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NEUROGENESIS EFFECT OF TIANEPTINE VS VORTIOXETINE

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Abstract

Background: Depression, a debilitating psychiatric disorder, is characterized by enduring feelings of sadness and a diminished capacity to derive pleasure or interest from everyday activities. While the exact causes and comprehensive comprehension of the neurochemical processes that contribute to mood disorders are not fully understood, there is already significant evidence connecting mood problems to other conditions such as heart disease, osteoporosis, diabetes mellitus, and cerebral ischemia.

Aim: This study aims to assess the neurogenesis effect of tianeptine vs vortioxetine

Method: Eighty white albino male rats (200-225 g) were used. Induction of depression by reserpine, then determine the brain serotonin content in each group of rats and evaluate the antidepressant and antioxidant parameters for tianeptine and vortioxetine treated groups.

Results: Tianeptine exhibited superior outcomes compared to vortioxetine in the majority of assessments.

Conclusion: The findings obtained from the study indicate that the use of tianeptine exhibits superior antidepressant effects than vortioxetinein in the treatment of depressive disorder because it has an antidepressant effect that might be mediated in rats through neuroprotective effect evident as antioxidant activity and restoration of brain weight.

Keywords: Tianeptine, vortioxetin, Depression, anxiolytic, antidepressan

Introduction

Depression, a debilitating psychiatric disorder, is characterized by enduring feelings of sadness and a diminished capacity to derive pleasure or interest from everyday activities (Boas et al., 2019). While the exact causes and comprehension of the neurochemical processes that contribute to mood disorders are not fully understood, there is already significant evidence connecting mood problems to other conditions such as heart disease, osteoporosis, diabetes mellitus, and cerebral ischemia (Li et al., 2021).

After receiving immediate treatment, patients who continue to display signs of depression are at a higher risk of experiencing a relapse, recurrence, and long-term persistence of the condition. Treatment-resistant depression (TRD) patients, when compared to those with depression who respond well to therapy, have a twofold higher probability of being admitted to the hospital for general medical conditions and comorbid disorders. Additionally, they also exhibit increased utilization of medicines and healthcare services (Runia et al., 2022 and McIntyre et al., 2022). There is limited understanding regarding the molecular components and mechanisms that are responsible for the effects of the antidepressant. Historical evidence indicates that the use of antidepressants leads to changes in the expression of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). Furthermore, research has demonstrated that some proteins that are unique to the cytoskeleton and synaptic plasticity in the hippocampus and forebrain of rats can be influenced by tricyclic antidepressant medicines (TCAs) such imipramine and amitriptyline (Zavvari et al., 2020).

Problems have arisen in the development of novel antidepressant medications due to the limited knowledge of the fundamental biological processes that contribute to their actions (Halaris et al., 2021).

The research shows the various methods and formulations used in the development and clinical use of antidepressant medicines. When vortioxetine, a selective serotonin reuptake inhibitor (SSRI), is given to the adult central nervous system (CNS), it has been demonstrated to cause several types of plasticity. These effects include neurogenesis in the hippocampus, induction of long-term potentiation in the hippocampus, and alterations in the neuronal structure of the somatosensory cortex and medial prefrontal cortex (Zavvari et al., 2020). Furthermore, research has demonstrated that tianeptine, an adjunctive medicine employed for depression treatment, boosts energy-related processes in non-synaptic mitochondria located in the hippocampus. The enhancement in the energy function could perhaps be associated with its capacity to diminish anxiety and ameliorate symptoms of depression (Perić et al., 2020).

Neuroplasticity refers to the ability of brain cells to exchange and remodel themselves in order to enhance the brain's adaptability to new environments. Neuroplasticity is crucial in both the initial genesis and subsequent advancement of neurodegenerative illnesses (Mar et al., 2022). Extensive study has been conducted on the impact of the unconventional antidepressant tianeptine on the ability of the amygdala and hippocampus to change and adapt, known as neuroplasticity (Alamo et al., 2019). In addition, tianeptine does not impact the Kappa receptor, but it strongly activates the mu-opioid receptor and, to a lesser extent, the delta-opioid receptor. Tianeptine likely activates transduction pathways that are different from those of other opioids when it binds to the mu-opioid receptor.

This may indirectly contribute to its antidepressant effects. The unique action of tianeptine on opioid receptors may explain the release of dopamine in the limbic system and also play a role in modulating glutamatergic mechanisms. Therefore, tianeptine's distinctive properties as an opioid may contribute to its antidepressant effects [24].

This study aims to assess the neurogenesis effects of tianeptine versus vortioxetine.

