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Delayed Antidepressant Efficacy and the Desensitization Hypothesis

Kathryn G. Commons*, **Sofia E. Linnros**

Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Boston, Massachusetts 02115, United States

Department of Anesthesia, Harvard Medical School, Boston, Massachusetts 02115, United States

Abstract

Many conventional antidepressants can quickly raise the levels of extracellular serotonin, yet their positive effects on mood ensues only weeks later. This delay in efficacy is a clinical problem that has proven difficult to overcome. Early investigation noted that the initial increases in extracellular serotonin engaged strong feedback inhibition of serotonin neurons via 5-HT_{1A} autoreceptors, resulting in a profound reduction in their firing rate. Over the course of chronic treatment, however, firing rate returned to normal and the inhibition via 5-HT_{1A} receptor agonists was attenuated. The coincident timeline of these phenomena led to the influential hypothesis that the relationship was causal and that gradual loss of feedback inhibition mediated by 5-HT_{1A} receptors was critical to the delayed therapeutic onset. Simple and appealing, the desensitization hypothesis has taken strong hold, yet much of the supporting evidence is circumstantial and there are several observations that would refute a causal relationship. In particular, even though 5-HT_{1A} receptors may desensitize, there is evidence that feedback inhibition mediated by remaining receptors persists. That is, baseline serotonin firing rate returns to normal not because of 5-HT_{1A} desensitization but rather despite ongoing feedback inhibition. Thus, while 5-HT_{1A} receptors remain important for emotional behavior, it may be other slow-adaptive changes triggered by antidepressants that allow for therapeutic effects, such as those involving glutamatergic synaptic plasticity.

Graphical Abstract

*Corresponding Author: kathryn.commons@childrens.harvard.edu. Mailing address: 300 Longwood Ave, Boston, MA 02115. Phone: 617-919-2220.

Author Contributions

S.E.L. wrote the first draft. K.G.C. modified and extended the manuscript to its final form.

Notes

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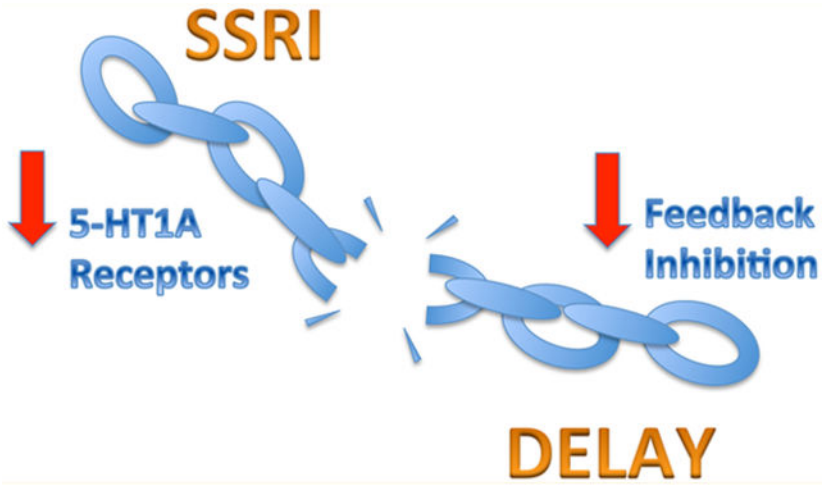

Keywords

Serotonin; glutamate; feedback; depression; fluoxetine; antidepressants

Serotonin-selective and serotonin-nonselective reuptake inhibitors (SSRIs and SNRIs) are widely prescribed classes of antidepressants that exert their pharmacological action entirely or in part by blocking the serotonin transporter (SERT). The simplistic idea is that blocking SERT would increase the concentration of extracellular serotonin, theoretically enhancing its signaling capacity.[1,2] The ability of SSRIs and SNRIs to increase extracellular serotonin is rapid, within hours.[3] However, the clinical efficacy of these drugs is only obtained with chronic use, typically several weeks, which is a major disadvantage and a problem that has proven difficult to overcome.[4]

