

Therapeutic Potential of Serotonin in Ischemic Stroke

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Abstract

Stroke is a leading cause of death and neurological disability worldwide. Survivors of ischemic stroke usually suffer from impairment in motor function, visual field defect, speech disorders and depression. Cerebral levels of several neurotransmitters such as dopamine, 5-hydroxytryptamine (5-HT) or serotonin, norepinephrine (NE) and glutamate alter during ischemia and contribute to the pathophysiology of cerebral ischemia. The overall effect of serotonin in cerebral ischemia is still unclear but there are evidences that enhancement of serotonin activity in the hippocampus exerts protection against neuronal damage after ischemia. Besides, several studies showed that selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs) and serotonin agonists reduced cerebral infarct size and improved functional recovery after stroke. There are different mechanisms that may explain the neuroprotective effect of SSRIs such as fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram and escitalopram in cerebral ischemia. They exert antioxidant, antiapoptotic and anti-inflammatory activities which are responsible for their effectiveness in stroke. In this review, we will discuss in detail the role of serotonin in ischemia and the proposed mechanisms of the neuroprotective role of SSRIs in stroke.

Keywords

Stroke, SSRIs, serotonin, glutamate, antioxidant.

1. Introduction

Ischemic stroke is one of the medical emergencies which is associated with a high rate of mortality. Each year, about 800 thousand patients experience a new or a recurrent stroke, approximately 610000 of these cases are first attacks and 185000 are recurrent attacks. In Egypt, the crude prevalence rate of stroke is 963/100 000 inhabitants [1]. Ischemic stroke accounts for 85% of all stroke cases, 45% are caused by thrombi and about 20% are caused by emboli while hemorrhagic stroke is less prevalent [2]. Patients who survived after ischemia usually suffer from deterioration in their motor functions and inability to understand or formulate speech [3, 4]. Stroke-induced depression is usually associated with increased disabilities and suicidality which make its treatment a target of interest [5].

2. Role of brain neurotransmitters in ischemic stroke

Cerebral ischemia triggers the release of several excitatory and inhibitory neurotransmitters that participate in neuronal ischemic damage and cell death as glutamate, dopamine, norepinephrine and serotonin.

2.1 Glutamate

Neuronal depolarization and Ca^{+2} overload induced by ischemia are the main reasons for the release of non-physiological amounts of the excitatory neurotransmitter glutamate [6]. Glutamate acts on both ionotropic and the metabotropic receptors, increases Na^+ , K^+ , and H^+ influx which causes membrane depolarization and

excessive Ca^{+2} entry [6, 7]. Loss of calcium homeostasis causes irreversible neuronal damage by induction of lipolysis, protein phosphorylation, proteolysis and disaggregation of cytoskeletal components. It also alters gene expression and induces expression of immediate genes as c-fos and c-jun that are activated in ischemia [8, 9]. These processes lead to mitochondrial dysfunction, disturbance of axon transport, membrane disruption, apoptosis and cell death.

2.2 Catecholamines

Massive release of several monoamine neurotransmitters as NE, dopamine and serotonin also occurs after ischemia. Extracellular dopamine levels are highly elevated during cerebral ischemia then returned to their normal levels after reperfusion [10]. It exacerbates neuronal damage through formation of several free oxygen radicals that increase blood brain barrier permeability and damage cellular proteins, nucleic acids and poly unsaturated fatty acids [11-13].

As dopamine, cerebral norepinephrine levels are also temporary increased during ischemia [14]. Selective depletion of NE in the brain before induction of ischemia in male rats showed a reduction in cerebral infarct size [15] which suggested the deleterious effect of NE in development of stroke. Inhibition of ischemia-induced NE release by dexmedetomidine, an α_2 -agonist, ameliorated the neuronal death in the hippocampal cornu ammonis (CA)1 and CA3 regions after BCCAO [16]. On the other hand, several studies showed neuroprotective effect of NE after ischemia. Chen and Russo-Neustadt [17] reported that

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NE promotes cell survival in the hippocampus through increasing the expression of brain derived neurotrophic factor (BDNF) and several pro-survival signaling molecules. Stimulation of NE system by the administration of atipamezole, a selective α_2 -adrenoceptor antagonist, showed an improvement in sensorimotor performance of rats after focal cerebral I/R injury [18].

In addition to the previously stated neurotransmitters, serotonin or 5-HT also plays an important role in the pathophysiology of stroke.

