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Histamine may contribute to vortioxetine's procognitive effects; possibly through an orexigenic mechanism

Gennady N. Smagin [a], Dekun Song [a], David P. Budac [c], Jessica A. Waller [b], Yan Li [b], Alan L. Pehrson [b], Connie Sánchez [b,*]

[a] Neuroinflammation Biology In vivo, Lundbeck Research USA, 215 College Rd, Paramus, NJ, USA
[b] Brintellix Science Team, Lundbeck Research USA, 215 College Rd, Paramus, NJ, USA
[c] Bioanalysis, Lundbeck Research USA, 215 College Rd, Paramus, NJ, USA

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ABSTRACT

Vortioxetine is a novel multimodal antidepressant that acts as a serotonin (5-HT)$_3$, 5-HT$_7$, and 5-HT$_{1D}$ receptor antagonist; 5-HT$_{1B}$ receptor partial agonist; 5-HT$_{1A}$ receptor agonist; and 5-HT transporter inhibitor *in vitro*. In preclinical and clinical studies vortioxetine demonstrates positive effects on cognitive dysfunction. Vortioxetine's effect on cognitive function likely involves the modulation of several neurotransmitter systems. Acute and chronic administration of vortioxetine resulted in changes in histamine concentrations in microdialysates collected from the rat prefrontal cortex and ventral hippocampus. Based on these results and a literature review of the current understanding of the interaction between the histaminergic and serotonergic systems and the role of histamine on cognitive function, we hypothesize that vortioxetine through an activation of the orexinergic system stimulates the tuberomammilary nucleus and enhances histaminergic neurotransmission, which contributes to vortioxetine's positive effects on cognitive function.

1. Introduction

Vortioxetine is a multimodal antidepressant (Adell, 2010; Alvarez et al., 2012) approved for the treatment of major depressive disorder. It is a serotonin (5-HT)$_3$, 5-HT$_7$ and 5-HT$_{1D}$ receptor antagonist, 5-HT$_{1B}$ receptor partial agonist, 5-HT$_{1A}$ receptor agonist and 5-HT transporter (SERT) inhibitor (Bang-Andersen et al., 2011). Vortioxetine's *in vitro* and *ex vivo* target related potencies are summarized in Table 1 (adapted from (Mork et al., 2012; Sanchez et al., 2015)). Preclinical studies have demonstrated that vortioxetine positively impacts cognitive function at doses that are clinically relevant, based on their level of SERT occupancy (reviewed by (Sanchez et al., 2015). In a clinical study in elderly (≥65 years old) patients with major depressive disorder, vortioxetine showed superiority to placebo in neuropsychological tests of speed processing, verbal learning and memory (Katona et al., 2012). We have previously reported that acute treatment of rats with vortioxetine modulated several neurotransmitter systems that are essential for the regulation of cognitive function, *i.e.*, 5-HT, glutamate, gamma butyric acid (GABA), acetylcholine ACh), histamine (HA), dopamine and norepinephrine (Sanchez et al., 2015; Mork et al., 2013; Pehrson et al., 2013).

The aim of the present paper is to elaborate further on vortioxetine's potential to modulate HA transmission and the putative contribution of this neurotransmitter system to vortioxetine's overall effects on cognitive function. Based on a review of the literature we elaborate on the serotonergic mechanisms by which vortioxetine potentially may modulate histamine, and we review the current understanding of histamine's role in regulation of cognitive function.

2. Histamine and its receptors

Histamine neurons in the brain comprise a divergent system that arises from the tuberomammillary nucleus (TMN) in the posterior hypothalamus (Panula et al., 1984) and projects into many cerebral areas. When released from these neurons, HA triggers its effects in the brain by activating HA H1-receptor (H1R), H2-receptor (H2R), and H3-receptor (H3R) subtypes, all of which are G-protein-coupled receptors. The HA H4 receptor (H4R) is mainly expressed on the surface of immune and hematopoietic cells, but may also play a role in the brain, since it is expressed in CNS neurons (Strakhova et al., 2009). HA is transmethylated to tele-methylhistamine (t-MeHA) by histamine N-methyltransferase (Brown et al., 2001). CNS expression and function of HA receptors have been thoroughly reviewed (Nuutinen and Panula, 2010; Panula and Nuutinen, 2013) and are summarized in Table 2. Neuronal HA originating from the TMN innervates almost

Abbreviations: 5-HT, serotonin; ACh, acetylcholine; GABA, gamma-aminobutyric acid; HA, histamine; IN, interneuron; LC, locus coeruleus; LH, lateral hypothalamus; PFC, prefrontal cortex; SCN, suprachiasmatic nucleus; SERT, serotonin transporter; TMN, tuberomammillary nucleus; VH, ventral hippocampus; VTA, ventral tegmental area.

