the Greek word “orexis” when the orexin/hypocretin peptides were studied for effects on appetite. However, the more salient biological aspect of the orexin system later was realized to be altering sleep and arousal. More specifically, mutations of genes for the orexin-2 (OX$_2$) receptor, orexin peptides, and loss of orexin-containing hypothalamic cell bodies were demonstrated to be the genetic cause of narcolepsy in canines, mice and humans. The first approved medication targeting the orexin system, suvorexant, blocks both orexin-1 (OX$_1$) and OX$_2$ receptors as a dual orexin receptor antagonist (DORA) and is indicated for the treatment of insomnia [78, 79]. Several other DORAs have been shown to be efficacious in treating primary insomnia [80–82]. The overlapping and diverging distribution for the OX$_1$ and OX$_2$ mRNA and protein has inspired several decades of past/ongoing research exploring these receptors for sleep, arousal, feeding,
alcohol and drug self-administration, stress, anxiety and depression models [83].

The involvement of OX$_2$ receptors in arousal together with the presence of OX$_2$ receptor mRNA in the non-specific midline and intralaminar thalamic nuclei and the interactions of the orexin system with brainstem nuclei with overlapping monoamine projections makes the OX2 receptor an especially interesting target for mood disorder therapeutics [78, 83]. As discussed below, OX$_2$ or hypocretin-2 receptor blockade appears to be a mechanism of action that provides a means of testing the hypothesis discussed above where a drug appropriately modifying multiple levels of biological effects for 5-HT$_{2A}$ receptor activation in the mPFC would be a putative antidepressant medication.

Electrophysiological effects of OX$_2$ receptor activation in the prefrontal cortex appear to parallel certain effects of 5-HT$_{2A}$ receptor activation when recording from layer V pyramidal neurons. The orexin-B (hypocretin-2) peptide was found to increase spontaneous EPSC/EPSPs in layer V pyramidal neurons of the prefrontal cortex that were blocked by postsynaptic AMPA receptor antagonists as well as by TTX and u-opioid agonists on the presynaptic side similar to the case for 5-HT$_{2A}$ receptor stimulation [84]. Experiments to delineate the origin of afferents in the PFC from which orexin induced glutamate release from suggested that the cells of origin were in the midline and intralaminar thalamic nuclei [84]. Further, the relative potency for orexin-B compared to orexin-A (hypocretin-1) at inducing spontaneous OX-induced EPSCs/EPSPs in PFC layer V pyramidal cells is similar to that found in the intralaminar and midline thalamic nuclei with OX$_2$, not OX$_1$, receptor responses [84–86]. The tetrodotoxin sensitivity of the orexin-induced EPSCs/EPSPs is in keeping with earlier studies suggesting that thalamocortical projections from these “non-specific” thalamic nuclei associated with arousal were prone to the generation of terminal spikes as previously suggested [87, 88]. This dependence on thalamocortical pathways originating in the midline and intralaminar thalamic nuclei and terminating in layers I and Va of the prefrontal cortex is consistent with features for the spontaneous 5-HT-induced EPSCs/EPSPs [26, 27]. One difference between OX-induced spontaneous EPSCs and 5-HT-induced EPSCs is that OX does not appear to induce postsynaptic depolarization (consistent with absence of OX$_2$ mRNA in layer V pyramidal cells) unlike the case for 5-HT$_{2A}$ receptor activation in the majority of layer V pyramidal cells [84, 89]. However, studies characterizing the ability of orexin-B induced EPSCs/EPSPs to be blocked with selective OX$_2$ receptor antagonists or selective OX$_1$ receptor antagonists would be useful to unambiguously identify the OX receptor subtype involved in this response.

Limited work has been done exploring effects of OX$_2$ receptor antagonists on immediate early gene (IEG-like) responses in the prefrontal cortex. However, the OX$_2$ receptor antagonist LSN2424100 did suppress restraint stress-induced increases in c-Fos protein expression without having any effects on baseline Fos protein expression in the home cage [90]. These effects of the OX$_2$ receptor antagonist LSN2424100 on restraint stress-induced increases Fos expression in the prelimbic cortex are similar to an effect of the mGlu$_2$ receptor agonist LY354740 on restraint stress-induced increases in Fos expression [45]. As discussed above, 5-HT$_{2A}$ receptor agonists induce a number of immediate IEG-like responses in the prefrontal cortex. Activation of mGlu$_2$ receptors appears to suppress the DOI-induced increases in a number of IEG-like responses in the prefrontal cortex [40, 41, 44, 91].

