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FEATURE ARTICLE

Neurobiology of mood, anxiety, and emotions as revealed by studies of a unique antidepressant: tianeptine

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Recent studies have provided evidence that structural remodeling of certain brain regions is a feature of depressive illness, and the postulated underlying mechanisms contribute to the idea that there is more to antidepressant actions that can be explained exclusively by a monoaminergic hypothesis. This review summarizes recent neurobiological studies on the antidepressant, tianeptine (S-1574, [3-chloro-6-methyl-5,5-dioxo-6,11-dihydro-(*c,f*)-dibenzo-(1,2-thiazepine)-11-yl) amino]-7 heptanoic acid, sodium salt), a compound with structural similarities to the tricyclic antidepressant agents, the efficacy and good tolerance of which have been clearly established. These studies have revealed that the neurobiological properties of tianeptine involve the dynamic interplay between numerous neurotransmitter systems, as well as a critical role of structural and functional plasticity in the brain regions that permit the full expression of emotional learning. Although the story is far from complete, the schema underlying the effect of tianeptine on central plasticity is the most thoroughly studied of any antidepressants. Effects of tianeptine on neuronal excitability, neuroprotection, anxiety, and memory have also been found. Together with clinical data on the efficacy of tianeptine as an antidepressant, these actions offer insights into how compounds like tianeptine may be useful in the treatment of neurobiological features of depressive disorders.
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Depression is a complex, heterogeneous disorder, and the mechanisms underlying its pathogenesis are the subject of intensive investigation using pharmacological and genetic tools and animal models. The antidepressant effect of one of the early antidepressants, imipramine, discovered by a clinical team,[1] was initially linked to an inhibition on monoamine reuptake. This led to research on the role of imbalances in neurotransmission by the monoamines, which are extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits.[2] The monoamine hypothesis, that is, depression involves imbalances in serotonergic, noradrenenergic, and possibly dopaminergic function, has led the way for many years as the primary explanation for depressive illness. However, monoamine deficits are only part of the story and events beyond monoamine imbalance must be taken into account.[3,4]

For example, certain brain regions are reported to undergo structural changes in depression[5,6] and, thus, pharmacological treatments should be sought to reverse structural changes in brain. A decrease in hippocampal and prefrontal cortical volumes is reported in patients suffering from recurrent major depression.[7–10] That morphological changes in the hippocampus can be observed in patients in a first episode of depression remains a matter of debate.[11,12] Structural imaging studies have demonstrated reduced gray matter volumes in areas of the orbital and medial prefrontal cortex, ventral striatum, and hippocampus, and enlargement of the third ventricle of patients with mood disorder.[12–15] Atrophy of prefrontal cortical cells (ie both neurons and glia) has been reported in post-mortem studies.[16–18] Although the amygdala appears to shrink with prolonged depression,[19] amygdala enlargement has been reported in the first episode of major depression.[10,20]

Neurogenesis in the dentate gyrus of the hippocampal formation may be involved in the mechanism of action of a wide range of antidepressants.[21–23] This fascinating finding requires further research in order to understand how the mechanism of antidepressant treatments might converge to regulate common events such as neurogenesis and other forms of structural plasticity. Moreover, the concept of a serotonergic deficit in depression is particularly challenged by the drug tianeptine (S-1574, [3-chloro-6-methyl-5,5-dioxo-6,11-dihydro-(*c,f*)-dibenzo-(1,2-thiazepine)-11-yl) amino]-7 heptanoic acid, sodium salt), an antidepressant with structural similarities to the tricyclic antidepressant agents but with different pharmacological

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properties. Collectively, these data require that we look beyond the monoamine hypothesis of depression. The goal of this review is to summarize recent neurobiological studies of tianeptine that have uncovered potentially useful effects on structural plasticity, neuronal excitability, neuroprotection, anxiety, and memory (Table 1). Together with clinical data on the efficacy of tianeptine as an antidepressant, these actions offer insights into how tianeptine may be useful in the treatment of depressive disorders.

Pharmacological and clinical features of tianeptine

Tianeptine shows no affinity for neurotransmitter receptors and does not inhibit the uptake of serotonin or noradrenaline in the central nervous system.[24] Chronic tianeptine administration did not alter the concentration and affinity of alpha2, beta1, 5-HT1, 5-HT2, benzodiazepine, or GABA-B receptors[24] but increased the responsiveness of the alpha1-adrenergic system.[25] Tianeptine does not inhibit MAOa and MAOb activity in the cortex, hippocampus, and hypothalamus. Interestingly, the uptake of 5-HT but not of dopamine or noradrenaline from cortical or hippocampal rat synaptosomes was reported to be increased by tianeptine *ex vivo* after acute and chronic administration, while no effect on 5-HT release was observed.[26,27] More recently, it has been demonstrated that tianeptine also reduced both the number of transporter sites and their mRNA levels in the dorsal raphe nucleus.[28] From an electrophysiological point of view, sustained administration of tianeptine did not modify the spontaneous firing rate of dorsal raphe 5-HT neurons nor did it alter the sensitivity of somatodendritic 5-HT autoreceptors to LSD. Tianeptine did not modify the activity of postsynaptic 5-HT1A receptors nor the effectiveness of the terminal 5-HT autoreceptor antagonist in increasing the efficacy of the stimulation of the 5-HT pathway, despite prolonged treatment.[29]

However, tianeptine does exert positive effects in several animal models of depression.[30,31] Moreover, the clinical efficacy of tianeptine in the treatment of depression together with its good tolerance in terms of anxiolytic effect without sedation, rate of sexual disturbances and weight gain, have been clearly demonstrated in controlled trials up to 18 months in duration. The efficacy of tianeptine has been established against placebo and reference antidepressants of different classes, mainly tricyclics and SSRIs.[32–40] In addition, tianeptine alleviates anxious symptoms associated with depression,[34,39,41–46] a property not associated with sedative effects.[47] The alleviation of inner tension is also more rapid than fluoxetine effects.[48] Actually, the use of tianeptine is not associated with the adverse effects commonly reported with tricyclic antidepressants (sedation, effects on attention and memory) or SSRIs (sexual dysfunction, nausea).

