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Serotonin's Potential as a Treatment for Ischemic Heart Disease

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ABSTRACT
The largest cause of mortality and neurological impairment in the world today is stroke. Survivors of an ischemic stroke often have impairment in motor function, visual field defect, speech difficulties, and depression, among other symptoms. While cerebral ischemia is occurring, the levels of many neurotransmitters in the brain, including dopamine, 5-hydroxytryptamine or serotonin, norepinephrine, and glutamate, change, and these changes contribute to the pathophysiology of cerebral ischemia. Despite the fact that the overall impact of serotonin in cerebral ischemia is still unknown, there is evidence that increased serotonin activity in the hippocampus protects neurons from damage after ischemia. Furthermore, multiple studies have shown that selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, and serotonin agonists may decrease the size of brain infarcts and enhance functional recovery after stroke. When it comes to cerebral ischemia, there are a variety of mechanisms that might explain the neuroprotective impact of SSRIs such as fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram, among others. They have antioxidant, anti-apoptotic, and anti-inflammatory properties, which are responsible for their success in the prevention and treatment of stroke. In this review, we will go through the function of serotonin in ischemia as well as the potential mechanisms underlying the neuroprotective effects of selective serotonin reuptake inhibitors (SSRIs) in stroke.

Keywords: *Stroke, selective serotonin reuptake inhibitors, serotonin, glutamate, antioxidant*

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INTRODUCTIONS
When it comes to medical crises, ischemic stroke is one of the most dangerous since it is connected with a high death rate. In the United States, around 800 thousand people have a new or recurrent stroke each year; roughly 610,000 of these instances are initial attacks and 185,000 are recurring attacks. According to the Egyptian Ministry of Health, the crude prevalence rate of stroke is 963/100 000 inhabitants[1]. Stroke is caused by thrombi in 45 percent of cases, and emboli in approximately 20 percent of cases [2], with hemorrhagic stroke being less common. Ischemic stroke accounts for 85 percent of all instances of stroke.

In most cases, patients who survive ischemia have a worsening in their motor capabilities as well as an inability to comprehend or construct speech [2, 3]. As a result of its association with greater impairments and suicidal ideation, stroke-induced depression is becoming more popular as a therapy option [5, 6].

2. The role of neurotransmitters in the brain during an ischemic stroke
Neuronal ischemic damage and cell death are caused by the release of many excitatory and inhibitory neurotransmitters, such as glutamate, dopamine, norepinephrine, and serotonin, when the brain is ischemia-inducible.

2.1 Glutamate is a kind of amino acid.

It has been shown that ischemia-induced neuronal depolarization and calcium ion excess are the most important factors contributing to the release of non-physiological levels of the excitatory neurotransmitter glutamate. Increased sodium ion, potassium ion and hydrogen ion inflow produces membrane depolarization and excessive calcium ion entry [6, 7]. Glutamate acts on both ionotropic and metabotropic receptors, causing increased sodium ion, potassium ion and hydrogen ion influx and membrane depolarization. Increased lipolysis, protein phosphorylation, proteolysis, and disaggregation of cytoskeletal components are all caused by a disruption in calcium homeostasis, which results in irreparable neuronal injury. This also affects gene expression, causing it to increase in the expression of immediate genes such as c-fos and c-jun, which are activated during ischemia [8, 9]. These mechanisms result in mitochondrial failure, disruption of axon transport, membrane disruption, apoptosis, and cell death, among other things.

2.2 Catecholamines: A class of neurotransmitters that are found in the brain.

Following ischemia, a large amount of monoamine neurotransmitters such as norepinephrine (NE), dopamine, and serotonin are released. Extracellular dopamine levels are significantly raised after cerebral ischemia and then rapidly revert to normal levels following reperfusion [10]. In addition, it exacerbates neuronal damage by the generation of numerous free oxygen radicals, which enhance the permeability of the blood brain barrier and damage cellular proteins, nucleic acids, and polyunsaturates [11-13].

Cerebral norepinephrine levels are temporarily elevated following ischemia in the same way as dopamine levels are [14]. The selective depletion of norepinephrine in the brain before induction of ischemia in male rats resulted in a decrease in the extent of the cerebral infarct [15], indicating that norepinephrine has a detrimental influence on the development of stroke. A neuronal death study in the hippocampus cornu ammonis (CA)1 and CA3 areas following BCCAO found that inhibition of ischemia-induced norepinephrine release by dexmedetomidine, an α_2-agonist, reduced neuronal death in the CA1 and CA3 regions [16]. norepinephrine, on the other hand, has been shown in multiple studies to have a neuroprotective impact following ischemia. It was stated by Chen and Russo-Neustadt that brain derived neurotrophic factor and numerous pro-survival signaling molecules are increased in the hippocampus as a result of norepinephrine's ability to increase the expression of these molecules[17]. When the norepinephrine system was stimulated with atipamezole, a selective β_2-adrenoceptor antagonist, sensorimotor performance in rats after focal cerebral Ischemia/ Reperfusion damage was examined [18], it was discovered that the rats' sensorimotor performance improved. In addition to the neurotransmitters previously mentioned, serotonin plays an essential role in the pathogenesis of ischemic stroke.

