Tianeptine: A Novel Atypical Antidepressant that May Provide New Insights into the Biomolecular Basis of Depression

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Abstract: Tianeptine, an atypical antidepressant patented and developed by Servier, enhances the synaptic reuptake of serotonin, without affecting norepinephrine and dopamine uptake, while it lacks affinity for neurotransmitter receptors. This mechanism for an antidepressant is apparently paradoxical, since the currently employed antidepressants enhance serotonin by inhibiting its breakdown or by inhibiting monoaminergic reuptake. Although tianeptine has been shown to reduce central 5HT availability and to indirecty modulate central adrenergic and dopaminergic systems and to indirectly inhibit cholinergic hyperactivity, its antidepressant action is believed to be more directly related to central neuronal remodeling and restoration of neuronal plasticity. In reliable animal models of depression tianeptine has been shown to prevent neurodegeneration and decreases in hippocampal volume in response to chronic stress. These effects on neuroplasticity are suspected to involve the normalization of the hypothalamic-pituitary-adrenal axis and modulatory effects on excitatory amino acids and *N*-methyl-D-aspartate receptors. Together with a body of related studies, these data provide further support for the hypothesis that depression may involve dysregulation of pathways controlling cellular resilience and that treatment should be directed towards the reversal thereof. Importantly, tianeptine is not anxiogenic and has also been shown to be effective in treatment-resistant depression, which may lead the way to a major breakthrough in the treatment of depression.

Keywords: Tianeptine, depression, antidepressants, biological basis, patents, trends.

INTRODUCTION

Tianeptine (S-1574) is marketed for the treatment of major depression by the pharmaceutical company Servier (inventors Antoine Deslandes & Michael Spedding) under the trade name Stablon® in Europe. This peculiar atypical antidepressant has drawn much attention, challenging traditional monoaminergic hypotheses of depression [1] and opening new windows of opportunity to investigate the biomolecular basis of this mood disorder. In fact, several new experimental, potential antidepressants are devoid of monoamine action, with modulation of the actions of neuropeptides (substance P, corticotrophin-releasing factor, neuropeptide Y, vasopressin V1b, melanin-concentrating hormone-1), *N*-methyl-D-aspartate (NMDA), nicotinic acetylcholine, dopaminergic, glucocorticoid, delta-opioid, cannabinoid and cytokine receptors, gamma-amino butyric acid (GABA) and intracellular messenger systems, transcription, neuroprotective and neurogenic factors [2].

Structurally, tianeptine can be viewed as a modified tricyclic antidepressant, with its chemical structure given in (Fig. **1**). Tianeptine exists as two isomers, of which the *l*-isomer seems to be the therapeutically active form [3]. Its primary metabolites have the same main structure, but less two and four carbons on the side chain, respectively.

The initial hype about tianeptine in the late 1980s and early 1990s was due to the puzzling fact that, as an effective antidepressant, it enhances serotonin uptake [4-6] (i.e. opposite to the action of other antidepressants such as the serotonin reuptake inhibitors), without significant activity at any receptors or other monoamine transporters. Thereby it has challenged the monoaminergic hypothesis of depression, as well as the proposed monoaminergic mechanisms whereby the action of most known antidepressants was explained. Furthermore tianeptine has been shown to be clinically effective, also in severe depression, in elderly and during alcohol withdrawal, and to possess anxiolytic properties, while it lacks common side-effects of most antidepressants, notably sedative effects or sleep disruption, anticholinergic effects, sexual dysfunction or adverse cardiovascular effects [7-11]. These findings, together with the realization that depression may be a neurodegenerative disorder [12-14], stimulated extensive research and lead to the discovery of the neuroprotective properties of tianeptine [15-17].

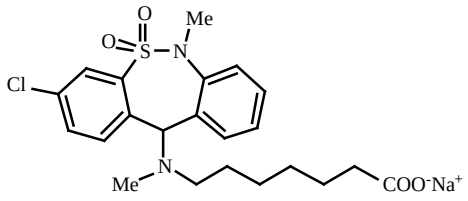

Fig. (1). Chemical structure of tianeptine, chemically described as [3-chloro-6-methyl-5,5-dioxo-6,11-dihydro-(*c,f*)-dibenzo-(1,2-thia-zepine)-11-yl) amino]-7 heptanoic acid, sodium salt.

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The current review will focus on the patents for tianeptine and their claims, evidence for its therapeutic effectiveness in the treatment of depression, proposed mechanisms of action and the implications thereof for our current understanding of the biomolecular basis of depression. It will conclude with a summary of what we know, but also point out the remaining uncertainties, especially as this relates to the claims in the patents under discussion.

PATENTS

Summary of Most Relevant Patents

Current patent applications and/or registrations regarding tianeptine have been published for (a) the therapeutic use of tianeptine in the treatment of neurodegenerative pathologies, (b) an original and a "new" process for the synthesis of tianeptine and (c) the pharmaceutical formulation of matrix-type oral sustained-release tablets of tianeptine sodium salt. These patents have been published in several countries since 1997, including Australia, Austria, Brazil, Canada, China, Denmark, Eurasia, Europe, France, Germany, Greece, Hong Kong, Hungary, Japan, New Zealand, Norway, Poland, Slovenia, South Africa and the United States of America [18] and is presented in (Table **1**). In view of its current use as an antidepressant, we have not been able to track a patent specifically registered for the use of tianeptine in the treatment of depression.