Materials and Methods

1. Drugs: Tianeptine Servier pharmaceutical company (France) supplied in the form of tablets each contains 12.5 mg, each dissolved in distilled water. Vortioxetine (Lundbeck Limited) supplied in the form of tablets each contains 20 mg, each dissolved in distilled water. Reserpine (Mallinckrodlt. Inc., Martin Luther King Jr. Blvd, Paris-Kantucky) was dissolved in glacial acetic acid (1 μg/μl) and then completed to 25 ml with distilled water. All other reagents were obtained from Sigma Chemical Co. (St. Louis MO, USA).

2. **Chemicals and reagents:** For determination of brain content of reduced glutathione (GSH), thiobarbituric acid reactive substances (TBARS), superoxide dismutase (SOD) activity, total protein content; the following chemical (analytical grade) were used: Catalase, ellman'sreagent, glutathione, malondialdehyde, thiobarbituric acid (TBA), trichloroacetic acid (TCA) 10% (Sigma Co. USA); dipotassium hydrogen phosphate anhydrous, orthophosphoric acid (1%), potassium dihydrogen phosphate (El-Nasr Co. Egypt); n-butanol, pyrogallol, tris-HCL (Merk Co. Germany).

Determination of brain serotonin content: Acidified n-butanol (0.85 conc. HCL in 1 litre of n-butanol), 0.2 N-acetic acid (1.2 ml 100 ml), n-heptane (Merk Co. Germany), O-phthalaldhyde (OPT) (4 mg% solution in distilled water), standard stock solution of serotonin creatinine sulphate (Sigma Co. USA).

Total protein reagent: (Stanbio Laboratory, Inc., USA):

a) Total protein reagent: A solution consist of copper sulfate pentahydrate, 0.3 g/dL, in aqueous sodium hydroxide, 0.8 g/dL. Also contains potassium iodide and potassium sodium tartarate.

b) Total protein standard (10 g/dL) Aquous solution of bovine albumin, with sodium azide as preservative

Animal Species and Dosages: Eighty white albino male rats (200-225 g) were used. Doses of tianeptine and Vortioxetine were calculated according to Paget and Barnes transformation table (1964) who calculated the dose in relation to surface area. Doses for animals comparable to the human therapeutic daily oral dose of tianeptine (12.5-37.5 mg) and that of vortioxetine is (20 mg) were included.

Animal groups

Eighty male rats, weighing 200-225g, were singly housed and maintained in a 12/12 hours light/dark cycle. Food and water were provided ad libitum. The animals were allowed to acclimatize with the last conditions for one week before the start of the experiments.

Rats were divided into 4 groups (10 rats in each), the design of the study will provide comparisons regarding the following groups:

***Group I*:** Control group, animals injected i.p. with 1 ml distilled water twice/ day (equal to volume used as a vehicle for the test drugs).

***Group II*:** Depressed animals (Depression was induced by administering intraperitoneal reserpine of 0.2mg/kg/14days (Antkiewicz-Michaluk et al., 2014), injected with distilled water as group I.

***Group III*:** Tianeptine treated group, depressed animals injected with tianeptine (0.25 ug/kg i.p. twice/day) for 4 weeks.

***Group IV*:** Vortioxetine treated group, depressed animals injected with vortioxetine (0.25 ug/kg i.p. once/day) for 4 weeks.

Then, determination of brain content of serotonin in non treated and treated depressed animals (Bogdanski et al., 1956) and Evaluation of an antioxidant activity of tianeptine and vortioxetine.
Statistical analysis Mean ± SEM is how the data is presented. To establish whether the differences between the groups were statistically significant, we utilized one-way analysis of variance (ANOVA) and then the post hoc Tukey test. A P-value <0.05 was considered significant. Values in tables carrying different letters (a,b) within a row are considered statistically significant different (P<0.05) while values with the same letter are considered statistically insignificant (P>0.05).

Results

Evaluation of Antidepressant Effect

In evaluating the antidepressant effects of tianeptine and vortioxetine, Stressed rats experienced a significant reduction in body weight compared to controls, but both tianeptine and vortioxetine treated groups showed significant weight gain, nearing control levels. Tianeptine maintained brain serotonin (5-HT) levels similar to controls, whereas vortioxetine significantly increased 5-HT content. Tianeptine also significantly improved brain antioxidant parameters (GSH, SOD, and TBARS) more effectively than vortioxetine.

Table (1): Mean % changes in body weight (g) of depressed, tianeptine treated and vortioxetine treated rat groups compared with control group.

Group	Control group	Depressedgroup	Tianeptine treated group	Vortioxetinetreated group
Means±SEM	210.31±6.22b	128.35±2.61a	190.53±3.01ab	210.16±6.01b
P		< 0.001	< 0.001	< 0.001

Values are expressed as means ± SEM.
a) Significantly different from control group at p < 0.001.
b) Significantly different from depressed group at p < 0.001.

