Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): actions at serotonin receptors may enhance downstream release of four pro-cognitive neurotransmitters

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Take-Home Points

- Vortioxetine has a complex mechanism of action that includes not only inhibition of serotonin (5HT) transporters (SERT), but also direct actions at multiple 5HT receptor subtypes (5HT1A, 5HT1B, 5HT1D, 5HT3, and 5HT7 receptors).
- Vortioxetine has direct actions at 5HT1A and 5HT1B heteroreceptors that may explain in part how vortioxetine causes the downstream release of dopamine (DA), norepinephrine (NE), histamine (HA), and acetylcholine (ACh).
- Enhanced release of neurotransmitters in the prefrontal cortex and hippocampus could hypothetically help to explain vortioxetine’s antidepressant actions and unique procognitive properties in patients with major depression.

Vortioxetine is a “multimodal” agent that simultaneously acts at 6 pharmacologic targets with 3 modes of action (Figure 1):1–5:

1. Inhibition of the serotonin (5HT) transporter or SERT
2. Actions at several G-protein linked receptors (agonist actions at 5HT1A receptors, partial agonist actions at 5HT1B receptors, antagonist actions at 5HT1D and 5HT7 receptors)
3. Inhibition of a ligand-gated ion channel (the 5HT3 receptor)

We have previously described the mechanisms whereby vortioxetine’s actions at 5HT receptors work together to enhance the release of 5HT,2 glutamate,7 acetylcholine (ACh),8 and norepinephrine (NE)9 and to inhibit the release of GABA (gamma amino butyric acid).7 Here we discuss how the interaction of vortioxetine at populations of 5HT1A and 5HT1B receptors (Figure 1) may also hypothetically contribute to the release of ACh and NE and furthermore lead to release of dopamine (DA) and histamine (HA) in the prefrontal cortex (Figures 2 and 3). Enhanced release of neurotransmitters may theoretically “tune” malfunctioning brain circuits.6–11 Specifically, enhanced release of 5HT, NE, DA, ACh, and HA by vortioxetine could theoretically improve the efficiency of information processing in maladaptive brain circuits by facilitating long-term potentiation, synaptic plasticity, and enhanced pyramidal neuron activity leading to improvement not only of mood but also of cognitive symptoms in major depressive disorder.

Improving the Efficiency of Information Processing in Neuronal Networks by Enhancing the Release of Key Neurotransmitters

In this series of articles on the mechanism of action of vortioxetine, we have discussed how the many modes of action of this agent interact with multiple 5HT receptor subtypes localized at various critical nodes that connect 5HT neurons to a network of several other neurons.6–8
Actions of neurotransmitters, drugs, and psychiatric illnesses can be understood not only within “microcircuits”—eg, connections between a presynaptic 5HT neuron and a postsynaptic site—but also within “macrocircuits,” eg, where serotonergic neurons are part of a neuronal network that connects many neurons with each other. The sites where neurons connect with each other are also called the “nodes” of a neuronal network, and in the case of 5HT nodes, are linked by many different 5HT receptor subtypes. Not only does 5HT acting at these nodes regulate its own release, but it modulates the release of every major neurotransmitter. We have previously discussed the role of 5HT1A autoreceptors located in the midbrain raphe and on soma and dendrites of 5HT neurons. These receptors desensitize over time when either SSRIs or vortioxetine are given, leading to disinhibition of 5HT release. By contrast, when these same 5HT1A receptors are localized on postsynaptic sites, they do not seem to desensitize over time after the administration of SSRIs or vortioxetine, but they regulate the release of many other neurotransmitters.

5HT1A Postsynaptic Heteroreceptors in Prefrontal Cortex: Potential Modulation of DA, ACh, and NE Release

We have previously discussed the role of 5HT1A presynaptic autoreceptors located in the midbrain raphe and on soma and dendrites of 5HT neurons. These receptors desensitize over time when either SSRIs or vortioxetine are given, leading to disinhibition of 5HT release. By contrast, when these same 5HT1A receptors are localized on postsynaptic sites, they do not seem to desensitize over time after the administration of SSRIs or vortioxetine, but they regulate the release of many other neurotransmitters.

