J Pharm Biopharm Res, 2023, 4(2): 318-325
DOI: 10.25082/JPBR.2022.02.003

REVIEW

How antidepressants affect the cerebral ischemic injury and ischemic stroke

Xiaohui Sun[1] **Tian Wang**[1] **Lin Zhou**[1] **Yawen Yu**[1] **Zhaofeng Liu**[1] **Runchen Ma**[1] **Fenghua Fu**[1*]

[1] School of Pharmacy, Key Laboratory of Molecular Pharmacology and Drug Evaluation (Yantai University), Ministry of Education, Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, Yantai University, Yantai, Shandong 264005, China

Correspondence to: Fenghua Fu, School of Pharmacy, Yantai University, Yantai, Shandong 264005, China; Email: fenghua@luye.com

Received: January 7, 2023;
Accepted: February 13, 2023;
Published: February 17, 2023.

Citation: Sun X, Wang T, Zhou L, *et al*. How antidepressants affect the cerebral ischemic injury and ischemic stroke. *J Pharm Biopharm Res*, 2023, **4**(2): 318-325. https://doi.org/10.25082/JPBR.2022.02.003

Abstract: Ischemic stroke is the main cause of long-term disability and death worldwide. Studies have pointed out that antidepressants not only can be used to treat depression, but also promote nerve regeneration, nerve plasticity, and recovery of nerve function after stroke. Some evidences indicated that antidepressants have beneficial effects on ischemic stroke. At the same time, there are also risks in treatment process. The mechanisms of the effects of antidepressants on ischemic stroke are complicated and rarely reported. This review summarizes the roles of antidepressants in patients and animal models of stroke, the possible mechanisms of antidepressants against brain injury induced by stroke, and the risks and challenges of antidepressants treatment in patients with ischemia.

Keywords: ischemic stroke, antidepressants, brain protection

1 Introduction

Ischemic stroke characterized by the focal loss of nerve functions is the main cause of disability and mortality worldwide [1]. Despite a great deal of preclinical and clinical efforts by researchers, there is still limited progress to promote the recovery of ischemic stroke [2]. Existing evidences suggest that antidepressants seem to be beneficial for stroke recovery. Animal experiments indicated that antidepressants improved functional outcomes after ischemic stroke by promoting nerve regeneration, nerve plasticity, and recovery of nerve function after stroke [3]. Experiments in animals showed that antidepressants could not only inhibit hippocampal neurons apoptosis, but also reduce cerebral infarct size, thus promoting cognition dysfunction and motor abilities after cerebral ischemia reperfusion. However, antidepressants increase the concentration of neurotransmitters in synaptic space. It may induce local vasoconstriction and then aggravate the injury of ischemic stroke. What's more, the risk of stroke or mortality associated with antidepressants is inconsistent. The increased stroke risk may be related to antidepressants, especially in the elderly [4]. This paradoxical result is mainly due to the fact that antidepressants have a range of side effects that can be detrimental to stroke recovery. In addition to antidepressants, the depression is also an important factor to hinder the recovery from stroke. There are few reports on the mechanism of the effects of antidepressants on ischemic stroke. In order to explain the influence of antidepressants on ischemic stroke, we summarize the benefits and risks of antidepressants and the associated mechanisms in stroke in the present review.

2 Clinical evidences of efficacy of antidepressants on recovery from stroke

The benefit of antidepressants is to improve overall outcomes after stroke, not just mood disorders, and this effect is long-lasting. After the fluoxetine-treated for 90 days, the patients had significant improvement in motor recovery, as measured on the Fugl-Meyer motor score [5]. The oral citalopram with a dose of 10 mg/day in ischemic stroke patients also improved neurofunctional, especially speech elements, after 1-month treatment [6]. Reboxetine could result in inhibiting the reuptake of noradrenaline. In ten chronic stroke patients, dexterity, grip strength, and hand-tapping speed were tested. After been administered a single dose of 6 mg reboxetine, patients had an obvious improvement in tapping speed and grip strength. The combination of methylphenidate and physical therapy improved motor functions of 21 patients early after stroke [7]. Trazodone improved motor functional outcome, showed an improvement of activities of daily living and a less cognitive difficulty, and decreased mortality in patients after ischemic stroke [8].

Some studies have shown that the antidepressants are used in the early stage of stroke are related to the better recovery effect of ischemic stroke. If antidepressants can be used within four

weeks of stroke, physical, cognitive and neurological functions will have significant improvements [7]. A clinical trial of 97 hospitalized-patients suffered for acute ischemic stroke found that the prophylactic use of escitalopram might exhibit significant therapeutic effects, has few side effects, ameliorate the degree of neurological deficit and depression, and prevent post-stroke depression, which will be beneficial to the prognosis of patients with acute cerebral infarction [9].