The current review, however, will focus on the therapeutic application of tianeptine and will not discuss the patents for its synthesis or pharmaceutical formulations. Patents regarding the therapeutic effectiveness of tianeptine in neurodegenerative pathology (originally registered in France, priority no. FR1999000004313 of 1999-04-07), as registered in different countries, are similar. The current review will therefore focus on and use as basis for discussion the patent US6599896 [19] for the "use of tianeptine in the production of medicaments to treat neurodegenerative pathologies", as registered in the United States of America.

Claims and Supporting Evidence Provided in the Patent

Patent US6599896 [19] claims that tianeptine may be useful in the treatment of "cerebral ischaemia, cerebral traumatism, cerebral aging, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, demyelating pathologies, encephalopathies, chronic fatigue syndrome, myalgic encephalomyelitis post-viral fatigue syndrome, the state of fatigue following a bacterial or viral infection, and the dementia syndrome of AIDS". There are also claims of effectiveness in the treatment of psychoneurotic disorders, pain and cough (patent FR2104728 – see US6599896 [19]). Studies that suggest significant effects on memory, including data from Jaffard and co-workers [20], are referenced, while the intended use of the (+) isomer of tianeptine for mnemo-cognitive disorders is also mentioned (patent FR2716623 – see US6599896 [19]).

The patent US6599896 [19] describes novel data that could provide a biochemical basis for the claimed neuroprotective properties of tianeptine, mostly involving observed effects on cellular entities that control calcium (Ca^{2+}) entry into the cell. In particular the patent mentions data that would implicate tianepine as a positive modulator of ionotropic alpha-amino-3-hyroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate type glutamate receptors (i.e. potentiation of kainate-mediated receptor activation). There is a growing body of evidence to strongly suggest that over stimulation (i.e. pathological stimulation) of these receptors may lead to excessive influx of Ca^{2+} into the cell, being associated with neurodegeneration [21,22], while normal (physiological) activation facilitates memory and cognition [23,24]. The AMPA and kainate receptor ion channels are permeable to monovalent cations such as sodium (Na^{+}) [25] and their activation may depolarize cells, thereby disinhibiting and then hyperactivating ionotropic N-methyl-D-aspartate (NMDA) receptors, opening the associated ion channels, to result in excessive Ca^{2+} influx and cell damage [26,27], or cellular homeostasis when at physiological levels. On the basis of these findings, it is argued in patent US6599896 [19] that tianeptine may find therapeutic application in several neurodegenerative disorders. The patent does, however, not speculate or present data to clarify the exact mechanism whereby the positive modulation of AMPA/kainate type glutamate receptors by tianeptine may modulate NMDA receptors and how this may (putatively) promote physiological, rather than pathological, intracellular Ca^{2+} levels, thereby exhibiting neuroprotective properties (see later for detailed discussion of literature).

Furthermore, patent US6599896 [19] describes several in-house experiments and results, suggesting that tianeptine (a) modulates AMPA/kainate receptors by potentiating kainate-mediated receptor activation, (b) protects cultured cortical cells against neurodegeneration due to hypoxia (c) or glutamate, (d) protects cultured astrocytes against degenerative effects of hypoxia, (e) protects cultured motoneurons from cell death during brain-derived neurotrophic factor (BDNF)-deprivation and (f) enhances the expression of mitochondrial genes in the amygdala of chronically treated rats. The latter results suggest improved cellular respiration and central oxidative metabolism, resulting in neuroprotective activity.

Finally patent US6599896 [19] gives the therapeutic dosage range as 12.5 to 300 mg per dose, depending on patient age and weight. The preferred salt of tianeptine is specified as the sodium salt.

Related Patents

Four hundred and eighty (480) patents in relation to depression, published during the past two years, have been screened for relevance to the current review. About 5% were relevant to the current topic, mostly covering augmentation strategies (utilizing an antidepressant in combination with the augmenting agent), or diverse indications (other than depression) for antidepressants or a combination of an antidepressant with a second agent.

Augmentation Strategies

Patents have been published for the co-administration of the analeptic modafinil and an antidepressant, to enhance antidepressant efficacy, reduce side-effects during antidepressant treatment or withdrawal or during a strategy to reduce the onset of antidepressant action. The rationale behind the claims is based on the reduced sedation and

Table 1. Published Patents for the Clinical Application, Synthesis and Pharmaceutical Formulation of Tianeptine (Priority no. FR1999000004313 of 1999-04-07), as Listed by Thomson Delphion

Country / Region	Therapeutic Use in Neurodegenerative Pathologies		Synthesis (Original & New)		Sustained-Release Oral Dosage Form	
	Patent no.	Date	Patent no.	Date	Patent no.	Date
Australia	AU0038248	2002-05-29	AU0133368A5 AU0777616	2001-10-04 2004-10-21	AU1904197 AU0719822	1997-10-30 2000-05-18
Austria					AT0205715	2001-10-15
Brazil	BR0008703					
Canada	CA2361988	2001-08-22	CA2342950	2001-09-30	CA2203310	2001-10-23
China	CN1342082	2004-04-30	CN1319593 CN1157387	2001-10-31 2004-10-14	CN1168792 CN1116029	1997-12-31 2003-07-30
Denmark			DK1138677	2003-09-29		
Eurasia			EA0003770	2003-08-28		
Europe	EP1165089 (WO0059511)	2004-06-28		2003-06-04	EP0803253 EP0803253	1997-10-29 2001-09-19
France	FR2791891	2003-07-29	FR2807039	2001-10-05	FR2747921 FR2747921	1997-10-31 1998-10-30
Germany					DE69706748 DE69706748	2001-10-25 2002-07-04
Greece					GR3037043	2002-01-31
Hong Kong			HK1039618	2004-12-31	HK1039618	2004-12-31
Hungary	HU0200145		HU0101334AB	2002-03-28	HU9700806 HU9700806	1997-06-30 1998-10-28
Japan	JP2002541110				JP10036268	1998-02-10
New Zealand	NZ513565		NZ0270566 NZ0510857	1996-01-26 2001-08-31	NZ0314662	1998-12-23
Norway	NO20014081		NO20011598	2001-10-01	NO0971860 NO0315407	1997-10-27 2003-09-01
Poland	PL356739					
Slovenia			SI1138677	2003-10-31	SI1138677T1	2003-10-31
South Africa	ZA200106690	2002-11-14	ZA0102642A	2001-10-05	ZA9703495A	1997-11-18
USA	US6599896	2003-07-29	US20010037021 US6441165	2001-11-01 2002-08-27	US5888542	1999-03-30