* Corresponding author.
E-mail address: cs@lundbeck.com (C. Sánchez).

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Table 1
In vitro pharmacological profile and *in vivo* target occupancies of vortioxetine.
Adapted from Mork et al. (2012); Sanchez et al. (2015).

Target	Activity	*In vitro* affinity, Ki		*In vivo* affinity, ED_{50}	
		Human, nM	Rat, nM	Human, mg	Rat, mg/kg
5-HT_3R	Antagonist	3.7	1.1	ND	0.004
5-HT_7R	Antagonist	19	200	ND	40% @ 10 mg/kg
5-HT_{1D}R	Antagonist	54	3.7	ND	ND
5-HT_{1B}	Partial agonist	33	16	ND	3.1
5-HT_{1A}	Agonist	15	230	ND	40% @ 10 mg/kg
SERT	Inhibitor	5.4*	5.3*	5	0.38

ND: not determined, 5-HT: serotonin, 5-hydroxytryptamine, R: receptor *IC_{50}.

every brain region, including the cerebral cortex, hippocampus, striatum, and amygdala (Haas et al., 2008). TMN neurons are heterogeneously modulated by several neurotransmitter systems, including GABA, glycine and cannabinoids and respond to stress and other environmental stimuli (Haas et al., 2008; Haas and Panula, 2003). The effects of the central histaminergic system were extensively studied using knock-out mice and are summarized in a recent review by Schneider (Schneider et al., 2014).

3. Effect of vortioxetine on histamine

In the early preclinical studies of vortioxetine, it was important to determine its modulation of the major brain neurotransmitter systems and the histaminergic system was among those studied. Administration of vortioxetine increased HA levels in the medial prefrontal cortex (PFC) of freely-moving rats in acute microdialysis studies (Mork et al., 2013) presented in Fig. 1. In the chronic dosing study presented here, vortioxetine was formulated into food pellets and given over a period of 14 days at a dose of 18 mg/10 g of food. In the vortioxetine group, this produced 99 ± 0.7% target occupancy at the rat SERT, and 81 ± 2.6% at the rat 5-HT_{1B} receptor, as determined by *ex vivo* autoradiography performed as previously described (Pehrson et al., 2013). Chronic administration of vortioxetine resulted in changes in HA concentrations in microdialysates collected from the PFC and ventral hippocampus (VH), which are key brain areas implicated in pro-cognitive function (experimental were approved by Lundbeck research USA Institutional Animal Care and Use Committee and methods were similar to those described in (Mork et al., 2013)). In control animals, HA concentrations were 0.6 ± 0.03 ng/mL in the PFC and 0.46 ± 0.05 ng/mL in VH. After vortioxetine treatment, concentrations were significantly higher: 0.95 ± 0.06 ng/mL in PFC and 0.85 ± 0.13 ng/mL in VH ($p < 0.05$). Thus, in addition to its acute effect (Mork et al., 2013), chronic vortioxetine treatment produced a sustained increase in HA levels in rats in these two brain regions (Figs. 2–3). *In vitro* studies of vortioxetine's receptor binding properties excludes the possibility that this effect is mediated through a direct effect on HA receptors (Sanchez et al., 2015).

