# TIANEPTINE'S ACTION ON NEURONAL PLASTICITY

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***Abstract***

Neuroplasticity can be seen at different levels: structural plasticity (plastic changes in spine and dendrite morphology as well as adult neurogenesis), functional synaptic plasticity, and the molecular and cellular mechanisms accompanying such changes. Tianeptine has specific neurotrophic properties, and the antidepressant effect is well established. Long term antidepressant treatment raise granulate cells in hipocampus and blocks the stress inhibitory effect on neurogenesis.

**Keywords**: neuroplasticity, tianeptine, hippocampus

Neuronal plasticity or remodeling is a fundamental process by which the brain acquires information and makes the appropriate adaptive responses in future-related stressful situations. The concept of neuroplasticity refers to the central nervous system function by which a person selects stimuli from different areas, such as sensory, cognitive, emotional, endocrine, and social and adapts to them.

Clinical studies have shown that remodeling plays an important role in the pathophysiology of mood disorders, as well as in their treatment [1].

Neuronal structural changes encountered in patients with mood disorders, or in the case of responses to stressful events are reversible by administration of antidepressants such tianeptine. The hippocampus plays a significant role in the processes of memory and learning, as well as in the control of autonomic and vegetative functions. Decrease of neurons in the hippocampus observed in patients with unipolar depression or bipolar disorder is the result of several factors, of which we mention: hypothalamic-pituitary-adrenergic hyperactivity, glutamatergic excitotoxicity, hypoxia and cerebral ischemia, or vulnerability to stress. Exposure to psychological trauma cause different changes in the number of neurons, atrophy of the

hippocampus CA3 pyramidal neurons, reduced number and length of apical dendrites. The hippocampus is a brain region where cell division process continues into adulthood. Brain imaging techniques in depressive disorders showed different degrees of cerebral atrophy, decreased volume of hippocampus and of prefrontal cortex. In adults, the hippocampus presents a structural neuroplasticity and shows great sensitivity and vulnerability to stressful situations [2]. Data from literature reports hippocampal atrophy in patients with post traumatic stress disorder (PTSD), major depressive disorder, or borderline personality disorder as a result of stress agents [3].

Initially, these disorders determine a neurogenesis down regulation of the granulated neurons in the dentate gyrus and their prolonged action produces a remodeling of the dendrites in CA3 region involved in memory processing. Hippocampic neuronal restructuring processes are mediated by adrenal hormones, which act in two ways:

- they are involved in the process of neurogenesis regulation of the granulate neurons in the dentate gyrus. This process is influenced by stressful experiences and reflects itself on the functional and anatomical connections between amygdale and the dentate gyrus. Amygdala is involved in memorizing the experiences that produce fear.

- they take part in the stress-induced reversible remodeling of apical dendrites in the hippocampus region, which plays an important role in learning short-term tasks and in spatial orientation. Neurons in the hippocampus have two types of receptors: type I (mineralocorticoid), type II (glucocorticoid) that interact with adrenal hormones in the blood and influence neuronal excitability and structural plasticity.

These receptors are involved in the destruction of pyramidal neurons, which is common in epilepsy, brain trauma, cerebral ischemic attacks, and changes in calcium homeostasis. Acute and chronic stress models have highlighted the role of neurotransmitters such as serotonin, and gamma-aminobutyric acid (GABA), which act synergistically with corticosteroids. High concentrations of glucocorticoids occur in stressful conditions. Adrenal hormones induce a biphasic and reversible modulation of the excitability of neurons in the hippocampus region, determining an initial rise in its amplitude, followed by a decrease of it under persisting trauma. Neural responses are influenced by adrenal gland secretion, whose activity depends on the action of various stress agents.

Exposure to stressful events changes the structure of presynaptic endings in striatum, and the inhibiting interneurons in this area control the neuronal excitability in the hippocampus. Cell destruction during stroke represents a stimulus for local neurogenesis in particular for granulated neurons. Receptors for circulating insulin-like growing factor-1 and -2, involved in neurogenesis, are expressed in the hippocampus.

Various studies have shown that acute and chronic psychosocial stress inhibits neurogenesis. Atrophy of the dentate gyrus is caused by dendritic remodeling process produced by glucocorticoids and exposure to trauma, which affects both dendrites from the dentate gyrus and those of CA3 and CA1 pyramidal neurons [4].

Neuronal plasticity is very useful in explaining the effects of drugs, which are not correlated with neurochemical mechanisms [5]. Unlike other antidepressants such as selective serotonin inhibitors, tianeptine reverses hippocampus atrophy observed in patients suffering from depressive disorders.

