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A hormetic approach to understanding antidepressant effectiveness and the development of antidepressant tolerance – A conceptual view

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Summary

Antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) have complex temporal effects. They may worsen symptoms during early treatment, they may reduce depressive symptoms over several weeks of treatment, and they may lose effectiveness over more prolonged treatment or after repeated treatment trials. Conceptually, these effects fall within the domain of hormesis, which refers to a biphasic or multiphasic response to a drug or toxin. Hormetic effects are commonly triggered when a drug interacts with homeostatic mechanisms. We develop and evaluate a theoretical framework for understanding how adaptations to SSRIs that restore synaptic homeostasis may partially contribute to their hormetic effects. Specifically, the serotonin system adapts to SSRIs by suppressing the firing of serotonergic neurons, inhibiting the synthesis of serotonin, and reducing the overall content of serotonin in the brain. Moreover, rodent models such as inescapable shock show that serotonin neurotransmission to specific forebrain regions is a necessary, but insufficient cause of depressive symptoms. Our review suggests: (1) early worsening of symptoms may be related to the direct effects of SSRIs on synaptic serotonin; (2) the symptom-reducing effects could be related to the loss of serotonin content in the brain during SSRI exposure; (3) the loss of efficacy over prolonged exposure could be related to the central nervous system equilibrating to the SSRIs. The serotonin system's adaptations to SSRIs may play a clinically meaningful role in their hormetic effects on depressive symptoms. A complete understanding of SSRIs' hormetic effects will require exploring temporal dynamics in other neurotransmitter systems.

Key words: adaptation, antidepressants, hormesis, oppositional tolerance, tachyphylaxis, stepwise resistance

Introduction

The hypothesis that depression is caused by low levels of monoamines, particularly norepinephrine [1] and serotonin [2, 3], was proposed more than 50 years ago. While the low monoamine hypothesis has been very influential, there has been no consistent support for this hypothesis from either animal or human studies [4–6]. The low monoamine hypothesis was largely based on evidence that certain drugs had depression-reducing effects and they caused synaptic levels of monoamines to increase [5, 6]. However, a long-recognized problem with this hypothesis is the fact that antidepressant drugs have complex and puzzling temporal effects on depressive symptoms (Table 1).

Table 1. **Predicted or observed effects of SSRIs on various parameters as a function of the phase of treatment**

Parameter	Phase						
	Premedication Baseline	SSRI Treatment			Discontinuation		
		Acute	Chronic	Prolonged	Acute	Chronic	Prolonged
Depressive symptoms	—	↑* (early worsening)	↓*	—* (return of symptoms)	↓	↑* (rebound or relapse)	—
Extracellular 5-HT	—	↑*	—*	—	↓*	—	—
Total brain 5-HT	—	—	↓*	↓	↓*	—	—
5-HT neuron firing	—	↓*	—*	—	↑	—	—
5-HT synthesis	—	↓*	↓*	↓	↑*	—	—
5-HIAA/5-HT	—	↓*	↓*	↓	↑*	↑*	—

All parameters in the premedication phase are set to "—", and effects in the other phases are relative to the premedication baseline. Because antidepressants lose efficacy over multiple bouts of treatment (see text), these patterns assume that the organism is medication naïve. An asterisk denotes an effect that is empirically supported (see text for details).

For instance, the selective serotonin reuptake inhibitors (SSRIs) increase synaptic serotonin within minutes to hours of administration [7, 8], but they do not usually produce clinically significant reductions in depressive symptoms except over several weeks of chronic treatment—a phenomenon called the *therapeutic delay* [9, 10]. In fact, some individuals may experience a worsening of symptoms during early (acute) SSRI treatment [11–13]. Over the course of more prolonged treatment (months or years) antidepressants may lose effectiveness [14, 15], which is sometimes referred to as *tachyphylaxis* [16, 17]. Relatedly, antidepressants may lose effectiveness after repeated treatment trials (*stepwise resistance*). Thus, antidepressants that were effective during prior depressive episodes may be less effective in treating new episodes [18–22]. In contrast, repeated antidepressant treatment trials may not diminish the response to future psychotherapy [23]. Finally, the likelihood of depressive relapse is high after discontinuation of long-term antidepressant therapy [14, 24], and higher than after discontinuation of psychotherapy [25].

We currently lack a mechanistic understanding of how antidepressants interact with the central nervous system (CNS) to produce these complex temporal effects. While the multiphasic effects of SSRIs have been puzzling to pharmacologists and neuroscientists, they fall within the domain of hormesis. *Hormesis* refers to the biphasic or multiphasic effects that a drug or toxin has on a biological parameter as a function of the dose or the duration of exposure [26–29]. For instance, chemicals that inhibit the growth of organisms at high concentrations often stimulate growth at low concentrations [30]. Psychotropic drugs often produce hormetic responses in receptor systems [31], and antidepressants often have biphasic effects on diverse biological parameters over acute and chronic treatment (Table 2).

