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REVIEW

Selective serotonin reuptake inhibitors for functional recovery after stroke: similarities with the critical period and the role of experience-dependent plasticity

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Abstract

There has been a growing interest in the potential for plasticity-inducing pharmacological interventions to enhance post-stroke recovery. One group of drugs that continues to garner a great deal of attention in this regard is a class of antidepressants called the selective serotonin reuptake inhibitors. Here we propose a model for the mechanism by which these drugs may enhance plasticity after ischemic brain injury. First, we review the research in animal models demonstrating how selective serotonin reuptake inhibitors reopen the critical period for ocular dominance plasticity in adulthood. We then compare this period of heightened plasticity to the cellular and biochemical milieu of perilesional tissue after an ischemic event in the adult brain. We argue that selective serotonin reuptake inhibitors administered acutely after an ischemic stroke alter excitatory–inhibitory balance in perilesional tissue and reinstate a type of plasticity reminiscent of the critical period in development. Finally, we discuss opportunities for future research in this area in both the preclinical and clinical realms.

Keywords Serotonin uptake inhibitors · Stroke · Neuronal plasticity · Critical period · Rehabilitation · Monocular deprivation

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Stroke is a leading cause of long-term adult disability in the United States. While many stroke patients experience significant functional recovery in the first few months after a stroke, residual deficits persist beyond the first year in most patients [1, 2]. Given the attractiveness of a pharmacological approach for enhancing post-stroke recovery, many groups have explored the therapeutic potential of a class of antidepressants called selective serotonin reuptake inhibitors (SSRIs). The first large-scale randomized clinical trial of SSRIs in acute stroke patients (FLAME) found that initiating fluoxetine acutely after an ischemic stroke improved motor outcomes at 90 days [3]. Furthermore, a meta-analysis of over 4000 stroke patients showed a similar benefit of SSRIs in recovery [4]. The improvement in motor outcomes appears to be specific to the SSRI class of antidepressants [5] and independent of the antidepressant effects of these drugs [3].

These findings raise an important question: What is the mechanism by which SSRIs enhance post-stroke recovery? To understand the effects of SSRIs at the molecular level, we discuss animal studies that have shown that SSRIs are capable of reopening the critical period for ocular dominance

plasticity in adulthood by altering excitatory–inhibitory balance. Next, we extrapolate these findings to understand how SSRIs may improve recovery after stroke. We argue that, in the presence of rehabilitative therapy, SSRIs operate through the strengthening of unmasked connections and the creation of new ones in an experience-dependent fashion by decreasing inhibitory tone, which increases plasticity; the excitatory–inhibitory balance is then re-established afterwards. This proposed mechanism not only helps explain the effects of SSRIs on motor recovery after stroke, but also suggests that SSRIs may facilitate post-stroke recovery in other functional domains such as vision, language, and cognition.

Critical period in development

Critical periods in neural development occur in many functional domains and are characterized by the potential for large-scale synaptic plasticity and cortical reorganization. Understanding the cellular and molecular underpinnings of this process can help us find ways to reopen the critical period in adulthood, which could in turn facilitate post-stroke recovery. A commonly used system for the study of critical period plasticity is the visual cortex, where perturbations to visual experience cause changes in ocular dominance during a well-defined period of development [6], whereas similar perturbations fail to alter visual circuitry to the same degree in adulthood [7]. Recent animal studies show that SSRIs are capable of reopening the critical period in adulthood [8–10].

The balance between excitatory and inhibitory signaling governs the opening and closing of the critical period, as well as the changes in ocular dominance that result from monocular deprivation during the critical period. The beginning of the critical period is marked by an initial maturation of parvalbumin-positive gamma-aminobutyric acid (GABA)-ergic neurons. Increasing GABA type A signaling using diazepam causes a precocious opening of the critical period for ocular dominance plasticity, while the attenuation of synaptic GABA synthesis in glutamic acid decarboxylase-65 knockout mice prevents the onset of the critical period altogether [11, 12].

Monocular deprivation during the critical period shifts the excitatory–inhibitory balance of visually deprived cortex towards excitation to compensate for the sudden loss of activity from the deprived eye [11]. After monocular deprivation, pyramidal neurons become disinhibited due to a rapid loss of parvalbumin-positive inhibitory input [12]. Structural changes also promote the remodeling of cortical responsiveness to the two eyes: monocular deprivation induces the retraction or elongation of interneuron dendritic branch tips and axonal boutons [8], and the changes in eye-specific axonal and dendritic arborization of excitatory neurons [13]. The circuit refinement that normally occurs during the critical period does not happen, however, if the inhibitory tone is too high at the onset of the critical period [12].

