Antidepressant Pharmacotherapy and Poststroke Motor Rehabilitation: A Review of Neurophysiologic Mechanisms and Clinical Relevance

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**Recommended Citation**
Elzib H, Pawloski J, Ding Y, and Asmaro K. Antidepressant Pharmacotherapy and Poststroke Motor Rehabilitation: A Review of Neurophysiologic Mechanisms and Clinical Relevance. Brain Circ 2019; 5(2):62-67.

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Antidepressant pharmacotherapy and poststroke motor rehabilitation: A review of neurophysiologic mechanisms and clinical relevance

Haya Elzib¹, Jacob Pawloski¹², Yuchuan Ding¹, Karam Asmaro²

Abstract:
According to the National Stroke Association, stroke is the leading cause of adult disability in the United States, where it is estimated that about 795,000 strokes occur on an annual basis. Minimizing the disability burden of a stroke routinely involves behavioral therapies such as physical and occupational therapy, as well as pharmacologic interventions. The positive effect of antidepressants on functional outcomes for patients with poststroke depression is well known and practiced. In the past 15 years, a growing body of evidence has demonstrated that antidepressant pharmacotherapy and selective serotonin reuptake inhibitors specifically have a role in the functional recovery from strokes even in the nondepressed population. The mechanisms by which antidepressants improve motor recovery following stroke are multifactorial, but it is clear that the process involves augmentation of cerebral blood flow, cortical excitation, and potentiation of neural growth factors all resulting in enhancement of neurogeneration. This review will examine the existing evidence and mechanisms behind antidepressant use for motor recovery in stroke patients and discuss the major human clinical trials that have been conducted surrounding this topic. The evidence clearly suggests that antidepressants have a positive impact on poststroke functional recovery regardless of the presence of depression, and although large-scale randomized, controlled trials are still ongoing, antidepressants are emerging as a promising pharmaceutical means of actively lessening the burden of disability following stroke.

Keywords: Antidepressants in stroke, pharmacotherapy of antidepressants, poststroke motor rehabilitation, stroke

Introduction
Poststroke depression (PSD) is a well-studied phenomenon that affects up to 30% of stroke patients and is associated with reduced quality of life and increased rates of disability and mortality.¹² The etiology of PSD is complex and multifactorial. While psychosocial factors such as poor social support, sleep disturbance, and disability have been implicated, multiple biological models for PSD have been described. The monoamine theory of depression, implicating a decreased availability of serotonin, norepinephrine, and dopamine in the natural disease process, has also been used to understand PSD.³ Following an ischemic insult, interruption of ascending axons from the brainstem and midbrain decreases the availability of monoamines in limbic structures of the frontal and temporal lobes.⁴ Alternatively, increased pro-inflammatory cytokine production following ischemia causes activation of enzymes that metabolize tryptophan and therefore deplete serotonin, potentially acting as an independent mechanism to precipitate the onset of PSD.⁵ Selective serotonin reuptake inhibitors (SSRIs)

How to cite this article: Elzib H, Pawloski J, Ding Y, Asmaro K. Antidepressant pharmacotherapy and poststroke motor rehabilitation: A review of neurophysiologic mechanisms and clinical relevance. Brain Circ 2019;5:62-7.
such as fluoxetine and paroxetine have been shown to counteract these neurobiological phenomena by directly increasing the availability of monoamines, as well as decreasing the expression of pro-inflammatory markers in animal models of cerebral ischemia. While SSRIs are now widely used as a treatment for PSD, there has been a growing interest in the neurophysiologic effects of SSRIs on the rehabilitation and motor recovery of the nondepressed stroke patient.

The current methods of rehabilitating patients following a stroke generally focus on behavioral or activity-based treatments such as physical and occupational therapies. While these practical, movement-based therapies can induce cortical reorganization, improve strength, and help patients maximize their remaining functional capacities, the high rate of disability following major stroke has warranted the search for ways to further improve the functional outcomes of stroke patients. Efforts to salvage motor function in this population have focused largely on ways to enhance neurogeneration in the peri-infarct zones, which improve motor recovery through neuronal production and increased synaptic connectivity in the lesioned brain. It is becoming clear that antidepressants, especially SSRIs, can play a significant role in improving motor recovery even in the absence of depression. Although the mechanisms underlying their effect in nondepressed stroke patients are multifactorial and not fully understood, there is evidence demonstrating that antidepressants improve stroke outcomes through augmenting cellular neuroprotective mechanisms, modulating cerebral excitation and inhibition, and inducing neural growth factor activity all resulting in potentiation of natural neurogeneration. This review will focus on these mechanisms and the evidence behind them and then summarize the major clinical trials [Table 1] demonstrating the efficacy of SSRIs in motor recovery of the nondepressed stroke patient.