3. Serotonin: a neurotransmitter.

Serotonin is a neurotransmitter that has a broad variety of actions in the body, including the regulation of mood. This compound is produced by the hydroxylation of the amino acid tryptophan to provide 5-hydroxytryptophan, which is then decarboxylated [19]. In humans, serotonin is found mostly in the blood platelets, enterochromaffin cells of the intestinal mucosa, and particular parts of the brain [20, 21]. Serotonin operates on 5-hydroxytryptamine receptors, which are classified into seven subtypes: 5-hydroxytryptamine 1, 5-hydroxytryptamine 2, 5-hydroxytryptamine3, and 5-hydroxytryptamine 4, 5-hydroxytryptamine 5, 5-hydroxytryptamine6 and 5-hydroxytryptamine7. These receptors are found in a broad variety of organs throughout the body, including the brain. It has been discovered that the 5-hydroxytryptamine2A receptor subtype is found in platelets, but the 5-hydroxytryptamine 2A receptor subtype is found in the stomach. 5-hydroxytryptamine1B and 5-hydroxytryptamine2C receptor subtypes are found in the substantia nigra area, while 5-hydroxytryptamine1E and 5-hydroxytryptamine2C receptor subtypes are found in the CA1 region of the hippocampus, respectively.

5-hydroxytryptamine causes platelet aggregation [21] and modulates the motility of the gastrointestinal tract [22]. Besides that, it controls cerebral and peripheral vascular tone [23], regulates blood pressure [24, 25], and has a role in the pathogenesis of hypertension as well as pulmonary hypertension. It is involved in the regulation of sleep, body temperature, sexual behaviour, and emesis in the central nervous system [26-29]. Low serotonin levels in the brain have been linked to mania, depression, schizophrenia, and anxiety disorders [23, 26].

3.1 Serotonin-inhibiting medications

Drugs that impact the serotonin system work by either increasing its effect (agonists or reuptake blockers) or decreasing its effect (antagonists). Many of these medications are used in clinical settings to treat a variety of disorders. In addition to selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors (SNRIs), and5-hydroxytryptamine1 partial agonists such as buspirone and gepirone, several depressive disorders, such as generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), depression, and panic disorder, are clinically indicated [30]. [31] Sumatriptan, a 5-hydroxytryptamine 1B agonist, is a medication that is often used to treat migraine attacks.
5-Hydroxytryptamine3 binding antiemetic agents such as ondansetron, granisetron, and tropisetron are frequently used in the treatment of acute chemotherapy-induced emesis as well as postoperative nausea and vomiting. Risperidone is an antipsychotic medication that works by blocking 5-Hydroxytryptamine 2A/2C receptors.

3.2 Post cerebral ischemia: Changes in the levels of serotonin in the brain.

Cerebral ischemia results in changes in the concentration of serotonin in the cerebral cortex. The description of these adjustments, on the other hand, is fraught with controversy. An animal model of neonatal hypoxia-ischemia was used in the studies by Buller, Wixey [31] and Wixey, Reinebrant [32], and the results showed a disturbance of the serotonergic system and a drop in the 5-Hydroxytryptamine level in the forebrain. According to [33], an increase in the extracellular concentration of serotonin in the corpus striatum and hypothalamus of gerbils after heat stroke-induced cerebral ischemia was seen in the corpus striatum and hypothalamus. A rise in 5-Hydroxytryptamine levels has also been documented by Sarna and Obrenovitch [34] after temporary global cerebral ischemia. A modification in the 5-Hydroxytryptamine1A receptor which was time-dependent was observed in global cerebral ischemia, there was a significant increase in receptor expression in the hippocampus. During the first two days of ischemia insult, the expression was decreased, but after five days of ischemia and reperfusion, the expression was dramatically raised [35].