3. Serotonin

Serotonin is a neurotransmitter that has a wide range of functions in the body. It is synthesized by hydroxylation of the amino acid tryptophan to 5-hydroxytryptophan followed by decarboxylation [19]. In human, serotonin presents mainly in the blood platelets, enterochromaffin cells of the intestinal mucosa and in specific areas of brain [20]. Serotonin acts on 5-HT receptors which are subtyped as 5-HT₁ to 5-HT₇. These receptors are widely distributed in various organs of the body. 5-HT_{2A} receptor subtype is present in platelets while 5-HT_{2B} receptor subtype is distributed in the stomach. Both 5-HT_{1B} and 5-HT_{2C} receptor subtypes are present in the substantia nigra region and 5-HT_{1E} and 5-HT_{2C} in the CA1 region of hippocampus.

5-HT induces platelet aggregation [21] and regulates GIT motility [22]. It also modulates cerebral and peripheral vascular tone, regulates blood pressure [23] and participates in the pathophysiology of hypertension and pulmonary hypertension [24, 25]. In the CNS, it regulates sleep, body temperature, sexual behavior and emesis [26-29]. Low cerebral level of 5-HT causes mania, depression, schizophrenia and anxiety disorders [23, 26].

3.1 Drugs affecting serotonin

Drugs that affect the serotonin system act by either enhancing its effect (agonists or reuptake blockers) or inhibiting its effect (antagonists). Many of these drugs are clinically used for various diseases. For example, SSRIs, serotonin/norepinephrine reuptake inhibitors (SNRIs) and 5-HT₁ partial agonists as buspirone and gepirone are clinically indicated for several depressive disorders as generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), depression and panic disorder [30]. Sumatriptan, a 5-HT_{1B} agonist, is widely used for migraine attack. 5-HT₃ antagonists as ondansetron, granisetron and tropisetron are widely used in acute chemotherapy induced emesis and postoperative nausea and vomiting. Risperidone blocks 5-HT_{2A/2C} receptors and used as an antipsychotic.

3.2 Alterations in serotonin level after cerebral ischemia

Cerebral ischemia induces alterations in the cerebral level of serotonin. The description of this alterations, however, shows controversies. Buller, Wixey [31], Wixey, Reinebrant [32] reported a disruption in the serotonergic system and a reduction in the 5-HT level in the forebrain in a rodent model of neonatal hypoxia-ischemia. On the other hand, as mentioned in [33], there was an increase in the extracellular concentration of serotonin in the corpus striatum and hypothalamus of gerbils during heatstroke-induced cerebral ischemia. Sarna, Obrenovitch [34] also reported an increase in 5-HT level after transient global cerebral ischemia. A time-dependent change in the 5-HT_{1A} receptor expression was reported after transient global cerebral

ischemia in the hippocampus. The expression was reduced in the first and second days of ischemic insult then highly increased after 5 days of I/R [35].

3.3 Role of modulation of serotonin in cerebral ischemia

The overall effect of serotonin in the neuronal damage induced by cerebral ischemia is still unclear. Several studies supported its neuroprotective role with little evidence which assumed its detrimental effects. Wester et al Globus, Wester [36] reported that serotonin exerted an excitatory effect on neurons at the CA1 region and induced neuronal damage through acting on 5-HT₂ receptors. They also reported that administration of ritanserin, a 5-HT₂ antagonist, attenuated the ischemia-induced neuronal damage in the two-vessel occlusion plus hypotension model of ischemia. In a bilateral carotid arteries occlusion model, administration of naftidrofuryl, another 5-HT₂ antagonist, to gerbils 5 minutes before surgery also reduced neuronal damage induced by ischemia [37]. Moreover, depletion of brain serotonin in heatstroke rats prolonged the survival time and attenuated heatstroke-induced ischemia and neuronal damage [38].

On the other hand, several reports proved its role in reducing excitotoxicity and neuronal damage after cerebral ischemia. Different SSRIs were used as protective or therapeutic agents in different animal models of cerebral ischemia. An improvement in neurobehavioral outcomes and histopathological results, an increment in antioxidant capacity and a reduction in cerebral infarct volume and cerebral protein expression of several inflammatory mediators and apoptotic markers have been observed [30].

4. Selective serotonin reuptake inhibitor in cerebral ischemia

Selective serotonin reuptake inhibitors as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram and escitalopram are the treatment of choice in different mood disorders as major depression, bipolar depression, panic disorder, obsessive-compulsive disorder and dysthymia. They are also used in premenstrual dysphoric disorder and eating disorders. They are highly tolerable, have a good side effect profile, and safe in overdoses [39].

In this review, we will discuss the neuroprotective role of SSRIs in cerebral ischemia.