Modulation of 5-HT$_{2A}$ receptor agonist-induced head twitches is a behavioral measure that is suppressed by a range of antidepressants blocking/regulating 5-HT$_{2A}$ receptors as discussed above; these DOI-induced head twitches are also suppressed by the selective OX$_2$ receptor antagonist LSN2424100 (Figure 1). LSN2424100 possesses approximately 200-fold functional OX$_2$ receptor antagonist activity at both human recombinant OX$_2$ vs. OX$_1$ receptors or rat OX$_2$ vs. OX$_1$
receptors [90]. Administration of LSN2424100 (10 mg/kg, i.p.) 30 min prior to administration of DOI (3 mg/kg, i.p.) with behavioral observations beginning 5 min later for a 30 min period resulted in over a 67% statistically significant reduction in the frequency of DOI-induced head twitches in CD-1 mice (n = 8/group; **Figure 1**) using conditions/methods/statistical analyses reported elsewhere in greater detail [52]. Head twitches were observed in 8/8 vehicle/DOI treated mice but in only 3/8 LSN2424100/DOI treated mice (p < 0.05, Fisher’s Exact Test). This experiment demonstrating that a Gq/G11-coupled GCPR OX2 receptor antagonist (like 5-HT2A receptor antagonists) suppress DOI-induced head twitches fits in with evidence that agonists or positive allosteric modulators of Gi/Go-coupled GCPRs (mGlu2, mGlu4, adenosine A1, and μ-opioid receptors) similarly suppress DOI-induced head twitches [28, 31, 48, 50, 52, 92, 93]. Thus, the effects of these drugs on spontaneous EPSCs/EPSPs upon layer V pyramidal neuron apical dendrites in layers I and Va of the prefrontal cortex all produce directionally consistent effects on DOI-induced head twitches [37]. These results imply that adequate orexin, glutamate, adenosine and endogenous opioid release is present from or onto thalamocortical afferents under the in vivo experimental conditions employed to engender salient changes in dendritic integration of the principle output layer V pyramidal cells.

OX2 receptor antagonists also appear to modulate at least certain aspects of executive function mediated by the prefrontal cortex, namely impulsivity and biasing operant responding for DRL schedules in rodents [69, 90]. The OX2 receptor antagonist LSN2424100 increased reinforcers obtained and decreased total responses by Sprague-Dawley rats performing under a DRL 72-s schedule of reinforcement (**Figure 2**) [90]. These antidepressant-like responses were largely replicated in wild-type CD-1 mice and OX1 receptor knockout mice responding on a DRL 36-s schedule of reinforcement rate [90]. However, no changes in the reinforcement rate or response rate

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**Figure 1.**
The effect of (±)-DOI (3 mg/kg, i.p.) and the selective OX2 receptor antagonist LSN2424100 (10 mg/kg, i.p.) on head twitches in CD-1 wild-type mice observed for 30 min following drug administration. LSN2424100 was administered 30 min prior to DOI. Each bar represents the mean (± SEM) of eight mice. Significantly different from the mean number of head twitches for the vehicle/DOI group, *p < 0.05. Significantly different from the number of mice displaying head twitches for the vehicle/DOI group, # p < 0.05 by the Fisher exact test.
were observed in OX$_2$ receptor knockout mice when testing LSN2424100 doses up to twice as large as those used for wild-type and OX$_1$ receptor knockout mice [90]. A similar antidepressant-like profile was observed in rats, wild-type CD-1 mice, and OX$_1$ receptor KO mice with the non-selective OX$_1$/OX$_2$ receptor antagonist almorexant [90]. In contrast, a selective OX$_1$ receptor antagonist failed to produce an antidepressant-like response in rats performing on a DRL 72-s schedule or wild type mice or OX$_2$ receptor knockout mice responding on a DRL 36-s schedule [90]. However, the well-established tricyclic antidepressant drug imipramine tested as expected in these experiments as a positive control (e.g., antidepressant-like effects) in Sprague-Dawley rats, wild-type mice, OX$_1$ receptor knockout mice, or OX$_2$ receptor KO mice trained to lever press under a DRL 72-s schedule (rats) or a DRL 36-s (mice) schedule.

3. Clinical trials with orexin receptor antagonists in patients with MDD

Thus far only a single small double-blind, placebo-controlled, diphenhydramine-controlled, parallel group, phase 1b/2a trial of a selective OX$_2$ receptor antagonist, JNJ-42847922/MIN-202 or seltorexant, has been conducted [94].
Only 47 men and women with a diagnosis of MDD (DSM-IV) were randomized to received either diphenhydramine, 25 mg q.d. (n = 13), seltorexant, 20 mg q.d. (n = 22) or placebo (n = 12) for 10 nights. Sleep polysomnography was also performed to provide objective assessment of improvements on sleep. There were improvements from baseline in the seltorexant treatment group for the HAMD-17 total score (−3.6 points) as well as the HAM-17 adjusted total score accounting for sleep improvement in addition to changes in the HAMD-6 item score (−1.5 points). This resulted in effect sizes of −0.48, −0.55 and −1.05 for the OX<sub>2</sub> receptor antagonist compared to placebo. However, one caveat is that the subjects assigned to the histamine H<sub>1</sub> receptor antagonist diphenhydramine showed highly comparable improvement compared to placebo. To answer these questions/concerns, a phase 2b randomized, double-blind parallel group, placebo-controlled, adaptive dose-finding trial for seltorexant adjunctive treatment to antidepressants scheduled to enroll about 280 adult subjects at 85 US, European, Russian and Japanese sites began in September 2017 (NCT03227224).