Mechanism of Antidepressant Activity in Motor Recovery Following Stroke

Neural excitation and inhibitory modulation

Following a stroke, regulation of cortical excitation and inhibition is impacted by ischemia-induced neuronal death. The period following a stroke is punctuated by disinhibition of neural circuits and exaggerated neural excitation over both hemispheres. A balance between excitation and inhibition of neural circuits in the cerebral cortex is essential for motor learning and synaptic plasticity. Recovery from stroke requires a significant amount of cerebral reorganization, and this can be compared to the process of synaptic remodeling that occurs in motor learning. It has been suggested that SSRIs promote normalization of cerebral overexcitation and re-establishment of the natural inhibitory tone, which results in an improved capacity for cerebral plasticity and functional recovery.

The underlying mechanism is debated, but it has been suggested that many of these changes can be attributed to modulation of cortical γ-aminobutyric acid (GABA), a primary inhibitory neurotransmitter. Fluoxetine has been shown to augment cerebral excitation and inhibition by increasing levels of GABA via promoting neurogenesis of GABAergic interneurons. The same effect likely also contributes to the antidepressant effect of SSRIs in patients with major depression, who are known to have decreased cortical GABA. A randomized, controlled trial by Acler et al. using transcranial magnetic stimulation to detect cortical excitation following stroke demonstrated that patients who received citalopram in addition to physical therapy during their rehabilitation period had decreased cortical excitation and improved motor recovery as measured by their NIH Stroke Scale (NIHSS) when compared to those who received physical therapy alone.

A similar study was conducted to observe differences in the cortical levels of GABA in healthy individuals as well as patients 3–12 months poststroke and correlate changes in GABA signaling with exercise therapy to motor scores on the Wolf Motor Function Test (WMFT). GABA was found to be significantly decreased in patients following stroke. In addition, after 2 weeks of exercise therapy, the patients’ WMFT scores were improved in a magnitude comparable to the increase in cortical GABA measured by magnetic resonance spectrometry. This supports the idea that a decrease in cortical excitation or increase in inhibition has a positive effect on poststroke motor recovery. Although this study did not examine the effect of antidepressants on their study population, SSRI administration has previously been shown to increase cortical GABA concentrations. By increasing GABA activity, SSRIs could be preventing an imbalance of excitatory and inhibitory signaling that would normally impair poststroke neural plasticity and regeneration.

While this discussion has focused on the role of SSRIs in increasing cortical GABA and affecting neural inhibitory tone, the activity of SSRIs on the regulation of neural excitation and inhibition is multifactorial and complex, especially when considered in the setting of ischemic injury to the brain. In addition to the indirect effect on cortical inhibitory tone, increased levels of serotonin in the synaptic cleft with SSRI treatment enhance signal transmission directly, also leading to increased synaptic connectivity and enhanced neurogenesis through excitatory mechanisms. Pinto et al. included an excellent in-depth discussion on the mechanisms and effects of SSRIs on excitatory and inhibitory pathways involved in neurogenesis.
Augmentation of cerebral blood flow

SSRIs are known to augment cellular defense pathways that are initiated during ischemic injury as well as regulate cerebral blood flow through the direct activity of vasoactive monoamines. Both of these mechanisms result in improvement of stroke recovery either by a neuroprotective effect against ischemic injury or increase in cerebral blood flow to limit neuronal death in the peri-infarct area.

During ischemia, the hypoxic state initiates a cascade of cellular events that results in the induction of proteins that allow cells to protect themselves from ischemic injury. Specifically, heme oxygenase-1 (HO-1) and hypoxia-inducible factor-1α (HIF-1α) have been studied as an innate mechanism by which neurons and neuroglia combat ischemic injury. The connection between this innate neuroprotection and treatment with SSRIs was demonstrated by Shin et al. using a mouse model for cortical ischemia. In their study, mice were treated with sertraline or fluoxetine daily for 2 weeks following photothermotic vascular occlusion causing permanent ischemia. Mice treated with either SSRI demonstrated improved cerebral blood flow autoregulation, as demonstrated by the ability to maintain cerebral blood flow at lower mean arterial pressures as compared to control mice. This effect on cerebral blood flow was associated with a reduction in infarct size. These results were then correlated with increased expression of HIF-1α and HO-1 in the SSRI treatment group. In addition to induction of HIF-1α and HO-1, the direct vasodilatory effects of this increased serotonin on small cerebral vessels in the treatment group likely also contribute to the reduced infarct size and improved blood flow. These results suggest that prompt administration of an SSRI in the acute phase following stroke can have a potentially neuroprotective effect in addition to the long-term benefits associated with chronic administration.