fatigue, as well as antidepressant effects found with the use of modafinil. By reducing the side-effects, it is claimed that compliance with antidepressant treatment may improve. The types of antidepressants to be used in combination with modafinil, as mentioned in the patent, may include tianeptine when it is classified as a tricyclic antidepressant [28-31].

Another patent claims the effectiveness of the combination of "newer antidepressants", such as SSRIs, with an antipsychotic or a dopamine system stabilizer during initiation of therapy for major depressive disorder, or other unipolar (non-bipolar, non-psychotic and non-treatment resistant) depression, to prevent suicide, disease progression, development of tolerance toward the antidepressants and alleviating cognitive distortion and related functional impairment or health risks. The drug combination is also claimed to be useful for smoking cessation or nicotine withdrawal [32]. A patent is also published for the combination of an antidepressant or anxiolytic with a dopamine D_4 receptor antagonist for the treatment of depression, anxiety or psychosis [33].

A reduction in the onset of action of an antidepressant is claimed by a patent for the combination of oral

antidepressants (including serotonin and norepinephrine reuptake inhibitors and specified receptor antagonists) with acetylsalicylic acid or derivatives thereof, or with heparin or heparin-like compounds. While the proposed mechanism whereby earlier onset of action may be accomplished by the combination (i.e. improved hemodynamics to enhance central bioavailability and improved central susceptibility to antidepressant action) could theoretically apply to any antidepressant, tianeptine, being a serotonin reuptake enhancer, is clearly excluded from this patent [34,35].

Another patent has been published for the combination of a GABA receptor modulator, such as eszopiclone, with a serotonin, norepinephrine or dopamine reuptake inhibitor or with a serotonin $5HT_{2A}$ receptor modulator, for the intention of treating depression and/or insomnia, a sleep abnormality, augmenting antidepressant therapy, eliciting a dose-sparing effect, reducing depression relapse, improving the efficacy of antidepressant therapy or improving the tolerability of antidepressant therapy. Although not specifically mentioned, tianeptine could be included in this patent, since it modulates serotonin $5HT_{2A}$ receptors. The rationale for including antidepressants in the treatment regime for insomnia is based on the modulation of the central neurotransmitters by the antidepressants in anxiety and mood disorders that in turn affect sleeping behavior [36,37].

Diverse Indications

The combination of an analgesic (which may include an NMDA antagonist or tricyclic antidepressant) plus a nicotinic receptor antagonist has been patented for the treatment of acute, chronic and/or neuropathic pain and migraine. Theoretically the analgesic, as described in the patent, may include tianeptine [38]. Similarly, a patent has been published for topical preparations comprising an antidepressant (including the possibility of tianeptine specified) and a NMDA receptor antagonist, for the treatment or prevention of pain, for example neuropathic pain [39,40].

A patent for administering any antidepressant, including tricyclic antidepressants, per inhalation for the treatment of premature ejaculation has been published. The rationale is that serotonin, in particular *via* stimulation of serotonin $5HT_{2A}$ receptors or inhibition of serotonin $5HT_{1A}$ receptors, may delay ejaculation. Inhalation is believed to give a prompt response on an "as-needed" basis, with fewer systemic side-effects than associated with chronic oral therapy with these drugs [41].

Another patent for the co-administration of a cholinesterase inhibitor with an antidepressant claims effective treatment of obesity [42].

CLINICAL EVIDENCE FOR THE EFFECTIVENESS OF TIANEPTINE AS ANTIDEPRESSANT AND ANXIOLYTIC

Since its discovery, relatively few scientists, besides the French speaking, knew and read much about tianeptine [43], most likely since much, although not all, of the initial work was published in French, making some data inaccessible to a large proportion of the scientific community. To the best of our knowledge, the earliest reports of the clinical efficacy of tianeptine in the treatment of depression dates back to 1981, as reported at congress podiums [44,45]. Since then, its clinical efficacy has been shown in several clinical trials. The earliest review of relatively small clinical trials (based on reports at congress podiums or in expert reports) was published in 1988, with more than three quarters of treated depressed patients reported as responders, including the elderly, and also showing anxiolytic properties of tianeptine [7]. Early systematic investigations in very small clinical trials also showed that tianeptine is generally well tolerated, lacking significant sedation, anticholinergic effects and cardiovascular effects, while it does not disturb hematological parameters or parameters of renal and hepatic function, even in alcoholic patients during withdrawal [46].