At the end of the critical period, a second wave of inhibitory maturation stabilizes established cortical connections. This wave is triggered, in part, by brain-derived neurotrophic factor (BDNF). Transgenic overexpression of BDNF accelerates the maturation of inhibitory neurons in young mice and prematurely opens and closes the critical period [14].

SSRIs reopen the critical period in adulthood

Restoration of the juvenile form of ocular dominance plasticity in adulthood can be achieved using a variety of methods that reduce cortical inhibition, including treatment with SSRIs [9, 10]. In this section, we review the animal and human literature that shows that SSRIs promote a type of plasticity in adulthood reminiscent of the critical period for ocular dominance plasticity in the juvenile visual system. These studies suggest that the SSRI-induced acute increase in the local concentration of serotonin causes a decrease in long-range horizontal inhibition, facilitating synaptic plasticity.

Animal SSRI studies

Serotonin can modulate the homeostatic response of visual circuits by decreasing inhibition [15, 16], thereby tipping excitatory–inhibitory balance in favor of excitation. Similarly, SSRIs have been shown to decrease inhibitory tone in the adult rat visual cortex [10] in a serotonin-dependent manner [17], by decreasing extracellular GABA concentrations and reducing the number of parvalbumin-positive GABAergic interneurons [18–20]. In addition, fluoxetine facilitates the degradation of the perineuronal nets surrounding parvalbumin-positive interneurons [18, 19, 21], thus removing an important structural component of synaptic stabilization.

With SSRIs decreasing the inhibitory tone of the circuit, the cortex becomes hyperexcitable [22, 23], which creates a permissive environment for novel visual experiences, such as monocular deprivation, to affect circuit organization in a way that is not typically seen in adulthood. For example, this type of SSRI-mediated hyperexcitability facilitates LTP in adult rat hippocampal neurons [24] and promotes remodeling of pyramidal cell dendritic spines [22, 25].

Like the end of the critical period, inhibitory tone rises again in the cortex of fluoxetine-treated adult animals on the order of days after monocular deprivation. This increase in inhibition, which re-establishes excitatory–inhibitory balance, is mediated by an SSRI-dependent increase in BDNF

[10] through either 5-HT_{1A} receptors [17] or the activity-dependent expression of the immediate early gene Npas4 [26], a transcription factor that promotes BDNF-dependent [27] inhibitory synaptogenesis [14, 28]. The restoration of homeostatic balance in the visual cortex of fluoxetine-treated, monocularly-deprived adult animals allows for the persistence and consolidation of these synaptic changes.

Human SSRI studies

The consequences of SSRI treatment appear to be similar in humans and animals. In the motor system of non-depressed healthy adults, a single dose of an SSRI decreases intracortical inhibition and cortical excitability (reviewed by 29) and decreases functional connectivity of a variety of brain networks [30, 31]. In contrast, long-term administration of SSRIs seems to stabilize new circuits that perform a given task more efficiently. For instance, chronic SSRI treatment reduces the spread of motor cortex activation induced by a difficult finger tapping task in a manner that is proportional to how well the task is performed [32, 33] and increases sensitivity to repeated visual stimulation as evidenced by larger visual evoked potential amplitudes after treatment [34].

Taken together, animal and human studies suggest that a single dose of an SSRI decreases intracortical inhibition to unmask pre-existing connections and establish new ones in an experience-dependent fashion, leading to the expansion of the cortical representation. On the other hand, chronic treatment leads to an increase in inhibition, a contraction of the cortical representation, and persistence of the novel and more efficient pathway. These two phases of SSRI-induced plasticity (Fig. 1) may be driven by the divergent effects of SSRI-induced BDNF expression, which depend on whether BDNF is up-regulated transiently or chronically [35].

SSRIs during monocular deprivation versus after stroke

In adult animal studies, SSRIs reopen the critical period by decreasing cortical inhibitory tone, which allows for an altered experience such as monocular deprivation to promote reorganization and reweighting of the cortical circuit. The type of plasticity characteristic of the critical period is also seen after ischemic injury in adulthood. Ischemia immediately reduces inhibitory synaptic transmission in perilesional tissue [36] through ipsilesional intracortical disinhibition [37, 38] and contralesional hyperactivation [39, 40]. These changes facilitate the unmasking and recruitment of pre-existing cortical connections to rewire the circuit [41]. On top of the decrease in inhibitory tone produced by ischemia, SSRIs given to mice shortly after an ischemic event reduces the expression of inhibitory markers in perilesional tissue