Neurobiological properties of tianeptine

Regulation of hippocampal structural plasticity

Tianeptine is able to modify the structural plasticity induced by stress in animal models including an animal model of depression. This was demonstrated for the first time in the model of stress-induced atrophy, or remodeling, of hippocampal neurons. The remodeling (ie decreased number and length of the apical dendritic branches) is observed in CA3

Table 1 Summary of the main recent neurobiological properties of tianeptine

Structural plasticity

Hippocampus
- Prevents stress-[52] and corticosterone-[51] induced dendritic atrophy in the hippocampus (CA3)
- Opposes stress-induced decrease in proliferation rate of precursor cells (dentate gyrus)[22]
- Opposes stress-induced decrease in the hippocampal volume[22]
- Opposes stress-induced decrease in concentrations of *N*-acetylaspartate[22]

Amygdala
- Prevents dendritic hypertrophy in the BLA[116]

Neuronal excitability
- Overcomes the block of hippocampal LTP induction by inescapable stress[108]
- Reverses the inhibitory effects of stress on LTP at hippocampal–prefrontal synapses[110]
- Reverses the stress-induced suppression CA1 PB[113]

Neuroprotection
- Reduces apoptosis in the hippocampus and temporal cortex[84]

Memory
- Blocks stress-induced impairments of spatial memory performance[97]
- Antagonizes the deleterious effects of alcohol[22]
- Facilitates focused attention behavior[99]
- Enhances memory retention[95,100]

pyramidal neurons of rodents and tree shrews, occurs after 2–3 weeks of exposure to restraint stress, long-term social stress, or upon exposure to high levels of glucocorticoids (suggesting a role for HPA axis).[49,50] Tianeptine prevents this dendritic atrophy in hippocampal pyramidal CA3 neurons [51,52] (Figure 1). This was measured as a prevention of the stress-induced decrease in the number and length of apical dendrite branch points.

The remodeling in the CA3 region is reversible after termination of 3 weeks of stress and is not a form of permanent hippocampal damage.[53] Indeed, tianeptine treatment was able to reverse dendritic remodeling caused by corticosterone in the drinking water for 3 weeks even while the corticosterone treatment continued[52] (Figure 2). In being able to prevent or reverse, stress- and corticosterone-induced dendritic remodeling, tianeptine differs from other antidepressants like serotonin-selective reuptake inhibitors for which no inhibition of stress-induced dendritic remodeling has been demonstrated.[52] Only one descriptive study, unfortunately not using a quantitative approach, has reported that fluoxetine was able to reverse the atrophy of hippocampal neurons caused by chronic mild stress in rats.[54]

Tianeptine's effects of preventing or even, to some extent, reversing stress-induced structural plasticity have also been demonstrated in a more naturalistic psychosocial stress model. Czéh *et al*[22] have investigated whether administration of tianeptine would oppose stress-induced adverse effects in the hippocampal formation in the chronic psychosocial stress model of adult male tree shrews (*Tupaia belangeri*). This animal model has a high validity to investigate the pathophysiology of depressive disorders.[55,56] To

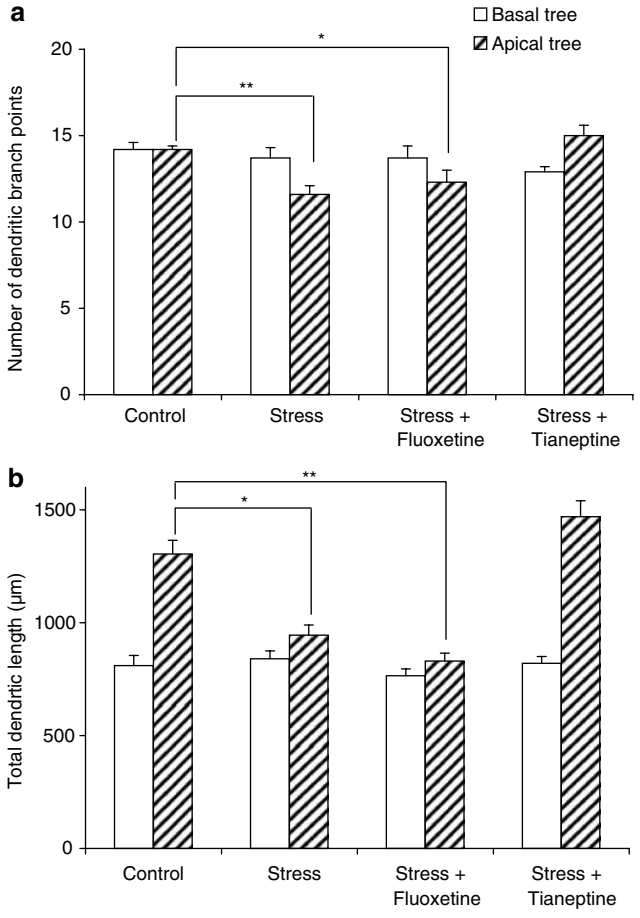

Figure 1 Effect of repeated restraint stress and cotreatment with fluoxetine and tianeptine on the number of dendritic branch points (panel a) and total dendritic length (panel b) of CA3 pyramidal neurons. After 21 days of daily restraint stress, a decrease in the number of branch points and total dendritic length of CA3 apical dendritic trees was observed. While the antidepressant fluoxetine, 10 mg/kg i.p. prior each restraint–stress session, was without effect, tianeptine, 10 mg/kg i.p. prior each restraint–stress session, prevented the hippocampal atrophy induced by stress. $*P<0.05$, $**P<0.01$, compared with controls. One-way ANOVA, Tukey's *post hoc* test. Bars represent means + SEM (reprinted from Magariños *et al. Eur J Pharmacol* 1999; **371:** 123–122).

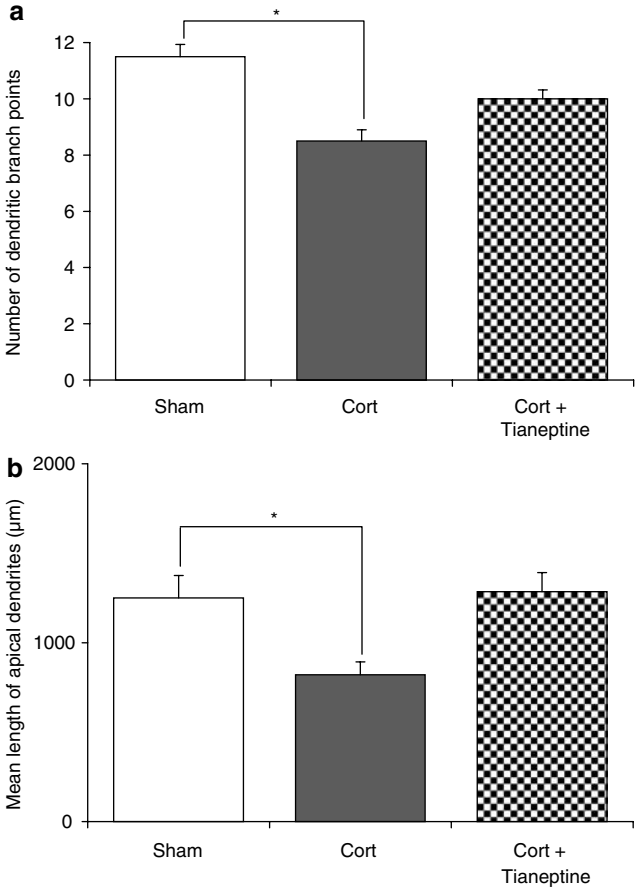

Figure 2 Effects of tianeptine (15 mg/kg/day i.p. for 21 days) and corticosterone on the number of branch points (a) and total length (b) of apical CA3 dendrites. For both measures, tianeptine prevents the significant decrease induced by corticosterone. $*P<0.05$, Tukey after one-way ANOVA (reprinted from Watanabe *et al. Eur J Pharmacol* 1992; **222:** 157–162).