The clinical effectiveness of tianeptine in the treatment of major depression, bipolar disorder, dysthymia or adjustment disorder, and its comparison with other drugs, have been extensively reviewed [47] and some of the individual studies contributing to the current body of data on tianeptine's use in depressive disorders includes the following. Comparative clinical trials suggest that tianeptine is as effective as amitriptyline in the treatment of depression, but associated with fewer side effects [48] and also as effective as mianserin in elderly [49]. From a clinical trial involving the treatment of 186 patients with major depression with tianeptine, imipramine or placebo for 42 days, it was reported that both imipramine and tianeptine were more efficacious than placebo and that there were more responders in the tianeptine group than in the imipramine group [50]. In a comparative trial between tianepetine and paroxetine with 277 patients, it was shown that these drugs were equally effective in treating depression and anxiety symptoms [51,52]. In a controlled, double blind study of tianeptine against placebo for 42 days in 126 patients with major depression or bipolar disorder, tianeptine showed greater antidepressant efficacy than placebo and equal general tolerance, with only headache as a more prominent complaint in the tianeptine group [53]. In a randomized, double-blind study involving 212 patients with major depression (single episode and recurrent) and bipolar depression, there was no difference in either efficacy or tolerability between 42 days of treatment with either sertraline or tianeptine [54].

In an 18-month follow-up trial involving 173 unipolar depressed patients, relapse was 2 to 3 times less frequent in the tianeptine group, while tianeptine was well tolerated also in the long term [55]. Similar results were yielded in a 16.5 month trial involving 268 patients receiving tianeptine or placebo [56]. There are, however, also trials that did not prove tianeptine's superior efficacy over the standard drugs. For example, in a trial comparing fluoxetine to tianeptine in 237 elderly with major depression, fluoxetine was superior to tianeptine in terms of efficacy [57]. To the contrary, a multinational trial involving 387 patients with a depressive episode, recurrent depressive disorder, or bipolar affective disorder showed no difference between the efficacy or safety after six weeks of treatment with fluoxetine or tianeptine [58,59]. In another 6-week, multicentre, randomised, double-blind controlled study involving 178 patients with major depression similar results than in the multinational trial were obtained [60]. In a meta-analysis of five studies involving

1,348 patients with depression treated with either tianeptine or a selective serotonin reuptake inhibitor (SSRI), tianeptine was shown to be as effective as the SSRIs, with a trend for better tolerability [61].

In a small open clinical trial in elderly with depressive symptoms, tianeptine improved not only depressive symptoms, but also seemed to improve anxiety symptoms and cognitive function [62].

In summary, one may conclude that most of the data show clinical efficacy of tianeptine in the treatment of depression and that its efficacy is as least as good as seen with standard drugs.

Tianeptine is generally well tolerated and relatively few toxic effects in comparison to the traditional antidepressants were evident from clinical data. Tianeptine lacks sedation as side-effect and one study also suggests that tianeptine does not affect driving performance [63]. Given the high incidence of sexual dysfunction in depression, which is usually even higher with the therapeutic use of most antidepressants, the rate of sexual disturbances has been shown to be lower with the use of tianeptine compared to tricyclic antidepressants and selective serotonin reuptake inhibitors in a study involving 4, 557 patients [64].

Physical dependence and withdrawal reactions were reported following the misuse of tianeptine. One case-report where 50 times the prescribed dose was taken, described no serious toxic effects or hepatic dysfunction with reversal of adverse effects after withdrawal [65], while a second case-report suggested that a patient with a history of drug-dependency, who took 90 tablets of tianeptine daily, showed physical and psychological withdrawal symptoms when the prescription was not renewed [66]. A recent report of five cases of tianeptine misuse in patients with a history of drug abuse, also suggests physical dependence to tianeptine [67]. Although these reports are few and associated only with patients with a history of drug abuse, they cannot be ignored and prescribers should be alerted about this potential complication. Given the extremely high doses taken and mild associated side-effects, it does, however, also suggest less serious toxicity of overdosing.

ANIMAL BEHAVIORAL STUDIES

Chronic tianeptine treatment causes similar behavioral responses in recognized animal models of depression, however, apparently without inducing serotonin $5HT_{1A}$ receptor subsensitivity as seen with other antidepressants [68]. Tianeptine does not cause anxiogenic effects in rats, as seen with initiation of, for example, citalopram therapy [69]. Interestingly, the co-administration of fluoxetine and tianeptine to rats abolishes the anxiolytic effects of chronic fluoxetine or tianeptine when given alone [70].

Anxiolytic activity was also evident during alcohol withdrawal in animals, and it was found that anxious behavior was significantly reduced in rats [71] and mice [72,73] treated with tianeptine. Stress-induced impairment of spatial memory in rats is also attenuated by tianeptine [74,75], while fear-conditioning remains unaffected [76]. Learning in rats, however, does not seem to be affected by tianeptine, although retention of spatial memory is enhanced [77].

A BIOMOLECULAR BASIS FOR THE ANTIDEPRESSANT EFFECTS OF TIANEPTINE

It is clear from all the clinical and animal studies that tianeptine is an effective antidepressant with anxiolytic properties and an acceptable side effect profile. In the search for its antidepressant mechanism of action, tianeptine has been investigated with regard to many of the most popular hypotheses for antidepressant action. The following few paragraphs will summarize the literature reports regarding a biomolecular basis for tianeptine's possible mechanism(s) of antidepressant and anxiolytic activity.

