



Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): modifying serotonin's downstream effects on glutamate and GABA (gamma amino butyric acid) release

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ISSUE:

Vortioxetine is an antidepressant with multiple pharmacologic modes of action at targets where serotonin neurons connect with other neurons. These actions modify the release of both glutamate and GABA (gamma amino butyric acid) within various brain circuits.

Take-Home Points

- Like most known antidepressants, vortioxetine inhibits the serotonin (5HT) transporter (SERT).
- Unlike most known antidepressants, vortioxetine targets numerous additional 5HT receptors: 5HT1A, 5HT1B, 5HT1D, 5HT3, and 5HT7 receptors.
- These additional pharmacologic actions not only enhance the release of 5HT compared to blocking SERT alone, but also modify the release of numerous additional neurotransmitters.
- Specifically, vortioxetine's pharmacologic actions on 5HT receptors—unique compared to any other antidepressant—enhance the release of glutamate and inhibit the release of GABA (gamma amino butyric acid) from downstream neurons in various brain circuits such as the prefrontal cortex and hippocampus.

Vortioxetine is a “multimodal” agent that simultaneously acts at 6 pharmacologic targets with 3 modes of action (Figure 1)¹⁻⁴:

1. Inhibition of the serotonin 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)

Although vortioxetine has a complex pharmacologic mechanism of action, the combined effects of all actions can be conceptualized more simply by how they alter the downstream release of numerous neurotransmitters. We have previously described the mechanisms whereby vortioxetine's actions at 5HT receptors work together to enhance the release of 5HT.⁵ Here we describe how vortioxetine alters the downstream release of both glutamate and GABA from the prefrontal cortex and hippocampus. An explanation of vortioxetine's actions that enhance the release of dopamine, norepinephrine, acetylcholine, and histamine are discussed in other Brainstorms articles.^{6,7}

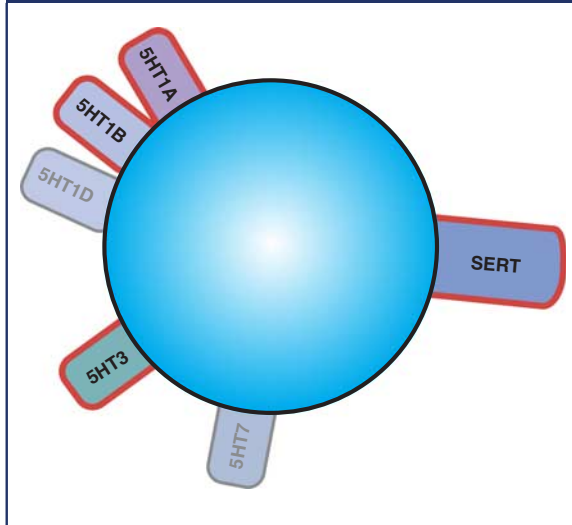
Modes and Nodes

Actions of neurotransmitters, drugs, and psychiatric illnesses can all be understood not only within a “microcircuit”—eg, a connection 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.⁵⁻⁹ The sites where neurons connect



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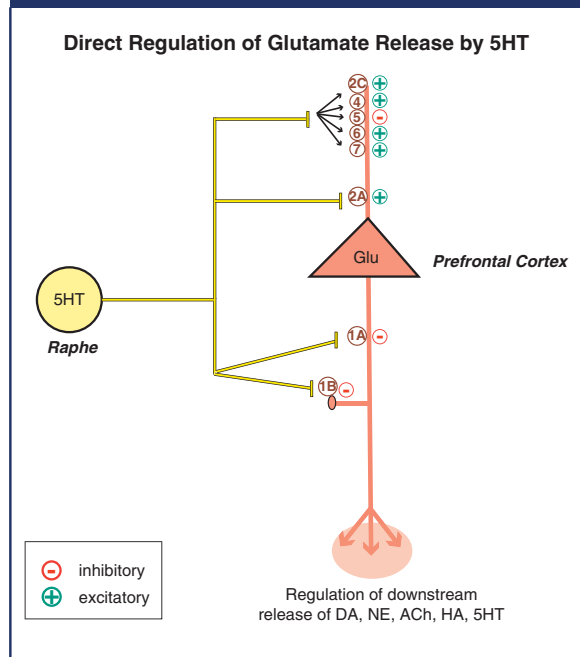
Figure 1. Icon of vortioxetine showing its 6 pharmacologic mechanisms. Highlighted here are the 4 actions principally linked to its hypothesized enhancement of glutamate release. Increased firing of pyramidal neurons of the prefrontal cortex and hippocampus hypothetically arises from the combination of SERT inhibition, 5HT1A agonism, 5HT1B partial agonism, and 5HT3 antagonism.