5HT1A postsynaptic receptors are inhibitory, so stimulating them either indirectly after SERT blockade by an SSRI or directly with a 5HT1A agonist such as vortioxetine will inhibit the firing of that neuron. We have already discussed how this specifically inhibits certain GABA interneurons regulating glutamate release. Here we discuss and illustrate the possible actions of 5HT at a different population of GABA neurons in prefrontal cortex, namely, those that possibly regulate the release of NE, DA, and ACh at their presynaptic nerve terminals (Figure 2A). GABA release is inhibited by 5HT1A input to these GABAergic interneurons, so when vortioxetine stimulates these 5HT1A receptors, this could potentially disinhibit the release of ACh, NE, and DA from their nerve terminals in the prefrontal cortex (Figure 2B).
Not shown because of the lack of data—but still a theoretical possibility—is the same regulatory system for histamine. Figures 2A and 2B are just hypothetical wiring diagrams that are consistent with the available data, but require much further investigation to confirm that this is how 5HT1A agonists actually increase ACh, NE, and DA release.

**5HT1B Postsynaptic Heteroreceptors in the Prefrontal Cortex: Potential Modulation of DA, ACh, NE, and HA Release**

We have also previously discussed the role of 5HT1B autoreceptors that are located on 5HT nerve terminals and inhibit 5HT release.6 When 5HT occupies these receptors, it inhibits further 5HT release from those 5HT nerve terminals.6,11,12 To the extent that vortioxetine blocks these 5HT1B receptors as a partial agonist or functional antagonist, the opposite effect occurs, namely enhanced 5HT release, as discussed previously.6 We have also previously discussed the possible role of 5HT1B heteroreceptors that may be localized on some GABAergic interneurons and may regulate GABA release.7

Here, however, we discuss and illustrate the actions of 5HT at a different 5HT1B receptor that is possibly localized directly upon the nerve terminals of neurons that release NE, DA, ACh, and HA (Figure 3A).12,24,25 Although the microanatomy is still being worked out, blockade of postsynaptic 5HT1B heteroreceptors on presynaptic nerve terminals could theoretically be another mechanism whereby ACh, NE, DA, and HA release is enhanced by vortioxetine (Figure 3B).8,10 This is somewhat speculative and is not yet a proven mechanism for regulating the release of these neurotransmitters, but is consistent with the known effects of vortioxetine enhancing the release of ACh, NE, DA, and HA. Few if any other agent has the broad neurotransmitter-releasing properties of vortioxetine, and a full explanation of the mechanism of this release will require a more complete clarification of the various
Psychopharmacologic agents such as vortioxetine that can change the release of many neurotransmitters and in more than one site (ie, multiple modes of action at multiple nodes within brain networks) theoretically have the possibility to change multiple symptoms linked to multiple circuits.\textsuperscript{9,10} Thus, it is possible that such actions of vortioxetine can explain not only its antidepressant actions,\textsuperscript{4} but also its unique procognitive actions in patients with major depression.\textsuperscript{27–29}

**References:**


7. Stahl SM. Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): modifying serotonin’s downstream effects on glutamate and GABA (gamma-aminobutyric acid) release by blocking 5HT3 and 5HT7 receptors. CNS Spectr. In press.


14. Assié MB, Lomentach H, Ravailhe V, Fauconil V, Newman-Tancredi A. Rapid desensitization of somatodendritic 5HT1A circuits involving 5HT receptors and other neurotransmitter systems. For example, some evidence suggests that stimulation of 5HT4 receptors may be in part responsible for 5HT’s regulation of HA and ACH release.\textsuperscript{26} For now, mechanisms such as the one illustrated in Figure 3B remain only theories as to how vortioxetine could potentially disinhibit the release of DA, NE, HA, and ACH in the prefrontal cortex and hippocampus.

**Clinical Implications**

Abnormal connectivity of brain circuits is theorized to cause symptoms of psychiatric disorders such as depression, and psychotropic drugs hypothetically reduce these symptoms by changing this connectivity, thus improving the efficiency of information processing in specific brain circuits.\textsuperscript{9,10} Since there are numerous symptoms in major depression, including both emotional symptoms and cognitive symptoms, it is likely that there are numerous networks with altered connectivity involved in major depression.\textsuperscript{9,10}