3.3 The role of serotonin regulation in the treatment of cerebral ischemia

It is currently unknown what role serotonin plays in the neuronal damage caused by cerebral ischemia on a systemic level, however. Several research supported its neuroprotective function, but only a small amount of data supported the assumption that it had negative effects. Globus and Wester [36] discovered that serotonin had an excitatory impact on neurons in the CA1 receptors and that it caused neuronal damage by acting on 5-Hydroxytryptamine receptors in the brain. They also discovered that the treatment with ritanserin, a 5-Hydroxytryptamine antagonist, significantly reduced the neuronal damage caused by ischemia in the two-vessel blockage plus hypotension model of ischemia. Another 5-Hydroxytryptamine antagonist, naftidrofuryl, administration of gerbils 5 minutes prior surgery which was used in a bilateral carotid artery blockage model, was shown to prevent neuronal damage generated by ischemia in the brain [37]. Furthermore, reduction of brain serotonin in heatstroke rats increased the length of time the animals survived and reduced the severity of heatstroke-induced ischemia and neuronal damage [38].

The opposite is also true, as shown by a number of studies demonstrating its ability to reduce excitotoxicity and neuronal damage after cerebral ischemia.

Animal models of cerebral ischemia were treated with a variety of selective serotonin reuptake inhibitors, some of which were protective, while others were therapeutic. Improvements in neurobehavioral outcomes and histological findings, as well as an increase in antioxidant capacity, along with a decrease in cerebral infarct volume and the expression of various inflammatory mediators and apoptotic markers in the cerebral cortex, have all been reported [30].

4. The use of a selective serotonin reuptake inhibitor in the treatment of cerebral ischemia

Various mood disorders, such as major depression, bipolar depression, panic disorder, obsessive-compulsive disorder, dysthymia, and others, are treated with selective serotonin reuptake inhibitors such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and escitalopram. Furthermore, they are utilized in the treatment of premenstrual dysphoric disorder and eating disorders. These drugs are quite tolerated, have a low occurrence of adverse effects, and are not harmful in large doses [39].

In this review, we will explore the neuroprotective effects of selective serotonin reuptake inhibitors in cerebral ischemia.

4.1 Fluoxetine: a prescription medication.

A number of animal investigations and clinical research have shown that fluoxetine has a neuroprotective effect in the context of stroke. According to previous studies [40-42], fluoxetine was found to alleviate cognitive and neurobehavioral impairments, improve long-term functional recovery, and reduce cerebral infarct volume in cerebral ischemic stroke caused by middle cerebral artery occlusion when administered for 3 days before induction of ischemia or used as a therapeutic agent and administered 30 minutes, 3 hours, or 6 hours after induction of ischemia in middle cerebral artery occlusion. Also, fluoxetine improved ischemia-induced memory deficits in the Y-maze task and inhibited ischemia-induced locomotor hyperactivity after global cerebral ischemia induced by a bilateral common carotid artery occlusion model [43, 44]. Aside from that, in a three-vessel occlusion model of global transient cerebral ischemia, the treatment with fluoxetine for 10 days before surgery increased neurogenesis and improved survival after ischemia [45].

In addition to experimental investigations, clinical trials have shown its efficacy in the treatment of stroke patients. A clinical investigation in individuals with acute ischemic stroke revealed that therapy with fluoxetine for 90 days at a 20 mg dose was effective in reducing the risk of 3 years recurrent stroke[46]. A further investigation found that a single dosage of fluoxetine was sufficient to dramatically enhance the sensory-motor abilities of the afflicted side in individuals who had had a stroke [47].

4.2 Paroxetine: a medication used to treat high blood pressure.

Paroxetine is another member of the selective serotonin reuptake inhibitor family that has shown to be neuroprotective against stroke. For example, it has been shown to attenuate memory losses and to demonstrate antioxidant activity after ischemia and reperfusion damage produced by bilateral common carotid artery occlusion[48]. Its treatment at a dosage of 10 mg/kg either before or after ischemia and reperfusion damage increased the number of viable cells in the CA1 hippocampal area, which resulted in better outcomes on the Morris water maze, which is a test used to measure learning and memory function [49]. In an in vitro oxygen-glucose deprivation model of ischemia, paroxetine alone or in combination with everolimus, an immunosuppressive drug, increased cell survival and decreased inflammation caused by ischemia[50]. Furthermore, in a mouse model of persistent focal ischemia, sertraline decreased the extent of the cerebral infarct and increased the antioxidant capacity [51].