Table 2. **Biphasic effects of antidepressants (AD) in response to acute treatment (single dose) and chronic treatment relative to the control condition (set to "—")**

Trait	AD	Animal	Control	Acute	Chronic	Refs
Aggression	Multiple classes	Rats	—	↓	↑	[120]
Anxiety	Citalopram	Humans	—	↑	↓	[90,121]
BDNF expression	Fluoxetine, desipramine	Rats	—	↓	↑	[122,123]
Microtubule structure	Fluoxetine	Rats	—	↑	↓	[124]
Potentiation of temporoammonic-CA1 synapse	Fluoxetine, citalopram, imipramine	Rats, mice	—	↑	↓	[125]
Excitability of motor cortex	Paroxetine	Humans	—	↑	↓	[126,127]

With the exception of BDNF expression, the data for each trait come from the same laboratory.

Hormetic responses are widespread in nature, and they are more common than linear dose responses [28, 32]. The multiphasic effects of SSRIs are not surprising when viewed from the lens of the hormesis literature, since hormetic responses tend to be the rule rather than the exception.

Hormetic responses are not limited to particular chemical agents, environmental or physiological stressors, or biological systems [29], which suggests that a common reason for hormesis resides in some process shared by many organisms [30, 33]. A common explanation for hormesis is that the drug interacts with a homeostatic mechanism [30, 34]. Homeostasis refers to the maintenance of internal physiological conditions within ranges necessary for survival and reproduction [29, 30]. All organisms have homeostatic control mechanisms.

At least two important hypotheses attribute the effects of antidepressants on depressive symptoms to the adaptations produced by homeostatic mechanisms [14, 35, 36]. Hyman and Nestler argued that homeostatic adaptations to SSRIs are responsible for the antidepressant effect that often occurs over chronic treatment. "It is the adaptive response of the nervous system to adequate repeated perturbations mediated through these initial targets that produces the therapeutic responses to antidepressants…" [ref.

35, p. 152]. Thus, Hyman and Nestler focus on the changes that occur from the early (acute) phase of treatment to the chronic phase. Vetulani and Sulser similarly argued that adaptations in the noradrenergic system were responsible for the symptom-reducing effects of tricyclic antidepressants, monoamine oxidase inhibitors, and electroconvulsive therapy [36]. In contrast, Fava has argued that the loss of effectiveness during prolonged antidepressant use is caused by recruitment of "processes that oppose the initial acute effects of a drug…" [ref. 14, p. 127]. Moreover, oppositional forces may take time to dissipate after antidepressants are discontinued and the residual adaptations can result in the "appearance of withdrawal symptoms and increased vulnerability to relapse" [ibid]. Thus, Fava's account also recognizes the multiphasic nature of the effects of antidepressants on depressive symptoms, focusing on the changes from chronic treatment to more prolonged treatment to discontinuation [37]. In principle, it is possible for both hypotheses to be correct because they refer to different phases of the hormetic response.

The CNS adapts to antidepressant exposure [35, 38–41], and these adaptations are sometimes referred to as *acquired tolerance* [23] or *oppositional tolerance* [14, 15]. However, the arguments of Hyman, Nestler, Vetulani, Sulser, and Fava require antidepressants to interact with a homeostatic mechanism. While Hyman, Nestler, Vetulani, and Sulser argue that the pertinent adaptations occur post-synaptically—in gene expression and receptor-mediated signaling pathways [35, 36]—it not clear that gene expression or receptor signaling pathways are under direct homeostatic control. However, synaptic monoamine levels are under direct homeostatic control [38, 40], and nearly all effective antidepressants perturb synaptic monoamine concentrations [24]. Because synaptic serotonin is under homeostatic control, and SSRIs directly perturb synaptic serotonin through a common mechanism (reuptake blockade), it is plausible that SSRIs trigger oppositional adaptations that eventually restore synaptic serotonin to equilibrium conditions. These adaptations may be particularly good candidates for exploring the hormetic effects of SSRIs.

In this paper, we briefly discuss how hormetic responses can be produced from homeostatic control mechanisms before reviewing several serotonergic adaptations that oppose SSRIs and return synaptic serotonin to the homeostatic equilibrium: the inhibition of serotonin synthesis, the suppression of serotonergic neuron firing rates, and the inhibition of serotonin transmission (which is related to neuronal firing, but nevertheless distinct).

We then review the dissipation of oppositional tolerance after SSRI discontinuation. We also review how SSRIs may cause permanent adaptations in the serotonergic system.

Finally, we consider whether and how the adaptations to SSRIs that eventually restore synaptic serotonin to homeostatic equilibrium are related to the hormetic effects on depressive symptoms. Resolving this issue requires an understanding of the causal role of synaptic serotonin in depression. The conventional wisdom is that serotonin transmission is reduced in depression [42, 43]. The primary foundation for the *low serotonin hypothesis* is the fact that most antidepressants have the pharmaco-

logical property of rapidly increasing synaptic serotonin. However, the homeostatic mechanisms of the CNS produce adaptations that oppose the serotonin-elevating effects of antidepressants [38]. Thus, if adaptations are responsible for the alleviation of depressive symptoms, then it is conceivably possible that serotonin is elevated (rather than diminished) in depression—the *high serotonin hypothesis* [4]. Several empirical findings in rodents, primates, and humans have led some researchers to suggest that serotonin neurotransmission is elevated in depression [44–46]. Finally, some have questioned whether serotonin is causally involved in depression at all [47, 48].