mimic a realistic situation of antidepressant intervention, animals were treated after 7 days of stress exposure, when stress-induced accommodation of the brain was being established, and the therapeutic action of tianeptine was followed across a clinically relevant time period of 4 weeks. The authors found in this paradigm significant decrease in the *in vivo* concentrations of cerebral metabolites like *N*-acetylaspartate (a putative marker of neuronal viability and function), the proliferation rate of the granule precursor cells in the dentate gyrus, and the hippocampal volume. Tianeptine reversed all these alterations: brain metabolites were normalized and stress-induced reduction in cell proliferation was reversed (Figure 3).

The histological analysis of Czéh's study could only evaluate the rate of cell proliferation since animals were killed 24 h after the administration of BrdU. Therefore, that the majority of these cells would have differentiated into mature neurons that are integrated into the hippocampal circuitry and, thus, may contribute to the therapeutic response of tianeptine remains to be demonstrated. Nevertheless, for the first time, Czéh's findings demonstrate regulation by an antidepressant of the decreased neuronal metabolism and function together with cell proliferation decrease, and that in a prosimian model of depression. More recently, the effects of other well-established antidepressants, such as fluoxetine and clomipramine, have been successfully investigated on neurogenesis in animals submitted to various stress.[21,23,57]

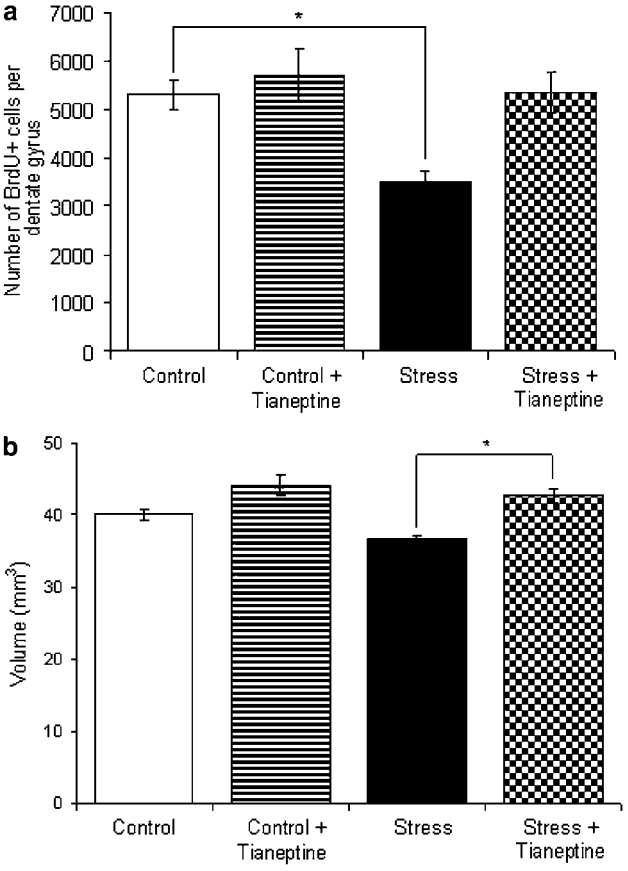

Figure 3 Tianeptine opposes the stress-induced adverse effects in the hippocampal formation in the chronic psychosocial stress model of adult male tree shrews (*T. belangeri*). (a) Chronic psychosocial stress significantly suppressed cell proliferation in the hippocampal dentate gyrus (stress), whereas chronic tianeptine treatment (50 mg/kg/day p.o. for 28 days) reversed the stress-induced effect (stress + tianeptine). Antidepressant treatment alone had an insignificant effect on hippocampal cell proliferation (control + tianeptine). Results are given as mean ± SEM number of BrdU-positive cells in the hippocampal dentate gyrus. $^*P<0.05$ *vs* controls. (b) Post-mortem volumetry of the hippocampus. Chronic psychosocial stress resulted in a decrease (7%) of the hippocampal volume compared with unstressed controls ($P<0.05$). This decrease was prevented by tianeptine treatment (stress + tianeptine *vs* stress; $^*P<0.05$) (reprinted from Czéh *et al. Proc Natl Acad Sci USA* 2001; **98:** 12796–12801).

What kind of mechanism could subserve these effects? Recent data suggest that antidepressants facilitate activity-dependent selection of functional synaptic connections in brain and, through their neurotrophic effects, improve information processing within neuronal networks compromised in mood disorders.[58] In fact, an increasing number of studies suggest that it is the ability to modify synaptic plasticity that is the crucial feature of clinically effective antidepressants, rather than the enhancement of neuronal survival alone. The emerging pharmacological profile of tianeptine suggests that this antidepressant may serve to organize synaptic function, thereby allowing the chemical signal to reinstate the optimal functioning of critical circuits necessary for normal affective functioning.

There are multiple pathways that may mediate the changes in connectivity induced by antidepressants. The underlying molecular and cellular mechanisms that contribute to hippocampal neurogenesis are not yet clearly understood. Among the candidate molecules that could mediate the trophic effect of tianeptine and other antidepressants are growth factors. Indeed, microinfusion of brain-derived neurotrophic factor (BDNF) or neurotrophin 3 (NT-3) into the hippocampus produces antidepressant effects in experimental models of depression.[59] However, Kuroda and McEwen[60] have shown that chronic tianeptine administration in a chronic restraint stress model does not modulate BDNF or NT-3 mRNA levels, suggesting that the mechanisms of action of tianeptine are distinct from those of SSRIs. Yet, other candidates are epidermal growth factor (EGF) and insulin-like growth factor (IGF-1). Indeed, dentate precursor cells are known to express EGF receptors and direct infusion of the growth factor into the dentate gyrus stimulates proliferation.[61] Selective induction of neurogenesis has also been achieved using IGF-1.[62,63] Further studies should elucidate the possible involvement of these molecules in the

mechanism of action of tianeptine and other antidepressants.