with each other are also called the “nodes” of a neuronal network.^{8,9} Two important sets of nodes that are uniquely distributed in various brain regions include the connections that 5HT neurons make with glutamate and GABA neurons^{10–14} (Figures 2 and 3). These connections allow 5HT to regulate downstream release of glutamate and GABA, with both direct effects on glutamatergic pyramidal neuron firing (Figure 2) and indirect effects on pyramidal neuron firing via modulating GABA neurotransmission of inhibitory cortical interneurons (Figure 3).^{10–14}

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.^{10,15,16} Since there are numerous symptoms in any given psychiatric condition, it is likely that there are numerous networks with altered connectivity involved in every psychiatric disorder.^{15,16} Psychopharmacologic agents that can change more than one neurotransmitter’s release 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.^{4–7,15,16} Thus, it is useful to understand the net effect of the multiple simultaneous actions of

Figure 2. Direct regulation of glutamate release in the prefrontal cortex and hippocampus by 5HT. This figure shows how glutamate release is regulated directly by 5HT actions on pyramidal neurons. Release of 5HT at apical dendrites of pyramidal neurons can be either excitatory at 5HT2C, 5HT4, 5HT6, or 5HT7 receptors or inhibitory at 5HT5 receptors (shown at the top of the figure). A key excitatory 5HT receptor is also the 5HT2A receptor. A key inhibitory 5HT receptor is the 5HT1A receptor. The net actions of 5HT at all these sites regulate the final common pathway of glutamate release (shown at the bottom of the figure), which in turn regulates downstream release of numerous neurotransmitters including DA, NE, ACh, HA, and 5HT.



vortioxetine on downstream release of both glutamate and GABA in order to gain insight into its pharmacologic mechanism of therapeutic action in improving mood, cognition, and other symptoms of major depressive disorder.

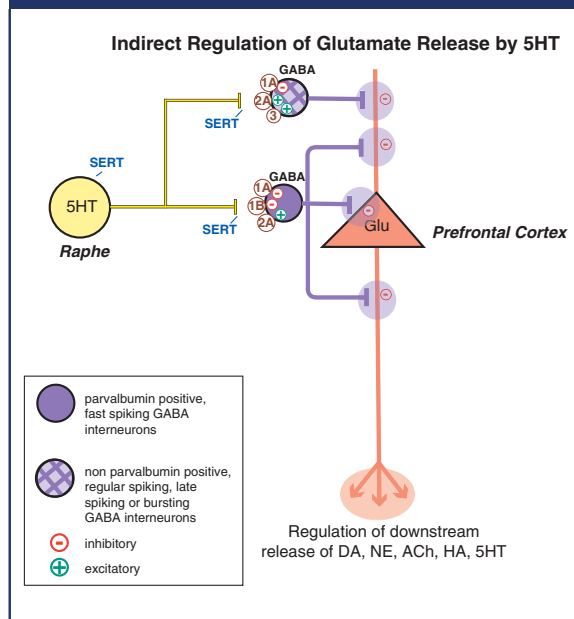
5HT Neuronal Connections to Glutamate and GABA Neurons in the Prefrontal Cortex and Hippocampus

5HT neurons project widely throughout the brain and notably to the prefrontal cortex and hippocampus and interact there with many glutamate and GABA neurons.^{10–14} The prefrontal cortex and hippocampus are hypothesized to be the sites of critical nodes within malfunctioning brain circuits responsible for various symptoms of major depressive disorder, from cognitive



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Figure 3. Indirect regulation of glutamate release in the prefrontal cortex and hippocampus by 5HT acting via GABA interneurons. This figure shows how glutamate release from pyramidal neurons is regulated indirectly by 5HT acting through two types of interneurons. At the top is shown a GABA interneuron that does not stain for parvalbumin, and is regular spiking, late spiking, or bursting in its firing pattern. Release of 5HT at this population of GABA neurons can both inhibit them via 5HT1A receptors, or excite them via either 5HT2A or 5HT3 receptors. Below the first GABA neuron is another class of GABA interneuron that does stain for parvalbumin and is fast spiking in firing pattern. The 5HT receptors that are populated on this second type of GABA interneuron include inhibitory 5HT1A receptors, inhibitory 5HT1B receptors, and excitatory 5HT2A receptors. When GABA is released after stimulation of any excitatory 5HT receptor, glutamate release is inhibited. When GABA release is blocked by 5HT acting at any inhibitory 5HT receptor, glutamate release is disinhibited (ie, enhanced). The net actions of 5HT at all these sites regulate the final common pathway of glutamate release (shown at the bottom of the figure), which in turn regulates downstream release of numerous neurotransmitters including DA, NE, ACh, HA, and 5HT.



inhibitory actions of the neuronal network of the prefrontal cortex.