Modulation of Monoaminergic and Cholinergic Systems

The monoamine hypothesis, which postulates a deficit in serotonin and noradrenaline in key areas of the brain in affected patients, is one of the best known hypotheses of depression and has formed the basis for the antidepressant activity of many of the known drugs. However, administration of tianeptine to pregnant rats does not significantly bind to or alter the concentration of α-adrenoceptors, serotonin $5\text{-}HT_2$ and $5\text{-}HT_{1B}$ receptors or dopamine D_2 receptors and does not modify serotonin-induced inositol phosphate formation in the cerebral cortex of the pups as measured after birth [78]. Following two week's treatment with tianeptine, but not with fluoxetine, the α_1-adrenoceptor concentration (B_{max} value) in rat brain cortex was slightly increased, without any effect on affinity values (K_D and K_i values) [79].

Serotonin

Tianeptine has been shown to selectively enhance the synaptic uptake of serotonin, but not of norepinephrine or dopamine, in rat cortex, hippocampus and hypothalamus [4-6,80]. It also attenuates potassium-induced elevation of serotonin levels in rat hippocampus [81]. In addition, tianeptine decreases free plasma concentrations of serotonin in rats after subchronic administration [82]. Human studies are inconsistent and there are reports of increased serotonin uptake into platelets after acute or chronic administration of tianeptine to humans [83] and of decreased serum serotonin after acute but not chronic treatment [84]. Acute stress-induced decrease of serotonin uptake in rat hypothalamus, hippocampus and cerebral cortex synaptosomes, but not the concomitant rise in corticosterone levels, is prevented by tianeptine administration 1 hour prior to the stressor [85]. However, very interestingly, acute and chronic administration of tianeptine did not change extracellular serotonin concentrations in rat frontal cortex and raphe nuclei, as measured by *in vivo* microdialysis [86]. In an electrophysiological investigation in rat dorsal raphe neurons, tianeptine was shown to inhibit the serotonin-induced inwardly rectifying K^+ current. This results in an increased excitability of serotoninergic neurons in the dorsal raphe where serotoninergic neurons mainly originate from [87]. It should be noted that many antidepressants, including selective serotonin reuptake inhibitors cause an increase of serotonin release from the frontal cortex only after chronic treatment. These two mechanisms may therefore contribute to increasing synaptic serotonin levels and a resulting

antidepressant action. However, it is generally accepted that antidepressant action is not dependent on the acute effects of the antidepressant on synaptic monoamine levels, but on long-term changes in synaptic neuroplasticity [88].

Similar to serotonin reuptake inhibitors, chronic tianeptine reduces the expression of serotonin transporter mRNA and serotonin transporter binding sites in rat dorsal raphe nucleus, but not in the median raphe nucleus [89]. Results, however, may be inconsistent if different brain regions are used and one study found no changes in serotonin transporter mRNA in the rat midbrain raphe region after 21 days treatment with saline, tianeptine or fluoxetine [90]. Unlike other antidepressants, tianeptine does not seem to modify serotonin synaptic transmission in rat hippocampus [91].

In dogs tianeptine diminishes behavioral effects induced by the serotonin precursor *l*-5-hydroxytryptophan, without modulating the effect of serotonin agonists that are insensitive to the serotonin reuptake system [92,93], thereby supporting *in vitro* data confirming the serotonin reuptake enhancing effects of tianeptine.

Interestingly, reduced susceptibility of serotonin to breakdown by central monoamine oxidase type A, but not by type B, has been shown to result from treatment of rats with tianeptine, sertraline and clomipramine, which may add to the mechanism of action of tianeptine [94].

One rat study showed that, while stress as well as serotonin enhancing drugs, such as serotonin reuptake inhibitors, block long-term potentiation (LTP) in the CA1 area, *l*-tianeptine induced recovery of such stress-induced LTP blockage, while its effect is prevented by simultaneous administration of fluoxetine [95]. The positive effect of tianeptine on long-term potentiation in the CA1 area of anesthetized rats is also prevented by fluoxetine [95], supporting the findings that co-administration of fluoxetine abolishes the anxiolytic effect of tianeptine in rats, as mentioned above. Another study also showed that tianeptine, and to a lesser extent fluoxetine, is able to reverse the stress-induced impairment in LTP at synapses from the rat hippocampus to prefrontal cortex [96].

l-Norepinephrine and Dopamine

Besides changes in the serotonin levels after short-term tianeptine treatment, increases in *l*-norepinephrine levels were also observed in the rat brain, suggesting that this may also be involved in the antidepressant action of tianeptine [97], although the mechanism whereby these levels may be altered is not known.

Studies in rat brain suggest that acute and chronic administration of tianeptine increases dopamine levels in the nucleus accumbens (and at higher doses also in the striatum) in a serotonin-independent manner, suggesting that increased dopamine levels in the nucleus accumbens may contribute to the antidepressant action of tianeptine [98,99]. It is clear, however, that tianeptine does not exhibit its effect on brain dopamine levels by an inhibitory effect on the dopamine transporter [100]. One study suggests that the functional responsiveness of dopamine D_2/D_3 receptors may be enhanced by tianeptine [101].

Cholinergic System

In line with the cholinergic hypothesis of depression [102-107], data suggest that the serotoninergic effects of tianeptine may also impact on the cholinergic system, contributing to antidepressant effects. Administration of high doses (30 mg/kg), but not lower doses of tianeptine, decreases the release of acetylcholine from rat dorsal hippocampi and frontal cortices, an effect which can be prevented by the co-administration of the serotonin antagonist metergoline [108] and whereby a serotoninergic-cholinergic system interdependency in the mechanism of action is suggested. Stimulation of serotonin $5HT_{1B}$ presynaptic heteroreceptors, located on cholinergic terminals, enhances the release of acetylcholine and studies on rat hippocampal synaptosomes suggest that tianeptine inhibits this process [109]. However, it seems that this inhibitory effect of tianeptine on $5HT_{1B}$ receptors is independent of its effect on serotonin availability in the synapse [110].