The atrophy of the hippocampus might involve steroid modulation of neurotransmitter activity in the hippocampus including the serotonergic, GABAergic, and glutamatergic systems.[64] Regarding the latter, there is evidence that antidepressants may regulate the excitatory amino-acid systems that underlie changes in synaptic connection strength (in addition to enhancing BDNF expression). A number of antidepressants have regulatory actions at the *N*-methyl-D-aspartate (NMDA) receptor complex and some NMDA receptor antagonists not only have antidepressant properties[65] but also prevent stress-induced dendritic remodeling of CA3 pyramidal neurons.[66,67] In line with this, tianeptine prevents the stress-induced reorganization of glutamatergic synaptic vesicles in the mossy fibers abutting CA3 neurons.[68] Thus, for tianeptine as for a number of other antidepressants, the modulation of the glutamatergic system could underlie its normalization effect on synaptic function.

Reagan *et al*[69] have explored the regulation of glial-specific excitatory amino-acid transporter (GLT-1a) under conditions that produce hippocampal dendritic remodeling (chronic stress) and found increases in GLT-1a mRNA expression in the dentate gyrus and the CA3 regions of the rat hippocampus, an effect which is inhibited by tianeptine (Figure 4). Increases in GLT-1a may result from stress-mediated increases in glutamate[70,71] and normalization of synaptic concentrations of glutamate by tianeptine would eliminate the stimulus for increased GLT-1a expression. Modulation of GLT-1a expression does not result from changes in hippocampal morphology, but rather reflects fundamental changes in the underlying neurochemical or molecular activities of the hippocampus in response to stress. Reagan's findings thus provide additional support for the hypothesis that stress-induced changes in the hippocampus involves a critical role in glutamate metabolism, disposition, and plasticity, and a dynamic interplay between numerous neurotransmitter systems, especially excitatory amino acids.[72,73]

Electrophysiological studies focusing on hippocampal synaptic plasticity further demonstrated similar protective effect of tianeptine application both *in vivo* and *in vitro*. Using a combined approach of repeated stress and electrophysiological recording, Kole *et al*[74] found that restraint stress for 21 days persistently enhances the NMDA-receptor component of EPSCs of the commissural/associational synapses onto CA3 pyramidal neurons, and that, when rats were concomitantly treated with tianeptine, several specific changes in NMDA and AMPA/kainate receptor-mediated currents are induced. First, tianeptine selectively counteracted the stress-induced increase in the NMDA-AMPA/kainate ratio (Figure 5). Moreover, as the enhancement of EPSCs could be blocked by the intracellular presence of the kinase inhibitor, staurosporine, the involvement of a postsynaptic

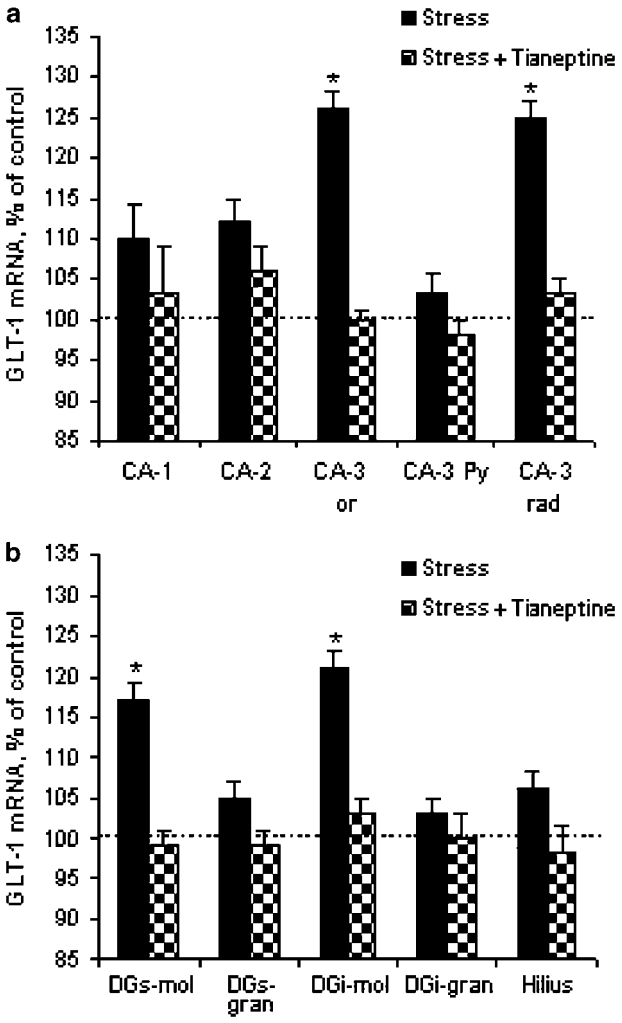

Figure 4 GLT-1a mRNA expression in the hippocampus of rats subjected to chronic stress. (a) Chronic stress (stress) did not modulate GLT-1a mRNA levels in the CA1 and CA2 regions of Ammon's Horn but increased GLT-1a mRNA levels in CA3 (CA3-or: stratum oriens; CA3-rad: stratum radiatum). These increases were reversed by daily tianeptine (10 mg/kg i.p. prior each restraint–stress session) administration (+tianeptine). (b) In the dentate gyrus, chronic stress increased GLT-1a mRNA levels in the molecular layers of the superior blade of the dentate gyrus (DGs-mol) and the inferior blade of the dentate gyrus (DGi-mol). Daily tianeptine administration inhibited stress-mediated increases in GLT-1a mRNA expression. All comparisons to vehicle-treated, nonstressed controls; $^{*}P \leq 0.01$ (modified from Reagan *et al. Proc Natl Acad Sci USA* 2004; **104:** 2179–2184).

phosphorylation cascade rather than presynaptic release mechanisms at the CA3 commissural/associational synapses may be involved.