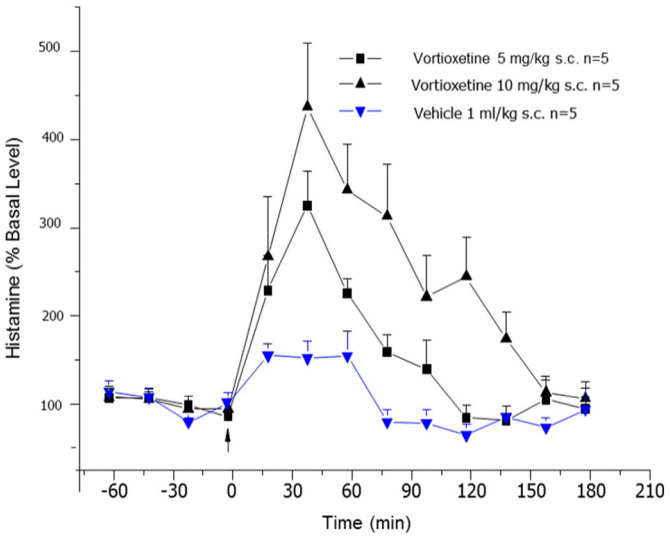

Fig. 1. Effects of subcutaneous administration of vortioxetine or vehicle control on extracellular histamine levels in mPFC (figure adapted from (Mork et al., 2013)). Data are expressed as mean ± SEM. Arrows indicate time of administration. There was a treatment and time-dependent increase in histamine extracellular levels in response to drug administration [$F(27.143) = 4.281$; $p < 0.001$]. Extracellular concentrations of histamine were significantly increased following all treatments relative to their respective baselines from $t = 20$ until $t = 40$ min ($p < 0.05$). The response of the histamine levels to 10 mg/kg was significantly different when compared to the other treatments.

4. Serotonergic regulation of histamine

Serotonergic regulation of histamine is not understood in great detail, but previously it has been shown that histaminergic and cholinergic systems can be activated by serotonergic agents such as the 5-HT_4 receptor agonists prucalopride and PRX-03140 (Johnson et al., 2012) along with an increase in ACh levels in microdialysates in the PFC. It has been suggested that activation of histaminergic and cholinergic systems is desirable for cognitive enhancement (Philippu and Prast, 2001a, 2001b; Blandina et al., 2004). The exact pharmacological mechanism of activation of the histaminergic system by serotonergic agents, including vortioxetine, is not clearly understood, but here we discuss points of possible interaction.

5. Regulation of histaminergic neurons in the TMN, the orexins

Since chronic vortioxetine does not increase ACh, one possible way of linking vortioxetine's HA enhancing effect to its primary serotonergic targets may be through the orexin system. Administration of orexin-A into the TMN produces a significant increase in HA levels, as measured by microdialysis (Huang et al., 2001). These studies expanded the role of orexins in the CNS beyond the regulation of feeding behavior (Sakurai et al., 1998). Orexins also regulate energy intake or storage

Table 2
Histamine receptors.
Adapted from Naddafi and Mirshafiey (2013).

	CNS expression	General function	Binding affinity to HA (pKi)	Signaling pathway
H1R	Thalamus, hippocampus, cortex, amygdala, basal forebrain	Wakefulness, inflammatory responses, decreasing blood pressure	4.2	PLC
H2R	Basal ganglia, hippocampus, amygdala, pyramidal cells, raphe nuclei, substantia nigra	Regulation of gastric acid secretion, decreasing blood pressure, relaxation of airway and vascular smooth muscle, excitation, fluid balance, regulation of hormonal secretion	4.3	Activation of PKC
H3R	CNS, cerebral cortex, basal ganglia and hypothalamus	Regulation of histamine release and generation	8.0	Inhibition of PKA, activation of PLA2, MAPK
H4R	Cerebellum, hippocampus	Modulation of immune system	7.8	Inhibition of PKA, activation of PLC, MAPK

CNS: central nervous system, MAPK: mitogen-activated protein kinase, PKA: protein kinase A, PLA2: phospholipase A2, PKC: protein kinase C, PLC: phospholipase C.