The only other MDD clinical trial for an OX receptor antagonist was negative [95]. Filorexant (MK-6096), a dual orexin receptor antagonist, was evaluated in a 6-week, double-blind, placebo-controlled, parallel-group phase 2a proof-of-concept trial where subjects with MDD were randomized 1:1 to once-daily oral filorexant 10 mg or matching placebo. Subjects on antidepressants continued to take their prescribed antidepressant for the duration of the trial. This study was stopped after enrolling 129 (40%) of a planned 326 subjects. Less than a 1 point numerical improvement was observed for filorexant compared to placebo using the mean change from baseline to week 6 MADRS total score. Exploratory analyses also failed to reveal statistically significant changes in the Insomnia Severity Index (ISI). Regarding safety, there were no deaths, drug-related serious adverse events (SAEs) and only one discontinuation due to AEs in both treatment groups. There were no other problematic safety issues reported.

This negative filorexant MDD study may be related to an issue of inadequate power as the planned study was designed with 80% power to detect a 3.5-point difference between treatments with a 2-sided 5% level of significance and a fully enrolled trial. However, the enrollment of only 129 subjects while using 61 sites (United States, Canada, Finland, France, Germany, Norway and Sweden) speaks to the recruitment challenges in this study. The dose chosen for this MDD trial appears reasonable based on positive effects reported for filorexant in a phase 2 randomized, double-blind, placebo-controlled adaptive crossover polysomnography dose-ranging study evaluating approximately 80 subjects each at nightly doses of 2.5, 5 and 10 mg [81]. All doses showed significant effects on sleep efficiency and wakefulness after persistent sleep onset while the two higher doses demonstrated significant effects on sleep onset. Filorexant was also well tolerated in this insomnia trial as well [81].

Preclinical results suggest that the combined OX<sub>1</sub>/OX<sub>2</sub> receptor antagonism should not have compromised potential antidepressant action in patients with MDD. Namely, the OX<sub>1</sub>/OX<sub>2</sub> receptor antagonist almorexant acted similarly to the OX<sub>2</sub> receptor antagonist LSN2424100 and the known tricyclic antidepressant imipramine in rats and mice performing on DRL 72-s or DRL 36-s schedules [90]. In addition, the non-selective OX receptor antagonist almorexant also tested similarly to known antidepressants in mice subjected to unpredictable chronic mild stress (UCMS) and then evaluated with the tail suspension test, the resident-intruder test, and the elevated plus maze [96]. However, opposing antidepressant-like and “pro-depressant”-like effects were observed in OX<sub>1</sub> and OX<sub>2</sub> receptor knockout mice, respectively, studied with the forced swim paradigm [97]. In this same study, the selective OX<sub>2</sub> receptor antagonist SB-334867 also exerted an antidepressant like
effect in the forced swim test. No data has been published suggesting that selective OX2 receptor antagonists test as antidepressants in rodent forced swim tests. Nevertheless, the balance of data are consistent with the hypothesis that adequate blockade of both OX1 and OX2 receptors, or OX2 receptors alone, should improve depressive symptoms in patients with MDD.

4. Conclusions

Activation of 5-HT2A receptors or OX2 receptors appears to induce glutamate release from thalamocortical terminals with cell bodies originating in the midline and intralaminar thalamic nuclei when recording from prefrontal cortical layer V pyramidal neurons (Figure 3). This 5-HT and orexin-B-induced glutamate release appears to dependent action potentials in the presynaptic terminals judging from the TTX-induced blockade of the 5-HT- or orexin-induced EPSC/EPSPs as

![Figure 3](image)

The model where activation of 5-HT2A or OX2 receptors depolarizes and releases glutamate from non-specific thalamocortical inputs to layer I and Vα of the apical dendrites from layer V pyramidal neurons. The majority of 5-HT2A receptors, apart from a minority of presynaptic receptors and those on GABAergic interneurons, are present on and also directly depolarize layer V pyramidal neurons. Other glutamatergic receptors (mGlu2 and mGlu4), μ-opioid receptors and adenosine A1 receptors that suppress the EPSCs/EPSPs induced by activation of 5-HT2A and OX2 receptors appear to be present on non-specific thalamocortical afferents. This circuitry (with additional positive modulator receptor such as mGlu5 and NK3 receptors and also additional negative modulators such as β2-adrenergic receptors) appears to underlie a similar valence of action for all these receptors for a behavior mediated by activation of 5-HT2A receptors in the prefrontal cortex, DOI-induced head twitches. This circuitry also appears to underlie impulsive behavior (DRL 72-s behavior) where a similar valence of GPCR mediated effects appears to drive antidepressant-like effects on this screening behavior as DOI-induced head twitches and 5-HT-induced EPSCs.
suggested previously for non-specific thalamocortical axons. Apical dendritic layer V pyramidal AMPA receptors appear to be activated postsynaptic to the thalamic terminals. The 5-HT or DOI-induced spontaneous EPSCs/EPSPs or DOI/electrically evoked EPSC/EPSPs also appear suppressed by mGlu$_2$, mGlu$_4$, adenosine A$_1$, 5-HT$_1$-like and β$_2$-adrenergic receptors.