Synthesis deficit in neurotrophic factors ((brain derived neurotrophic factor (BDNF), Neurotrophin NT3, 4/5, Bcl-2) is responsible for increased apoptosis in the hippocampus and prefrontal cortex, areas which are involved in cognitive impairment described in depression [6]. Neurotrophic factors, such as BDNF, CREB (cAMP response element binding protein), nerve growth factor and neutrophin 3 play a specific role in the development and maturation of neurons. Stress causes a pronounced decrease of BDNF in the hippocampus, especially in CA3 and CA1 pyramidal cells. Long-term antidepressant treatment increases BDNF not only in the hippocampus but also in the cerebral cortex.

Depression and chronic exposure to stress agents cause a decrease in the levels of growth factors, BDNF and Bcl 2, and reduce neurogenesis. Involvement of cytokines in depression is supported by their increase in major depressive disorder, or after exposure to stress agents. Immunotherapy with cytokines (interferon alpha) exacerbates depressive symptoms resistant to antidepressant treatment [7]. Tianeptine is highly effective in depressive disorders. It reduces and controls the dendritic remodeling process of the hippocampus caused by stress and glucocorticoids and thus it prevents cognitive impairment.

Chronic psychosocial stress causes glutamate and serotonin release, which are involved in the dendritic remodeling processes. Serotonin interacts pre- or post-synaptic with glutamate and a receptor interaction of the two neurotransmitters occurs in the CA3 neuron dendrites [8]. Tianeptine alters receptor structure, which is reflected in stress-induced dendritic remodeling.

Although long-term social conflicts do not determine the loss of main cells, hippocampus alteration is accompanied by changes in cell apoptosis. Suppressant effect of social conflicts on hippocampic structures can be reversed by tianeptine treatment [9].

Long-term administration of antidepressant treatment increases granular cell proliferation in the hippocampus and blocks the effect of decreased neurogenesis that occurs in response to stress. Several studies show that antidepressants induce a reversibility of the hippocampus atrophy in patients with depressive disorder. They also produce an increase of neurotrophic factors in the hippocampus and in the cerebral cortex. Behavioral models found out that BDNF infusion in the midbrain produces strong and

durable antidepressant effect. Tianeptine has specific neurotrophic properties, and its antidepressants effects are well documented [10].

Recent studies provide evidence that tianeptine modulates the effects of stress on glutamate neurotransmission. For example, tianeptine inhibits stress-induced decreases in cell proliferation and hippocampal volume, as well as the reductions in cerebral metabolites elicited by chronic stress [11]. Tianeptine also prevents stress induced alterations in the electrophysiological properties of glutamatergic synapses after acute [12] and chronic stress [13]. These results demonstrate that tianeptine effectively inhibits stress-mediated neurological changes related to neurochemical adaptations that may involve modulation of the phosphorylation state of glutamate receptors in the CA3 region [13]. Interestingly, tianeptine administration to no stressed control rats has no effect on these morphological [11,14], electrophysiological [12], cellular [11,15], or pharmacological [17] parameters. These results support the hypothesis that tianeptine may act to normalize glutamatergic function during stressful stimuli and may, therefore, have distinct clinical advantages when compared with other antidepressant treatments [16].

Clinically, Tineptin effective in reducing symptoms of depression in mild to moderate-to-severe major depression, including over the long term. Tianeptine is also effective in alleviating the symptoms of depression-associated anxiety.

Tianeptine prevents or reverses stress-associated structural and cellular changes in the brain and normalizes disrupted glutamatergic neurotransmission. In particular, in the hippocampus, it prevents stress-induced dendritic atrophy, improves neurogenesis, reduces apoptosis and normalizes metabolite levels and hippocampal volume.

Tianeptine also has beneficial effects in the amygdala and cortex and can reverse the effects of stress on neuronal and synaptic functioning. The neurobiological properties of tianeptine may provide an explanation not only for its antidepressant activity, but also for its anxiolytic effects in depressed patients and its lack of adverse effects on cognitive function and memory.

It is given in oral doses of 12.5 mg three times daily in the treatment of depression. Doses should be reduced to a total of 25 mg daily in elderly patients and in those with renal impairment.

It is generally well tolerated, with little sedation or cognitive impairment. Isolated cases of hepatitis have been reported during treatment with tianeptine.

**Conclusion**

Neuronal plasticity or remodeling is a fundamental process by of appropriate adaptive responses in future-related stressful situations. Various studies have shown that acute and chronic psychosocial stress

inhibits neurogenesis. Long-term administration of antidepressant treatment increases granular cell proliferation in the hippocampus and blocks the effect of decreased neurogenesis that occurs in response to stress. These results point to the importance of understanding the effects of chronic stress on structural plasticity as well as the neuroprotective properties of agents such as tianeptine.

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