The CA3 commissural/associational synapses are characterized by their autoinnervation from the cell body and collateral axons of neighboring CA3 cells providing a strong excitatory associative feedback network.[75] These hippocampal recurrent synapses could store autoassociative episodic memories.[76,77] A direct block by tianeptine at the NMDA channel, such

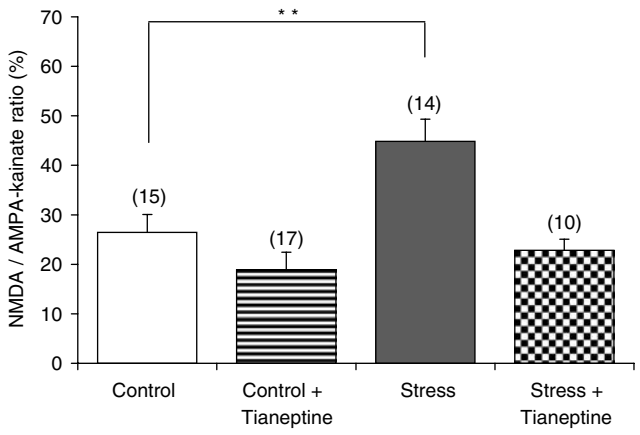

Figure 5 Chronic stress resulted in an enhanced ratio of the NMDA-receptor component of EPSCs of the commissural/associational synapses onto CA3 pyramidal neurons. When rats are concomitantly treated with tianeptine (10 mg/kg i.p. in saline daily), the stress-induced NMDA-AMPA/kainate ratio increase is selectively counteracted ($P<0.03$). Data are the mean $\pm$ SEM; numbers indicate the cells obtained from six animals per group (reprinted from Kole *et al. Eur J Neurosci* 2002; **16:** 807–816).

as the antidepressant imipramine produces,[78,79] is not likely to have caused this normalized ratio of glutamate receptor-mediated currents since tianeptine did not bind to excitatory amino-acid receptors.[24] On the other hand, a concurrent downregulation of selective NMDA-receptor subunits by tianeptine could be suggested, as already observed with tricyclic compounds and selective serotonin reuptake inhibitors.[65] Audinat *et al*[80] found that, on hippocampal slices, tianeptine increased field potential recorded in the CA1 region (following Schaffer collateral stimulation) and increased the amplitude of postsynaptic responses of both CA1 pyramidal cells and interneurons. Thus, although direct effects of tianeptine on glutamatergic receptors can be excluded, the antidepressant increases both NMDA- and AMPA-mediated current. Collectively, Kole's and Audinat's data suggest that tianeptine-enhanced hippocampal pyramidal activity is most probably attained by strengthening the conductance for receptor-mediated EPSCs, thereby increasing subthreshold voltage propagation and reducing action potential threshold.

Tianeptine-induced EPSC enhancement is obtained rapidly, but repeated exposure to tianeptine resulted in an enduring expression of EPSC increase.[80] Tianeptine may target the phosphorylation state of glutamate receptors at the CA3 commissural/associational synapse. Tianeptine-induced phosphorylation of intracellular kinases could provide a priming signal for the activity-dependent structural shaping of dendrites, either by promoting dendritic outgrowth or providing enhanced structural stability. For example, the calcium-calmodulin-dependent protein kinase II (CaMK II) is involved in stabilizing structural rearrangements.[81] Chronic, but not acute treatment with tianeptine caused increased phosphorylation of the CaMK II-PKC site (Ser831) on GluR1 subunit of AMPA receptors in the hippocampus (CA3 and dentate gyrus) and cerebral cortex of mice. Although there was a trend for an increase, the PKA site (Ser845) was not significantly affected by tianeptine.[82] CaMK II is markedly enriched at synapses, where it is involved in the control of synaptic transmission, transmitter release, and synaptic plasticity. CaMK II has also been found to be involved in the long-term action of a wide variety of antidepressant treatments including electroconvulsive treatment. Thus, the findings obtained with tianeptine add physiological evidence to the hypothesis that kinase phosphorylation, more particularly changes in CaMK II activity, following chronic antidepressant treatment might represent an important step in the expression of their antidepressive action.

A number of other critical molecules in neurotrophic signaling cascades (most notably cyclic adenosine monophosphate (cAMP), response element binding protein (bcl-2), and mitogen-activated protein (MAP) kinases) are also potential targets for tianeptine potentiating modalities. Tianeptine-induced phosphorylation of such kinases could thus explain how the drug reverses and/or prevents the stress-induced reduction of CA3 apical dendrites. Moreover, it will be important to determine which pathways are shared by other antidepressants, or, alternatively, how other antidepressants may converge on the same end point, such as AMPA receptors, via different pathways.

Thus, at the present time, the contribution of these molecules to the mechanism of action of tianeptine remains to be demonstrated, but the novel signal transduction mechanisms that have been recognized so far may provide a mechanistic resolution for the neuroprotective properties of tianeptine and, moreover, suggest a pharmacological trajectory for the memory-enhancing and/or antidepressant activity of tianeptine (see below).

Cytoprotective effects

Tianeptine exhibits cytoprotective effects against the potentially deleterious effects of proinflammatory cytokines in both the cortex and white matter.[83] Moreover, Lucassen *et al*[84] have hypothesized that tianeptine may have putative cytoprotective effects in chronically stressed animals and they investigated the effect of tianeptine treatment on apoptosis in the hippocampus and temporal cortex of adult tree shrews. Both stress and tianeptine had region-specific effects and tianeptine treatment reduced apoptosis in the dentate granule cell layer and subgranular zone, most likely on non-neuronal cells, but had no effect in the Ammon's Horn. These effects were not restricted to the hippocampus alone, as in the temporal cortex, chronic stress alone increased the numbers of apoptotic cells,[85] while tianeptine treatment had an antiapoptotic effect both in the stressed and unchallenged animals[84] (Figure 6).

The most pronounced effects of tianeptine are exerted in the dentate granule cell layer and in the

