# ANTIDEPRESSANT ACTION OF TIANEPTINE IS CONNECTED WITH ACCELERATION OF SEROTONIN TURNOVER IN THE SYNAPSE: A HYPOTHESIS

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**ÚJ HIPOTÉZIS A TIANEPTIN ANTIDEPRESSZÁNS HATÁSÁRÓL, A SZEROTONIN SZINAPSZISBAN TÖRTÉNŐ FELSZABADULÁS GYORSÍTÁSÁVAL**

A szerotonerg antidepresszánsokkal kezelt szorongásos depressziós betegek vizsgálatának eredményeiből kiindulva, az irodalomban elsőként felvetjük, hogy a tianeptin hatás a szerotonin visszavétel serkentésén alapul. Eszerint a tianeptin nemcsak a szerotonin visszavételt aktiválja a szinapszisban, hanem a felszabadulást is, ennélfogva gyorsítja a szerotonin turnovert. Az általunk felvetett főként a szerotonerg neurotranszmisszió normalizálására irányuló hatás első, akut fázisára vonatkozik.

**KULCSSZAVAK:** tianptin, neurokémiai hatásmechanizmus, szorongásos depresszió

**SUMMARY**

Based on the results of our investigation of patients with anxious depression under the treatment with serotonergic antidepressants with different mechanism of action on serotonin reuptake we, the first time in the literature, propose the hypothesis about neurochemical mechanism of tianeptine action. According to this hypothesis tianeptine not only activates serotonin reuptake into the synaptic ending but also activates its release from the ending into the synaptic cleft thus accelerating serotonin turnover rate in the synapse. Proposed mechanism mainly refers the first, acute phase of its action directed to the normalization of serotonergic neurotransmission.

**KEYWORDS:** tianeptine, neurochemical mechanisms of action, anxious depression

Tianeptine is a serotonin (5-hydroxytryptamine, 5-HT) reuptake enhancer. It exhibits a mechanism of action totally opposite to selective serotonin reuptake inhibitors (SSRI), such as sertraline, but paradoxically both mechanisms of action are associated with a therapeutic efficacy in depressive disorders, in particular in anxious depressions. In spite of a numerous experimental and clinical trials the neurochemical mechanism of tianeptine action is not enough clear (Ansseau, 1993; Stahl, 1999; Kasper, 2006). Ansseau (1993) had analyzed the different effects of tianeptine and discussed the approaches, mainly clinical, which could help to understand "the paradoxical activity of tianeptine". But he did not express his views on the ways to solve the problem of the neurochemical and therapeutic mechanisms of action of this antidepressant. Stahl in his "Essential Psychopharmacology" (1999, p. 160) wrote: "Tianeptine is an example of an agent that allosterically modifies serotonin reuptake in a manner that is almost the opposite to that of the SSRIs. Although this might theoretically seem to have the potential to cause depression rather than treat it, tianeptine in fact appears to be antidepressant."

All these prompt us to carry out the comparative clinical-biochemical investigation of patients with anxious depression under the treatment of tianeptine and sertraline and on the basis of results of the study develop possible mechanism of tianeptine action. Some clinical and biochemical aspects of this work are described elsewhere (Maximova et al. 2000; Uzbekov et al. 2006).

In this paper we want to stress the attention on the working hypothesis of the neurochemical mechanisms of tianeptine action. Some preliminary as-

pects of this hypothesis were published earlier (Uzbekov et al., 2002).

Shortly, in 43 patients with anxious depression we have revealed significant almost twofold increase of platelet monoamine oxidase (MAO) activity as compared with healthy volunteers. These disturbances in monoaminergic systems were accompanied by the significant twofold decrease of serum semicarbazide-sensitive amine oxidase (SSAO) activity, significant increase of the level of plasma middle-mass endotoxic molecules (MMEM) and significant decrease of albumin functional properties (Uzbekov et al. 2006). There were found significant changes in blood serum concentrations of cortisol, estradiole and testosterone (Uzbekov et al. 2003). All these disturbed parameters indicate on the pronounced endogenous intoxication (Uzbekov and Misionzhnik, 2000; Uzbekov et al. 2006).

Anxious depression is characterized by the decrease in serotonergic activity (Kasper, 2001) and possibly by the decrease in serotonin concentration in the synapses. Twofold increased platelet MAO activity in anxious patients indirectly supported this view. It is thought that the platelet MAO activity in some instances reflects the similar enzyme activity in the brain (Stahl, 1985).