Future work is required to establish that orexin-B-induced glutamate release from non-specific thalamic afferents is also suppressed by mGlu$_2$, mGlu$_4$, adenosine A$_1$, 5-HT$_1$-like and β$_2$-adrenergic receptors. Blockade of OX$_2$ and 5-HT$_{2A}$ receptors also both appear to suppress DOI-induced head twitches, a behavioral response that appears to be mediated by activation of prefrontal cortical 5-HT$_{2A}$ receptors. A selective OX$_2$ receptor antagonist tested similar to the tricyclic antidepressant imipramine in rats and mice responding under an operant DRL 72-s schedule of reinforcement. Another question for future preclinical research with rodent DRL behavior is whether blockade of OX$_2$ receptors is additive/synergistic with tricyclic antidepressants or SSRIs in the same manner as blockade of 5-HT$_{2A}$ receptors. The ongoing clinical antidepressant trial with the OX$_2$ receptor antagonist seltorexant are important to understanding whether the circuitry involving orexin-containing cells in the hypothalamus together with orexin-containing axon terminals in the intralaminar and midline thalamic nuclei and the prefrontal cortex are necessary and sufficient by themselves to augment the antidepressant effects of tricyclic antidepressants and SSRIs. If this ongoing and other clinical antidepressant trials with selective OX$_2$ receptor antagonists or additional adequately powered clinical trials testing OX$_1$/OX$_2$ receptor antagonists are negative, then future work will be required to begin to ask whether additional actions of OX$_2$ receptor antagonists in other circuitry are functionally opposed to the brainstem/thalamic/prefrontal cortical circuits.

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Conflict of interest

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References

[1] Bradley AJ, Lenox-Smith AJ. Does adding noradrenaline reuptake inhibition to selective serotonin reuptake inhibition improve efficacy in patients with depression? A systematic review of meta-analysis and large randomized pragmatic trials. Journal of psychopharmacology (Oxford, England). 2013;27:740-758

[2] Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: A multiple-treatments meta-analysis. Lancet. 2009;373:746-758

[3] Papakostas GI, Charles D, Fava M. Are typical starting doses of the selective serotonin reuptake inhibitors sub-optimal? A meta-analysis of randomized, double-blind, placebo-controlled, dose-finding studies in major depressive disorder. The World Journal of Biological Psychiatry. 2010;11:300-307

[4] Mayers AG, Baldwin DS. Antidepressants and their effect on sleep. Human Psychopharmacology. 2005;20:533-539

[5] Nakano Y, Baba H, Maeshima H, Kitajima A, Sakai Y, Baba K, et al. Executive dysfunction in medicated, remitted state of major depression. Journal of Affective Disorders. 2008;111:46-51

[6] Paelecke-Habermann Y, Pohl J, Leplow B. Attention and executive function in remitted major depression patients. Journal of Affective Disorders. 2005;89:125-135

[7] Winokur A, Gary KA, Rodner S, Rae-Red C, Fernando AT, Szuba MP. Depression, sleep physiology, and antidepressant drugs. Depression and Anxiety. 2001;14:19-28

[8] Blier P, Gobbi G, Turcotte JE, de Montigny C, Boucher N, Hebert C, et al. Mirtazapine and paroxetine in major depression: A comparison of monotherapy versus their combination from treatment initiation. European Neuropsychopharmacology. 2009;19:457-465

[9] Carpenter LL, Yasmin S, Price LH. A double-blind placebo-controlled study of antidepressant augmentation with mirtazapine. Biological Psychiatry. 2002;51:183-188

[10] Ferreri M, Lavergne F, Berlin I, Payan C, Peuch AJ. Benefits from mianserin augmentation of fluoxetine in patients with major depression non-responders to fluoxetine alone. Acta Psychiatrica Scandinavica. 2001;103:66-72

[11] Han C, Wang S-M, Kato M, Lee S-J, Patkar AA, Masand PS, et al. Second-generation antipsychotics in the treatment of major depressive disorder: Current evidence. Expert Review of Neurotherapeutics. 2013;13:851-874

[12] Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorders: A meta-analysis of placebo-controlled randomized trials. The American Journal of Psychiatry. 2009;166:980-991

[13] Marek GJ, Carpenter LL, McDougle CJ, Price LH. Synergistic action of 5-HT2A antagonists and selective serotonin reuptake inhibitors in neuropsychiatric disorders. Neuropsychopharmacology. 2003;28:402-412

[14] Marek GJ. Regulation of rat cortical 5-hydroxytryptamine2A-receptor mediated electrophysiological responses by repeated daily treatment with electroconvulsive shock or imipramine.
European Neuropsychopharmacology. 2008;18:498-507

[15] Marek GJ. Cortical 5-hydroxytryptamine_{2A}-receptor mediated excitatory synaptic currents in the rat following repeated daily fluoxetine administration. Neuroscience Letters. 2008;438:312-316

[16] DUAG. Citalopram: Clinical effect profile in comparison with clomipramine—A controlled multicenter study. Psychopharmacology. 1986;90:131-138

[17] DUAG. Paroxetine: A selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. Journal of Affective Disorders. 1990;18:289-299

[18] Drevets WC. Functional neuroimaging studies of depression: The anatomy of melancholia. Annual Review of Medicine. 1998;49:341-361