Table (2): Mean % change in whole brain weight (g) of depressed, tianeptine treated (0.25µg/kg) and vortioxetine treated (0.25 ug/kg) groups compared with control group.

	Control group	depressed group	Tianeptine treated group	Vortioxetine treated group
Means±SEM	1.72±0.01b	1.51±0.04a	1.69±0.01ab	1.50±0.01a
		< 0.001	< 0.001	< 0.001

Values are expressed as means ± SEM .
a) Significantly different from control group at p < 0.001.
b) Significantly different from depressed group at p < 0.001.

Table (3): Effect of intraperitoneal injection of tianeptine or vortioxetine on the content of 5-HT in rat brain compared to both control and depressed group.

Group	Control group	Depressed group	Tianeptine treated group	Vortioxetine treated group
Means±SEM	0.50±0.01b	0.28±0.01a	0.46±0.01b	0.70±0.01ab
P		< 0.001	> 0.05	< 0.001

Values are expressed as means ± SEM.
a) Significantly different from control group at p < 0.001.
b) Significantly different from depressed group at p < 0.001.

Table (4): Effect of tianeptine or vortioxetine on GSH, TBARS, and SOD content in rat brain.

Group dose (mg/kg)	GSH µmol/g tissue	TBARS nmol/g tissue	µ/mg SOD protein
Control group	0.52±0.01b	63.41±0.36b	12.14±0.02b
Depressed group	0.36±0.01a	158.24±3.68a	6.5±0.01a
Tianeptine treated group	0.94±0.01ab	81.26±1.19ab	11.41±0.03b
vortioxetine group	0.26±0.04a	148.96±0.47a	7.04±0.01a

Values are expressed as means ± SEM.
a) Significantly different from control group at $p < 0.001$.
b) Significantly different from depressed group at $p < 0.001$.

Discussion

Mental health disorders are significant global public health concerns and a contributing factor to the diminished quality of life experienced by patients worldwide. Major depressive disorder (MDD) is a multifaceted condition that arises from a range of biological, psychological, genetic, social, and familial factors (Spellman & Liston, 2020).

Prior research has established a correlation between specific brain regions and alterations in both structure and function in individuals with depression. The hippocampus has been the primary focus of research on depression in both humans and animals (Runia et al., 2022). This increases its vulnerability to chronic stress. The dysfunction of the hippocampus may be responsible for inappropriate emotional responses, as it plays a crucial role in the processes of learning and memory (Boas et al., 2019; Zavvari et al., 2020).

The hippocampus area has a high capacity for neuroplasticity because it is believed to be one of the few brain regions where neurogenesis continues to occur in the adult brain. Given that the hippocampus includes all three primary opioid receptors and associated chemicals, as well as an abundance of opioids, it stands to reason that the opioid system influences the hippocampus's ability to adapt and function. All of this points to the possibility that antidepressants help normalize hippocampal function, which is severely impaired in depression (Puryear et al., 2020).

It is possible that the precognitive impact of tianeptine might be attributed to its neurobiological properties, among which are its ability to repair impairments in synaptic glutamate transmission and to restore normal neuroplasticity in certain regions of the brain. Glutamate is involved in the mechanism of action of the antidepressant tianeptine, which is in line with the findings of extensive preclinical research that demonstrates the essential role that glutamate plays in the altered neuroplasticity that is the root cause of the symptoms of Alzheimer's disease and depression. The favorable benefit that tianeptine has on cognition is particularly significant when taking into consideration the ongoing debate concerning the effects of antidepressants on cognitive functioning in older patients who are suffering from depression. 2018 research by Dudas et al. By doing so, it improves neuroplasticity, reverses changes in the brain that are brought on by stress, and prevents cognitive impairments that are brought on by chronic stress. According to Perić et al. (2019), it has the ability to enhance GABA-mediated neurotransmission and also functions as a positive modulator of the AMPA-type glutamate receptor. All of these properties make it a potential nootropic that can increase cognitive performance in those who are in good health.

Reductions in volume, shrinkage of neurons, and rearrangement of dendrites have been observed in the hippocampus of depressed individuals as well as animal models of depression, according to investigations that have been conducted using neuroimaging techniques. For the purpose of providing a physiological explanation for depression, the monoamine theory of depression proposes that there is a drop in the levels of serotonin, norepinephrine, and dopamine in the central nervous system (Hao et al., 2020).

It is possible for antidepressants to acutely increase monoamine transmission if they work by either reducing the reuptake of neurons or slowing the breakdown of monoamines in synapses. In order to adequately explain the efficacy of antidepressants, it is not sufficient to merely attribute their efficiency to the monoaminergic system. Recent study on major depressive illness has indicated that prolonged use of antidepressant medication may act by enhancing synaptic plasticity and

neurogenesis. This was demonstrated in investigations that were carried out during the recent decade (Cuijpers et al., 2020; Sajjadian et al., 2021).