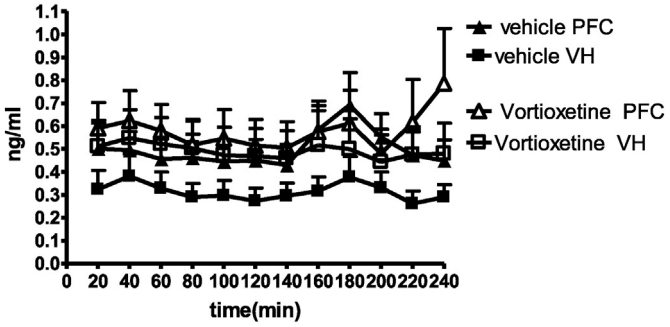

Fig. 2. Time course of basal extracellular concentrations of histamine in ventral hippocampus (VH) and prefrontal cortex (PFC) of rats treated with standard rat chow (vehicle, n = 17) and food containing vortioxetine (18 mg/10 g) for 14 days (n = 17). Rats were anesthetized and intracerebral guide cannulas/microdialysis probes were implanted, followed by a 2-day recovery period. For each animal, the average of the 3–4 consecutive samples collected immediately preceding compound administration was used as the basal level and was set to 100%. Microdialysis experiments were conducted on day 15. Samples were collected after a 4 h stabilization period. Data are presented as means ± SEM, n = 15–17.

and expenditure by modulating feeding and energy homeostasis-related circuits.

Orexin neurons are specifically localized in the lateral hypothalamus (LH) and perifornical areas, and secrete the peptides orexin-A and orexin-B. The TMN is heavily innervated by orexin neurons (Eriksson et al., 2001; Torrealba et al., 2003). The orexin-A peptide consists of 33 amino acids, while orexin-B is a 28 amino acid peptide. Both orexins derive from precursors (prepro-orexins) with 26% sequence identity (de Lecea et al., 1998; Chen et al., 2015). The orexin receptors OX_1 and OX_2 can couple to Gq, Gs (stimulatory), and Gi (inhibitory) G-proteins (Magga et al., 2006; Tang et al., 2008). Orexinergic fibers originate from the LH and are spread over different brain areas (Chen et al., 2015; Song et al., 2005). Orexin receptors are widely distributed in brain and peripheral organs, but interestingly, they are abundantly present in the dorsal raphe nucleus (Soffin et al., 2004), locus coeruleus and in the neurons of the TMN (Marcus et al., 2001).

The effect of orexin on appetite requires intact arcuate nucleus activity (Moreno et al., 2005), partially due to its dependence on activation of the neuropeptide Y pathway (Yamanaka et al., 2000). In line with the hypothesis that vortioxetine interacts with the orexinergic system, we have unpublished observations of the effect of chronic administration of vortioxetine on the body weight of rats. The results of one such study are presented in Fig. 4. Animals receiving vortioxetine have a significantly lower body weight compared to animals receiving the control diet. The difference in the body weight between the vehicle- and vortioxetine-treated animals was approximately15%. The drop in body weight was not due to an anorexigenic effect since food intake was unchanged. It may be that vortioxetine treatment through an action on the orexin system changes the metabolism (possibly set point), and thereby results in the body weight reduction. The most plausible explanation of this effect is an activation of the orexigenic system by vortioxetine, through $5\text{-}HT_{1A}$ receptors (Muraki et al., 2004), since $5\text{-}HT_{1A}$ receptor immunoreactivity has been observed in orexin-containing neurons (Collin et al., 2002) and the effect of 5-HT was inhibited by the $5\text{-}HT_{1A}$ receptor antagonist WAY100635 (Muraki et al., 2004). Proper studies measuring body weight, food intake and metabolic activity would clearly need to be done to substantiate the hypothesis. Clinical data indicate that vortioxetine is weight neutral (Sanchez et al., 2015).

The involvement of other 5-HT receptors in the regulation of histaminergic neurotransmission is not well understood. The $5\text{-}HT_4$ receptor agonists prucalopride and PRX-03140 increase HA levels in the PFC (Johnson et al., 2012), but the effect might be indirect. The $5\text{-}HT_{2C}$ receptor inverse agonist, α2-adrenoceptor antagonist, and $5\text{-}HT_{2A}$ receptor antagonist S32212 also increased HA release in the PFC as well as levels of many other neurotransmitters (Dekeyne et al., 2012). It is also proposed that activation of $5\text{-}HT_7$ receptors on terminals of histaminergic neurons of the TMN leads to release of HA, which in turn activates H2Rs on neurons of the suprachiasmatic nucleus (SCN) and leads to stimulation of the cyclic adenosine monophosphate–protein kinase A pathway (Jacobs et al., 2000).