Confusion over this issue can be reduced by being clear about our precise causal claim. If we could fully map out the neurological chain of events that trigger depression, we would probably find that some steps involve serotonin, while other neurotransmitters (e.g., norepinephrine, glutamate, GABA) are involved in other steps. Disabling the brain's ability to transmit serotonin to forebrain regions—by lesion, pharmacological inhibition, or *Tph2* gene knockout—prevents rodents from developing depression-like symptoms in rodent models of depression [49–52]. Serotonin is therefore a *necessary cause* for depression in these rodent models, but it is not a *sufficient cause* since there are also positive mood states in which serotonin neurotransmission is elevated [4]. Given an elevation in serotonin transmission, other neurological events must determine whether depression or some other state is induced. In inescapable shock, the transmission of serotonin to the rat's amygdala and striatum play crucial roles in the development of depressive symptoms, but it does this by affecting post-signaling receptor pathways involving the 5-HT_{2C} receptor [53]. Thus, serotonin transmission to the amygdala and striatum are more *distal causes* of depression in the inescapable shock model, while post-signaling receptor pathways within these regions are more *proximal causes* of depression. We will return to the precise causal role that serotonin plays in depression later in this paper. Finally, we reiterate the involvement of norepinephrine as another causal factor in affecting depressive symptoms [24], but we focus on adaptations to SSRIs in the serotonin system because they have been more widely studied. Even so, the principles of hormesis, homeostasis, and adaptation that we apply to SSRIs may also apply to antidepressants with noradrenergic properties.

Search strategy and selection criteria

We searched for relevant articles in PubMed and Google Scholar using "serotonin", "adapt", "adaptation", "oppositional tolerance", "acquired tolerance", "hormesis", "homeostasis", "5-HIAA/5-HT", "discontinuation", "cessation", "acute SSRI", "chronic SSRI", "fluoxetine", and related terms. In the references of relevant articles, we sometimes found other relevant articles. We also searched articles that cited relevant articles.

Homeostasis and hormesis

A common way to produce hormetic responses is through the dynamical interplay between two opposing forces [26, 33, 34, 54]. The first force is the load that the drug puts on the system, which perturbs a physiological parameter from homeostatic equilibrium. This is the direct effect of the drug and it often produces the first part of the biphasic response. The second force is the negative feedback produced by the homeostatic mechanism to bring the parameter back into equilibrium. This negative feedback is responsible for the tolerance or adaptation to the drug [26, 55]. It often takes time for a homeostatic mechanism to build up oppositional tolerance, which is why there may be a delay in the control of the parameter.

The oppositional tolerance that accrues over the duration of drug exposure can cause a physiological parameter to overshoot or undershoot its equilibrium [55]. Over time, the parameter can show a dampened overshoot and undershoot oscillation pattern until it eventually re-equilibrates (Figure 1). The oscillation reflects the interplay between the load caused by the drug and fluctuating degrees of oppositional tolerance. The adaptive value of a control mechanism that responds to perturbations with a dampened oscillation pattern is that it brings the parameter back into equilibrium more rapidly, but it comes at some cost to stability [56].

Because synaptic serotonin is under homeostatic control [35, 38–41], oppositional tolerance to SSRIs could trigger a dampened oscillation in synaptic serotonin or other parameters that affect synaptic serotonin, and these might be related to the hormetic effects on depressive symptoms.

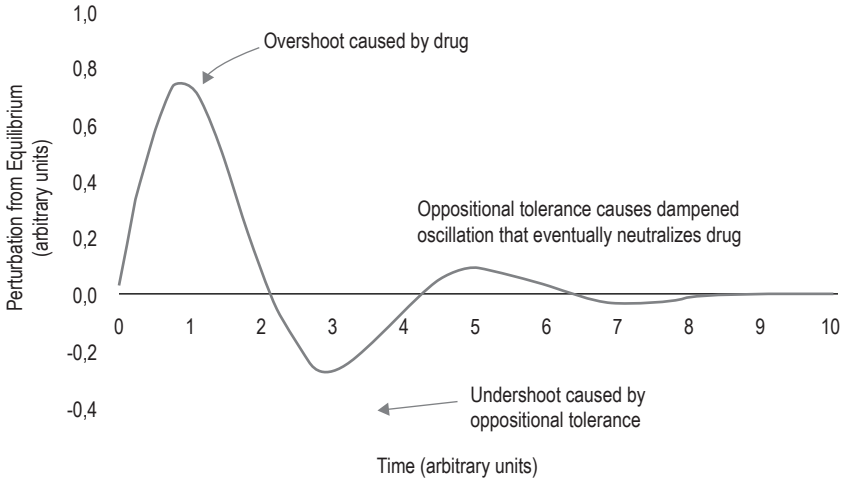

Figure 1. **Hypothetical time course of a parameter (process variable) as it is disturbed from equilibrium (setpoint) by a drug, and as homeostatic control processes bring it back to equilibrium**

Oppositional tolerance to restore synaptic homeostasis

If SSRIs are interacting with a system under homeostatic control, then the drugs should trigger responses in the CNS that return the system to equilibrium. The direct effect of SSRI molecules is to block serotonin transporter (SERT) sites, which prevents the reuptake of serotonin into the pre-synaptic neuron. SSRIs cause synaptic serotonin to significantly increase within minutes to hours after the first dose [7, 8]. Thus, if the total level of brain serotonin is the sum of the intracellular and extracellular (synaptic) pools, the direct effect of initial SSRI therapy must be to shift the allocations, increasing the extracellular pool of serotonin while reducing the intracellular pool (Figure 2).