Tianeptine and vortioxetine are two examples of drugs that are frequently prescribed for the treatment of depression. Both vortioxetine, which is a selective serotonin reuptake inhibitor (SSRI), and tianeptine, which is a novel antidepressant, have been extensively studied for their effectiveness in alleviating depressive symptoms (Perić et al., 2020). Tianeptine is distinguished from conventional antidepressants by its distinctive ability to increase serotonin reuptake, as stated by Allain et al. in 2022.

In the research carried out by Pekarskaya and colleagues (2021), the antidepressant effects of tianeptine were examined using a mouse model that had been exposed to fluoxetine during the early stages of development. The findings demonstrated that mice that were given fluoxetine during their early stages of development had behavioral resistance to the antidepressant-like effects that were induced by the administration of SSRIs to adults. However, chronic treatment with tianeptine resulted in a significant improvement in avoidant behaviors in these mice. This finding suggests that tianeptine may be a promising alternative treatment option for individuals who do not respond to conventional antidepressants, particularly those who have altered serotonergic systems as a result of being exposed to SSRIs while they were still in utero.

Tianeptine's can modulate various biochemical pathways involved in mood regulation. Perić et al. (2020) found that chronic tianeptine treatment normalized depressive and anxiety-like behaviors induced by chronic social isolation stress in rats. Proteomic analysis revealed that tianeptine increased the expression of proteasome system elements, redox system enzymes, and enzymes involved in energy metabolism in hippocampal non-synaptic mitochondria. This enhancement of mitochondrial function may contribute to tianeptine's anxiolytic effects.

On the other hand, vortioxetine may offer a unique clinical profile distinct from SSRIs, perhaps owing to the novel multimodal mechanism of action, including direct 5-HT_{1A} agonis, modulation of norepinephrine and dopamine as well as 5-HT may contribute to its anxiolytic. Vortioxetine increased norepinephrine levels in the ventricular hippocampus and medial prefrontal cortex of rats (Inoue et al., 2021).

For example, tianeptine was able to keep serotonin levels in the brain close to control levels, whereas vortioxetine was able to considerably raise serotonin levels, which is consistent with its mechanism of action as an SSRI. Additionally, tianeptine increased antioxidant markers in the brain more efficiently than vortioxetine, indicating possible neuroprotective advantages.

The research conducted by Pekarskaya and colleagues (2021) shown that tianeptine has the potential to serve as an alternative treatment for individuals who are resistant to traditional antidepressants. This is especially true for those who have changed serotonergic systems as a result of prenatal exposure to selective serotonin reuptake inhibitors (SSRIs). Tianeptine was able to significantly reduce avoidant behaviors in a mouse model of early developmental exposure to selective serotonin reuptake inhibitors (SSRI). On the other hand, chronic SSRI treatment either failed to ameliorate or made these behaviors worse. It is possible that tianeptine could provide therapeutic effects in groups that are resistant to conventional antidepressants. This would be a source of hope for those who are experiencing depression that remains unresponsive to treatment.

Nevertheless, it is of the utmost importance to look into the potential negative effects that are connected with antidepressant medication. The research conducted by Lopez-Castroman and colleagues (2020) looked into the activation syndrome (AS) that was brought on by tianeptine and the connection that it had with suicidal ideation (SI). Treatment-emergent schizophrenia was found

to have a substantial association with symptoms of attention deficit hyperactivity disorder (AS), specifically sleep issues and impulsive upsurges. Underscoring the significance of properly monitoring AS symptoms during the commencement of antidepressant treatment is the fact that this is especially important for individuals who have experienced depressive episodes for an extended period of time.

Han et al. (2022) explored the one-of-a-kind mechanism of action of tianeptine, indicating that, in contrast to vortioxetine, tianeptine requires mu opioid receptors (MORs) in order to produce effects that are similar to those of a chronic antidepressant. Not only does this distinction provide vital insights into potential targets for the creation of new antidepressant medications, but it also suggests a novel avenue for antidepressant treatment that goes beyond the monoamine hypothesis.

Conclusion

Because tianeptine has an antidepressant effect that may be mediated in rats through neuroprotective effect evident as antioxidant activity and restoration of brain weight, the findings obtained from the study indicate that the use of tianeptine exhibits superior antidepressant effects than vortioxetinein in the treatment of depressive disorder. This is because vortioxetinein has been shown to have antidepressant effects. These findings provide evidence that tianeptine has the potential to be a flexible drug that is both safer and more effective in a wide range of applications.

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