Previously conducted research on the use of paroxetine as a prophylactic or as a therapeutic therapy for depression were remarkable for their comparison. Paroxetine administration as a therapeutic drug after temporary bilateral common carotid artery occlusion resulted with greater improvement in neurological outcomes, better expression of antioxidant enzymes, and higher levels of brain derived neurotrophic factor than administration of paroxetine prior to induction of bilateral common carotid artery occlusion[48]. On the other hand, Paroxetine was also substantially identical whether administered before or after brief bilateral common carotid artery occlusion, the improvement in memory impairments and the percentage of viable cells in the hippocampus were virtually the same [48, 49].

4.3 Fluvoxamine

A study in rats showed that fluvoxamine decreased the size of the infraction in a model of focal cerebral ischemia. It also showed improvement in somatosensory function, as shown by the hindlimb and forelimb placement tests.

Following middle cerebral artery occlusion surgery, the administration of fluoxetine resulted in the same decrease in infarct volume and improvement in neurobehavioral outcomes [52, 53]. Another research found that administering fluvoxamine to poststroke patients decreased the depression as well as their central poststroke pain when measured using a visual analogue scale, which is a tool used to determine the frequency or severity of different symptoms [54].

4.4 Citalopram: an antidepressant medication.

It was discovered that citalopram has anti-inflammatory and antioxidant effects in a rat model of focal cerebral ischemia when it was tested. In a 2 h middle cerebral artery occlusion model of ischemia, it was shown to diminish cerebral infarct volume, grip test score, and neurological impairment score when given before and post, pre and post administration [55]. A second study found that citalopram protected CA1 pyramidal cells after transient cerebral ischemia in gerbils by preventing the accumulation of excitatory amino acids, glutamate and aspartate, during and after forebrain ischemia [56]. It also found that citalopram decreased glutamate release from lipopolysaccharide-activated microglia, which in turn increased the survival of oxygen-glucose deprived-injured neurons [57]. More specifically, citalopram was shown to increase neurogenesis and improve somatosensory function in the peri-infarct area of the brain after ischemia and reperfusion damage [58]. Furthermore, clinical reports have demonstrated that daily oral administration of citalopram at a dose of 20 mg improved motor recovery in patients with acute ischemic stroke, as measured by the National Institutes of Health Stroke Scale (NIHSS) scores, and facilitated the rehabilitation of these patients [59, 60]. Recurrent vascular events, such as those that might occur after an ischemic stroke, were also decreased by this treatment [60].

Escitalopram, the therapeutically active S-enantiomer of citalopram, was found to have a neuroprotective effect in the presence of cerebral ischemia in rats. Pre- and post-treatment with this agent reduced the amount of neuronal death in the CA1 hippocampal region caused by ischemia and reperfusion injury in the CA1 region. On the other hand, when it was given as a preventive agent after 5 minutes of common carotid occlusion, brain derived neurotrophic factors were shown to be produced at much greater levels [61]. Clinical studies have also shown the efficacy of the drug. Patients with acute ischemic stroke who received escitalopram for three months had better neuronal function, according to a recent study [62].

5. Serotonin/norepinephrine reuptake inhibitors and other antidepressants: Evidence to have a protective effect against cerebral ischemia in animal models.

Some experimental research has proven the neuroprotective benefits of serotonin/norepinephrine reuptake inhibitors and other antidepressants following cerebral ischemia and reperfusion damage, in the same way that selective serotonin reuptake inhibitors have. A four-day therapy with desipramine, a tricyclic antidepressant, venlafaxine, a serotonin/norepinephrine reuptake inhibitor, and trazodone, an atypical antidepressant, dramatically reduced mitochondrial dysfunction and oxidative stress in mice following a partial global cerebral ischemia and reperfusion injury. They were able to restore normal levels of catalase and superoxide dismutase and to mediate their actions via the nitric oxide-cGMP pathway [63]. Furthermore, pretreatment with duloxetine, an serotonin/norepinephrine reuptake inhibitor, inhibited the activation of astrocytes and microglia in the ischemic (CA1) area and increased the production of superoxide dismutase in CA1 pyramidal neurons following acute global cerebral ischemia [64]. In addition, after

transitory ischemia in the CA1 area, duloxetine, either before or following the administration of atomoxetine, reduced glial activation in the CA1 region and enhanced neuronal outcomes in the CA1 region after hypoxic ischemia [65]. Atomoxetine increases the expression of brain-derived neurotrophic factor, which increases the activity of various antioxidant enzymes and has antiapoptotic properties[66,67,67,69]. These findings suggested that increasing both serotonin and norepinephrine transmission in the brain might be a potentially viable therapeutic approach for the treatment of cerebral ischemia in the future.

6. Proposed mechanisms of neuroprotective action of selective serotonin reuptake inhibitors and serotonin/norepinephrine reuptake inhibitors in case of cerebral ischemia .