Effects on the Hypothalamo-Pituitary-Adrenal Axis

The HPA-axis plays a major role in the response of organisms to stress and a hallmark of anxiety and depression is the malfunction of the HPA-axis. Under stress conditions, the hypothalamus secretes corticotropin-releasing hormone/factor (CRH/CRF), which in turn, stimulates the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary that in turn stimulates the release of glucocorticoids from the adrenal cortex [111]. There has been a growing body of evidence that, directly or indirectly, antidepressants can modulate the function of the HPA axis [112]. The effect of tianeptine on the HPA-axis was therefore also thoroughly investigated. As a starting point, antidepressants (imipramine, amitriptyline, desipramine, fluoxetine, tianeptine, mianserin and moclobemide) inhibit corticosterone-induced gene transcription, as was demonstrated in an appropriate cultured cell line [113].

As far as animal studies are concerned, it has been shown that acute administration of tianeptine in rats can reduce the stress-induced elevation of ACTH and corticosterone levels (i.e. activation of the hypothalamo-pituitary-adrenal (HPA) axis) [114]. One study found no modulation of stress-induced corticosterone levels in several rat brain regions by tianeptine at doses where it induced antidepressant-like behavioral effects [115]. A later study found that chronic, but not acute administration of tianeptine to rats decrease corticotropin-releasing factor in the hypothalamus, but not in the cerebral cortex and hippocampus and that it increased adrenocorticotropin in the anterior lobe of the pituitary [116]. Results from the latter study also confirmed that chronic tianeptine reduces the stress-induced rise in corticosterone levels (i.e. tianeptine attenuates the stress-induced activation of the HPA-axis). The rise in lipopolysaccharide-induced increase in corticosterone levels in rat plasma and induction of Fos expression in the paraventricular nucleus of the hypothalamus, is attenuated after chronic treatment with tianeptine. These results suggest that tianeptine may exert its effect on the hypothalamic-pituitary-adrenal axis by inhibiting the release of corticotropin-releasing hormone (CRH) and that it may interfere with cytokine-induced behavioral effects of stress

[117]. However, another study using neuro-2A cells, transfected to express CRH acetyl transferase, suggests that, while imipramine and fluoxetine inhibit human CRH gene promoter activity, tianeptine has no effect [118].

Acute moderate to high stress has been shown to activate serotoninergic neurons to release serotonin in the hypothalamus, where the resulting activation of $5HT_{1A}$ receptors will stimulate the release of corticotrophin, resulting in the secretion of glucocorticoids [119]. By virtue of tianeptine's ability to decrease synaptic serotonin levels, one may speculate that it may decrease HPA-axis activity through suppression of stress-induced serotonin release in the hypothalamus. Clearly we do not yet have an answer on the mechanism whereby tianeptine affects the HPA-axis and more work is needed to confirm the abovementioned hypothesis.

Neuroprotective Properties of Tianeptine

One of the most thoroughly studied hypotheses of tianeptine's antidepressant action is the effects it has on central neuroplasticity and as a neuroprotective agent [120]. The relationship between stress and neurodegeneration, especially in CA3 pyramidal neurons, resulting in atrophy of the hippocampus [121], has been described and reviewed extensively [16,17,120,122-127]. This is of particular relevance given the recent evidence from literature that depression is associated with hippocampal volume loss and that the disorder may present a degenerative component [14,16,128]. From the literature it seems that, amongst the antidepressants, tianeptine has been the most extensively investigated (primarily in pre-clinical studies) for its prominent and consistent protective effect against stress-induced neurodegeneration. It should, however, be noted that the clinical significance and data suggesting the positive relationship between hippocampal volume loss and depression in humans has also been criticized [129].

Histological studies have demonstrated that tianeptine is able to prevent chronic restraint stress or corticosterone-induced hippocampal neurodegeneration in rats [130]. In particular, the reduction in the length and number of branch points of hippocampal CA3c pyramidal dendrites is prevented by tianeptine [74,130]. It would appear that BDNF, neurotrophin-3 (NT-3), basic fibroblast growth factor (bFGF), GAP-43 and MAP2 are not involved in stress-induced neurodegeneration in rat hippocampus, as indicated by a lack in any change of mRNA expression, and that these factors are also not altered by tianeptine [131]. It has also been shown that chronic treatment with paroxetine reduces hippocampal volume loss in patients with post-traumatic stress disorder [132], supporting (but not finally proving) the idea that modulation of neuroplasticity may be a common mechanism of antidepressants.

In a psychosocial stress model of adult male tree shrews (*Tupaia belangeri*), tianeptine prevents the stress-induced changes in cellular markers of neuronal integrity, including *N*-acetyl-aspartate, creatine, phosphocreatine and choline-containing compounds [15]. Tianeptine also prevents the reduced proliferation rate of the granule precursor cells in the dentate gyrus and the reduction in hippocampal volume in these animals [15]. In a recent study tianeptine was found to prevent stress-induced apoptosis in the temporal cortex and dentate gyrus of tree shrews, in support of neuroprotection as a putative antidepressant mechanism [133], as well as stress-induced structural changes in the hippocampus, reduction of hippocampus volume and alterations in cerebral metabolites [134]. Preliminary evidence for apoptosis in depression has been documented [135].

