The Augmentation Hypothesis for Improvement of Antidepressant Therapy

Is Pindolol a Suitable Candidate for Testing the Ability of 5HT₁₅ Receptor Antagonists to Enhance SSRI Efficacy and Onset Latency?

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Abstract

The development of selective serotonin reuptake inhibitors (SSRIs) provided a major advancement in the treatment of depression. However, these drugs suffer from a variety of drawbacks, most notably a delay in the onset of efficacy. One hypothesis suggests that this delay in efficacy is due to a paradoxical decrease in serotonergic (5-HT) neuronal impulse flow and release, following activation of inhibitory presynaptic 5-HT₁₅ autoreceptors, following acute administration of SSRIs. According to the hypothesis, efficacy is seen only when this impulse flow is restored following desensitization of 5-HT₁₅ autoreceptors and coincident increases in postsynaptic 5-HT levels are achieved. Clinical proof of this principal has been suggested in studies that found a significant augmenting effect when the β-adrenergic/5-HT₁₅ receptor antagonist, pindolol, was coadministered with SSRI treatment. In this article, we review preclinical electrophysiological and microdialysis studies that have examined this desensitization hypothesis. We further discuss clinical studies that utilized pindolol as a test of this hypothesis in depressed patients and examine preclinical studies that challenge the notion that the beneficial effect of pindolol is due to functional antagonism of the 5-HT₁₅ autoreceptors.

Index Entries: 5-HT₁₅ receptor; serotonin; depression; dorsal raphe nucleus; pindolol; fluoxetine; WAY-100635.

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Introduction

Selective Serotonin Reuptake Inhibitors (SSRIs)

Antidepressant therapy, the treatment of major depression by pharmaceutical agents with demonstrated antidepressant activity, has been a feature of psychiatric treatment regimens since the 1950s. In the last 15 years, however, the field has been revolutionized by the introduction of the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, sertraline, and citalopram (for review, see 1). These compounds are rationally designed molecules that rely upon data implicating serotonin (5-HT), and possibly other monoamine neurotransmitters, in the etiology and treatment of depression, and modulation of 5-HT in its treatment. The logic is straightforward; 5-HT release and reception at central sites appears to be involved in affect, and may be significantly suppressed in many depressed patients. Several earlier treatment directions had a serotonergic component, so a general hypothesis emerged that enhancement of some or all aspects of 5-HT-mediated neurotransmission may be beneficial with respect to antidepressant therapy (2). Because at the time of the development of SSRIs (and to the present for the most part), the specific postsynaptic 5-HT receptors mediating these effects had not been unequivocally identified, or specific agonists had not been discovered for receptors believed to be involved, inhibition of 5-HT reuptake provided a mechanism whereby serotonergic transmission could be effectively enhanced at all targets for this important neurotransmitter. Inhibition of 5-HT reuptake results in a longer synaptic dwell time for the 5-HT released by serotonergic neurons, effectively increasing the amount and duration of 5-HT available for interaction with 5-HT receptors.

The success of these compounds underscores both the importance of 5-HT in depression and the enormous benefit of rational drug design; these compounds are arguably the most successful psychiatric drug therapies to date. Nevertheless, they are fraught with side-effects (notably sleep disturbances and sexual dysfunction), they have an apparent significant delay in the onset of therapeutic benefit, and there are significant numbers of patients that are refractory to SSRI treatment (3,4). The desire to improve upon the speed of therapeutic onset and to increase the proportion of patient response prompted the search for a hypothesis to explain the drawbacks of SSRI monotherapy and ultimately a mechanism for improvement.

Presynaptic 5-HT$_{1A}$ Receptor-Mediated Inhibition of 5-HT Release and Delayed Onset of SSRI Action

Serotonin neurons are largely localized within a small number of nuclei in the brainstem, notably the dorsal raphe nucleus (DRN). A prominent feature of their physiology is the presence of 5-HT autoreceptors that contribute to a feedback inhibitory loop for the regulation of this transmitter’s release (5). In the 1990s, several groups proposed that the initial period of SSRI treatment could be ineffective due to 5-HT autoreceptor activation in the presence of the drug, which could significantly reduce any potential immediate benefit of the SSRI by reducing impulse propagation of 5-HT neurons. The delay in drug action could reflect a desensitization of these receptors in the continued presence of elevated 5-HT at the autoreceptor (see 6). Some data indicating that this desensitization occurs with prolonged SSRI treatment has been presented (see below). This suggested that a more rapid onset of action, and perhaps a greater proportion of responders, could result from the combination of a 5-HT$_{1A}$ autoreceptor antagonist with an SSRI, negating the need for autoreceptor desensitization. Of course if postsynaptic 5-HT$_{1A}$ receptors are also important for anti-depressant response, one must postulate that they are unaffected or sensitized by chronic SSRI treatment or any benefit of autoreceptor desensitization would be offset by desensitization of receptors participating in SSRI response.