[19] Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME. A functional anatomical study of unipolar depression. Journal of Neuroscience. 1992;12:3628-3641

[20] Mayberg HS. Limbic-cortical dysregulation: A proposed model of depression. Journal of Neuropsychiatry & Clinical Neurosciences. 1997;9(3):471-481

[21] Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dilley G, Pittman SD, Meltzer HY, et al. Morphometric evidence for neuronal and glia prefrontal cell pathology in major depression. Biological Psychiatry. 1999;45:1085-1098

[22] Price JL. Prefrontal cortical networks related to visceral function and mood. Annuals of New York Academy of Sciences. 1999;877:383

[23] Price JL, Drevets WC. Neurocircuitry of mood disorders. Neuropsychopharmacology. 2010;35:192-216

[24] Aghajanian GK, Marek GJ. Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. Neuropharmacology. 1997;36(3/4):589-599

[25] Zhang C, Marek GJ. AMPA receptors involvement in 5-hydroxytryptamine_{2A} receptor-mediated prefrontal cortical excitatory synaptic currents and DOI-induced head shakes. Progress in Neuropsychopharmacology & Biological Psychiatry. 2008;32:62-71

[26] Lambe EK, Aghajanian GK. The role of Kv1.2-containing potassium channels in serotonin-induced glutamate release from thalamocortical terminals in rat frontal cortex. The Journal of Neuroscience. 2001;21:9955-9963

[27] Marek GJ, Wright RA, Gewirtz JC, Schoepp DD. A major role for thalamocortical afferents in serotonergic hallucinogen receptor function in the rat neocortex. Neuroscience. 2001;105:379-392

[28] Benneyworth MA, Xiang Z, Smith RL, Garcia EE, Conn PJ, Sanders-Bush E. A selective positive allosteric modulator of metabotropic glutamate receptor subtype 2 blocks a hallucinogenic drug model of psychosis. Molecular Pharmacology. 2007;72:477-484

[29] Marek GJ, Aghajanian GK. 5-HT-induced EPSCs in neocortical layer V pyramidal cells: Suppression by μ-opiate receptor activation. Neuroscience. 1998;86:485-497

[30] Marek GJ, Wright RA, Schoepp DD, Monn JA, Aghajanian GK. Physiological antagonism between 5-hydroxytryptamine_{2A} and group...
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DOI: http://dx.doi.org/10.5772/intechopen.82544

II metabotropic glutamate receptors in prefrontal cortex. The Journal of Pharmacology and Experimental Therapeutics. 2000;292:76-87

[31] Slawinska A, Wieronska JM, Stachowicz K, Marciniak M, Lason-Tyburkiewicz M, Gruca P, et al. The antipsychotic-like effects of positive allosteric modulators of metabotropic glutamate mGlu4 receptors in rodents. British Journal of Pharmacology. 2013;169:1824-1839

[32] Stutzman GE, Marek GJ, Aghajanian GK. Adenosine preferentially suppresses serotonin2A receptor-enhanced excitatory postsynaptic currents in layer V neurons of the rat medial prefrontal cortex. Neuroscience. 2001;105:55-69

[33] Zhang C, Marek GJ. Group III metabotropic glutamate receptor agonists selectively suppress excitatory synaptic currents in the rat prefrontal cortex induced by 5-hydroxytryptamine2A receptor stimulation. The Journal of Pharmacology and Experimental Therapeutics. 2007;320:437-447

[34] Marek GJ, Zhang C. Activation of metabotropic glutamate 5 (mGlu5) receptors induces spontaneous excitatory synaptic currents in layer V pyramidal cells of the rat prefrontal cortex. Neuroscience Letters. 2008;442:239-243

[35] Marek GJ, Aghajanian GK. 5-HT2A or α1-adrenoceptor activation induces excitatory postsynaptic currents in layer V pyramidal cells of the medial prefrontal cortex. European Journal of Pharmacology. 1999;367:197-206

[36] Marek GJ, Aghajanian GK. The electrophysiology of prefrontal 5-HT systems: Therapeutic implications for mood and psychosis. Biological Psychiatry. 1998;44:1118-1127

[37] Marek GJ. Interactions of Hallucinogens with the Glutamatergic System: Permissive Network Effects Mediated through Cortical Layer V Pyramidal Neurons. Current Topics in Behavioral Neuroscience. Berlin, Heidelberg: Springer; 2017

[38] Aghajanian GK, Marek GJ. Serotonin, via 5-HT2A receptors, increases EPSCs in layer V pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release. Brain Research. 1999;825:161-171

[39] Lambe EK, Aghajanian GK. Hallucinogen-induced UP states in the brain slice rat prefrontal cortex: Role of glutamate spillover and NR2B-NMDA receptors. Neuropsychopharmacology. 2006;31:1682-1689

[40] Gewirtz JC, Chen AC, Terwilliger R, Duman RC, Marek GJ. Modulation of DOI-induced increases in cortical BDNF expression by group II mGlu receptors. Pharmacology, Biochemistry, and Behavior. 2002;73:317-326

[41] Gonzalez-Maeso J, Ang RL, Yuen T, Chan P, Weisstaub NV, Lopez-Gimenez JF, et al. Identification of a serotonin/glutamate receptor complex implicated in psychosis. Nature. 2008;452:93-97