The increase in synaptic serotonin concentration during initial SSRI treatment represents peak values, and extracellular serotonin levels gradually return to pre-SSRI values over time, despite continued administration (see, e.g., Figure 2 from [57] and Figure 2 from [58]). This return to premedication levels during chronic SSRI treat-

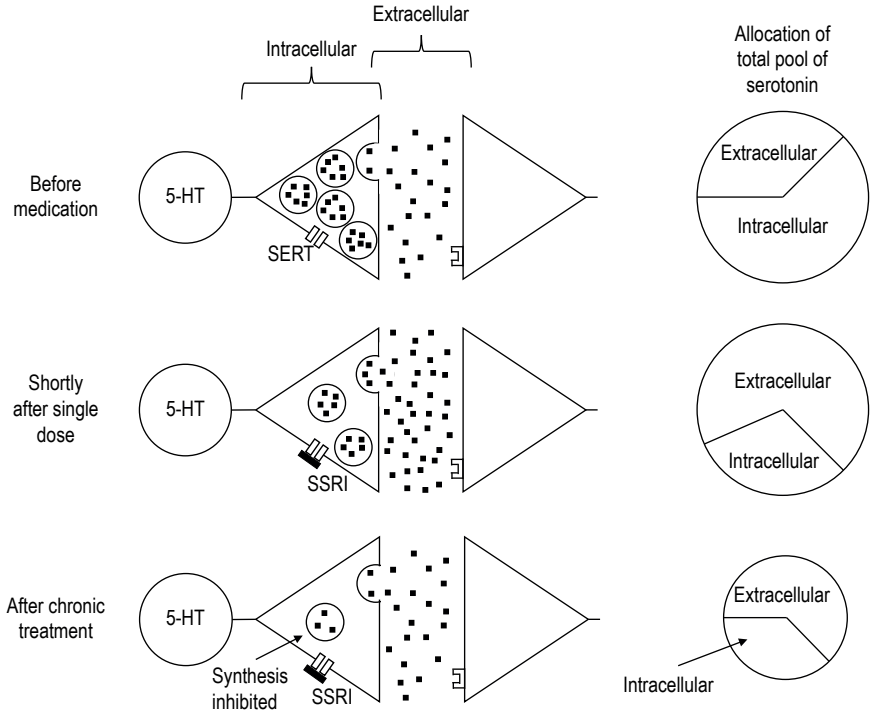

Figure 2. **The effect of a single dose of an SSRI is to shift the relative allocation of intracellular and extracellular serotonin. With chronic SSRI treatment, extracellular serotonin concentrations eventually return to the premedication baseline. This effect is at least partly attributable to the inhibition of the synthesis of serotonin, which reduces the pool of intracellular serotonin available for neurotransmission and the total pool of serotonin in the brain**

ment has been demonstrated in rats, mice and primates [57–59]. Several adaptations contribute to the return of synaptic serotonin to pre-SSRI levels.

Synthesis of serotonin

Numerous studies show that total serotonin content in brain regions decrease (rather than increase) during chronic antidepressant therapy [60–69]. Because extracellular serotonin does not go below the premedication equilibrium level during SSRI exposure, the decline in total brain serotonin content must be caused by a reduction in the intracellular serotonin pool (Figure 2). All classes of effective antidepressants inhibit the synthesis of serotonin, which reduces the intracellular pool of serotonin available for neurotransmission [62, 66, 70–72]. One study showed the dose-dependent inhibition of serotonin synthesis, with higher doses of fluoxetine causing greater inhibition [73].

Firing of serotonergic neurons

The inhibition of serotonin synthesis happens quickly after SSRI administration is initiated, but the effects accumulate slowly. SSRI administration also causes a rapid suppression of the firing rates of serotonergic neurons, which reduces the release of serotonin into the synapse [74]. The decrease in neuronal firing, however, is insufficient to bring synaptic serotonin concentrations back to premedication baseline. As noted above, extracellular serotonin levels decline slowly during chronic SSRI administration and serotonin concentrations only come back to pre-drug baseline after several weeks of treatment. This occurs because SSRI doses are usually upward titrated to occupy 70-80% of available SERT sites [39, 75]. The brain cannot fully compensate for this by decreasing neuronal firing rates, which is why it takes several weeks for synaptic serotonin concentrations to return to pre-drug levels. Without suppression of neuronal firing, however, synaptic serotonin would be even more perturbed from equilibrium. Over several weeks—as the inhibition of serotonin synthesis gradually causes synaptic serotonin to return to normal—serotonergic neurons also return slowly to their normal firing rates [74].