3 Efficacy of antidepressant on cerebral ischemic animal model

3.1 Selective serotonin reuptake inhibitors

Studies have shown that selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, increased neurogenesis in the ischemic brain. SSRIs not only improved functional recovery after ischemic stroke, including neurological scores, spatial memory, cognitive function, and sensorimotor functions but also decreased the infarct size in the middle cerebral artery occlusion model [10]. The mechanism of action of SSRIs is possibly related to regulating 5-hydroxytryptamine and its receptors [11]. Paroxetine enhances the antioxidant capacity and then protects neurons against oxidative stress in rats. Administration of paroxetine may enhance the level of brain-derived neurotrophic factor (BDNF) in hippocampus [12].

3.2 Serotonin-noradrenaline reuptake inhibitors

Serotonin-noradrenaline reuptake inhibitors (SNRIs) have anti-painful physical effects due to the action of noradrenergic compared to SSRIs [13]. Venlafaxine has neuroprotective activities and increases the content of BDNF, Bcl-2, and Copper-zinc superoxide dismutase [14]. Neuronal cells treated with duloxetine for 24 h attenuate the activation of oxidative stress. At the same time, pretreatment with duloxetine for 3 days decreased the production of reactive oxygen species and had neuroprotective effect on transient global cerebral ischemia [15].

3.3 Monoamine oxidase inhibitors

It is of great significance to inhibit the activity of monoamine oxidase (MAO) to attenuate brain injury induced by ischemic stroke. Inhibition of MAO in the brain will result in neuroprotective properties and antidepressant effects. If monoamine oxidase inhibitors (MAOIs) are used to treat ischemic injury, the metabolites of neurotransmitters are inhibited. Therefore, MAOIs reduce the brain damage caused by ischemic injury. A study shows that MAOIs can reduce oxygen-glucose deprivation and ischemia reperfusion caused neuronal injury, which is closely associated with ameliorating mitochondrial damage [16]. MAO-B inhibitors, selegiline and rasagiline, also exert a neuroprotective effect in Parkinson's disease or Alzheimer's disease [17].

3.4 Tricyclic antidepressants

Treatment with clomipramine at 5 min before transient ischemia in gerbil reduced the loss of neurons in hippocampal CA1, which showed that clomipramine may have a neuroprotective effect. Nortriptyline reduced infarct volume by approximately 55% and improved motor functional outcomes in MCAO mice [18]. Tianeptine, a tricyclic antidepressant (TCA), has antioxidant properties and brain protection. It can decrease malondialdehyde levels and increase the content of antioxidant enzymes in the brain [19]. Previous report also indicated that desipramine enhanced motor recovery after cortical lesions in rats [18].

3.5 Other antidepressants

Trazadone belongs to 5-HT_{2A} and 5-HT_{2C} receptor antagonists and selective serotonin reuptake inhibitor. The neuroprotective effects of trazodone have been reported by previous studies. Trazadone improved depressive disorder and transient global ischemia in animal models [20]. Trazadone could also exhibit neuroprotective effect during inflammation and prevent injury of nerve cells in mice with cerebral ischemia [21]. N-methyl-D-aspartate receptor antagonists can block the harmful cascade reaction mediated by glutamate (Glu) and the release of dopamine during anoxia, thus exerting effects of neuroprotection [22]. In addition, amphetamine, a sympathomimetic drug, promotes long-term recovery after stroke [18].

4 Neuroprotective mechanisms of antidepressants

4.1 Anti-inflammation

Many studies have investigated the effects of antidepressants on the inflammation in the central nervous system (CNS). SSRIs reduce inflammation to protect neurons through inhibiting microglia and neutrophil granulocytes [23]. Treatment with antidepressants resulted in a marked

decrease in pro-inflammatory factors releasing including NO, IL-1β, IL-6, and TNF-α [24]. Furthermore, *in vitro* studies also found that fluoxetine protected neurons from damage by mediating the inflammatory characteristics of microglia [25].

Antidepressants showed beneficial effects on ischemic stroke by playing an anti-inflammatory role through classic anti-inflammatory pathways. NF-κB activated by different stress conditions after ischemic stroke can upregulate the expression of pro-apoptotic genes. Antidepressants may exert a neuroprotective effect dose-dependently by suppressing NF-κB activity [26]. Antidepressants binding to the targets will elevate the neurotransmitter, and then inhibit JAK/STAT pathway. JAK/STAT signaling pathway is involved in mediating several functions of CNS including neurogenesis, synaptic plasticity, and microglial activation, which are related to the development of ischemic stroke [27]. Antidepressants suppress signaling downstream of the toll-like receptor family of innate immune receptors which plays a key role in the process of inflammatory response after ischemic injury [28, 29].