The neuroprotective effects of selective serotonin reuptake inhibitors after ischemia and reperfusion damage are thought to be caused by a variety of different mechanisms. According to some theories, the anti-inflammatory and antioxidant properties of fluoxetine may be responsible for its neuroprotective effects after cerebral ischemia. It inhibits the production of various inflammatory mediators, including interleukin-1, tumor necrosis factor-α, and cyclooxygenase-2. It also has the additional effect of decreasing the activity of the proinflammatory mediator NF-κB after ischemia and reperfusion damage [42]. On the other hand, fluoxetine enhances the production of the brain derived neurotrophic factor, which supports the survival of neurons while also increasing the activity of several antioxidant enzymes such as glutathione peroxidase, catalase, and superoxide dismutase-1[44]. Fluoxetine also has an antiapoptotic effect, as it decreases the expression of various apoptotic markers, such as caspase-3 and caspase-12, in the hippocampus following ischemia and reperfusion damage, and thus suppresses the induction of endoplasmic reticulum stress-induced apoptosis in the hippocampus [40]. In a study conducted by Hu, Liu [41], Shin, and Kang [51], it was shown that fluoxetine stimulates the expression of heme oxygenase-1 (HO-1), which catalyzes the synthesis of biliverdin and bilirubin, both of which have antioxidant properties. It also stimulates the production of hypoxia-inducible factor-1α, which improves neuronal survival and enhances angiogenesis after ischemic brain injury or insult. Moreover, it promotes hippocampus regeneration, reduces neuronal loss, and increases the number of microglial cells, after cerebral ischemia[45, 67].
It was also reported that fluoxetine improves the blood-brain barrier integrity by inhibiting the expression of several matrix metalloprotease enzymes (2 and 9), as well as reducing the disruption caused by ischemia [43]. Fluoxetine has also been shown to improve the blood-brain barrier integrity.

Fluoxetine, paroxetine, and sertraline are anti-inflammatory and antioxidant medications, and it is these qualities that are responsible for their neuroprotective benefits after ischemia and reperfusion damage. Paroxetine and sertraline, according to Sheikholeslami, Ghafghazi [48], Gaur, and Kumar [68], lower malondialdehyde and nitric oxide levels in the brain while increasing the activity of antioxidant enzymes glutathione peroxidase, catalase, and superoxide dismutase-1 in the brain. Paroxetine also causes an increase in the expression of brain-derived neurotrophic factor and an increase in the proportion of viable cells in the hippocampus after ischemia [48, 49].

According to Tanimukai et al. [53], the drug fluvoxamine induces the expression of sigma-1receptor, a receptor that is expressed on the endoplasmic reticulum membranes and inhibits calcium ion influx through the N-methyl-D-aspartate receptor while also regulating the release of neurotransmitters such as dopamine [69]. This reduces endoplasmic reticulum stress and reduces cerebral infarct volume. Malondialdehyde and nitric oxide levels are decreased as a result of the action of the apoptotic markers caspase-3, caspase-9, matrix metalloproteinase enzyme2, and matrix metalloproteinase enzyme9, and the activity of caspase-3 is reduced, when citalopram is administered. It also has the additional effect of decreasing the production of inflammatory mediators such as tumor necrosis factor-α and interleukin-1β, which help to alleviate ischemia-induced cell death and inflammation [55-57]. Escitalopram, like fluoxetine and paroxetine, increases the expression of brain-derived neurotrophic factor and decreases ischemia-induced oxidative stress. It also has the additional effect of decreasing microglial activity in the CA-1 hippocampus area [61].

Anti-oxidant, anti-apoptotic, and anti-inflammatory properties of serotonin/norepinephrine reuptake inhibitors and other antidepressants are also involved in the neuroprotective impact of these medications. The antidepressants atomoxetine, duloxetine, and venlafaxine increase the expression of various antioxidant enzymes such as catalase and superoxide dismutase, among others. Atomoxetine also increases the production of brain-derived neurotrophic factor, which protects neurons from injury and promotes cell survival [65, 66, 68].

All of the previously discussed processes explained the neuroprotective effects of different selective serotonin reuptake inhibitors in experimental cerebral ischemia generated in various animal models, and they were all valid. The anti-inflammatory, anti-oxidative, and anti-apoptotic activities of these compounds decreased cerebral infarct extent, increased neuronal survival in the CA1 hippocampal area, alleviated neurobehavioral impairments, and improved functional results with traumatic brain injury. To summarize, additional clinical studies are needed to determine whether or not selective serotonin reuptake inhibitors are an effective treatment option for ischemic stroke.

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