4.1 Fluoxetine

Several animal experiments and clinical studies indicated the neuroprotective role of fluoxetine in stroke. Previous reports [40-42] showed that when fluoxetine was administered for 3 days before induction of ischemia or used as a therapeutic agent and administered 30 minutes, 3 hr or 6 hr after ischemia, it alleviated cognitive and neurobehavioral impairments, improved long-term functional recovery and reduced cerebral infarct volume in cerebral ischemia induced by middle cerebral artery occlusion (MCAO). Furthermore, fluoxetine ameliorated ischemia-induced memory deficits in the Y-maze task and also inhibited ischemia-induced locomotor hyperactivity after global cerebral ischemia induced by bilateral common carotid artery occlusion (BCCAO) model [43, 44]. Moreover, in a three-vessel occlusion model of global transient cerebral ischemia, administration of fluoxetine 10 days over surgery enhanced neurogenesis and improved survival after ischemia [45].

In addition to experimental studies, clinical studies also showed its effectiveness after stroke. A clinical study in patients with acute ischemic stroke showed that treatment with fluoxetine at a

dose of 20 mg for 90 days after ischemia significantly reduced the three-year recurrence rate of ischemic stroke [46]. Another study showed that only one dose of fluoxetine is enough to significantly improved the sensory-motor skills of the affected side in patients after stroke [47].

4.2 Paroxetine

Paroxetine is another member of the SSRI family exhibiting neuroprotective effect against stroke. For example, it reduced memory deficits and exerted antioxidant activity after I/R injury induced by BCCAO [48]. Its administration in a dose of 10 mg/kg pre or post- I/R injury increased the percentage of viable cells in the CA1 hippocampal region and subsequently improved the results of the Morris water maze, a test for assessment of learning and memory function [49]. In an *in vitro* oxygen-glucose deprivation model of ischemia, paroxetine alone or in combination with everolimus, an immunosuppressant agent, improved cell survival and reduced inflammation induced by ischemia [50]. Furthermore, sertraline reduced cerebral infarct volume and enhanced the antioxidant capacity in a mouse model of permanent focal ischemia [51].

It is noteworthy that the use of paroxetine either as prophylaxis or as treatment therapy was compared in previous studies. Using paroxetine as a therapeutic agent after transient BCCAO achieved higher improvement in neurological outcomes, higher expression of antioxidant enzymes and BDNF than using it prior to induction [48]. On the other hand, the improvement of memory deficits and the percentage of viable cells in hippocampus were nearly the same when paroxetine was administered pre or post transient BCCAO [48, 49].

4.3 Fluvoxamine

In a rat model of focal cerebral ischemia, fluvoxamine reduced the infarction volume. It also improved somatosensory function as indicated by the hindlimb and forelimb placing test. Administration of fluoxetine pre or post MCAO achieved similar reduction in the infarct volume and similar an improvement in neurobehavioral outcomes [52, 53]. On the other hand, a clinical study reported that administration of fluvoxamine for poststroke patients reduced depression as well as central poststroke pain, assessed via a visual analog scale, an instrument which is used to measure the frequency or the intensity of various symptoms [54].

4.4 Citalopram

Citalopram exerted anti-inflammatory and antioxidant activities in a rat model of focal cerebral ischemia. Pre, post and pre and post administration of it reduced cerebral infarct volume, grip test score and neurological deficit score in a 2 h MCAO model of ischemia [55]. Another study showed that citalopram protected CA1 pyramidal cells after transient cerebral ischemia in gerbil through prevention of excitatory amino acids, glutamate and aspartate, accumulation during and after forebrain ischemia [56] and also decreased glutamate release from lipopolysaccharide-activated microglia which in turn increased the survival of oxygen-glucose deprivation injured neurons [57]. Furthermore, citalopram enhanced neurogenesis and improved somatosensory function in the peri-infarct region of the brain after I/R injury [58]. Moreover, clinical reports showed that daily oral administration of citalopram at a dose of 20 mg improved the motor recovery, assessed using the National Institutes of Health

Stroke Scale (NIHSS) scores, in patients with acute ischemic stroke and facilitated the rehabilitation of these patients [59]. It also reduced the risk of recurrent vascular events that may occur after ischemic stroke [60].

Escitalopram, the therapeutically active S-enantiomer of citalopram, also exerted a neuroprotective effect in cerebral ischemia. Pre- and post-treatment with this agent reduced the neuronal death in the CA1 hippocampal region induced by I/R injury. However, when it was used as a prophylactic agent after 5 minutes common carotid occlusion, BDNF was expressed in higher level [61]. Its effectiveness has also been proved in clinical trials. Treatment with escitalopram for three months improved neuronal function in patients with acute ischemic stroke [62].