4.2 Inhibition of glutamate release and antioxidation

Ischemic stroke leads to the destruction of antioxidant defense system and the production of reactive ROS, which results in the dysfunction and death of neurons [25]. Antidepressants have antioxidant effect and down-regulate the content of Glu, which may be one of the mechanisms to improve stroke. Nrf2 is a pharmacological target in pathologies with neuroinflammatory and oxidative features. It can be partially modulated to treat ischemic stroke by antidepressants [30]. What's more, this has been confirmed by TCA, SSRI, and SNRIs. Fluoxetine and citalopram can improve the viability of weakened neurons after ischemia injury, which is related to the reduced release of Glu and D-serine [31]. Treatment with antidepressants significantly decrease lipid peroxidation [30]. The therapeutic concentrations of antidepressants exhibit a protective effect against oxidative stress. At the same time, the high concentration of antidepressants may inhibit mitochondrial function and deplete cellular ATP levels, causing cells damage [32]. This finding illustrates the importance of dose when using antidepressants for ischemic stroke.

4.3 Neurogenesis

Antidepressant treatment is associated with neurogenesis that occurs in some specific brain areas and contributes to the recovery from ischemic stroke. There are studies showing antidepressants may increase hippocampal cell proliferation and neurogenesis in a chronic phase [33]. The stimulation of neurogenesis mediated by SSRI may promote to structural and functional recovery from ischemic cerebral injury. And generated-neurons migrating from the neurogeneration brain areas to the damaged region, which may be potentially useful for stroke recovery, is also related to antidepressants. In rat brain, fibroblast growth factor 2 (FGF2), vascular endothelial growth factor (VEGF) and BDNF can trigger neurogenesis and improves outcome of stroke. Administration of tranylcypromine, desipramine, sertraline, or mianserin for 3 weeks increased BDNF in rat hippocampus. Both FGF2 and VEGF levels in the hippocampus were increased in rats treated with fluoxetine. In addition, the level of FGF2 were increased in the cerebral cortex and hippocampus after desipramine or mianserin treatment for 3 weeks, and VEGF levels also increased in the hippocampus with desipramine administration [18].

4.4 Neuroplasticity

Poststroke recovery is involved in the activation of plasticity in adjacent neurons which is related to several neurotransmitters, including norepinephrine, dopamine, and serotonin [34]. Since antidepressants can modulate neurotransmitters in central system, this effect may be one of the reasons for the brain protection of antidepressants. BDNF, a neurotrophic factor, is regulated by the phosphorylation of diverse nuclear proteins and involved in neuronal survival and plasticity. Several antidepressants have been shown to increase BDNF levels in the brain [35]. Venlafaxine increased the synaptophysin which is considered necessary for synaptic plasticity density in the hippocampus of rats [36], which further confirms the neuroprotective potential of antidepressants in neurological diseases.

4.5 Motor cortical excitability regulation

A good many of stroke survivors have persistent motor functional deficits and the underlying mechanism is related to the alteration of motor cortical excitability in the primary motor cortex [37]. Antidepressants affect motor cortical excitability, which is associated with monoamines [38]. Fluoxetine improved hand motor function by affecting the overactivation of motor cortices on functional in patients treated with a single dose of 20 mg and recovering from poststroke hemiplegia [7]. Sertraline also increased excitability of the cortico-spinal neuron in healthy subjects [39]. Paroxetine increased the executive motor area activation and the motor performance in post-stroke patients [40]. A trial with healthy individuals showed that a single dose of paroxetine led to the

excitability of the primary motor cortex, while long-term intake was related to hypoexcitability of the brain motor cortices [7]. Therefore, the effects of antidepressant administrating on motor cortical excitability that occur with the progression from acute to chronic stroke may be different. Long term antidepressant use may have not affecting motor cortical excitability of post-stroke [38].

4.6 Cerebral blood flow regulation

As a potent vasoactive amine, serotonin participates in the development of ischemic brain edema and protect against blood-brain barrier dysfunction after ischemia. Fluoxetine interferes with the Ca^{2+} signaling mechanisms, which benefit the collateral circulation in the ischemic penumbra and the vascular smooth muscle of small cerebral arteries. Citalopram significantly increases vascular endothelial growth factor levels and the density of microvessels in the peril-infarct region [41]. By normalizing the lower boundary of cerebral mean arterial pressure administrating fluoxetine daily reduced extravasation and infarction size and improved cerebral blood flow regulation. In addition, acute peripheral administration of SSRIs results in changes in vascular function mediated by inhibiting the activation of sympathetic, presumably via a central mechanism. However, it remains speculative whether SSRI improving vasomotor reactivity might associate with post stroke recovery in humans [23].