Tianeptine has been shown to normalize the stress-induced changes in the amplitude ratio of NMDA receptor to AMPA/kainate receptor-mediated currents in rat hippocampal CA3, most likely by altering the phosphorylation status of glutamate receptors, which may contribute to its neuroprotective properties [136]. In a study involving mouse cortical neuronal cultures, tianeptine, similar to the N-methyl-D-aspartate (NMDA) antagonist, MK-801, inhibits hypoxia-increased lactate dehydrogenase. However, tianeptine does not protect against NMDA-induced apoptosis, but does protect against interleukin-1β-induced neurodegeneration. These results suggest that tianeptine may possess neuroprotective effects against hypoxia *via* a mechanism different from NMDA channel inhibition and may protect against the deleterious effects of cytokines [137]. Of particular significance is that tianeptine has been found to inhibit the activity of nitric oxide synthase (NOS) in the hippocampus [138], an important subcellular signaling system for the glutamate-NMDA receptor. Nitric oxide (NO) is a recognized neurotoxin, which has been found to be elevated in depressed patients [139] and which may underlie the neuroprotective actions of tianeptine. Furthermore, inhibition of NOS may also be directly involved in the antidepressant actions of tianeptine, since NOS inhibitors have distinct antidepressant activity in animal models [140]. It should, however, be noted that various classes of antidepressants, including tricyclics and SSRIs, inhibit NOS, in addition to established actions on serotonin, suggesting a cross-talk between serotonin-glutamate-NO in antidepressant action [138]. These findings should be read in conjunction with the suggestion of the modulating effect of tianeptine at AMPA/kainate type glutamate receptors, as mentioned in the discussion of the patent above.

Tianeptine inhibits the chronic restraint stress-induced increase in glia glutamate transporter GLT-1 mRNA expression in rat hippocampus (also prominently in the CA3 region), suggesting a mechanism for the neuroprotective effects (reversal of stress-induced neuronal remodelling) by tianeptine [141]. Tianeptine also alters peripheral, but not central cytokine effects, suggesting that tianeptine probably does not influence central proinflammatory processes *via* modulation of lipopolysaccharide or interleukin-1β [142]. It also attenuated lipopolysaccharide-induced expression of TNFα in the spleen and hypothalamus, as well as plasma levels of this cytokine, and altered the central balance between pro- and anti-inflammatory cytokines (interleukins IL-1β/IL-10) [143].

In mice, tianeptine has been shown to reverse cognitive impairment induced after chronic alcohol administration and to reduce certain cognitive impairments, such as diminished spatial learning capacity after ageing [144].

A few recent patents also illustrate the postulated role of neuroplasticity in depression and the neuroprotective effects of antagonists at the NMDA receptor. In this regard a patent has been published for the use of adamantine derivatives for the treatment of various pathologies, including neurodegenerative pathologies (also including depression), based on their activity on NMDA receptor complexes and iNOS enzymes. This putative mechanism of action would overlap with that proposed for tianeptine [145-149]. Very interestingly, a recent patent claims that the use of a protein kinase B (also Akt) activator will be effective for the prevention or treatment of depression, anxiety, manic-depressive psychosis and posttraumatic stress disorder. The rationale for the invention is the known role of protein kinase B in neuroprotection and the putative role of neuro-degeneration in these disorders [150].

Other Biological Effects

In one study, the levels of triiodothyronine were increased in the rat amygdala after chronic administration of desipramine, paroxetine, venlafaxine, tianeptine, lithium or carbamazepine or partial sleep deprivation, suggesting central thyroid hormone action as a putative common target for these psychotropic drugs [151]. This is of relevance considering the use of thyroid hormone as augmentation therapy in treatment-resistant depression [152].

DIVERSE THERAPEUTIC CLAIMS AND HYPOTHESES

Brain Disorders

Effectiveness of tianeptine during alcohol withdrawal has been shown clinically, while pre-clinical animal (see above) and *in vitro* studies support this application [153]. Considering the important role of glutamatergic mechanisms in alcohol addiction and abstinence [154], this further confirms the importance of glutamate in the pharmacological actions of tianeptine.

Based on findings of its neuroprotective properties, there are several claims for the use of tianeptine as an anti-aging agent. In a small retrospective study of elderly treated with tianeptine, results suggest that tianeptine may be a useful alternative to serotonin reuptake inhibitors in the treatment of depression in elderly with co-morbid Alzheimer's disease [155]. Dysfunction and atrophy of the hippocampus are associated with ageing and Alzheimer's disease and clinical data support the suggestion that tianeptine may protect against such neurodegenerative phenomena.

A small preliminary study in 68 patients showed that tianeptine may be mildly beneficial in the treatment of attention-deficit hyperactivity disorder, with minimal side-effects [156].

In a small placebo-controlled, double-blind crossover trial of tianeptine, involving 12 autistic children that did not respond to other psychotropic drugs, tianeptine showed a small reduction of irritability. Although the study was small and without pronounced effectiveness, it does point towards a possible therapeutic application for future investigation [157].

Tianeptine, but not fluoxetine, inhibits pentylene-tetrazole-induced seizures in rats [158]. Whether this points to possible therapeutic application, needs further investigation. Because of the well-recognized importance of glutamate in the genesis of seizure activity and in the action of antiepileptic drugs, this study again highlights the involvement of glutamate in the action of tianeptine [159].