[42] Gonzalez-Maeso J, Weisstaub NV, Zhou M, Chan P, Ivic L, Ang R, et al. Hallucinogens recruit specific cortical 5-HT2A receptor-mediated signalling pathways to affect behavior. Neuron. 2007;53:439-452

[43] Scruggs JL, Patel S, Bubser M, Deutch AY. DOI-induced activation of the cortex: Dependence upon 5-HT2A heteroreceptors on thalamocortical glutamatergic neurons. The Journal of Neuroscience. 2000;20:8846-8852

[44] Wischhof L, Koch M. Pretreatment with the mGlu2/3 receptor agonist LY379268 attenuates DOI-induced impulsive responding and
regional c-Fos protein expression. Psychopharmacology. 2012;219:387-400

[45] Menezes MM, Marek GJ, Benvenga MJ, Chaney S, Svensson KA. The mGlue2/3 receptor agonist LY354740 attenuates the restraint-stress induced Fos expression and DOI-induced Fos expression in prefrontal cortex. In: Neuroscience Meeting Planner Society for Neuroscience. Chicago, IL: Society for Neuroscience; 2009. pp. 417-423

[46] Canal CE, Morgan D. Head-twitch response in rodents induced by the hallucinogen 2,5-dimethoxy-4-iodoamphetamine: A comprehensive history, a re-evaluation of mechanisms, and its utility as a model. Drug Test Analysis. 2012;4:556-576

[47] Willins DL, Meltzer HY. Direct injection of 5-HT2A receptor agonists into the medial prefrontal cortex produces a head-twitch response in rats. The Journal of Pharmacology and Experimental Therapeutics. 1997;282:699-706

[48] Gewirtz JC, Marek GJ. Behavioral evidence for interactions between a hallucinogenic drug and group II metabotropic glutamate receptors. Neuropsychopharmacology. 2000;23:569-576

[49] Klodzinska A, Bijak M, Tokarski K, Pile A. Group II mGlue receptor agonists inhibit behavioral and electrophysiological effects of DOI in mice. Pharmacology Biochemistry & Behavior. 2002;73:327-332

[50] Marek GJ. Behavioral evidence for μ-opioid and 5-HT2A receptor interactions. European Journal of Pharmacology. 2003;474:77-83

[51] Marek GJ. Activation of adenosine1 receptors induces antidepressant-like, anti-impulsive effects on differential reinforcement of low-rate 72-s behavior in rats. The Journal of Pharmacology and Experimental Therapeutics. 2012;341:564-570

[52] Benvenga MJ, Chaney S, Baez M, Britton TC, Hornback WJ, Monn JA, et al. Metabotropic glutamate2 receptors play a key role in modulating head twitches induced by a serotonergic hallucinogen in mice. Frontiers in Pharmacology. 2018;9:208

[53] Rojoz Z. Effect of co-treatment with mirtazapine and risperidone in animal models of the positive symptoms of schizophrenia in mice. Pharmacological Reports. 2012;64:1567-1572

[54] Blackshear MA, Sanders-Bush E. Serotonin receptor sensitivity after acute and chronic treatment with mianserin. The Journal of Pharmacology and Experimental Therapeutics. 1982;221:303-308

[55] Friedman E, Cooper TB, Dallob A. Effects of chronic antidepressant treatment on serotonin receptor activity in mice. European Journal of Pharmacology. 1983;89:69-76

[56] Maj J, Rogoz Z, Skuza G, Sowinska H. The effect of repeated administration of imipramine, citalopram and mianserin on responsiveness of central serotonergic, alpha 2-adrenergic and cholinergic system in mice. Polish Journal of Pharmacology and Pharmacy. 1989;41:313-319

[57] Ogren SO, Fuxe K, Agnati LF, Gustafsson JA, Jonsson G, Holm AC. Reevaluation of the indoleamine hypothesis of depression. Evidence for a reduction of functional activity of central 5-HT systems by antidepressant drugs. Journal of Neural Transmission. 1979;46:85-103

[58] Taylor DP, Carter RB, Eison AS, Mullins UL, Smith HL, Torrente JR, et al. Pharmacology and neurochemistry
of nefazodone, a novel antidepressant drug. Journal of Clinical Psychiatry. 1995;56(Suppl 6):3-11

[59] Clements-Jewery S, Robson PA, Chidley LJ. Biochemical investigations into the mode of action of trazodone. Neuropharmacology. 1980;19:1165-1173

[60] Cioli V, Corradino C, Piccinelli D, Rocchi MG, Valeri P. A comparative pharmacological study of trazodone, etoperidone and 1-(m-chlorophenyl) piperazine. Pharmacological Research Communications. 1984;16:85-100

[61] Nacca A, Guiso G, Fracasso C, Cervo L, Caccia S. Brain-to-blood partition and in vivo inhibition of 5-hydroxytryptamine reuptake and quipazine-mediated behaviour of nefazodone and its main active metabolites in rodents. British Journal of Pharmacology. 1998;1998:1617-1623