Serotonin transmission

Elsewhere, we have reviewed evidence that the ratio of the concentrations of 5-hydroxyindoleacetic acid (5-HIAA) to serotonin (5-HT) is a useful surrogate index for measuring regional serotonin neurotransmission, although sometimes 5-HIAA concentrations by themselves are used for this purpose [4]. One study involving primates [57] reported a reduced 5-HIAA/5-HT ratio in multiple brain regions during chronic fluoxetine treatment (Figure 3). Moreover, there appears to be a dampened oscillation in the 5-HIAA/5-HT ratio around the lower equilibrium (Figure 3). The inhibition of transmission appears to be quite rapid since another study involving mice reported

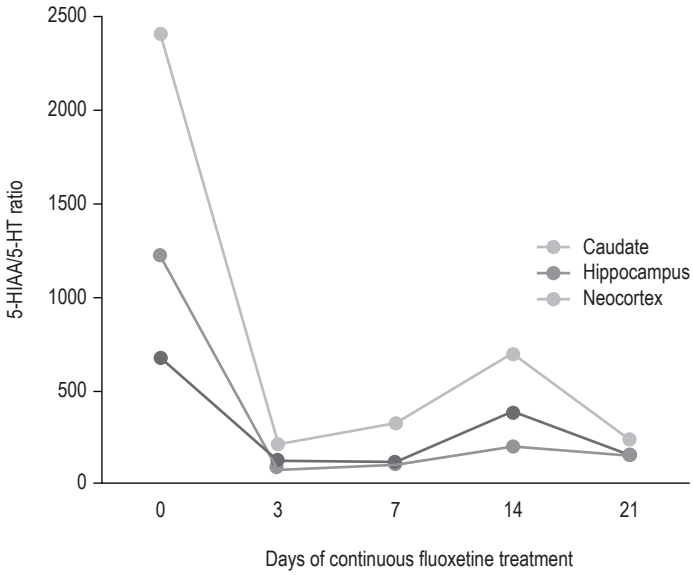

Figure 3. **The 5-HIAA/5-HT ratio in three regions (caudate, hippocampus, neocortex) is reduced following the initiation of fluoxetine treatment and remains reduced for the duration of treatment. The ratio seems to show a dampened oscillation around the new, lower equilibrium [data are from ref. 59]**

a decrease in the 5-HIAA/5-HT ratio after a single injection of fluoxetine [73]. Another study involving humans showed that chronic SSRI use reduced 5-HIAA levels in the jugular vein, which directly drains the brain with little peripheral contamination [44].

The effects of SSRIs on firing rates of serotonin neurons (i.e., initial suppression, followed by return to baseline) and on neurotransmission (i.e., continued suppression indexed by the 5-HIAA/5-HT ratio) may appear paradoxical. Should not the return of serotonin neuronal firing rates to normal also result in a return of transmission to normal? These two observations can be reconciled by the fact that synthesis is suppressed during treatment as well. The return of neuronal firing rates to normal will not increase transmission if there is less serotonin available for transmission.

Dissipation of oppositional tolerance after discontinuation

After SSRI discontinuation, the load on the system caused by the drug is relaxed, and oppositional tolerance should gradually dissipate. Thus, we predict changes to brain serotonin content, neuronal firing, and neurotransmission after drug discontinuation (Table 1). For instance, shortly after discontinuation when the drug has been effectively cleared from the system, there should be a shift in the allocation of the brain's serotonin where the intracellular pool of serotonin increases and the extracellular pool decreases. This should cause synaptic serotonin to fall below equilibrium and

trigger adaptations to restore equilibrium (increase in serotonergic neuron firing rate, increase in synthesis, increase in 5-HIAA/5-HT). During the chronic discontinuation phase, these adaptations will eventually restore overall serotonin content in the brain to premedication levels. As the discontinuation period becomes more prolonged, the system should eventually return to premedication conditions.

Few studies have examined what happens to the serotonin system after SSRI discontinuation, but two are relevant. In the first study, mice were injected with fluoxetine for three weeks and then followed for up to 17 days after discontinuing treatment [73]. After discontinuation, the synthesis of serotonin and the 5-HIAA/5-HT ratio exhibited a dampened oscillation pattern in three regions—hypothalamus, hippocampus, and frontal cortex. Specifically, there was an overshoot that peaked at day 3, followed by a gradual return to pre-fluoxetine values by day 17.

In the second study (discussed in more detail in the Supplement), rats were treated with fluoxetine for three weeks [76]. The drug was then discontinued, and the rats were followed for varying periods of time before they were sacrificed to measure serotonin and 5-HIAA concentrations in four brain regions—hippocampus, cortex, hypothalamus, and pons medulla (Supplement, Figures S1 and S2). During fluoxetine treatment, there was a loss in the total serotonin content of the brain and a reduction in the 5-HIAA/5-HT ratio, consistent with the patterns noted above. After discontinuation, total brain serotonin content gradually returned to premedication levels. Also, the 5-HIAA/5-HT ratio exhibited an overshoot several days after discontinuation before returning to premedication levels.