5. The role of serotonin norepinephrine reuptake inhibitors (SNRIs) and other antidepressants on cerebral ischemia

As SSRIs, some experimental studies demonstrated the neuroprotective effects of SNRIs and other antidepressants after cerebral I/R injury. A four day treatment with desipramine, a tricyclic antidepressant, venlafaxine, an SNRI, and trazodone, an atypical antidepressant, significantly attenuated mitochondrial dysfunction and oxidative stress induced after partial global cerebral I/R injury in mice. They restored the normal levels of catalase and superoxide dismutase and mediated their effects through nitric oxide-cGMP pathway [63]. Moreover, pretreatment with duloxetine, an SNRI, reduced the activation of astrocytes and microglia in ischemic (CA1) region and increases the expression of superoxide dismutase in CA1 pyramidal neurons after transient global cerebral ischemia [64]. As duloxetine, pre or post treatment with atomoxetine, a selective norepinephrine reuptake inhibitor, attenuated glial activation in ischemic CA1 region after transient ischemia and improved neuronal outcomes after hypoxic ischemia [65]. Atomoxetine overexpressed BDNF that upregulates several antioxidant enzymes and exerts antiapoptotic activity [66]. These results indicated that enhancement of both serotonin and norepinephrine signaling in brain could be a potential effective therapeutic strategy for cerebral ischemia treatment.

6. Proposed mechanisms of the neuroprotective role of SSRIs and SNRIs in cerebral ischemia

Different mechanisms may explain the neuroprotective role of the SSRIs after I/R injury. For example, the anti-inflammatory and the antioxidant characters of fluoxetine may be responsible for its neuroprotective role after cerebral ischemia. It reduces the induction of several inflammatory mediators as interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α) and cyclooxygenase-II (COX-II). It also reduces the activity of the proinflammatory mediator NF- κ B after I/R injury [42]. On the other hand, fluoxetine overexpresses the BDNF that promotes neurons survival and increases the activity of different antioxidant enzymes like glutathione peroxidase, catalase and superoxide dismutase-1 [44]. Fluoxetine also exerts an antiapoptotic role as it reduces the expression of different apoptotic markers, caspase-3 and caspase-12, which inhibits endoplasmic reticulum stress-inducing apoptosis in the hippocampus after I/R injury [40]. Hu, Liu [41], Shin, Kang [51] reported that fluoxetine increases the expression of hemoxygenase-1 (HO-1) which catalyzes the formation of biliverdin and bilirubin that exerts an antioxidant character. It also upregulates the formation of hypoxia-inducible factor-1 α (HIF-1 α) that increases neuronal survival and promotes angiogenesis after ischemia. Moreover, it also enhances hippocampal neurogenesis, decreases neuronal loss and increases

the number of microglial cells after cerebral ischemia [45, 67]. It was also reported that fluoxetine increases the blood brain barrier integrity through inhibition of the expression of several matrix metalloprotease enzymes (MMP-2 and MMP-9) and reduces the disruption induced after ischemia [43].

As fluoxetine, paroxetine and sertraline exert anti-inflammatory and antioxidant properties which are responsible for their neuroprotective effects after I/R injury. Sheikholeslami, Ghafghazi [48], Gaur and Kumar [68] reported that paroxetine and sertraline reduce cerebral malondialdehyde (MDA) and nitric oxide (NO) levels and increase the activity of the antioxidant enzymes, glutathione peroxidase, catalase and superoxide dismutase-1. Paroxetine also overexpresses BDNF and increases the percentage of viable cells in the hippocampus after ischemia [48, 49].

Tanimukai *et al.* [53] reported that fluvoxamine induces the expression of sigma-1 receptor (Sig-1R), a receptor that is expressed on the endoplasmic reticulum (ER) membranes which inhibits Ca²⁺ influx through NMDA receptor and regulates the release of neurotransmitters such as dopamine [69], which suppresses endoplasmic reticulum stress and reduces cerebral infarct volume after I/R injury. Citalopram alleviates the activity of the apoptotic markers, caspase-3, caspase-9, MMP-2 and MMP-9 and reduces the levels of MDA and NO. It also reduces the release of the inflammatory mediators; TNF- α and IL-1 β which ameliorate the ischemia-induced cell death and inflammation [55-57]. As fluoxetine and paroxetine, escitalopram overexpresses BDNF and reduces ischemia-induced oxidative stress. It also alleviates microglial activation in the CA-1 hippocampal region [61].

SNRIs and the other antidepressants also exert their neuroprotection role through anti-oxidant, anti-apoptotic and anti-inflammatory effects. Atomoxetine, duloxetine and venlafaxine upregulate the expression of several antioxidant enzymes as catalase and superoxide dismutase. Atomoxetine also overexpresses BDNF that attenuates neuronal damage and enhances cell survival [65, 66, 68].

All these previous mechanisms explained the neuroprotective role of different SSRIs in experimental cerebral ischemia induced by different animal models. They reduced cerebral infarct volume, increases neuronal survival in the CA1 hippocampal region, ameliorated neurobehavioral deficits and improved the functional outcomes through their anti-inflammatory, anti-oxidative and anti-apoptotic effects. To conclude, further clinical studies are required to elicit the SSRIs as an effective option for the management of ischemic stroke.

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