Specifically, 5HT neurons act directly at glutamate pyramidal neurons and can be both excitatory (eg, at 5HT2A, 5HT2C, 5HT4, 5HT6, and 5HT7 receptors)^{19–37} and inhibitory (at 5HT1A, 5HT5, and possibly postsynaptic 5HT1B heteroreceptors)^{32–37} (Figure 2). Additional control of glutamate output from pyramidal neurons is provided by multiple 5HT receptor actions on inhibitory GABAergic interneurons^{19–37} (Figure 3). One major population of GABAergic interneurons is “fast spiking” and contains inhibitory 5HT1A receptors, and excitatory 5HT2A and 5HT3 receptors^{19–37} (Figure 3). These so-called “basket” and “chandelier” interneurons stain for the calcium binding protein parvalbumin and each innervate 200–1000 pyramidal cells. Basket cells comprise about half of non-pyramidal cells in the cortex.^{10–14,18} A second major population of GABAergic interneurons stains for different neurochemical markers (eg, calbindin, calretinin, cholecystokinin, vasoactive intestinal peptide, somatostatin, and/or neuropeptide Y) and fire with electrical activity that is regular spiking, late spiking, or bursting in character^{10–14,18} (Figure 3). They contain inhibitory postsynaptic 5HT1A and possibly inhibitory postsynaptic 5HT1B heteroreceptors, as well as excitatory 5HT2A receptors^{19–37} (Figure 3).

With so many ways to stimulate and to inhibit the glutamate neuron, and with some 5HT receptors doing the opposite thing to glutamate release indirectly via GABA neurons that they do to glutamate release directly upon pyramidal neurons, the question arises as to which action of 5HT upon glutamate release will prevail at any one time. Analysis of the neuronal macrocircuitry (Figures 2 and 3) suggests that 5HT can induce mixed effects both upon glutamate (Figure 2) and GABA (Figure 3) in the prefrontal cortex and hippocampus.^{19–37} The net effects of 5HT upon glutamate will therefore depend upon the regional and cellular expression patterns of 5HT receptor subtypes, the density of 5HT receptors, and the local concentration of 5HT. 5HT affinity is different for its various receptors, eg, 2- to 6-fold higher for 5HT1A receptors over 5HT2A receptors and even higher over 5HT3 receptors.^{18–20,38–45} Thus, low 5HT concentrations in a given location within a neuronal network will skew the effects of 5HT release there more heavily toward inhibition from 5HT1A receptors, with excitation mediated by 5HT2A and 5HT3 receptors becoming more prominent as 5HT concentrations increase. 5HT seems to be well positioned to act as a neuromodulator whose function could be to maintain homeostasis in the

functions such as learning, working memory, attention, and behavioral flexibility, to mood and other emotions.^{15–17} 5HT neurons terminate both directly upon glutamatergic pyramidal neurons (Figure 2) and indirectly upon GABAergic inhibitory interneurons that in turn terminate upon pyramidal neurons (Figure 3).^{10–14,18} What results is an elegant array of excitatory and



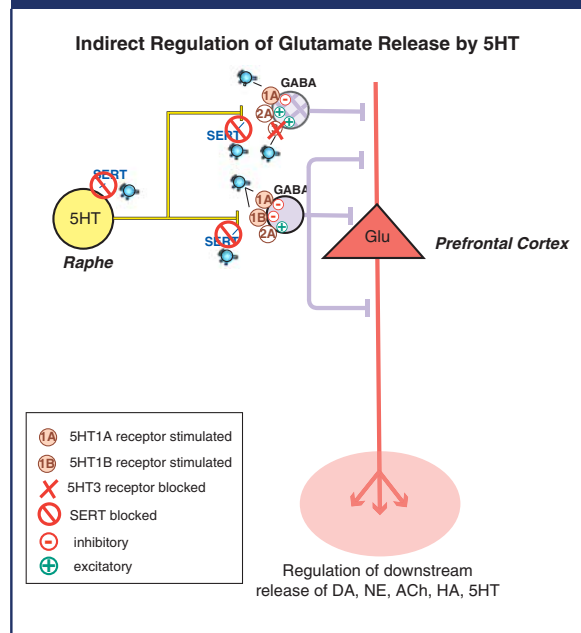
brain, fine-tuning the glutamate in prefrontal cortical networks up or down as needed and thus acting as a “buffer” to “normalize” output of pyramidal neurons. In other words, keeping glutamatergic pyramidal neurons “in tune” (neither too quiet nor too excited) could be the task of 5HT acting in a coordinated manner at all of its receptors.