5 The safety of antidepressants in cerebral ischemia

5.1 Antidepressants and stroke risk

The results of clinical studies are conflicting about the relationship between antidepressants and cerebral ischemia. SSRI was associated with the risk of hemorrhagic and fatal stroke, especially in patients treated with antithrombotic, antiplatelet, or nonsteroidal anti-inflammatory drugs [42,43]. Studies have shown that the risk may be high at the initiation of treatment, but the risk of stroke was reduced with long-term antidepressant treatment [43]. As antidepressants were accompanied by an increased blood pressure, which was usually considered as a risk factor for hemorrhage, a more pronounced risk of bleeding has been found in patients treated with SNRI. It has been observed that SSRI and SNRI have fibrinolytic properties, which could impair the adhesion of platelets to collagen. Although serotonergic antidepressants may alter hemostasis due to their profibrinolytic properties, they may be beneficial in the treatment of cerebral ischemia. For example, nortriptyline and fluoxetine improve activities of daily living and mortality, and sertraline improves morbidity [42]. However, SSRIs also may increase the risk of ischemic stroke through vasoconstriction caused by serotoninergic activation. Paroxetine and sertraline with the highest affinity to the serotonin transporter seemed to lead to a high risk of ischemic stroke [44]. Taking tricyclic antidepressants was associated with an increased risk of idiopathic venous thromboembolism compared with control. In addition, patients taking other antidepressants did not increase the risk of venous thromboembolism, whereas there was no increased risk among users of other antidepressants. However, mirtazapine and paroxetine are often followed with side effects of weight gain, which will impair the profibrinolytic properties and increase the risk of cerebral ischemia [45]. Overall, antidepressants reduced the ischemic stroke events than hemorrhagic stroke events, which means that SSRIs are still a safer choice, especially for the elderly.

5.2 Antidepressants and the risk of death

Antidepressants were linked with an increased mortality in some, but not in all studies. Due to their antiplatelet effects, the use of SSRI/SNRI has been found the increased risk of abnormal bleeding, including intracranial hemorrhage [45]. Among ischemic stroke patients, patients who received SSRI treatment reduced the incidence of new cardiovascular events, but were more likely to die, which is probably related to the increased risk of bleeding [7]. Therefore, non-pharmacological treatments should be wiser for patients at high risk of hemorrhagic stroke. The elderly in France and Australia cohort have shown that they were more likely to be died after receiving antidepressant treatment. There are also studies showing that the risk of antidepressant-related death was significantly lower during treatment but the risk was significantly increased after withdrawal of antidepressants. However, the current research on antidepressant treatment was found that antidepressants could reduce mortality, which reduced the rate of mortality by 10% compared with non-users [4]. This contradictory finding might be explained by the high risk of death of the elderly and the limitations of the survey. Therefore, careful long-term monitoring is still necessary to ensure timely prevention and treatment for patients.

5.3 Antidepressants and blood pressure

Because of anticholinergic activity of antidepressants, constipation and dry mouth are common with paroxetine administration [13]. Amitriptyline, nortriptyline, and clomipramine have high risk of occurrence of delirium [7]. In addition, hypertension can occur after venlafaxine treatment,

especially at doses of 225 mg or more per day [13]. For older patients, SNRIs are relevant if they present psychomotor retardation or pain, while keeping in mind to check blood pressure [46].

Studies suggest TCA users are at high risk of stroke than either non-users or SSRI users, while other reports demonstrate that there is no risk of stroke with TCA [47]. This inconsistent result may be explained by side-effect of TCA which is relevant to stroke risk including prolongation of the Q-T interval, increasing arrhythmia, heart rate, and orthostatic hypotension. Patients with stroke should be careful when choosing amitriptyline and nortriptyline, because of the occurrence of orthostatic hypotension and cardiac arrhythmia. Besides, glaucoma or prostatic hyperplasia may occur after amitriptyline and nortriptyline administration. At the same time, TCAs are often used for relieving depression, suggesting depressive symptoms, rather than the medication itself, may influence the effect of TCA on stroke [48]. Therefore, TCAs are not recommended for stroke patients.

5.4 Drug interaction

It's important to pay attention to drug-drug interactions because many antidepressants interact with the P450 cytochrome and the P-glycoprotein [7]. For example, fluoxetine inhibits cytochrome-P450, which affects the activation and metabolism of other drugs, possibly leading to toxic effects. What's more, fluoxetine might interact with warfarin, which would increase anticoagulant effect and lead to an high risk of bleeding [13]. Citalopram is prone to QT prolongation and should avoid combining it with other QT-prolonging drugs [46].

5.5 Other side effects of antidepressants

Gastrointestinal symptoms, hyponatremia, and sexual dysfunction are well-known side effects of SSRIs. Gastrointestinal is a common symptom of fluoxetine, such as anorexia occurs in the early stage of treatment. Sertraline and fluvoxamine may have more obvious gastrointestinal side effects among SSRIs [13]. However, a concern included the mechanisms that be explained by the inhibition of serotonin uptake in platelets. SSRIs might improve the risk of intracranial hemorrhage, stroke recurrence, bone fractures, and seizure risk [49, 50], which might be a direct consequence of the effects on the serotonin transporter by antidepressants.