These two studies suggest that, after SSRI discontinuation: (1) the oppositional tolerance that accumulated during chronic SSRI administration gradually dissipates until synaptic serotonin levels return to premedication equilibrium; and (2) as oppositional tolerance dissipates, the system exhibits a dampened oscillation in serotonin synthesis and 5-HIAA/5-HT ratio until it re-equilibrates.

SSRIs can permanently alter the serotonin system

The CNS sometimes responds to synaptic perturbations by making adjustments of a relatively permanent nature that restore equilibrium. This can happen, for instance, when organisms are exposed to psychotropic drugs during early development. Neonatal SSRI exposure can cause changes to the components of the serotonin system involved in synthesis and reuptake—Tph2 and SERT expression—that persist into adulthood [77–80]. The precise directional changes depend on other factors (e.g., the specific SSRI used), but these studies demonstrate the principle that exposure to SSRIs can induce permanent changes to the serotonin system.

Discussion

From a hormetic perspective, the worsening of symptoms that sometimes occurs during early SSRI treatment represents an overshoot relative to the premedication symptom level, while the therapeutic effect that develops during chronic SSRI treatment represents an undershoot. Tachyphylaxis over more prolonged treatment arguably represents a return of depressive symptoms to premedication levels, and it is possible that relapses after SSRI discontinuation may be overshoots. For instance, the risk of relapse after the discontinuation of effective cognitive behavioral therapy (CBT) is lower than the risk of relapse after the discontinuation of effective SSRI treatment [25].

The literature on hormesis suggests that this pattern could be caused by the SSRI interacting with one or more homeostatic control mechanisms. Synaptic serotonin is under homeostatic control, and we have reviewed several adaptations to SSRIs in the serotonin system that return synaptic serotonin to the premedication equilibrium.

Do these adaptations contribute to the hormetic effects of SSRIs on depressive symptoms? An answer to this question requires an assumption about the direction of association between serotonin and depression.

Serotonin and depression

The low serotonin hypothesis of depression originated with the discovery that certain drugs with antidepressant effects had the property of acutely increasing synaptic norepinephrine or serotonin [5, 6]. However, the therapeutic delay between treatment initiation and clinical response has long been recognized as problematic for the low serotonin hypothesis [10].

Nevertheless, researchers have attempted to explain the therapeutic delay by working within the low serotonin framework. One attempt relied upon the fact that the firing of serotonergic neurons is suppressed during acute treatment by activation of the 5-HT_{1A} autoreceptor, which is inhibitory. During chronic treatment, however, the autoreceptor becomes desensitized and firing rates return to normal [35, 74]. The suppression of neuronal firing that occurs with acute SSRI treatment should decrease neurotransmission to forebrain regions, which could possibly reconcile the therapeutic delay with the low serotonin hypothesis. The problem with the autoreceptor desensitization hypothesis is that synaptic serotonin increases rapidly after a single SSRI dose [7, 8]. Thus, irrespective of firing rates, SERT blockade is effective in increasing synaptic serotonin concentrations, and the low serotonin hypothesis predicts this should cause a rapid alleviation in symptoms, which it does not do.

The widespread acceptance of the low serotonin hypothesis is surprising because rodent models of depression have provided substantial evidence that contradicts it. Inescapable shock—perhaps the most widely studied rodent model of depression—increases extracellular serotonin concentrations in the prefrontal cortex, striatum, amygdala, periaqueductal gray, and other forebrain regions [49, 81]. Indeed, most studies of rodent models of depression have found elevated extracellular serotonin, 5-HIAA, or

the 5-HIAA/5-HT ratio in a number of forebrain regions [4]. Other researchers have also noticed how the direct measurements contradict the low serotonin hypothesis [44–46] (see also Supplement, Table S1).

More evidence against the low serotonin hypothesis comes from studies that disable the rodent brain's ability to transmit serotonin to forebrain regions via surgical lesioning, pharmacological inhibition, or *Tph2* gene knockout [49–52]. According to the low serotonin hypothesis, these manipulations should all induce depressive-like symptoms in rodents. In fact, they do not [4]. Instead, they prevent the rodent from developing depressive symptoms in response to otherwise depressogenic stressors (e.g., inescapable shock, chronic social defeat, chronic mild stress) [49–52]. In their review of 50 years of research on inescapable shock, Steve Maier and Martin Seligman review evidence that elevated serotonin transmission—particularly to the striatum and amygdala—is "necessary and sufficient" to produce the depressive symptoms uniquely triggered by inescapable shock [ref. 50, p. 352].

It could be argued that rodents are not good models for understanding human depression. However, inescapable shock produces most symptoms of depression, including some of the cognitive effects [49]. Moreover, the mammalian brain is highly conserved, and rodent models are extensively used in understanding the neurobiology of many depression-related phenomena, such as the reduction in hippocampal neurogenesis and the effects of antidepressants. It makes little sense to argue that rodents are not a good model for depression without also giving up everything we have learned from those models. Given the influential impact of the inescapable shock paradigm on the understanding of depression, it is puzzling how the effect of inescapable shock on serotonin has gone largely unnoticed by psychiatric and pharmacological researchers.