Effects of Antidepressants on Glutamate Release and Neuronal Firing of Pyramidal Neurons in Prefrontal Cortex and Hippocampus

Antidepressants that block 5HT reuptake (serotonin transporter or SERT inhibitors) such as SSRIs (selective serotonin reuptake inhibitors) increase 5HT concentrations everywhere there are 5HT nerve terminals. 5HT release is mitigated by 5HT’s stimulation of inhibitory 5HT autoreceptors on 5HT neurons as discussed in an earlier article.^{5,17} The net effect of *acute* elevations of 5HT upon glutamate release by SSRIs would therefore appear to be mixed, with both excitatory and inhibitory effects that largely cancel themselves out.^{46,47} Studies of *long-term* administration of SSRIs in animals, however, suggest a *reduction* of pyramidal neuron activity, and thus of glutamate release, possibly due to the pattern of desensitization of some serotonin receptor systems.^{46,47} In disease states such as depression with hypothetically dysregulated circuits of emotions and cognition, therapeutic actions of antidepressants may require instead *enhanced* pyramidal neuron firing in the prefrontal cortex or hippocampus in order to change the connectivity of one brain region to another and to rebalance the information processing of a neuronal network. For example, the actions of the novel rapid-acting antidepressant ketamine on mood are associated with increased downstream glutamate release.^{48–50} Also, enhanced neuronal output from pyramidal neurons promotes glutamate dependent neuronal plasticity and long-term potentiation, key components of cognition and memory, and possibly necessary actions to improve cognitive symptoms of depression.^{51–53}

Although long-term studies have not been reported, vortioxetine—in contrast to SSRIs—acutely *enhances* firing of pyramidal neurons,⁵⁴ presumably due to its additional receptor actions combined with SERT inhibition (Figure 4). Potent antagonism of vortioxetine at 5HT3 receptors may be the most relevant action in this regard, as this removes an important source of 5HT-mediated inhibition from a population of GABA interneurons, thus disinhibiting pyramidal neurons (Figures 3 and 4).⁵⁴ 5HT1A agonism by vortioxetine

Figure 4. Vortioxetine enhances glutamate release. Not only does vortioxetine block SERTs the same as SSRIs, but it also has numerous direct receptor actions that diminish GABA inhibition at both populations of GABA interneurons. At the top, agonist actions at 5HT1A receptors inhibit GABA release; also, antagonist actions at 5HT3 receptors inhibit GABA release. At the second GABA neuron below, agonist actions at 5HT1A receptors and possibly partial agonist actions at 5HT1B receptors inhibit GABA release from this interneuron. Combining what happens at both GABA neurons, glutamate release downstream is disinhibited. Perhaps the most robust of these actions is the blockade of 5HT3 receptors. When glutamate release is enhanced, it can lead to the enhanced downstream release of numerous neurotransmitters including DA, NE, ACh, HA, and 5HT.



inhibits both major subpopulations of GABA interneurons, further disinhibiting pyramidal neurons (Figures 3 and 4). Partial agonist actions of vortioxetine at presynaptic 5HT1B inhibitory autoreceptors on 5HT neurons should lead to greater 5HT release, and partial agonist actions at 5HT1B inhibitory postsynaptic heteroreceptors on glutamatergic cortical nerve terminals may directly enhance glutamate release (Figure 2).^{55,56} Weaker actions of vortioxetine at 5HT7 receptors and the relative lack of 5HT1D receptors in prefrontal cortex make vortioxetine’s actions at these receptors in cortical and hippocampal networks unclear. The result of all receptor actions of vortioxetine can hypothetically explain why glutamate output is



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increased (Figure 4). These actions can potentially explain why there is a differential effect of vortioxetine compared to SSRIs in the hippocampus and prefrontal cortex, presumably due to multiple actions at 5HT receptors, compared to SERT inhibitors such as SSRIs that stimulate every 5HT receptor in every site.

Summary

In summary, vortioxetine enhances the output of glutamatergic pyramidal neurons and reduces the output of GABAergic interneurons in the prefrontal cortex and hippocampus. Blockade of 5HT₃ receptors and SERTs while stimulating 5HT_{1A} receptors and (partially) 5HT_{1B} receptors at nodes within neural networks where 5HT neurons connect with glutamate and GABA neurons may account for these changes in neuronal activity. Improving information processing within neuronal networks could hypothetically result from these receptor actions and be the mechanism that leads to improvement in the symptoms of depression by vortioxetine. Enhanced release of glutamate from increased pyramidal neuron activity, which is unique for vortioxetine compared to SSRIs, could also enhance long-term potentiation, neuronal plasticity, and memory formation and could potentially explain not only the antidepressant/mood actions of vortioxetine but also its unique procognitive actions compared with other antidepressants.

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