SNRIs such as duloxetine and milnacipran were found to have genotoxic and cytotoxic effects in different test systems [51]. Duloxetine ranks first for hyponatremia, severe skin reactions and life-threatening liver injury [52], but citalopram or escitalopram ranks first for cardiovascular complications. Mirtazapine leads to significant weight gain, mild elevation of alanine aminotransferase, and neutropenia in rare cases [13].

6 Other factors influencing the usage of antidepressant in stroke

Depression and depressive symptoms are associated with a high risk of stroke, especially the repeated occurrences of depressive symptoms [53]. The biological mechanisms include neuroendocrine dysregulation which is characterized by the activation of sympathetic nervous system, dysregulation of the hypothalamic pituitary adrenocortical axis, neurotransmitter-mediated platelet aggregation dysfunction, and immunologic/inflammatory factors [54]. In addition to the above reasons, obesity or hypertension is also common in depression, increasing the risk of stroke. Furthermore, weight gain and metabolic disturbances are also induced by drug. This factor may be one of the reasons that antidepressants are not promoting to the recovery of stroke. Developing depressive symptoms or long-term high depression symptoms may indicate the occurrence of cerebrovascular events in the future, suggesting a possible role for antidepressant in stroke prevention [53]. Therefore, antidepressants are of great significance for the prevention and treatment of stroke.

7 Summary

The existing literature have studied and evaluated the beneficial effects of antidepressants on alleviating cerebral ischemia, involving in neurogenesis, neuroprotection, inhibition of hippocampal neurons apoptosis, reduction of cerebral infarct size, improvement of sensory-motor deficit, and promotion of cognition dysfunction after cerebral ischemia reperfusion [33]. The data from animal experiments are in line with the available clinical data, supporting antidepressants facilitated recovery of function [55]. These findings may involve complicated mechanisms, such as anti-inflammatory, antioxidation, neurogenesis, neuroplasticity, promotion of motor cortical excitability regulation, and regulation of cerebral blood flow.

The research about antidepressants protecting cerebral ischemia is increasing. So far, the relationship between antidepressants and stroke occurrence and death in stroke patients remains to

be explored. Overall, the usage of antidepressants in patients with cerebral ischemia is promising. Especially, SSRIs and SNRIs were the preferable to TCAs and MAOIs. Although antidepressants have shown beneficial effects on cerebral ischemia, they should be used in patients with caution. Particularly, we should pay attention to the manifest characteristics of patients and timely adjust the dosage and type of medication. The mechanism of neuroprotective effect of antidepressants is complex and even a combination of multiple ones. This will encourage us to be careful in the clinical use of antidepressants. Furthermore, the beneficial role of antidepressants in ischemic stroke will also be of guiding the treatment of post-stroke depression. Administration of antidepressants in stroke patients will be more mature in the future. However, the age, stroke severity, drug class, and potential side effect profile should be considered when antidepressants are administered.

Author contributions

Xiaohui Sun: conceptualization, investigation, writing – original draft.
Tian Wang: writing – review & editing.
Lin Zhou, Yawen Yu, Zhaofeng Liu and Runchen Ma: writing – review & editing.
Fenghua Fu: Writing – review & editing, conceptualization, supervision, project administration.

Conflict of interest

All authors declare no conflicts of interest.

Funding

This study was supported by grants from the Taishan Scholar Project of Shandong Province.

References

[1] Randolph SA. Ischemic Stroke. Workplace health & safety, 2016, **64**(9): 444. https://doi.org/10.1177/2165079916665400

[2] Ginsberg MD. Current status of neuroprotection for cerebral ischemia: synoptic overview. Stroke, 2009, **40**(3): 111-114. https://doi.org/10.1161/strokeaha.108.528877

[3] Jin Y, Lim CM, Kim SW, *et al*. Fluoxetine attenuates kainic acid-induced neuronal cell death in the mouse hippocampus. Brain research, 2009, **1281**: 108-116. https://doi.org/10.1016/j.brainres.2009.04.053

[4] Ön BI, Vidal X, Berger U, *et al*. Antidepressant use and stroke or mortality risk in the elderly. European journal of neurology, 2022, **29**(2): 469-477. https://doi.org/10.1111/ene.15137

[5] Mortensen JK and Andersen G. Pharmacological management of post-stroke depression: an update of the evidence and clinical guidance. Expert opinion on pharmacotherapy, 2021, **22**(9): 1157-1166. https://doi.org/10.1080/14656566.2021.1880566