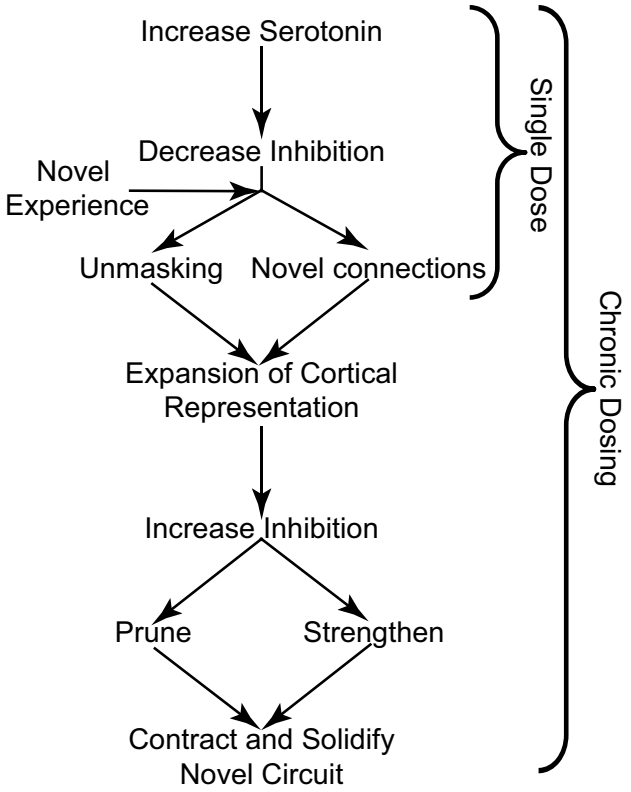

Fig. 1 Single-dose vs. chronic SSRI administration has different effects on cortical plasticity. The first dose of an SSRI decreases inhibition which allows a novel experience to impose changes in the cortical circuit through unmasking of existing connections or establishing new connections. Chronic SSRI treatment then completes the rewiring process and restores excitatory–inhibitory balance, thereby consolidating an efficient novel circuit

even further [20]. In addition, the extent of this reduction is associated with a prolongation of the sensitive period for successful forelimb rehabilitation [20]. Similarly, in subacute stroke patients, a single dose of fluoxetine causes hyperactivation of the ipsilesional primary motor cortex [42].

After rewiring and reweighting occurs in adult monocular deprivation SSRI experiments, chronic SSRI treatment re-establishes excitatory–inhibitory balance, which stabilizes the altered circuit. Similarly, in the months following the ischemic event in stroke patients with good recovery, excitatory–inhibitory balance of ipsilesional and contralesional tissue normalizes, with the return of normal levels of inhibition [39, 43, 44], and cortical recruitment disappears [41]. In contrast, stroke patients with poor recovery never show a restoration of excitatory–inhibitory balance, especially in the contralesional hemisphere [40]: it is as if the reopened critical period never closes and inhibition is chronically reduced. Other studies have found that restoration of excitatory–inhibitory balance, either through reducing inhibitory tone with GABA receptor agonists or increasing excitation with AMPA receptor modulators, can improve recovery after

stroke [45]. Since chronic SSRI treatment increases BDNF levels after stroke [46] and post-stroke BDNF levels are positively correlated with good functional outcomes [47], SSRIs may provide another way to address the excitatory–inhibitory imbalance in stroke patients with poor recovery. We propose that a three-month course of SSRI therapy improves recovery after stroke [3] because it completes the rewiring process and restores excitatory–inhibitory balance in both hemispheres, thereby consolidating an efficient and effective altered circuit in the ipsilesional hemisphere. Evidence for this proposal comes largely from studying the visual and motor domains; however, it is possible that similar processes are at play in the recovery of more complex, distributed functions after stroke: there is some evidence to suggest that SSRIs can also improve stroke patients' cognitive [48] and language [49] abilities.

A working model for SSRI-induced recovery after stroke

To summarize, we synthesize the following model to explain how SSRIs might enhance post-stroke recovery (Fig. 1). In the acute phase after a stroke, SSRIs enhance the excitability of perilesional cortex by decreasing inhibition, which allows for the reweighting of existing connections. In addition, SSRIs facilitate the development of new connections by removing the extracellular barriers to circuit remodeling (such as perineuronal nets) and boosting dendritic branch tip and axonal arborization dynamics. These changes, paired with rehabilitation therapies that challenge the damaged system, allow for greater experience-dependent plasticity, which facilitates functional recovery [50]. Finally, prolonged SSRI treatment leads to chronically elevated BDNF levels, which in turn increases local inhibition and restores the balance between excitation and inhibition. The restoration of the excitatory–inhibitory balance stabilizes the core of the novel circuit and prunes away redundant or inefficient components, leading to contraction of the cortical representation.

Future directions for studying SSRIs in post-stroke recovery

The current literature provides a rationale for using SSRIs to enhance recovery of neurologic function after an ischemic stroke. We see two opportunities for future research in this field: (1) investigation of the optimal dosing, timing and rehabilitation supplementation for this kind of treatment; and (2) exploration beyond the motor system to determine whether SSRIs can help enhance post-stroke recovery in other functional domains, such as vision and language.