Additionally, orexin-A activates the histaminergic system in mice after intracerebroventricular administration, with no effect on serotonergic or noradrenergic systems (Hong et al., 2005). The involvement of the orexinergic system in regulation of the histaminergic system becomes even more interesting when considering that alterations in orexins and their receptors are associated with decreased wakefulness, leading to narcoleptic symptoms in humans (Thannickal et al., 2000, 2003). Preclinical studies with knock-out mice have demonstrated that orexin receptors differentially modulate extracellular concentrations of specific neurotransmitters, including HA (Ortega et al., 2012). A proposed interaction of the histaminergic neurons of the TMN with other neurotransmitter systems affected by vortioxetine is illustrated in Fig. 5. The TMN is a key structure in the diagram: it provides direct output to the cortex, relays information from the LH to the cortex and other nuclei, and remains under control of the GABA-ergic neurons of the ventrolateral preoptic nucleus. The TMN cells project to cerebral cortex, hippocampus, septal region, amygdala, paraventricular thalamic nuclei, and supraoptic nuclei. These neurons activate most of the brain areas that are important for arousal, learning and memory (Inagaki et al., 1990). Histaminergic neurons extend to the ventral tegmental area (VTA), substantia nigra, amygdala, striatum, thalamus and cerebral cortex. In turn, orexinergic neurons of the LH project to the TMN, locus coeruleus (LC) and VTA. Systemic administration of vortioxetine may stimulate the orexinergic system through 5-HT receptors, which in

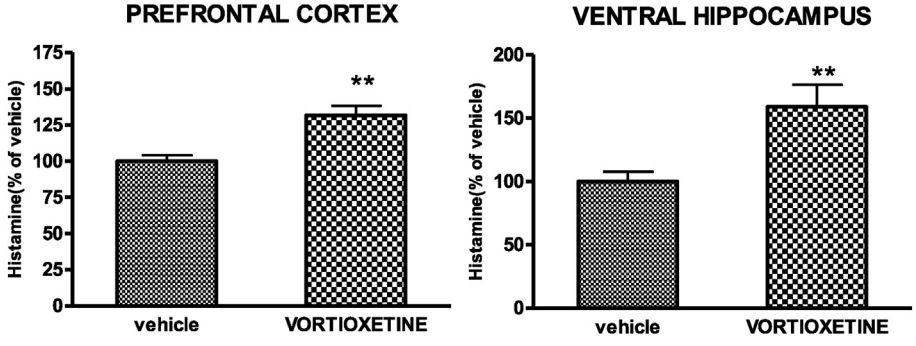

Fig. 3. Levels of extracellular concentrations of histamine in ventral hippocampus (VH) and prefrontal cortex (PFC) over the 240-min collection period. Rats were treated with standard rat chow (vehicle, n = 17) and food containing vortioxetine (18 mg/10 g) for 14 days (n = 17). Rats were anesthetized and intracerebral guide cannulas/microdialysis probes were implanted, followed by a 7-day recovery period. For each animal, the average of the 3–4 consecutive samples collected immediately preceding compound administration was used as the basal level and was set to 100%. Microdialysis experiments were conducted on day 15. Samples were collected after a 4 h stabilization period. Data are presented as means ± SEM, n = 15–17. **p < 0.01 for histamine in PFC and in VH in VOR group compared to vehicle group, one-way ANOVA followed by Tukey's test.

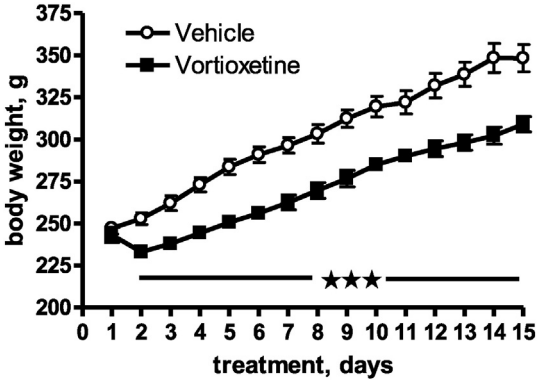

Fig. 4. Body weight change in rats receiving food pellets containing vortioxetine (18 mg/10 g) for 14 days *versus* a vehicle control group receiving standard food pellets. The mean body weight of vortioxetine-treated rats was significantly lower than the vehicle control group. (★★★) $p < 0.001$; mean ± SEM, $n = 8$; two-way repeated measures analysis of variance (ANOVA), followed by Bonferroni's multiple comparison test.

turn stimulate orexinergic projections to the TMN, LC and VTA. It is therefore hypothesized that activation of TMN resulting in increased HA concentrations in microdialysates collected from the PFC and hippocampus is driven largely by the activation of orexinergic system.

