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

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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.

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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).

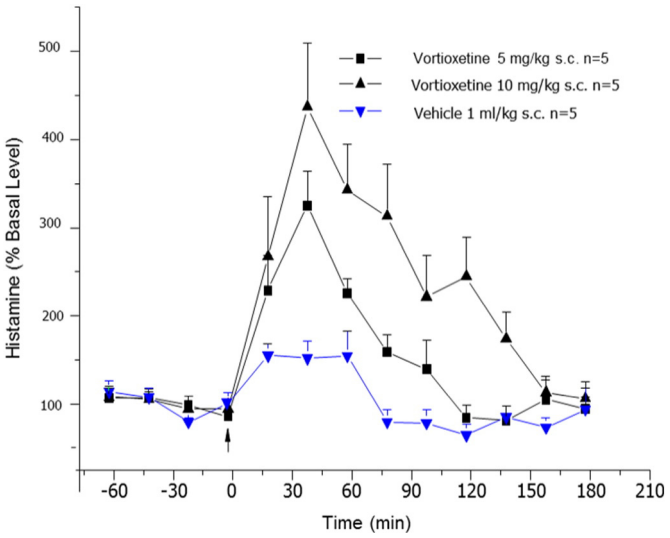

Fig. 1. Effects of subcutaneous administration of vortioxetine or vehicle control on extracellular histamine levels in mPFC (figure adapted from (Mork et al., 2013)). Data are expressed as mean ± SEM. Arrows indicate time of administration. There was a treatment and time-dependent increase in histamine 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.