[62] Wettstein JG, Host M, Hitchcock JM. Selectivity of action of typical and atypical anti-psychotic drugs as antagonists of the behavioral effects of 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI). Progress in Neuro-Psychopharmacology & Biological Psychiatry. 1999;23:533-544

[63] Goodwin GM, Green AR, Johnson P. 5-HT2 receptor characteristics in frontal cortex and 5-HT2 receptor-mediated head-twitch behavior following antidepressant treatment to mice. British Journal of Pharmacology. 1984;83:235-242

[64] Godfrey PP, McClue SJ, Young MM, Heal DJ. 5-hydroxytryptamine-stimulated inositol phospholipid hydrolysis in the mouse cortex has pharmacological characteristics compatible with mediation via 5-HT2 receptors but this response does not reflect altered 5-HT2 function after 5,7-dihydroxytryptamine lesioning or repeated antidepressant treatments. Journal of Neurochemistry. 1988;50:730-738

[65] Pawlowski L, Ruczynska J, Gorka Z. Citalopram: A new potent inhibitor of serotonin (5-HT) uptake with central 5-HT-mimetic properties. Psychopharmacology. 1981;74:161-165

[66] Pawlowski L, Melzacka M. Inhibition of head twitch response to quipazine in rats by chronic amitriptyline but not fluvoxamine or citalopram. Psychopharmacology. 1986;88:279-284

[67] Kawakami Y, Kitamura Y, Araki H, Kitagawa K, Suemaru K, Shibata K, et al. Effects of monoamine reuptake inhibitors on wet-dog shakes mediated by 5-HT2A receptors in ACTH-treated rats. Pharmacology, Biochemistry, and Behavior. 2005;81:65-70

[68] Kitamura Y, Araki H, Suemaru K, Gomita Y. Effects of imipramine and lithium on wet-dog shakes mediated by the 5-HT2A receptor in ACTH-treated rats. Pharmacology, Biochemistry, and Behavior. 2002;72:397-402

[69] Marek GJ, Day M, Hudzik TJ. The utility of impulsive bias and altered decision making as predictors of drug efficacy and target selection: Rethinking behavioral screening for antidepressant drugs. The Journal of Pharmacology and Experimental Therapeutics. 2016;356:534-548

[70] O'Donnell JM, Marek GJ, Seiden LS. Antidepressant effects assessed using behavior maintained under a differential-reinforcement-of-low-rate (DRL) operant schedule. Neuroscience and Biobehavioral Reviews. 2005;29:785-798

[71] Marek GJ, Li AA, Seiden LS. Selective 5-hydroxytryptamine2 antagonists have antidepressant-like effects on
differential-reinforcement-of-low-rate 72-second schedule. The Journal of Pharmacology and Experimental Therapeutics. 1989;250(1):52-59

[72] Marek GJ, Martin-Ruiz R, Abo A, Artigas F. The selective 5-HT2A receptor antagonist M100907 enhances antidepressant-like behavioral effects of the SSRI fluoxetine. Neuropsychopharmacology. 2005;30:2205-2215

[73] Marek GJ, Seiden LS. Effects of selective 5-hydroxytryptamine-2 and nonselective 5-hydroxytryptamine antagonists on the differential-reinforcement-of-low-rate 72-second schedule. The Journal of Pharmacology and Experimental Therapeutics. 1988;244(2):650-658

[74] Ardayfio PA, Benvenga MJ, Chaney SF, Love PL, Catlow J, Swanson SP, et al. The 5-hydroxytryptamine2A receptor antagonist R-(+)-a-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl-4-piperidinemethanol] (M100907) attenuates impulsivity after both drug-induced disruption (dizocilpine) and enhancement (antidepressant drugs) of differential-reinforcement-of-low-rate 72-s behavior in the rat. The Journal of Pharmacology and Experimental Therapeutics. 2008;327:891-897

[75] Fell MJ, Witkin JM, Falcone JF, Katner JS, Perry KW, Hart J, et al. N-(4-((2-(trifluoromethyl)-3-hydroxy-4-(isobutyryl)phenoxy)methyl)benzyl)-1-methyl-1H-imidazole-4-carboxamide (THIIC), a novel metabotropic glutamate 2 potentiator with potential anxiolytic/antidepressant properties: In vivo profiling suggests a link between behavioral and central nervous system neurochemical changes. The Journal of Pharmacology and Experimental Therapeutics. 2011;336:165-177

[76] Nikiforuk A, Popik P, Drescher KU, van Gaalen M, Relo A-L, Mezler M, et al. Effects of a positive allosteric modulatory of group II metabotropic glutamate receptors, LY487379, on cognitive flexibility and impulsive-like responding in rats. The Journal of Pharmacology and Experimental Therapeutics. 2010;335:665-673

[77] Li AA, Marek GJ, Hand TH, Seiden LS. Antidepressant-like effects of trazodone on a behavioral screen are mediated by trazodone, not the metabolite m-chlorophenylpiperazine. European Journal of Pharmacology. 1990;177(3):137-144

[78] Gotter AL, Webber AL, Coleman PJ, Renger JJ, Windrow CJ. International Union of Basic and Clinical Pharmacology. LXXXVI. Orexin receptor function, nomenclature and pharmacology. Pharmacological Reviews. 2012;64:389-420