[6] Savadi Oskouie D, Sharifipour E, Sadeghi Bazargani H, *et al*. Efficacy of Citalopram on Acute Ischemic Stroke Outcome: A Randomized Clinical Trial. Neurorehabilitation and Neural Repair, 2017, **31**(7): 638-647. https://doi.org/10.1177/1545968317704902

[7] Chollet F, Acket B, Raposo N, *et al*. Use of antidepressant medications to improve outcomes after stroke. Current Neurology and Neuroscience Reports, 2013, **13**(1): 318. https://doi.org/10.1007/s11910-012-0318-z

[8] Khouzam HR. A review of trazodone use in psychiatric and medical conditions. Postgraduate Medicine, 2017, **129**(1): 140-148. https://doi.org/10.1080/00325481.2017.1249265

[9] Cao JX, Liu L, Sun YT, *et al*. Effects of the prophylactic use of escitalopram on the prognosis and the plasma copeptin level in patients with acute cerebral infarction. Brazilian Journal of Medical and Biological Research, 2020, **53**(11): 8930. https://doi.org/10.1590/1414-431x20208930

[10] Lee JY, Lee HE, Kang SR, *et al*. Fluoxetine inhibits transient global ischemia-induced hippocampal neuronal death and memory impairment by preventing blood-brain barrier disruption. Neuropharmacology, 2014, **79**: 161-171. https://doi.org/10.1016/j.neuropharm.2013.11.011

[11] Hua Y, Li C, Hu J, *et al*. Fluoxetine adjunct to therapeutic exercise promotes motor recovery in rats with cerebral ischemia: Roles of nucleus accumbens. Brain Research Bulletin, 2019, **153**: 1-7. https://doi.org/10.1016/j.brainresbull.2019.07.022

[12] Sheikholeslami MA, Ghafghazi S, Pouriran R, *et al*. Attenuating effect of paroxetine on memory impairment following cerebral ischemia-reperfusion injury in rat: The involvement of BDNF and antioxidant capacity. European Journal of Pharmacology, 2021, **893**: 173821. https://doi.org/10.1016/j.ejphar.2020.173821

[13] Khawam EA, Laurencic G, Malone DA, *et al*. Side effects of antidepressants: an overview. Cleveland Clinic Journal of Medicine, 2006, **73**(4): 351-356.
https://doi.org/10.3949/ccjm.73.4.351

[14] Kumar A, Garg R, Gaur V, *et al*. Venlafaxine involves nitric oxide modulatory mechanism in experimental model of chronic behavior despair in mice. Brain Research, 2010, **1311**: 73-80.
https://doi.org/10.1016/j.brainres.2009.11.050

[15] Toda T, Yamamoto S, Umehara N, *et al.* Protective Effects of Duloxetine against Cerebral Ischemia-Reperfusion Injury via Transient Receptor Potential Melastatin 2 Inhibition. The Journal of Pharmacology and Experimental Therapeutics, 2019, **368**(2): 246-254.
https://doi.org/10.1124/jpet.118.253922

[16] Liu Y, Feng S, Subedi K, *et al*. Attenuation of Ischemic Stroke-Caused Brain Injury by a Monoamine Oxidase Inhibitor Involves Improved Proteostasis and Reduced Neuroinflammation. Molecular Neurobiology, 2020, **57**(2): 937-948.
https://doi.org/10.1007/s12035-019-01788-2

[17] Naoi M, Riederer P and Maruyama W. Modulation of monoamine oxidase (MAO) expression in neuropsychiatric disorders: genetic and environmental factors involved in type A MAO expression. Journal of Neural Transmission, 2016, **123**(2): 91-106.
https://doi.org/10.1007/s00702-014-1362-4

[18] Burns MM and Greenberg DA. Antidepressants in the treatment of stroke. Expert review of neurotherapeutics, 2010, **10**(8): 1237-1241.
https://doi.org/10.1586/ern.10.96

[19] Reeta K, Prabhakar P and Gupta YK. Anticonvulsant activity of the antidepressant drug, tianeptine, against pentylenetetrazole-induced seizures mitigates cognitive impairment in rats. Behavioural Pharmacology, 2016, **27**(7): 623-632.
https://doi.org/10.1097/fbp.0000000000000257

[20] Marinescu IP, Predescu A, Udriştoiu T, *et al*. Comparative study of neuroprotective effect of tricyclics vs. trazodone on animal model of depressive disorder. Romanian Journal of Morphology and Embryology, 2012, **53**(2): 397-400.