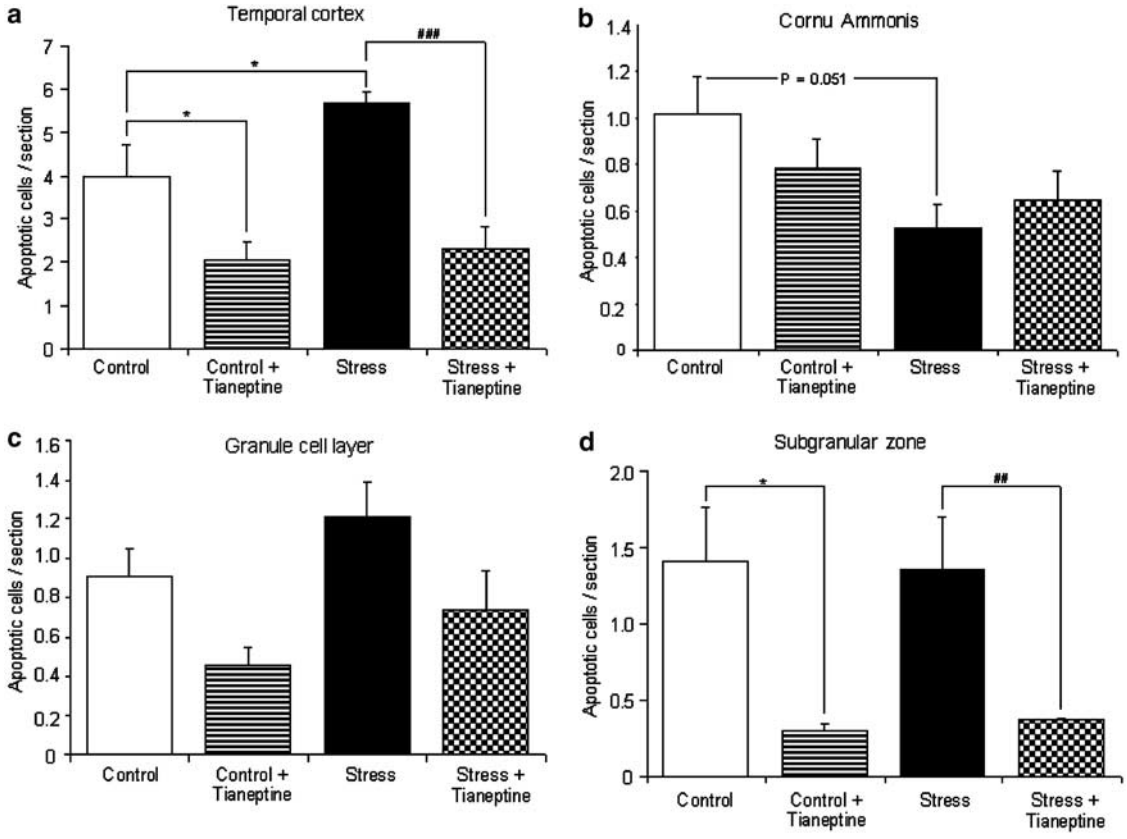

Figure 6 Effects of chronic psychosocial stress and concomitant tianeptine treatment (50 mg/kg/day p.o. for 28 days) on apoptosis in the temporal cortex (a), Cornu Ammonis (b), dentate granule cell layer (c), and subgranular zone (d) of the tree shrew. (a) In the temporal cortex, chronic stress resulted in a significantly increased occurrence of apoptotic cells, whereas antidepressant treatment had a significant antiapoptotic effect both in the control and stressed animals. (a) In the Ammon's Horn, the frequency of apoptosis was significantly suppressed after 5 weeks of psychosocial stress. (c and d) Both in the granule cell layer and subgranular zone of the dentate gyrus drug treatment significantly decreased the incidence of apoptosis (two-way ANOVA, main effect of drug treatment: $P<0.01$). Results are given as the mean number of ISEL-positive cells/section ± SEM. $^{*}P<0.05$, *vs* control: $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$, *vs* stress are results of the Newman–Keuls *post hoc* analysis (reprinted from Lucassen *et al. Biol Psychiatry* 2004; **55:** 789–796).

adjacent subgranular zone within the hippocampal formation, which gain special significance when considering the study of Czéh *et al*[22] in an animal model of depressive disorders. Thus, not only cytogenesis but also cell death, and therefore the entire process of adult dentate gyrus neuronal turnover, is affected by tianeptine treatment. In line with the antiapoptotic effect observed post-mortem by Lucassen *et al*,[85] tianeptine prevented the stress-induced reduction of the *in vivo* brain metabolite levels of *N*-acetylaspartate.[22] Several other studies have shown protective effects of antidepressants in different models, and mostly in the hippocampus.[58,86] In a maternal deprivation and a prenatal restraint stress model, alterations in granule cell number and neurogenesis as well as apoptosis occur[87,88] and these changes could be normalized by fluoxetine treatment.

The cortical effects of tianeptine are consistent with several reports on structural alterations in discrete human brain areas, like the anterior cingulate, dorsolateral prefrontal, subgenual, and orbitofrontal cortices, as well as the parahippocampal cortex and the amygdala, that are characterized by decreases in glia number or density.[89–91] Fuchs and Lucassen's data suggest that the cell survival-promoting effects of tianeptine may represent a more general mechanism of action that involves not only the hippocampus and cortical areas but may extend also to different brain regions of the limbic system, and that it involves glial cells as well as neurons.

Procognitive effects

Cognitive deficits, such as an impairment of attention, memory, and problem solving, have often been reported in patients with depressive disorders.[92] The magnitude of the hippocampal atrophy reported here in certain experimental conditions may partly underlie some of cognitive deficits that accompany major

depression. Conversely, any prevention or restoration of these morphological changes (volume loss) in the hippocampus should be parallel to procognitive/promnesiant effects. Accordingly, tianeptine has particularly favorable effects on cognitive functions and the positive effect of tianeptine may be mediated, at least in part, through its upregulation of neurogenesis and dendrite remodeling. Thus, tianeptine blocks the dendritic remodeling caused by stress or glucocorticoids,[51,52] blocks stress-induced impairments of spatial memory performance in radial and Y-maze,[93,94] and antagonizes the deleterious effects of alcohol.[95]

Yet, tianeptine effects can also be rapid. In a validated model of hippocampal-dependent memory impairment and synaptic plasticity changes by predator stress,[96] acute tianeptine can block the deleterious effects of stress on spatial memory,[97] an effect that does not depend on corticosterone levels.[98] Tianeptine also facilitates focused attention behavior in the cat in response to its environment or towards a significant stimulus.[99] It was shown to exert improving effects on learning as well as on working memory and on reference memory in rodents[95,100] and to exhibit vigilance-enhancing effects in rats[101] and monkeys.[102]

Moreover, Morris *et al*[103] found that acute tianeptine treatment can enhance memory retention in animals whose rate of forgetting of spatial memory in the water-maze has been increased through partial lesions of the diagonal band of Broca, which mainly supply the dentate gyrus and the adjacent CA3 and CA4 subfields of Ammon's horn[104] and provide direct and indirect (disinhibitory) excitatory inputs to the hippocampus. The behavioral findings of Morris *et al*[103] are consistent with findings that revealed that tianeptine prevents vesicular reorganization in mossy fibers caused by stress.[51,66–68] Morris' findings indicate that the input into the CA3 and dentate gyrus, that is, the main hippocampal areas where neurogenesis occurs, are key sites for the procognitive action of tianeptine.