Peripheral Disorders

In addition to the claims as mentioned under "related patents" above, the following therapeutic applications were also found in literature:

The use of tianeptine has been found to reduce bronchoconstriction in asthmatics [160-163] and a rapid and dramatic improvement of pulmonary function was seen in a small, double-blind, crossover trial with asthmatic children, associated with (but not necessarily causatively linked to) simultaneously reduced plasma serotonin levels [164,165]. It is claimed to have been successful in more than 20 000 severely asthmatic patients (adults and children), resulting in the reversal of asthma attacks within 30 – 60 minutes after oral administration [163]. This observed efficacy has been postulated to be related to its enhancing effect on serotonin re-uptake, whereby free plasma serotonin levels are also reduced, resulting in a reduction of serotonin-mediated stimulation of bronchial parasympathetic activity [162,163]. The relationship between elevated free plasma serotonin levels and asthma is well-recognized [160]. NO has important therapeutic relevance in the treatment of severe respiratory disorders [166,167] and considering the action of tianeptine on the glutamate-NO pathway, this may have relevance to the efficacy of tianeptine in asthma.

Since serotonin has been shown to cause pulmonary vasoconstriction, it has been suggested that tianeptine may find therapeutic application in the treatment of pulmonary hypertension [168,169]. These effects may involve tianeptine's effects on the glutamate-NO pathway. Patients with ischemic heart disease and comorbid depression, receiving tianeptine in addition to standard cardiovascular therapy had improved cardiovascular performance in comparison with those not receiving tianeptine [170]. Disturbances in platelet NO production have been linked to a positive association between depression and coronary artery disease [171,172]. Considering the NOS inhibitory action of tianeptine and the putative role of NO in the pathology and treatment of anxiety and stress-related disorders [119,139,173], one may speculate that the effects of tianeptine on NO may underlie its cardiovascular benefits in this group of patients. Furthermore, glutamatergic pathways, mobilized during stress, may also drive peripheral autonomic manifestations, specifically detrimental cardiac effects [174,175], which may be reversed by modulatory effects of tianeptine on glutamate pathways, as described earlier.

One study in animals suggests that tianeptine has prominent thermal antinociceptive activity in mice, as compared to saline, suggesting an analgesic property [176]. One case-study in humans also suggests this possibility [177].

CURRENT & FUTURE DEVELOPMENTS

It is clear from the data available that tianeptine has contributed greatly to our realization of the complexity of the etiology of depression. Studies with tianeptine strongly suggest that neuroprotection may potentially be an important mechanism whereby antidepressants exert their therapeutic effect. Clinical data have however been inconclusive so far. Nevertheless, many pre-clinical studies suggest a mechanism of action of tianeptine targeting serotonin and glutamate pathways, although its relation to tianeptine's antidepressant action requires further investigation. There is an urgent need for a more comprehensive, systematic preclinical investigation into the mechanism(s) of the proposed neuroprotective actions of tianeptine and all other known antidepressants and related psychotropic drugs. In addition, more conclusive clinical data to support (or reject) the hypothesis of reduced hippocampal volume in depression and the reversal thereof by antidepressants are urgently needed.

Furthermore, the complexity of investigating candidate genes that may encode for specific neurobiological pathways suspected to be involved in the patho-etiology of psychiatric disorders is tremendous, leading to studies with many variables and difficult statistical analysis [178]. The large sample sizes of human subjects to be included in studies and general costs may also be a stumbling block. One needs to study sizeable sets of genes, or rather haplotypes thereof, pertinent to each putative pathophysiological pathway [178]. Although some progress has been made, we have not had major breakthroughs that directly benefit the clinical treatment of, for example, depression. It is, however, likely that some significant answers may follow in the near future, as illustrated by a few recent patents: A patent has been published with a list of putative target genes that are commonly modified by antidepressants, as shown in DNA microarrays using rat hippocampus and hypothalamus tissue. The patent claims that particular modulation of these genes by antidepressants may suggest that a patient is predisposed to mental the disorder [179]. Another patent suggests that polymorphisms of the 5' region of the human serotonin $5HT_{1A}$ receptor gene may be associated with a decreased suppression of the pre-synaptic expression of this receptor in serotoninergic raphe neurons, thereby resulting in receptor upregulation. It is claimed that the identification of these polymorphisms in humans may be diagnostic for major depression and related mental disorders [180,181]. In yet another published patent it is claimed that patients having the Taq1A (A1) allele (A1 + allelic status) of the dopamine D_2 receptor, are candidates for treatment with high dose [182], while it is claimed in another that nucleotide polymorphisms in a haplotype block comprising the gene encoding FKBP51 may be associated with predisposition to depression and that its analysis may be used for diagnosis and classification [183].

Tianeptine does seem to hold the potential for all the therapeutic applications as claimed by the patent, but convincing and conclusive clinical data to support these claims are yet outstanding. Even more important than the realization of what we know about depression, neuroplasticity and tianeptine, is the realization of what we do NOT know:

1. We do not know whether all clinical manifestations of major depression result from the same biological pathology/dysfunction. In fact, no one has yet identified the key defective gene or genes or genetic haplotypes of depression. It may be that some or even most, but not all manifestations of depression result from, or are associated with neurodegeneration. In the same way it may be that some but not all manifestations of depression is associated with monoaminergic dysfunction.
2. We do not know for sure what the key mechanism of the therapeutic antidepressant effect of tianeptine is and we also have not identified a common action pathway for all antidepressants. Further we do not know whether the neuroprotective effects seen in tree shrews can be related directly to humans and whether this really is necessary for its antidepressant effects.
3. We do not know whether any unforeseen unwanted side-effects of tianeptine may become apparent in future, especially after long-term use in large populations. This is illustrated by the case reports on the abuse of tianeptine, as mentioned above.

In conclusion, the clinical relevance of pre-clinically observed neuroprotective properties of tianeptine needs to be established. Furthermore it should be determined whether this can be translated to other therapeutic claims stated in the patent of tianeptine.

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