[21] Settimo L and Taylor D. Evaluating the dose-dependent mechanism of action of trazodone by estimation of occupancies for different brain neurotransmitter targets. Journal of Psychopharmacology, 2018, **32**(1): 96-104.
https://doi.org/10.1177/0269881117742101

[22] Alkan T, Kahveci N, Buyukuysal L, *et al*. Neuroprotective effects of MK 801 and hypothermia used alone and in combination in hypoxic-ischemic brain injury in neonatal rats. Archives of Physiology and Biochemistry, 2001, **109**(2): 135-144.
https://doi.org/10.1076/apab.109.2.135.4271

[23] Siepmann T, Penzlin AI, Kepplinger J, *et al*. Selective serotonin reuptake inhibitors to improve outcome in acute ischemic stroke: possible mechanisms and clinical evidence. Brain and Behavior, 2015, **5**(10): 00373.
https://doi.org/10.1002/brb3.373

[24] Chung YC, Kim SR, Park JY, *et al*. Fluoxetine prevents MPTP-induced loss of dopaminergic neurons by inhibiting microglial activation. Neuropharmacology, 2011, **60**(6): 963-974.
https://doi.org/10.1016/j.neuropharm.2011.01.043

[25] Chen SD, Yang DI, Lin TK, *et al.* Roles of oxidative stress, apoptosis, PGC-1α and mitochondrial biogenesis in cerebral ischemia. International Journal of Molecular Sciences, 2011, **12**(10): 7199-7215.
https://doi.org/10.3390/ijms12107199

[26] Lim CM, Kim SW, Park JY, *et al*. Fluoxetine affords robust neuroprotection in the postischemic brain via its anti-inflammatory effect. Journal of Neuroscience Research, 2009, **87**(4): 1037-1045.
https://doi.org/10.1002/jnr.21899

[27] Shariq AS, Brietzke E, Rosenblat JD, *et al*. Therapeutic potential of JAK/STAT pathway modulation in mood disorders. Reviews in the Neurosciences, 2018, **30**(1): 1-7.
https://doi.org/10.1515/revneuro-2018-0027

[28] Sacre S, Jaxa-Chamiec A, Low CMR, *et al*. Structural Modification of the Antidepressant Mianserin Suggests That Its Anti-inflammatory Activity May Be Independent of 5-Hydroxytryptamine Receptors. Frontiers in Immunology, 2019, **10**: 1167.
https://doi.org/10.3389/fimmu.2019.01167

[29] Li M, Liu J, Bi Y, *et al*. Potential Medications or Compounds Acting on Toll-like Receptors in Cerebral Ischemia. Current Neuropharmacology, 2018, **16**(2): 160-175.
https://doi.org/10.2174/1570159x15666170601125139

[30] Martín-Hernández D, Bris ÁG, MacDowell KS, *et al*. Modulation of the antioxidant nuclear factor (erythroid 2-derived)-like 2 pathway by antidepressants in rats. Neuropharmacology, 2016, **103**: 79-91.
https://doi.org/10.1016/j.neuropharm.2015.11.029

[31] Dhami KS, Churchward MA, Baker GB, *et al*. Fluoxetine and its metabolite norfluoxetine induce microglial apoptosis. Journal of Neurochemistry, 2019, **148**(6): 761-778.
https://doi.org/10.1111/jnc.14661

[32] Elmorsy E, Al-Ghafari A, Almutairi FM, *et al*. Antidepressants are cytotoxic to rat primary blood brain barrier endothelial cells at high therapeutic concentrations. Toxicology in Vitro, 2017, **44**: 154-163.
https://doi.org/10.1016/j.tiv.2017.07.011

[33] Paolucci S. Advances in antidepressants for treating post-stroke depression. Expert Opinion on Pharmacotherapy, 2017, **18**(10): 1011-1017.
https://doi.org/10.1080/14656566.2017.1334765