Neurotrophic growth factor induction

A well-known mediator of neuroplasticity and regeneration, brain-derived neurotrophic factor (BDNF) is being actively investigated for its activity following ischemic stroke as well as a potential mediator of SSRI effect on major depression. BDNF is a member of the neurotrophin family that includes nerve growth factor and neurotrophins 3 and 4. One specific case of neuroplasticity in which BDNF is implicated is the memory and learning induced by long-term potentiation (LTP) of neurons in the hippocampus. BDNF-deficient mice demonstrated reduced early- and late-phase LTP in hippocampal CA1 synapses, and this was associated with poorer performance on certain learning tasks. BDNF exerts its effects through a variety of molecular pathways that result in augmentation of transcription and translation of mRNAs at the neural synapse which then induces neuron maturation and synaptic development and plasticity.

The BDNF signaling pathways are active during all forms of motor learning but are also implicated in the recovery from certain pathologic brain injuries such as stroke. Stroke-induced expression of BDNF in the cortical areas, adjacent to the infarct, has been shown to aid in the neurogenesis and motor recovery process. Deposition of BDNF into infarct areas of mice resulted in increased axonal sprouting, migration of immature neurons into the peri-infarct territory, and improved motor recovery following infarct. In addition to neurogeneration associated with motor learning and stroke recovery, BDNF has also been implicated in the positive effects associated with antidepressants in the treatment of depression.

Antidepressants directly affect the extracellular concentrations of monoamine neurotransmitters such as serotonin and norepinephrine, and these increases in concentration happen on the order of hours. However, the clinical benefit of antidepressants in depression can require up to 6–8 weeks to become evident. Because of this delay, it was thought that antidepressants may exert their clinically relevant activity via an alternative mechanism such as neurogeneration. It is now known that BDNF plays a crucial role in the neuroplastic changes that take place in the setting of antidepressant use and that the increased activity of BDNF may be a primary means by which antidepressants exert their positive effects. Antidepressants as well as electroconvulsive
therapy enhanced the expression of BDNF in the same time frame as the antidepressant effects of the drugs.\textsuperscript{[26]} Taken together, these studies suggest that BDNF is an important mediator of the neuroplastic changes required for motor learning and recovery following stroke and that administration of SSRIs is involved in inducing BDNF activity.

**Neurogeneration**

The ability of SSRIs to potentiate neurogenesis through a variety of pathways is likely a significant source of their efficacy in stroke rehabilitation. Many factors impact the degree of neurogenesis occurring in the brain including location, age, stress, ischemia, behavioral activities, and pharmacological agents.\textsuperscript{[27]} Animal models have demonstrated that neurogenesis occurs focally in the dentate gyrus of the hippocampal formation following cerebral ischemia.\textsuperscript{[28]} Chronic treatment with SSRIs has now been implicated in neurogenesis through variety of studies utilizing animal models.\textsuperscript{[9,29]} In a mouse model of cerebral ischemia, mice which were treated with fluoxetine for 28 days demonstrated improved performance in spatial cognitive performance testing and increased neurogenesis in the dentate gyrus compared to control group.\textsuperscript{[30]} Furthermore, the improvements noted in spatial cognitive functioning with treatment with fluoxetine were eliminated when mice were treated with a telomerase inhibitor to prevent cell division. This suggests that increased neurogenesis is at least partly implicated in the positive effects of fluoxetine on poststroke recovery. A similar, more recent study in rats that underwent transient cerebral vessel occlusion to induce ischemia demonstrated enhanced poststroke neurogenesis with SSRI treatment, as well as a decrease in inflammation at the cellular level and increase in the functional recovery of the animals.\textsuperscript{[31]} In addition to the effects of SSRIs, animal studies utilizing the atypical antipsychotic aripiprazole have demonstrated enhanced neurogeneration in the hippocampus and increased the recovery of dopaminergic neurons in the striatum following ischemic injury.\textsuperscript{[32,33]} These results may be due to the partial agonist activity of aripiprazole at D2 receptors and demonstrate that dopaminergic modulation can also play a role in neurogeneration.

Importantly, the individual mechanisms behind antidepressant drug activity already discussed have also been shown to potentiate neurogenesis, demonstrating how this induction of neurogenesis serves as a unifying feature associated with a variety of SSRI activities. Thus, while there are many individual mechanisms to explain the beneficial effects of antidepressants on stroke recovery, their impact on neurogenesis can be viewed as a common denominator or conduit by which these various neurophysiological activities produce a lasting improvement in motor function.