The putative effect of vortioxetine on the orexin system has not been studied to date. Obviously, studies need to be made to determine the role of vortioxetine in regulation of the orexin system and its contribution to both clinical and preclinical findings with vortioxetine.

6. Serotonin and cognition

Extensive literature supports the important role of the serotonergic system in regulation of cognitive processes (reviewed by (Leiser et al., 2015)). Serotonin regulates cognitive functions in a very complex manner inducing *via* its many 5-HT receptor subtypes. For example, 5-HT receptors are expressed on both excitatory neurons and inhibitory interneurons and function in either a stimulatory or inhibitory manner depending on cell type or brain localization of a given cell. The net effect of a decrease or increase 5-HT tone, *e.g.* through depletion of the 5-HT precursor, tryptophan, or administration of a selective serotonin reuptake inhibitor (SSRI), respectively, is generally speaking cognition neutral. On the other hand compound that act on a specific 5-HT receptor subtype (*e.g.* 5-HT_6 receptor antagonists) or a combination of 5-HT receptor subtypes (*e.g.* vortioxetine) have shown potential to enhance cognitive functions.

7. Histamine and cognition

The pro-cognitive effects of HA are relatively well-documented. They are mainly mediated by H1Rs and are mediated either directly *via* excitation of neocortical pyramidal neurons and thalamic relay neurons or indirectly *via* excitation of ascending cholinergic neurons (Haas and Panula, 2003). HA synthesis and release from nerve terminals is inhibited by the activation of presynaptic H3Rs, providing a potential mechanism for regulating the activity of HA in the CNS. This idea was explored with the use of the H3R antagonist thioperamide, which produced an increase of HA in the brain (Itoh et al., 1991). Studies with thioperamide on the reversal of pro-cognitive deficits and wake-promoting effects further supported the role of HA in this area and the hypothesis that H3R antagonists could have a therapeutic potential for treatment of conditions associated with cognitive dysfunction (Miyazaki et al., 1997; Monti et al., 1991).

Thus, enhancing histaminergic neurotransmission, improves cognition and facilitates various forms of learning (Passani and Blandina, 2011). Furthermore, interaction between the histaminergic and cholinergic systems is important to the ability of animals to learn and remember (Passani and Blandina, 2011), and many therapeutic strategies and successful treatments have been directed towards the restoration of cholinergic neurotransmission. The effect of vortioxetine on wakefulness is documented (Leiser et al., 2014). Administration of vortioxetine increased time spent in active wake with vortioxetine, and significant changes were found in EEG spectral analyses, demonstrating that vortioxetine alone and in combination with the 5-HT_{1A} receptor agonist flesinoxan increased θ (4–8 Hz), α (8–12 Hz) and γ (30–50 Hz) power. The authors concluded that increased frontal cortical activity associated with vortioxetine is most likely because of its 5-HT_7 and 5-HT_3 receptor