The 5-HT_{1A} receptor has been centrally implicated in contributing to the delayed efficacy of antidepressants. 5-HT_{1A} receptors are inhibitory and are richly expressed by serotonin neurons themselves, and thus, they play an important role in providing feedback inhibition of serotonin neurons. Since antidepressants elevate synaptic serotonin levels, they also lead to activation of 5-HT_{1A} autoreceptor-driven feedback inhibition of serotonin neurons, causing a decrease in serotonin neuron firing and serotonin release.[4–7] With chronic SSRI administration, the serotonin neuron firing rate recovers and at the same time there is desensitization of 5-HT_{1A} autoreceptors.[5–9] An appealing hypothesis is that the desensitization of 5-HT_{1A} autoreceptors and subsequent loss of feedback inhibition is causal in the restoration of serotonin neuron firing and this process in turn accounts for the delay in clinical efficacy.[5,10–12]

The attractive simplicity of this hypothesis has resulted in its widespread acceptance, perhaps to a greater degree than may have been originally anticipated. It should be pointed out that there are a number of implicit causative relationships involved in this hypothesis that are supported by only suggestive evidence such as coincident time-lines. For example, while it is well established that there is a slow recovery of baseline firing rate and desensitization of 5-HT_{1A} receptors, the precise contribution of each of these in delayed efficacy is not

clear. In addition, there is no direct evidence that reduced feedback inhibition directly *causes* the recovery of baseline firing-rate. That is, there is no reason to assume either that feedback inhibition has a linear relationship to the sensitization-state of 5-HT_{1A} receptors, or that feedback inhibition via 5-HT_{1A} receptors is the sole regulator of serotonin neuron firing rate.

With respect to feedback inhibition and 5-HT_{1A} receptor desensitization, recent evidence has provided new insight into how these are related over the time-course of antidepressant exposure. To understand this relationship, it is worth emphasizing how each of these factors, desensitization and feedback inhibition, are measured. Sensitization state is determined by the number of receptors and their capacity to signal, for example their capacity to activate second messengers or inhibit neuronal firing. Studies determining these end points use receptor agonists to measure receptors in isolation from their endogenous ligand. In contrast, the level of feedback inhibition relates to the endogenous function of the receptor, which is both a consequence of the receptor itself and the availability of its ligand as it is physiologically released. In order to probe receptor-ligand interactions, antagonists are used, compounds that disrupt the relationship between the receptor and its endogenous ligand. A few receptors in the presence of overwhelming ligand may have the same functional effect as many receptors activated by scant ligand. In addition, serotonin released during behavior may have unique local concentrations and kinetics that could regulate receptors in ways that are not mimicked by an agonist, or for that matter by nonphysiological neuronal activation. Thus, there is a fundamental difference between agonist-based studies that investigate receptors and antagonist-based studies that investigate receptor-ligand interactions. Pointedly one may not predict the other.

Many agonist-based studies provide convincing evidence for 5-HT_{1A} desensitization after chronic exposure to high levels of extracellular serotonin. For example, repeated administration of the SSRI fluoxetine decreases the sensitivity of dorsal raphe serotonin neurons to 5-HT_{1A} agonists as measured with single cell electrophysiology.[6,7,13,14] Fluoxetine treatment attenuates the ability of 5-HT_{1A} agonists to decrease in forebrain serotonin release measured by microdialysis.[8,15–17] In addition, fluoxetine treatment attenuates 5-HT_{1A} autoreceptor-stimulated second messenger activation in the dorsal raphe.[9,18–20] Many of these same effects have been observed in a model of life-long elevated extracellular serotonin where mice lack functional SERT, SERT-knockouts (KOs).[21,22]

Inhibition can be difficult to measure because the output can be silent. However, when inhibition is blocked an output of disinhibition can be measured. By disrupting receptor-ligand interactions with a 5-HT_{1A} antagonist, typically WAY-100635, feedback inhibition can be blocked and levels of disinhibition studied. In normal mice and rats, the effects of WAY-100635 on most end points can be subtle or difficult to detect, suggesting a modest function of 5-HT_{1A} receptors under normal conditions. However, in the SERT-KO, WAY-100635 has robust effects. For example, WAY-100635 strongly increases single unit activity recorded in the dorsal raphe nucleus in the SERT-KO indicating that WAY-100635 is disinhibiting raphe neurons by blocking 5-HT_{1A} receptor-dependent feedback inhibition.[23] Also in the SERT-KO mouse, pharmacologic evidence caused Fox and colleagues to propose the existence of maintained 5-HT_{1A}-mediated feedback inhibition.[24]