[79] Kuriyama A, Tabata H. Suvorexant for the treatment of primary insomnia: A systematic review and meta-analysis. Sleep Medicine Reviews. 2017;35:1-7

[80] Black J, Pillar G, Hedner J, Polo O, Berkani O, Mangialaio S, et al. Efficacy and safety of almorexant in adult chronic insomnia: A randomized placebo-controlled trial with an active reference. Sleep Medicine. 2017;36:86-94

[81] Connor KM, Mahoney E, Jackson S, Hutzelmann J, Zhao X, Jia N, et al. A phase II dose-ranging study evaluating the efficacy and safety of the orexin receptor antagonist filorexant (MK-6096) in patients with primary insomnia. The International Journal of Neuropsychopharmacology. 2016;19(8):1-10

[82] Murphy P, Moline M, Mayleben D, Rosenberg R, Zammit G, Pinner K, et al. Lemborexant, a dual orexin receptor antagonist (DORA) for the
treatment of insomnia disorder: Results from a Bayesian, adaptive, randomized, double-blind, placebo-controlled study. Journal of Clinical Sleep Medicine. 2017;13:1289-1299

[83] Marcus JN, Aschkenasi CJ, Lee CE, Chemelli RM, Saper CB, Yanagisawa M, et al. Differential expression of orexin receptors 1 and 2 in the rat brain. The Journal of Comparative Neurology. 2001;435:6-25

[84] Lambe EK, Aghajanian GK. Hypocretin (orexin) induces calcium transients in single spines postsynaptic to identified thalamocortical boutons in prefrontal slice. Neuron. 2003;40:139-150

[85] Bayer L, Eggermann E, Saint-Mleux B, Machard D, Jones BE, Muhlethaler M, et al. Selective action of orexin (hypocretin) on nonspecific thalamocortical projection neurons. The Journal of Neuroscience. 2002;22:7835-7839

[86] Lambe EK, Liu RJ, Aghajanian GKS. Hypocretin (orexin), and the thalamocortical activating system. Schizophrenia Bulletin. 2007;33:1284-1290

[87] Gutnick MJ, Prince DA. Thalamocortical relay neurons: Antidromic invasion of spikes from a cortical epileptogenic focus. Science. 1972;176:424-426

[88] Pinault D. Backpropogation of action potentials generated at ectopic axonal loci: Hypothesis that axon terminals integrate local environmental signals. Brain Research Reviews. 1995;21:42-92

[89] Araneda R, Andrade R. 5-Hydroxytryptamine<sub>2</sub> and 5-Hydroxytryptamine<sub>1A</sub> receptors mediate opposing responses on membrane excitability in rat association cortex. Neuroscience. 1991;40(2):399-412

[90] Fitch TE, Benvenga MJ, Jesudason CD, Zink C, Vandergriff AB, Menezes MM, et al. LSN2424100: A novel, potent orexin-2 receptor antagonist with selectivity over orexin-1 receptors and activity in an animal model predictive of antidepressant-like efficacy. Frontiers in Neuroscience. 2014;8(5):1-11

[91] Menezes MM, Santini MA, Benvenga MJ, Marek GJ, Merchant KM, Mikkelsen JD, et al. The mGlu2/3 receptor agonists LY354740 and LY379268 differentially regulate restraint-stress-induced expression of c-fos in rat cerebral cortex. Neuroscience Journal. 2013;36439:8

[92] Klodzinska A, Bijak M, Chojnacka-Wojcik E, Krocza B, Swieder M, Czuczwar SJ, et al. Roles of group II metabotropic glutamate receptor agonists in modulation of seizure activity. Naunyn-Schmiedeberg's Archives of Pharmacology. 2000;361:283-288

[93] Marek GJ. Activation of adenosine<sub>1</sub> (A<sub>1</sub>) receptors suppresses head shakes induced by a serotonergic hallucinogen in rats. Neuropharmacology. 2009;56:1082-1087

[94] Recourt K, Van Amerongen G, Jacobs G, Zuiker R, Luthringer R, Van der Ark P, et al. JNJ-42847922/MIN-202, a selective orexin 2 receptor antagonist, demonstrates beneficial effects on mood and sleep with major depressive disorder. European Neuropsychopharmacology. 2017;27(Suppl. 4):S866

[95] Connor KM, Ceesay P, Hutzelmann J, Snaively D, Krystal AD, Trivedi MH, et al. Phase II proof-of-concept trial of the orexin receptor antagonist filorexant (MK-6096) in patients with major depressive disorder. The International
Journal of Neuropsychopharmacology. 2017;20:613-618

[96] Nollet M, Gaillard P, Tanti A, Girault V, Belzung C, Leman S. Neurogenesis-independent antidepressant-like effects on behavior and stress axis response of a dual orexin receptor antagonist in a rodent model of depression. Neuropsychopharmacology. 2012;37:2210-2221

[97] Scott MM, Marcus JN, Pettersen A, Birnbaum SG, Mochizuki T, Scammell TE, et al. Hcrt1 and 2 signaling differentially regulates depression-like behaviors. Behavioural Brain Research. 2011;222:289-294