According to the literature (Avakjan, 1976; Hughes, 1972) it is supposed that at normal condition about 75% of serotonin released in the synaptic cleft undergoes functional inactivation by the reuptake in the presynaptic ending (neuron) by the reuptake mechanisms (reuptake receptor or serotonin transporter). Serotonin is accumulated in the synaptic vesicles and thus it becomes unavailable to the action of MAO localized in mitochondria of presynaptic ending. The remaining serotonin (approximately 25%) undergoes chemical (irreversible) inactivation by MAO localized in mitochondria of glial cells (astrocytes and/or microglial cells) that close the synaptic cleft and where the neurotransmitter is taken up (Hughes, 1972; Avakjan, 1976; Whitaker et al. 1983). As serotonin uptake in neuronal and glial cells proceeds through the receptors (or transporters) it is possible to suppose that serotonin affinity for the receptors on presynaptic ending (neuron) and on glial cells correlates as 3 to 1 (75% and 25%, see above). It is necessary to note that receptors for serotonin on astrocytes differ from those on the neurons (Hertz and Tamir, 1981).

It was earlier shown that in depressed patients the capacity (or activity) of the serotonin reuptake mechanisms were decreased (Bellivier et al. 2002; Slanley et al. 1982; Stahl, 1985). On the other hand in our study we have established that in anxious-depressed patients MAO activity was increased almost twofold (Uzbekov et al. 2006). The letter specifies that in this case serotonin is taken up more actively by the glial cells where MAO is localized. We can assume that the ratio – serotonin affinity for receptors on the presynaptic ending and the same on the glial cells in patients with anxious depression changes. The left part of the ratio is decreasing and the right part – is increasing, i.e. the ratio becomes, for example, 2 to 2 instead of 3 to 1 (as in norm). On the functional level it means that in anxious depression serotonin is taken up by glial cells in larger quantity where it chemically inactivated by MAO. Owing to this serotonin concentration in the synaptic cleft is reduced and as a result less quantity of serotonin is returned in the presynaptic ending. All this events lead to the disturbances in serotonergic activity and in particular serotonergic neurotransmission.

The therapeutic effects under tianeptine treatment (37,5 mg/day) is manifested after two weeks of therapy (Maximova et al. 2000; Uzbekov 2006) that is supported by literature data (Quitkin et al. 1984; Kato and Weitsch, 1988; Ansseau, 1993). At that time we have found changes in activity or levels of all investigated biochemical parameters. These changes were not very pronounced although they were significant (Uzbekov, 2006).

Elucidation of the antidepressive mechanism of tianeptine action is one of the most difficult problems. The analysis of available data has shown the lack of any information that could explain neurochemical mechanism of action of this antidepressant. It is well known that tianeptine activates serotonin reuptake in the presynaptic ending. Thus promoting for the more "energetic withdrawal" of serotonin from the synaptic cleft. In spite of all existing theories tianeptine on the clinical level reveals antidepressive, anxiolytic effects. Ansseau writes about this situation in such words: "The paradoxical finding that both tianeptine and selective 5-HT reuptake inhibitors exhibit antidepressant activity despite clearly antagonistic mechanisms is rather puzzling" (1993).

We think that the problem of tianeptine action is necessary to consider from the point of view of structural-functional unity of the synapse. Based

on this thesis the synapse has to be considered as a complex, multiple biological system but not only as a structure with "reuptake receptor".

According to our working hypothesis tianeptine, enhancing serotonin reuptake, decreases serotonin level in the synaptic cleft. Simultaneously with this process in responders we have established that a very high MAO activity starts to decrease. It is possible to suppose that tianeptine decreasing affinity of glial receptors for serotonin reduces activity of glial cells in serotonin uptake. That is followed by the inhibition of MAO activity. Our supposition is supported by results of Marinesco et al. (1996) who have found that tianeptine decreases serotonin availability to MAO which localized in glial cells. Because of that the ratio – serotonin affinity for the receptors on presynaptic endings and on glial cells changes. The left part of the ratio is increased (neuron) and the right part – decreased (glia), i. e. we have the ratio not 2 to 2 (peak of anxious depression) but, for example, 2,5 to 1,5 (beginning of the remission). Under tianeptine action two processes take place in the synaptic region: a) enhancing of serotonin reuptake in the synaptic ending, and b) inhibition of MAO activity that is followed by increase of serotonin concentration in the synaptic cleft. But in a whole it is possible to assume that serotonin concentration in the synaptic cleft appeared to be dropped because process (a) is more active then process (b). That is the "paradox" of the action of this antidepressant.