Also using the SERT-KO our lab found evidence for presence of 5-HT_{1A} dependent feedback inhibition using a slightly different approach. We studied the ability of WAY-100635 to disinhibit serotonin neurons as measured by expression of the immediate early gene product Fos, a marker of cellular activation. That is, we measured the appearance of Fos within serotonin neurons after feedback inhibition was blocked by WAY-1000635. In the SERT-KO WAY-100635 treatment caused a massive increase of Fos expression in serotonin neurons, more than in any other paradigm studied.[25]

In contrast to modest effects in normal rodents, WAY-100635 also had substantial behavioral effects in the SERT-KO acting like an antidepressant in the forced swim test.[25] Thus, 5-HT_{1A} mediated feedback inhibition appears functional despite the desensitization of 5-HT_{1A} receptors in this mouse model.

Feedback inhibition mediated by 5-HT_{1A} receptors has more than one mechanism.[26] Serotonin neurons themselves express high levels of 5-HT_{1A} receptors, referred to as autoreceptors. However, 5-HT_{1A} receptors are also present in forebrain areas where they can activate multisynaptic feedback inhibition of serotonin neurons. Thus, when WAY-100635 is administered systemically, as in many of the preceding studies, action at 5-HT_{1A} autoreceptors is very likely, but indirect mechanisms are possible. Worth noting is that there is additional evidence that 5-HT_{1A} autoreceptors specifically continue to provide feedback inhibition in the SERT-KO. That is, Araragi and colleagues[27] using electrophysiological approaches found evidence for desensitization in a reduced response of raphe neurons to a 5-HT_{1A} agonists, but they also found continued 5-HT_{1A} autoreceptor-mediated inhibition of serotonin neurons. They concluded that the magnitude of desensitization of 5-HT_{1A} autoreceptors does not necessarily translate to the degree of inhibition these receptors exert over serotonin raphe neurons.[27]

SERT-KO mice are an extreme model for studying the effects of elevated extracellular serotonin and thus may not be representative of chronic SSRI treatment. Two weeks of fluoxetine treatment in rats may be a model of greater face validity. That is, with initial treatment of fluoxetine, firing rate of serotonin neurons is depressed, but after a few weeks of treatment this baseline rate returns to normal. Using an experimental protocol for extended fluoxetine treatment where others had found that firing rate normalized,[6] we found that WAY-100635 still caused a profound increase in Fos expression in serotonin neurons.[28] Thus, the pharmacological treatment over weeks mimicked the effects seen after life-long increases in extracellular serotonin indicating that feedback inhibition persists in both models of sustained extracellular serotonin. This finding is consistent with others; for example, Arborelius and colleagues found that a 5-HT_{1A} antagonist disinhibited raphe neurons after chronic exposure to citalopram.[29]

These observations would suggest that the desensitization of 5-HT_{1A} autoreceptors and restoration of baseline firing rate of serotonin neurons are coincidental, not causative. That is, it is a mistaken idea that loss of feedback inhibition causes restoration of baseline firing because feedback inhibition remains functional. This suggests that there are compensatory changes occurring in parallel that over-ride feedback inhibition to restore baseline-firing rate. The continued presence of feedback inhibition is perhaps not a complete surprise as it

is long been known that 5-HT_{1A} autoreceptor desensitization is only partial and reflects a shift in the dose-response curve that can be overcome with increasing agonist concentration.[6] Indeed, ultrastructural studies have found that 5-HT_{1A} autoreceptors continue to have presence on the plasma membrane of neurons within the raphe nucleus after sustained antidepressant treatment although their trafficking in response to agonist treatment is altered.[30]