**Clinical Significance**

Several clinical studies have demonstrated that antidepressants improve physical recovery and motor function independent of the presence of depression in the study population.\textsuperscript{[34,35]} The FLAME trial demonstrated that among 113 patients randomized, the improvements in Fugl-Meyer motor scale scores were significantly higher in those patients receiving fluoxetine for 3 months versus those receiving placebo (34-point increase compared to 24-point increase). All patients in the study received physical therapy in addition, and the impact of fluoxetine was independent of the status of depression in the patients.\textsuperscript{[34]} Similarly, Mikami et al. reported on a double-blinded randomized trial in which patients recovering from stroke ($n = 83$) were randomized to receive fluoxetine, nortriptyline, or placebo for 3 months. During a 1-year follow-up period, depression was assessed using the Hamilton Depression Rating Scale and disability was measured using a modified Rankin Scale. After controlling for the presence of depression, age, and baseline stroke disability, patients receiving antidepressants demonstrated less disability at 1 year following stroke or 9 months following the discontinuation of their antidepressant treatment.\textsuperscript{[35]} These results are significant because they demonstrate clinically that the pharmacological effect of antidepressants in poststroke recovery has some degree of permanence. These results support the idea that these drugs have definite effects on neurogeneration and neurobiology as discussed above.

A recent randomized, controlled trial enrolled 144 poststroke patients to receive either citalopram or placebo for 3 months, and the NIHSS was measured upon enrollment and completion of the study period. Importantly, patients with depression were excluded from the study. Following 3 months, 79\% of patients who received citalopram compared to 54\% of patients who received placebo demonstrated a 50\% or greater improvement in their NIHSS, a statistically significant improvement.\textsuperscript{[36]}

Of note, several smaller studies have demonstrated that even a single dose of an SSRI can have a beneficial impact on hand dexterity. One such trial observed recovering stroke patients ($n = 8$) performing a clinical motor test before and after a single dose of fluoxetine and demonstrated improved motor functioning with the therapy.\textsuperscript{[11]} As mentioned above, a blinded, randomized controlled trial by Acler et al. demonstrated, in addition to decreased cortical excitation, an improved motor recovery following a single dose of citalopram.\textsuperscript{[12]}

The differing modes by which SSRIs augment neurobiology are important for understanding the
mechanism behind the beneficial effects of a single dose of antidepressant compared to chronic administration. The results of a single administration are more likely associated with the direct augmentation of cerebral blood flow and neurotransmitter concentrations at the cortical synapses and their associated effects on cortical excitability, as opposed to the effects of chronic administration in which their effects on neural growth factor induction and neurogenesis play a more significant role.

Conclusion

Antidepressants result in a variety of chemical modifications within the healthy and diseased brain that have important physiological consequences in the setting of stroke. Cerebral ischemia and infarct set off a chain of events at the cellular level in the entire brain that include: induction of proteins involved in cellular protection from ischemia, augmentation of the excitatory and inhibitory neural pathways leading to overall increased cortical excitability, and induction of neural growth factors and neurogenesis in the peri-infarct zones which contribute to synaptic development as the brain attempts to reorganize following the ischemic insult. These changes are all affected by the administration of SSRIs in the immediate poststroke period as well as chronically during the rehabilitation process. The neurophysiological effects of SSRIs have been well-studied both in the context of major depression and other pathologies such as cerebral ischemia, and the beneficial effects of SSRIs on the functional recovery process following stroke have been demonstrated in large clinical trials. Treatment with SSRIs has also been shown to be safe and even beneficial in stroke patients. The use of SSRIs following stroke in addition to traditional rehabilitation methods should be considered a safe and effective method to improve functional recovery, regardless of the presence of major depression. Interesting topics for future research in this area may focus on differentiating between the effects of different members of the SSRI drug class, as well as identifying the optimal time frame for initiation and discontinuation of pharmacologic treatment to give maximal benefit for patients undergoing stroke rehabilitation. Although SSRIs are generally safe to use and can improve stroke outcomes, objective evidence related to the effect of SSRIs on mood regulation and other associated psychiatric or neurocognitive changes in the nondepressed patient is currently lacking, and this represents an area of interest if SSRIs are to be used routinely for stroke rehabilitation. Ongoing large-scale clinical trials studying the role of fluoxetine, or other antidepressants, for poststroke recovery will continue to provide valuable evidence regarding the use of SSRIs following stroke. It is important to emphasize the need for future large-scale clinical trials to further strengthen the body of evidence supporting the efficacy and safety of antidepressant use in nondepressed stroke patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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