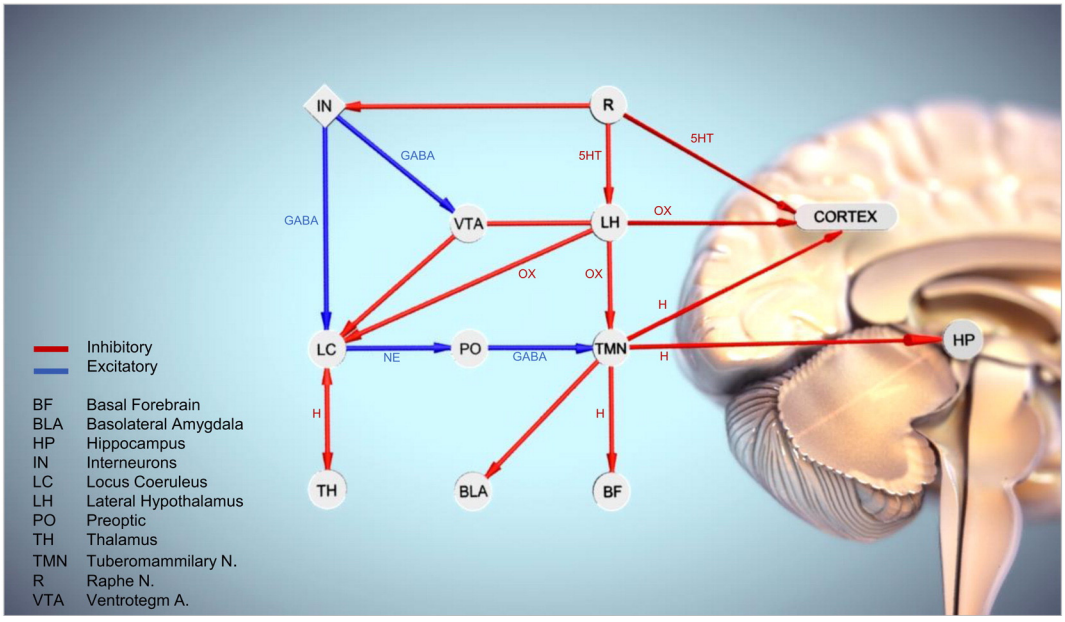

Fig. 5. Schematic diagram of the activation of the histaminergic system. See text for the details. BF, basal forebrain; TMN, tuberomammillary nucleus; LH, lateral hypothalamic area; TH, thalamus; LC, locus coeruleus; VTA, ventral tegmental area; R, raphe nuclei; VLPO, ventrolateral preoptic nucleus; PO, preoptic area; BLA, basolateral amygdala; IN, GABA-ergic interneurons. Neurotransmitters involved: H-histamine; OX, orexin; GABA, γ-aminobutyric acid, 5-HT, serotonin, 5-hydroxytryptamine; NE, norepinephrine (noradrenaline); DA, dopamine.

antagonism and 5-HT_{1A} receptor agonism. There is evidence that several clinically effective cognition-enhancing compounds induce an increase in the power of θ oscillations in rats (Hajos et al., 2008; Siok et al., 2006) while also increasing ACh and HA release (Hajos et al., 2008).

8. The orexins and cognition

The orexin system has been associated with numerous physiological functions. Li et al. reviewed the literature and proposed a hypothesis of how the orexin system orchestrates multifaceted physiological functions (Li et al., 2014). The role of the orexin system in cognition is mostly driven by its effects on the sleep/wake cycle (Yoshida et al., 2001), arousal (Chen et al., 2015), and reward (Song et al., 2005; Borgland et al., 2009). There is still no consistent conclusion about the role of orexins in learning and memory. While some studies indicate a positive role of the orexin system in avoidance (Jaeger et al., 2002), and water maze tests (Akbari et al., 2007), other studies showed the opposite or inconsistent results (Aou et al., 2003). Use of several orexin antagonists, such as 1-(2-methylbenzoxazol-6-yl)-3-(Adell, 2010; Sanchez et al., 2015) naphthyridin-4-yl urea (SB-334,867, OX_1 receptor antagonist) and almorexant, a dual antagonist of OX_1 and OX_2 receptors, also produced negative or inconsistent results in memory and learning tests (Dietrich and Jenck, 2010). Orexins may improve the attention and decision-making, since administration of orexin B has improved the performance of rats in the attention task (Lambe et al., 2005). It is also possible that the orexins play a role in the processes related to learning and memory because of their effect on arousal (Chen et al., 2015; Battleday and Brem, 2015; Redrobe et al., 2010).

9. Conclusion

All taken together, microdialysis studies in rats reveal that acute and subchronic vortioxetine significantly increases histamine level in cortical and hippocampal brain structures. Based on evidence from the literature we hypothesize that vortioxetine's effects on histamine may be mediated indirectly *via* a serotonergic modulation of the orexin system, and that increased histaminergic activity may contribute to the pro-cognitive effects observed in animal models.

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