Since the desensitization hypothesis was proposed there's been a considerable increase in the understanding of mechanisms that can take part in homeostatic plasticity that may underlie the return of baseline firing rate, and there are many.[31] That is, 5-HT_{1A} receptors do not change within a static background, rather there are a host of cellular changes, both within individual serotonin neurons and their networks, that could contribute to the restoration of baseline firing rate. Chronic exposure to SSRIs can induce changes in expression of trophic factors, intracellular signal pathways, excitability, microcircuitry and neurogenesis.[32–36] The observation that the most promising fast-acting antidepressant candidates interact with glutamate neurotransmission[37] raises the possibility that slowly induced plasticity in glutamatergic synapses produced by SSRIs could contribute to therapeutic efficacy. Serotonin neurons in the dorsal raphe nucleus innervate, and receive return glutamatergic innervation from cortical areas implicated in depression.[38] In addition, extended but not acute exposure to citalopram leads to an increase in strength of glutamatergic synapses onto serotonin neurons, an adaptation that could hypothetically override continuing feedback inhibition.[36] Thus, a tenable hypothesis is that restoration of baseline firing rate is caused by increased glutamatergic excitation of serotonin neurons, which could superseed ongoing feedback inhibition.

It is important not to discount the potential importance of 5-HT_{1A} receptor-dependent feedback inhibition and 5-HT_{1A} receptors as a therapeutic target. For example, it remains possible that feedback inhibition of serotonin neurons contributes to poor treatment response. This would be consistent with the results of one of the most careful genetic studies on the topic. Richardson-Jones and colleagues tested the effect of selective knockdown of 5-HT_{1A} autoreceptors on behavior in mice.[39] They found that mice with initially low levels of 5-HT_{1A} autoreceptors responded well to fluoxetine. However, the eventual desensitization of 5-HT_{1A} receptors did not predict treatment response. Thus, mice with higher levels of initial expression remained refractive to treatment even after desensitization occurred. Only the state of 5-HT_{1A} receptors before treatment with fluoxetine started was important, not the extent of desensitization.

The insight that receptor sensitization state and feedback inhibition do not have a linear relationship may be relevant to understanding additional observations in the literature. In particular, desensitization of 5-HT_{1A} receptors has been also reported as a consequence of depression alone, both in humans and in animal models, an observation hard to reconcile with the desensitization hypothesis. For example depressed patients have been reported to have blunted hormonal response to administration of the 5-HT_{1A} receptor agonist ipsapirone, suggesting reduced hypothalamic receptor sensitivity.[40–42] In addition, some studies have reported reduced 5-HT_{1A} receptor binding potential in the dorsal raphe for individuals with unipolar and bipolar depressive disorder.[42,43] Likewise, in several rodent

models, including rat inescapable shock model,[44] chronic mild stress model,[45–48] chronic sleep restriction,[49] and maternal separation,[50] evidence for desensitization of 5-HT_{1A} receptors has been reported. In addition, chronic fluoxetine treatment caused a greater level of desensitization in a chronic-corticosterone treatment model of depression than in control mice.[51] This desensitization provides a unique insight into the adaptive changes of serotonin neurons and may be functionally important, but it might not intuitively predict the state of feedback inhibition or serotonin neuron function.

We investigated how feedback inhibition functions in a model relevant to depression and as a consequence of chronic fluoxetine treatment, independently and in combination. Using a rat maternal separation model, we found that the WAY-100635 effect was slightly attenuated compared to control-reared rats, which might be consistent with loss of 5-HT_{1A} receptor function.[28] However, when maternally separated rats were treated with fluoxetine for 2 weeks, the effect of WAY-100635 was considerably more pronounced then in control-reared rats receiving fluoxetine. That is, it seemed feedback inhibition was greatest in fluoxetine-treated maternally separated rats.[28] These studies indicate the need for a deeper understanding of changes that occur in serotonin neurons in models of depression and as a consequence of antidepressant treatment.

Considerable evidence suggests 5-HT_{1A} receptors are important for mood disorders including depression and anxiety. They provide feedback regulation of serotonin neurons as well as direct influence of forebrain circuits to play an important role in mood disorders and treatment response.[39,52–57] Moreover, their function both during development and in adulthood has proven crucial to normal behavior.[39] Thus, 5-HT_{1A} receptors are important therapeutic targets. However, there is direct evidence for continuing 5-HT_{1A} receptor-dependent feedback inhibition of serotonin neurons after sustained exposure to high levels of extracellular serotonin indicating this is unlikely to explain the eventual efficacy of antidepressants. A better understanding of feedback inhibition would improve insight into the neurobiological basis of depression and the mechanism of action of common antidepressants.

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