In humans, research on the relationship between serotonin and depression is hindered by the inability to directly measure serotonin in the brain without invasive techniques [4]. Nevertheless, two well-designed studies suggest that serotonin transmission is elevated in unmedicated people with clinically diagnosed depression.

One neuroimaging study examined SERT expression in 20 depressed patients and 10 healthy volunteers who were either medication-naïve or medication-free for at least one year using a single photon emission computed tomography radioligand highly specific for SERT [82]. The depressed patients had lower levels of SERT in the midbrain, basal ganglia and temporal lobe. Moreover, responders to the non-pharmacologic intervention of CBT, versus non-response to CBT, showed a significant increase in SERT expression [83]. Because SERT clears serotonin from the synapse, these results are consistent with an increase in synaptic serotonin in depressed patients, and a decrease in synaptic serotonin with effective treatment.

While brain 5-HIAA levels can serve as a good proxy for serotonin transmission, 5-HIAA levels in the spinal fluid of human lumbar region are contaminated by peripheral sources [44]. To avoid this problem, another well-designed study examined brain 5-HIAA overflow in the jugular vein of humans, which comes from the brain with little peripheral contamination [44]. Investigators studied 21 depressed subjects, nearly all of

whom had been medication-free for at least one year, and 40 non-depressed controls. Relative to non-depressed controls, there was a higher overflow of 5-HIAA in the jugular veins of the depressed subjects. Moreover, 5-HIAA concentrations decreased over 12 weeks of SSRI therapy. This finding corroborates the evidence in non-human animals (discussed above) that SSRIs suppress serotonin neurotransmission (indexed by 5-HIAA or 5-HIAA/5-HT).

Some studies have attempted to test the low serotonin hypothesis in humans by providing participants with a drink that is depleted of tryptophan in an attempt to reduce the availability of brain serotonin. These studies have failed to trigger depressive symptoms in otherwise healthy people [84]. However, tryptophan depletion triggers depressive symptoms in remitted patients who have currently or previously used serotonergic antidepressants [84]. In such patients, it does not suppress DRN activity, as the low serotonin hypothesis predicts. Rather, it activates the DRN [85], which is consistent with the high serotonin hypothesis. This finding could be explained by the downregulation of the 5-HT_{1A} autoreceptor during acute tryptophan depletion, which may be a compensatory homeostatic response that disinhibits the DRN [86].

Altogether, these findings suggest that serotonin neurotransmission to certain forebrain regions is elevated in depression, and it may be necessary to the development of depressive symptoms.

How the serotonin system may contribute to the hormetic effects of SSRIs

In attempting to explain how serotonergic adaptations contribute to the hormetic effects of SSRIs, we therefore start with the assumption that serotonin transmission is elevated in depression, at least to forebrain regions like the striatum and basolateral amygdala.

Early worsening of symptoms

Although chronic SSRI treatment commonly reduces depressive symptoms, a worsening of symptoms is sometimes observed shortly after treatment is initiated [12, 13]. Perhaps the most potent demonstration of this is the increased risk of suicidal thoughts and behavior in the first few days after initiating antidepressant treatment [87]. The high serotonin hypothesis for depression provides a natural explanation for the early worsening of symptoms, because the earliest pharmacological effect of SSRIs is to increase synaptic serotonin even further.

The reason why many patients do not experience early worsening is unknown. Early worsening of anxiety or depression is sometimes studied experimentally with single-dose or sub-chronic SSRI treatments [88]. In both rodents and humans, a single dose of SSRIs increases the symptoms of anxiety [89, 90] and potentiates fear responses [91–93]. Two studies of human volunteers suggest that SSRIs may potentiate anhedonia during early treatment. In one, a sub-chronic dose of citalopram reduced

the neural response to chocolate in areas involved in reward [94]. In the other, a single dose of paroxetine reduced the neural signal involved in motivation for a monetary reward [88]. Similarly, single doses of SSRIs often decrease reward-related activity in rodents [95–97]. However, these studies usually involve non-depressed individuals, which raises the issue of whether SSRIs worsen symptoms in depressed patients. Anecdotally, the worsening of symptoms during early antidepressant treatment may be more likely when the symptoms are mild [88]. It is possible that potential ceiling effects limit early worsening in patients with more severe symptoms.

There is interesting experimental evidence suggesting that early worsening may be less likely to occur in patients with more severe symptoms. In non-depressed human controls and in non-stressed rodents, a single dose of an SSRI increases the activation of the hypothalamus-pituitary-adrenal (HPA) axis [98–104]. However, in stressed animals and depressed patients, single SSRI doses do not affect HPA activity [103, 105]. Since the HPA axis is often hyperactivated in depression, a single dose of an SSRI appears to have little effect on an already activated stress response, which is consistent with a ceiling effect. Of course, the HPA activity of depressed patients is reduced by chronic SSRI treatment [106].

The therapeutic delay

The therapeutic delay is also naturally explained by the high serotonin hypothesis in a way that is consistent with the adaptation framework that Hyman and Nestler espouse. Since SSRIs increase synaptic serotonin even further, one must resort to the gradual development of adaptations that oppose this elevation to explain the delayed therapeutic effect. The evidence that serotonin is necessary for the development of depressive symptoms suggests that the antidepressant effect could be linked to the gradual loss of serotonin content in the brain.