Tianeptine's effects involve a dynamic interplay between different brain regions

Whereas the hippocampus is one of the most intensely studied structures, other brain regions involved in stress, fear, emotions, and memory, which are involved in regulating the HPA axis through excitatory inputs, are beginning to receive increasing attention.[105,106]

Medial prefrontal cortex

There is also a clear relationship between the hippocampus and frontal cortex and dynamic changes in synaptic connectivity such as long-term potentiation (LTP) can be demonstrated in the medial frontal cortical areas.[107] When administered several hours after the stress, tianeptine overcomes the block of hippocampal LTP induction by inescapable stress at a dose level that did not affect LTP in nonstressed animals.[108] This finding is consistent with the report that tianeptine can reverse stress-suppressed exploration of a novel environment when injected after the stress.[109]

Rocher *et al*[110] have shown that severe acute platform stress in rats caused a long-lasting inhibition of LTP in the frontal cortex evoked by stimulation of hippocampal outflow. In agreement with the observed effects of acute tianeptine in intrinsic hippocampal circuits,[108] acute tianeptine rapidly reverses the inhibitory effects of stress on LTP at hippocampal–prefrontal synapses (Figure 7). Thus, while tianeptine has been shown to have a strong impact on the deleterious effects of stress in the hippocampus, Rocher's data reinforce this outcome to another brain region of interest for depression, the frontal cortex.

Repeated restraint stress, such as is used to cause remodeling of the hippocampus in rats, causes shortening of dendrites in the medial prefrontal cortex.[111] It remains to be determined whether chronic tianeptine treatment will prevent these changes as it does for atrophy of hippocampal neurons.

Amygdala

Conrad *et al*[53] have postulated that chronic stress would enhance cued conditioning but not context conditioning. They showed that repeated restraint stress facilitates fear conditioning to both context and tone independently of causing hippocampal CA3 dendritic atrophy. Tianeptine failed to prevent the stress effects on fear conditioning, even though it did prevent neuronal atrophy in the hippocampus. Conrad's findings indicate that the retraction of the CA3 dendrites was present 4 days, but not 10 or 20 days, after the cessation of the restraint stress. Consequently, changes in fear conditioning cannot be attributed to the CA3 atrophy having reversed itself before the end of the conditioning paradigm. However, restoration of normal dendritic morphology within 10 days emphasizes the importance of assessing possible stress-induced behavioral deficits before the atrophy disappears. The failure of tianeptine to block the stress-induced changes in fear conditioning and open-field behavior is an indication of dissociation between the behavioral and morphological consequences of repeated stress. Conrad suggests that dendritic atrophy is not a form of permanent hippocampal damage, but a type of structural plasticity, or 'remodeling', which could be an adaptation to chronic stress. Although these findings do not exclude the possibility that the stress-induced hippocampal CA3 atrophy affects some aspects of conditioned fear, they do indicate that repeated restraint stress over 21 days has a powerful enhancing effect on emotionality that may be attributable to the overriding effects of chronic stress on other brain regions such as the amygdala. There is evidence for a critical role for the amygdala in the stress circuitry, which comes from behavioral studies of learning and memory. Repeated stress that produces dendritic remodeling in the CA3 region impairs hippocampal-

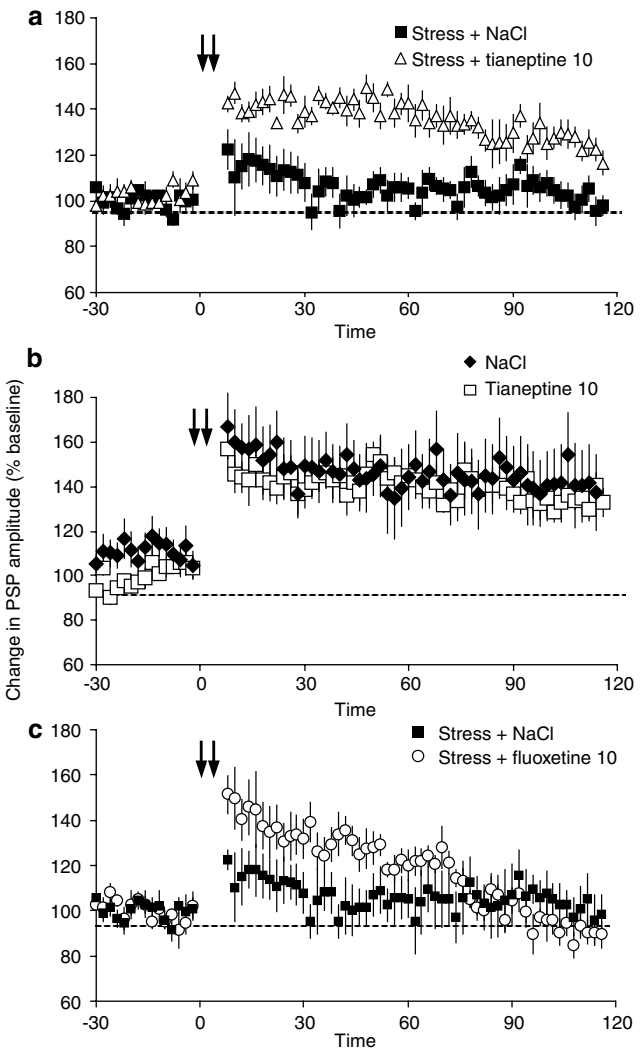

Figure 7 Severe acute platform stress in rats caused a remarkable and long-lasting inhibition of LTP in the frontal cortex evoked by stimulation of hippocampal outflow. Tianeptine (10 mg/kg i.p. in saline 40 min prior to induction of LTP) rapidly reverses the inhibitory effects of stress on LTP at hippocampal–prefrontal synapses. (a) Stressed rats. Tianeptine fully restores LTP from stress-induced impairment. (b) Unstressed rats. Tianeptine does not significantly affect LTP. Values are mean ± SEM of the normalized hippocampal–frontal cortex postsynaptic response amplitude. The high-frequency stimulation (HFS) is represented by arrows. (c) By comparison, fluoxetine (10 mg/kg i.p. in saline 40 min prior to induction of LTP) partially overcomes the stress-induced impairment of frontal LTP (reprinted from Rocher *et al. Cereb Cortex* 2004; **14:** 224–229).

dependent learning, but stress might also impair memory through nonhippocampal mechanisms such as enhanced emotionality.[53]

Anatomically, the amygdala is connected both directly (amygdalo-hippocampal bundles arise from the basolateral amygdala and terminate in the CA1, the CA3, and the subiculum) and indirectly (through the entorhinal cortex) to several hippocampal regions.[112] Diamond and colleagues also have studied the effects of acute tianeptine and stress on hippocampal and basolateral amygdaloid (BLA) plasticity. Rats were stressed by a cat intruder for 1 h and recordings in CA1 and BLA were performed. Primed burst (PB) or LTP stimulation was delivered to the hippocampal commissure for CA1 and BLA recordings or to the entorhinal cortex for BLA recordings. Tianeptine enhanced CA1 PB and increased baseline excitability in the nonstress group, and reversed the stress-induced suppression of CA1 PB. Neither stress nor tianeptine affected CA1 LTP. Stress alone enhanced LTP in the BLA of vehicle-treated rats, as well as in the stressed tianeptine-treated rats. Thus, these findings indicate that tianeptine can reverse the adverse effects of stress on hippocampal processing without interfering with the naturally enhancing effects of stress on amygdaloid processing.[113]