What is the fate of serotonin, which continues to take up in the presynaptic ending? Here it is necessary to make an assumption. Tianeptine is characterized by one more property that has a principle meaning. Carlsson et al. (1969) had described that 4-methyl-alpha-meta-tyramine caused the depletion of serotonin from the intraneuronal stores. They also had found that tianeptine markedly potentiated this type of serotonin depletion. Later Fattaccini et al. (1990) and Labrid et al. (1992) have shown in vivo and in vitro that tianeptine had significantly increased serotonin depletion from its intraneuronal stores.

Based on these data we can make the assumption that tianeptine directly or indirectly through any unknown mechanisms activates serotonin release from presynaptic ending in the synaptic cleft.

Thus, tianeptine enhances not only serotonin reuptake but also it activates its surge from the ending into the synaptic cleft. So it is possible to conclude that under tianeptine action serotonin turnover rate in the synapse is increased that promotes the increase in the unit of time serotonin concentration on postsynaptic receptors. Decreasing MAO activity supports serotonin concentration in the synaptic cleft on the minimally allowable level to display its neurotransmitter functions.

Proceeding from the offered neurochemical mechanism of tianeptine action it is possible to hypothesize of the interrelation between the dynamics of MAO activity and the clinical status of anxious depressed patients. In responders activation of serotonin turnover rate in the synapse is accompanied by decrease of MAO activity that allows on the minimally allowable serotonin level in the synaptic cleft to achieve pronounced therapeutic effects. The increase of the parameters of functional albumin activity and decrease of MMEM level are indicated to the decrease of degree of endogenous intoxication and the improvement of homeostasis as a whole (Uzbekov et al. 2006).

Analysis of our own and literature data make it possible to suppose that tianeptine antidepressant effects are characterized by two-phase action.

In the first, acute phase of its action there take place the neurochemical processes on the synaptic level, i.e. processes that were described as stated above. They lead to a relative normalization of serotonergic neurotransmission, moreover tianeptine does not induce the decrease of 5-HT1A receptors sensitivity for serotonin (Kelly and Leonard, 1994).

The second phase of tianeptine action begins, possibly, after a relative normalization of serotonergic neurotransmission. It is connected with such properties of this antidepressant as ability to decrease of degree of endogenous intoxication (Uzbekov et al. 2006) and mobilization and activation of compensatory and plastic mechanisms of the central nervous system. Thus, tianeptine reduces stress-induced atrophy of neuronal dendrites (Wagstaff et al. 2001; Watanabe et al. 1992), in stressed animals tianeptine attenuates the activation of the hypothalamo-pituitary-adrenal axis (Delbende et al. 1994; Droste et al. 2006), increases neuronal electric activity (Pineyro et al. 1995). It was shown that tianeptine prevents or reverses stress-associated structural and cellular changes in the brain and normalizes disrupted glutamatergic neurotransmission. In hippocampus, amygdala and

cortex it prevents stress-induced dendritic atrophy, improves neurogenesis, reduces apoptosis and normalizes metabolite levels (Lucassen et al. 2004; Kasper and McEwen, 2008).

The latent period for about 2 weeks, that is necessary to reveal tianeptine therapeutic effect, possibly is connected with the reorganization of different pathologically disturb brain system (Ansseau, 1993; Hirschfeld, 2001; Uzbekov et al. 2006). The results of our investigations indicate that indeed as early as in two weeks of tianeptine treatment we have revealed the improvement of investigated biochemical parameters; although these changes were not very pronounced they were significant (Maximova et al. 2000; Uzbekov et al. 2006).

In conclusion, we in the first time in the literature propose the hypothesis about neurochemical mechanism of tianeptine action. According to our hypothesis tianeptine not only activates serotonin reuptake but also activates serotonin release in synaptic cleft thus accelerating serotonin turnover in the synapse. Proposed mechanism mainly refers the first, acute phase of its action directed on the normalization of serotoninergic neurotransmission.

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