[34] Jun-O'Connell AH, Jayaraman DK, Henninger N, *et al*. Effects of Preexisting Psychotropic Medication Use on a Cohort of Patients with Ischemic Stroke Outcome. Stroke Research and Treatment, 2020, **2020**: 9070486.
https://doi.org/10.1155/2020/9070486
[35] Gaur V and Kumar A. Protective effect of desipramine, venlafaxine and trazodone against experimental animal model of transient global ischemia: possible involvement of NO-cGMP pathway. Brain Research, 2010, **1353**: 204-212.
https://doi.org/10.1016/j.brainres.2010.07.004
[36] Fang S, Yan B, Wang D, *et al*. Chronic effects of venlafaxine on synaptophysin and neuronal cell adhesion molecule in the hippocampus of cerebral ischemic mice. Biochemistry and Cell Biology, 2010, **88**(4): 655-663.
https://doi.org/10.1139/o10-015
[37] Robol E, Fiaschi A and Manganotti P. Effects of citalopram on the excitability of the human motor cortex: a paired magnetic stimulation study. Journal of the Neurological Sciences, 2004, **221**(1-2): 41-46.
https://doi.org/10.1016/j.jns.2004.03.007
[38] Li X and Morton SM. Effects of chronic antidepressant use on neurophysiological responses to tDCS post-stroke. Neuroscience Letters, 2020, **717**: 134723.
https://doi.org/10.1016/j.neulet.2019.134723
[39] Ilic TV, Korchounov A and Ziemann U. Complex modulation of human motor cortex excitability by the specific serotonin re-uptake inhibitor sertraline. Neuroscience Letters, 2002, **319**(2): 116-120.
https://doi.org/10.1016/s0304-3940(01)02563-0
[40] Gerdelat-Mas A, Loubinoux I, Tombari D, *et al*. Chronic administration of selective serotonin reuptake inhibitor (SSRI) paroxetine modulates human motor cortex excitability in healthy subjects. NeuroImage, 2005, **27**(2): 314-322.
https://doi.org/10.1016/j.neuroimage.2005.05.009
[41] Shin TK, Kang MS, Lee HY, *et al*. Fluoxetine and sertraline attenuate postischemic brain injury in mice. The Korean Journal of Physiology & Pharmacology, 2009, **13**(3): 257-263.
https://doi.org/10.4196/kjpp.2009.13.3.257
[42] Narushima K, Paradiso S, Moser DJ, *et al*. Effect of antidepressant therapy on executive function after stroke. The British Journal of Psychiatry, 2007, **190**(3): 260-265.
https://doi.org/10.1192/bjp.bp.106.025064
[43] Smoller JW. Do antidepressants raise the risk of stroke? The American Journal of Psychiatry, 2011, **168**(5): 457-459.
https://doi.org/10.1176/appi.ajp.2011.11020336
[44] Trifirò G, Dieleman J, Sen EF, *et al*. Risk of ischemic stroke associated with antidepressant drug use in elderly persons. Journal of Clinical Psychopharmacology, 2010, **30**(3): 252-258.
https://doi.org/10.1097/JCP.0b013e3181dca10a
[45] Hoirisch-Clapauch S and Nardi AE. Antidepressants: bleeding or thrombosis? Thrombosis Research, 2019, **181**(1): 23-28.
https://doi.org/10.1016/s0049-3848(19)30362-7
[46] Pericaud A, Straczek C, Montastruc F, *et al*. Use of antidepressants in unipolar depression in the elderly. L'Encephale, 2022, **48**(4): 445-454.
https://doi.org/10.1016/j.encep.2021.11.006
[47] Glymour MM, Gibbons LE, Gilsanz P, *et al*. Initiation of antidepressant medication and risk of incident stroke: using the Adult Changes in Thought cohort to address time-varying confounding. Annals of Epidemiology, 2019, **35**: 42-47.
https://doi.org/10.1016/j.annepidem.2019.04.010
[48] Tully PJ, Alpérovitch A, Soumaré A, *et al*. Association Between Cerebral Small Vessel Disease With Antidepressant Use and Depression: 3C Dijon Magnetic Resonance Imaging Study. Stroke, 2020, **51**(2): 402-408.
https://doi.org/10.1161/strokeaha.119.026712
[49] Legg LA, Rudberg AS, Hua X, *et al*. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. The Cochrane Database of Systematic Reviews, 2021, **11**(11): 009286.
https://doi.org/10.1002/14651858.CD009286.pub4
[50] Juang HT, Chen PC and Chien KL. Using antidepressants and the risk of stroke recurrence: report from a national representative cohort study. BMC Neurology, 2015, **15**: 86.
https://doi.org/10.1186/s12883-015-0345-x
[51] Avuloglu Yilmaz E, Unal F and Yuzbasioglu D. Evaluation of cytogenetic and DNA damage induced by the antidepressant drug-active ingredients, trazodone and milnacipran, in vitro. Drug and Chemical Toxicology, 2017, **40**(1): 57-66.
https://doi.org/10.1080/01480545.2016.1174870
[52] Braillon A. Antidepressants after stroke and patient centered care: An oxymoron. Research in Social & Administrative Pharmacy, 2019, **15**(9): 1187-1188.
https://doi.org/10.1016/j.sapharm.2019.04.050
[53] Soh Y, Tiemeier H, Kawachi I, *et al*. Eight-Year Depressive Symptom Trajectories and Incident Stroke: A 10-Year Follow-Up of the HRS (Health and Retirement Study). Stroke, 2022, **53**(8): 2569-2576.
https://doi.org/10.1161/strokeaha.121.037768
[54] Li H, Zheng D, Li Z, *et al*. Association of Depressive Symptoms With Incident Cardiovascular Diseases in Middle-Aged and Older Chinese Adults. JAMA Network Open, 2019, **2**(12): 1916591.
https://doi.org/10.1001/jamanetworkopen.2019.16591
[55] McCann SK, Irvine C, Mead GE, *et al*. Efficacy of antidepressants in animal models of ischemic stroke: a systematic review and meta-analysis. Stroke, 2014, **45**(10): 3055-3063.
https://doi.org/10.1161/strokeaha.114.006304