In view of the potentially contrasting impact of chronic stress on the hippocampus and amygdala at the behavioral level, and the different roles played by these two structures in the neural circuitry of stress, it is important to examine the effects of chronic stress at the level of single neurons. Using morphometric techniques, Chattarji *et al*[114] have demonstrated that chronic stress induce contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons.[114,115] Chronic immobilization stress elicited significant dendritic atrophy in hippocampal CA3 pyramidal neurons, as previously reported but, in striking contrast, chronic immobilization stress *increased* dendritic arborization in BLA neurons. This stress-induced enhancement in dendritic arborization did not represent a generalized increase in all classes of BLA neurons, but was restricted only to BLA pyramidal and stellate neurons, which are presumably excitatory projection neurons.

Stress-induced dendritic remodeling in the amygdala may provide a potential cellular substrate for depression caused by chronic stress. The effects of tianeptine on stress-induced dendritic remodeling in the basolateral amygdala have been investigated. Strikingly, stress-induced enhancement in dendritic arborization in the BLA neurons was completely prevented in tianeptine-treated animals.[116] Moreover, prevention of dendritic hypertrophy in the BLA by tianeptine was associated with a preventive effect of the antidepressant on potentiation of anxiety-like behavior in male rats. Nevertheless, Conrad *et al*[53] reported that repeated restraint stress enhanced freezing to context and tone and decreased open-field exploration irrespective of whether tianeptine was given or not, suggesting no association between morphological and behavioral effects. At present, there is no explanation for the difference in efficacy of tianeptine in the two studies. It remains to be seen whether the difference between these findings is due to the fact that Conrad used restraint stress for 21 days, whereas the Chatterji group used a 10-day immobilization (a more severe stressor).

Yet, there is other evidence for anxiety reduction by tianeptine. When administered acutely, tianeptine

counteracted the anxiogenic effect of benzodiazepine and alcohol withdrawal in the social interaction test, whereas no effects were observed in the stress-induced hyperthermia, elevated plus-maze, and social interaction test.[117,118] Recent data also provide some convergence on the potential efficacy of tianeptine in terms of its action on the amygdala. Wood *et al*[119] have shown that chronic tianeptine prevented stress-induced potentiation of aggressive conflicts, such that there was an interaction between chronic stress and tianeptine treatment throughout the study. Tianeptine also significantly reduced the incidence of aggressive conflicts in stressed and unstressed control rats during periods when aggression is high. Moreover, Burghardt *et al*[120] reported that chronic tianeptine given for 21 days before training can reduce conditioned freezing, very much as chronic SSRI treatment is able to do; however, tianeptine was devoid of anxiogenic effects after acute administration, whereas acute SSRI treatment increased anxiety. All these phenomena are likely to reflect amygdala function.

Conclusions

The clinical efficacy of tianeptine in the treatment of depression together with its good tolerance has been clearly demonstrated in controlled trials. However, the generally accepted theories about the biological basis of depression, for example, a serotonergic deficit, cannot explain its antidepressant activity and events beyond the monoaminergic regulation must be taken into account. The neurobiological properties of tianeptine involve a critical role of structural and functional plasticity in several brain regions of the limbic system, as well as the dynamic interplay between numerous neurotransmitter systems including excitatory amino acids. Some of these properties appear to be shared by other antidepressants. Moreover, the neurobiological properties of tianeptine, involving trophic effects on the alteration of plasticity in the hippocampus and amygdala, are relevant to its clinical efficacy for the treatment of depression as well as its reported effects on memory and anxious symptoms of depression. Collectively, it is of great interest that the antidepressant tianeptine acts on dendritic remodeling, both in amygdala and the hippocampus, two limbic regions, which are central and intimately linked to the full expression of emotional learning.

Cognitive deficits, such as an impairment of attention, memory, and problem solving, have often been reported in patients with depressive disorders.[92] The hippocampus plays a critical role in learning and memory and the magnitude of the hippocampal volume loss may partly explain some of the cognitive deficits that accompany major depression. Tianeptine has a unique impact on the alteration of plasticity in the hippocampus, which may thereby participate in accelerating neural adaptive mechanisms that may be deficient, and the improvement in memory function by tianeptine may represent the partial restoration of normal functional plasticity in the hippocampus. Interestingly, subjects with mild cognitive impairment (MCI) who subsequently developed clinical Alzheimer's disease exhibit a greater rate of hippocampal atrophy than those remaining clinically stable.[121,122] Therefore, tianeptine treatment, which is aimed at facilitating trophic function, may prove highly beneficial in attenuating the rate of neural degeneration leading to short-term memory loss observed in MCI.

Tianeptine is also effective in treating anxiety. It rapidly alleviates anxious symptoms of depressed patients[34,39,41–46] with no sedative-associated effects.[47]

Tianeptine and other antidepressants share some common effects such as those on neurogenesis. These findings reinforce the credibility of the neuroplasticity approach to the pathophysiology of depression. However, antidepressants of different classes may differ in their ability to produce other types of structural changes. Although neurogenesis seems to be a key point in the mechanism of action of antidepressants, the story is far from being complete in light of other forms of structural plasticity, such as dendritic remodeling and turnover of glial cells, that can also be involved in the mechanism of action of antidepressant drugs. To date, the schema underlying the effect of tianeptine on central plasticity is the most thoroughly studied among antidepressants. Insofar as data are still missing with most of the other antidepressants, it may be that some of the reported effects of tianeptine on brain plasticity do not represent a common feature of all antidepressants. However, while all drugs do not need to act by the same mechanism, the neurobiological properties of tianeptine, particularly the effects on various forms of neural plasticity, may be critical for its therapeutic effects.

Finally, concerning tianeptine and other antidepressants, it has recently been reported that the brain sites of change produced by successful antidepressant and cognitive behavior therapies (CBT) are different from each other, reflecting 'bottom-up' (ie limbic and subcortical brain regions) for antidepressants, and 'top-down' (frontal cortex) sites of alterations for CBT.[123] This means that it is the overall modulation of this complex network of neural circuits, rather than one focal site of action, that results in reduced depression. It is highly likely that different antidepressant medications, in producing their bottom-up effects, may affect some of the same as well as different limbic and subcortical areas and produce effects that sometimes converge on the same molecular and cellular targets, as may be the case for AMPA receptors (see above) and for effects on neurogenesis in the dentate gyrus.

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