Limited effectiveness

The symptom reducing effect of antidepressants during chronic treatment—relative to placebo—is not large [107–109]. This is also potentially explainable by the framework we suggest. Specifically, the oppositional tolerance that develops should be proportional to the strength of the drug [24]. In other words, a drug that is more effective in perturbing synaptic serotonin should trigger a stronger oppositional tolerance [24]. The fact that drug and the oppositional tolerance tend to cancel each other out could explain the limited effectiveness of antidepressants.

Tachyphylaxis

Over sufficiently long time periods, the CNS should fully equilibrate to the load imposed by SSRIs, so the return of depressive symptoms over the course of prolonged

SSRI use (tachyphylaxis) is somewhat to be expected [14]. However, it is difficult to explain tachyphylaxis solely in terms of adaptations in the serotonin system. For instance, if the loss of serotonin content is a sufficient, proximal cause of the antidepressant effect, then one might expect that tachyphylaxis would involve the return of serotonin content to premedication levels. However, the serotonin content of the brain remains depleted during prolonged SSRI use; it only returns to premedication levels sometime after discontinuation (Supplement, Figures S1 and S2). Somehow, the return of depressive symptoms must occur despite the loss of serotonin content. In this context, we note that total serotonin content is only reduced with chronic SSRI administration—it is not eliminated. It may be that adaptations in other neurotransmitter systems allow the brain to use what serotonin is available to bring about tachyphylaxis.

Again, we suggest that the transmission of serotonin to specific forebrain regions—such as the striatum and amygdala—is a necessary, somewhat distal cause of depression. In these regions, activity in post-synaptic neurons plays a more proximal role. Moreover, proper synaptic function requires maintaining the ratio of excitation and inhibition at a homeostatic equilibrium [110], which is modulated by both serotonin and dopamine [111]. By provoking adaptations in the serotonin system, it is possible that SSRIs may indirectly trigger dampened oscillations in neuronal activity in relevant forebrain regions that account for the hormetic overshoots and undershoots in depressive symptoms during SSRI therapy, as well as tachyphylaxis. Again, adaptations in other neurotransmitter systems may contribute to the hormetic effects in depressive symptoms.

Relapse after discontinuation

Upon SSRI discontinuation, the load caused by the drug is removed, and the oppositional tolerance that has accumulated causes the system to dis-equilibrate. As extracellular serotonin falls below equilibrium, there could be a reduction in depressive symptoms, which is a prediction that we believe has never been tested. Moreover, we suggest that the relapse that often occurs after discontinuation [14, 24, 25, 37] represents an overshoot caused by the increase in serotonin content and transmission during this period. This overshoot mirrors the undershoot in depressive symptoms that occurs during chronic SSRI treatment. As the period of discontinuation becomes more prolonged, the system should eventually return to premedication conditions.

Stepwise Resistance

Hyman and Nestler suggested that the adaptations induced by SSRIs can lock the system into a therapeutic state that outlasts the duration of drug treatment [35]. This suggestion is supported by the research discussed above in which neonatal SSRI exposure produces changes in the CNS that persist into adulthood. Unfortunately, the alterations to the system are often not therapeutic in the way that Hyman and Nestler

hoped. Many of the studies show that rats exposed as neonates develop a depressed or anxious symptom profile when they reach adulthood [78, 112].

The phenomenon of stepwise resistance—where there is a loss of treatment effectiveness over repeated antidepressant treatment trials [18–23, 113–115]—suggests that exposure to SSRIs and other antidepressants can permanently alter the CNS even in adulthood. This is a within-person effect; it cannot be explained by stable between-person differences. Moreover, stepwise resistance does not appear to be caused by new episodes that happen shortly after discontinuation when oppositional tolerance has not fully dissipated, as this phenomenon can occur years after previous episodes have resolved.

Mechanistically, it is not clear how stepwise resistance in adults is achieved. One possibility comes from evidence that chronic fluoxetine administration in adult rats can induce hippocampal and prefrontal cortex neurons into a less mature state [116, 117]. The neuroplasticity seen in de-matured rat neurons is similar to that seen during critical developmental stages [118, 119], which suggests that adult SSRI exposure in humans can push neurotransmitter systems into a sensitive developmental stage where they may be permanently altered by the drugs.

Conclusion

Hyman and Nestler [35] argued that adaptations to SSRIs explain the therapeutic delay, while Fava [14] argued that adaptations to SSRIs explain tachyphylaxis and the increased risk of relapse after discontinuation. The concepts of hormesis and homeostasis can provide a unifying framework for understanding how both proposals may be correct. When interacting with a drug that perturbs a system from equilibrium, a homeostatic control mechanism often causes the system to alternate between positive and negative responses until it eventually equilibrates to the drug. SSRIs disrupt synaptic serotonin from its homeostatic equilibrium, and we have reviewed several adaptations in the serotonin system that may contribute to the hormetic effects of SSRIs. A complete understanding of how SSRIs affect depressive symptoms will require a full exploration of their temporally dynamic effects on multiple neurotransmitter systems.

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