SSRI dosing, timing and supplementation with rehabilitative therapies

To date, most studies investigating a role for fluoxetine in post-stroke recovery have used 20 mg of fluoxetine daily [3, 5, 51–54]. However, if a lower dose demonstrates similar efficacy, the likelihood of adverse effects with this treatment would diminish, especially in older patients [55]; this is an important open question that should be studied in animal stroke models and future clinical trials.

Our current understanding of the ideal timing for starting SSRI treatment after a stroke is "the sooner the better". SSRIs are less effective at promoting recovery if started later than one week after a stroke, but one study suggests that they remain more effective than placebo for up to 6 months [52]. It is possible, however, that SSRIs may have beneficial effects even beyond six months given that chronic stroke patients who received a single dose of an SSRI had greater muscle activity in the paretic arm five hours later [56]. Whether SSRI treatment facilitates recovery in chronic stroke patients has yet to be investigated with a randomized double-blind placebo-controlled clinical trial. The question of optimal treatment duration also remains unanswered.

Another open question is whether patients already on an SSRI at the time of the stroke might show a different recovery trajectory compared to SSRI-naïve stroke patients. There are conflicting data on how SSRI use before an ischemic stroke affects functional recovery [57, 58]. The antiplatelet effects of SSRIs [59] may cause poor outcomes in hemorrhagic stroke patients or in ischemic stroke patients treated with intravenous thrombolysis when the patient was on an SSRI before the stroke [60, 61]. It is also possible that the benefit of SSRI treatment after stroke depends on the acute peak in synaptic serotonin levels upon commencing treatment [62], in which case there may be no SSRI-dependent boost in recovery, if the patient was taking an SSRI before the stroke.

Additionally, it is unclear whether SSRIs improve stroke recovery independent of a rehabilitation program. In the FLAME study, all patients, regardless of treatment group assignment, received rehabilitation therapies [3]. In contrast, the more recent negative clinical trial, FOCUS, did not require that all patients receive rehabilitative therapies, nor did it report the percentage of patients who did receive therapy [55]. The possibility that SSRIs need to be paired with rehabilitative therapy to be an effective treatment for stroke recovery is supported by the studies we have highlighted here showing that rewiring occurs when SSRIs are paired with novel experience (such as monocular deprivation or physical therapy). Future studies with three arms (drug alone, therapy alone, drug plus therapy) could shed light on whether SSRIs need to be paired with rehabilitation to be maximally effective at promoting functional recovery.

Can SSRIs promote vision recovery after stroke?

While past [3–5, 48, 51–55, 63–66] and current clinical trials (AFFINITY, EFFECTS, FLOW, SELEIS, CISS, RECONISE, ELISA, and NCT02208466) studying the effects of SSRIs on stroke recovery have largely focused on strokes affecting motor function, we are currently conducting a randomized, placebo-controlled phase IIa exploratory clinical trial investigating a potential role for fluoxetine in promoting vision recovery in acute ischemic stroke patients with homonymous visual field deficits [67] (FLUORESCE: NCT02737930). Given that only 7.5–26% of stroke patients with homonymous visual field deficits completely recover vision [1, 68, 69] and that visual restoration therapy remains experimental in nature, with no currently proven rehabilitative treatment that enhances vision recovery in this patient population [70], the results from this and future pharmacological studies have the potential to expand the realm of possibilities for post-stroke vision restoration [71].

We have reason to believe that SSRIs will enhance vision recovery in hemianopic stroke patients for multiple reasons. First, as reviewed above, much of the basic research demonstrating the neuroplastic effects of SSRIs has been conducted in the visual system. Second, stroke patients with persistent hemianopia exhibit similar neural markers of poor recovery when compared to those with poor motor recovery, including persistent expansion of cortical activity [72, 73] and contralateral hemisphere activation [74–76]. Third, evidence of reorganization of the visual circuit has been detected in patients with spontaneous vision recovery after a stroke [73, 77]. Taken together, these studies suggest that SSRI administration in the first week after a stroke may push those with less potential for spontaneous vision recovery towards a more favorable outcome in the same way that it supports greater post-stroke motor recovery. In addition, since visual ability can be quantified with a high degree of spatial resolution using standard clinical measures (automated perimetry), and reorganization of the visual cortex can be probed using functional neuroimaging [78, 79], we believe future studies in the visual system have the potential to demonstrate not only the effectiveness of fluoxetine in post-stroke vision recovery, but also the neural substrates of fluoxetine-mediated plasticity after stroke.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standard The manuscript does not contain clinical studies or patient data.

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