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# The paradox of tianeptine

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**Summary** – The classical biochemical hypothesis of depression posits a functional deficit in central neurotransmitter systems, particularly serotonin (5-HT) and/or noradrenaline. The major support for this theory was that antidepressants increase the amount of neurotransmitters in the synaptic cleft, by inhibiting reuptake mechanisms (tricyclics) or inhibiting enzymatic catabolism (MAOIs). The major role suggested for 5-HT in this theory led to the development of a large number of compounds which selectively inhibit 5-HT reuptake, such as fluvoxamine, fluoxetine, citalopram, sertraline, paroxetine, etc. Numerous clinical studies have demonstrated the antidepressant activity of such types of agents, supporting 5-HT deficit as the main origin of depression. Tianeptine is active in classical animal models of antidepressants. Its antidepressant efficacy has been established in controlled trials involving a large number of patients. Several biochemical studies however demonstrated that tianeptine induces in acute as well as in chronic conditions, a presynaptic increase of 5-HT reuptake, both in animal and human platelets and animal CNS. Therefore, as a 5-HT reuptake enhancer, tianeptine exhibits a mechanism of action totally opposite to 5-HT reuptake blockers such as fluoxetine but, paradoxically, both mechanisms of action are associated with a therapeutic activity in depressive disorders. Several hypotheses to explain these paradoxical findings and different methodologies to test them clinically are proposed.

**tianeptine / antidepressant / serotonin / selective serotonin reuptake inhibitor**

## Introduction

The current theory of the biological foundation of depression hypothesizes a decrease in central synaptic neurotransmission secondary to the deficiency in monoaminergic neurotransmitters, serotonin (5-HT) and/or noradrenaline (Schildkraut, 1965; Bunney and Davis, 1965). These hypotheses emerged from the serendipitous observation that depressive symptoms developed in approximately 15% of the patients who were treated for hypertension with the biogenic amine-depleting agent reserpine (Schildkraut, 1965; Bunney and Davis, 1965). Support for the 5-HT hypothesis was also derived from several reports of reduced cerebrospinal fluid 5-hydroxy-indol-acetic acid (5-HIAA) or plasma free tryptophan (Van Praag, 1982a) whereas the noradrenaline hypothesis was supported by several studies of reduced urinary excretion of 3-methoxy-4-hydroxy-phenylglycol (MHPG) (Maas *et al*, 1968). The 5-HT hypothesis was further supported by post-mortem findings of a decrease in 5-HT or in 5-HT metabolites in several brain areas of depressive patients as well as reports of positive antidepressant results with 5-HT precursors, such as tryptophan or 5-hydroxytryptophan (5-HTP) (Van Praag, 1982b). The major support for the monoaminergic theory came however from the demonstration that clinically effective antidepressants increased the amount of neurotransmitters available in the synaptic cleft, by inhibiting reuptake mechanism (tricyclics) or by inhibiting enzymatic catabolism (monoamine oxidase inhibitors) (Willner, 1985). The major role suggested for 5-HT in this theory led to the development of a large number of compounds which selectively inhibit 5-HT reuptake, such as zimeldine, indalpine, fluvoxamine, fluoxetine, citalopram, sertraline, paroxetine, etc (Johnson, 1991). Numerous clinical trials have demonstrated the antidepressant efficacy of such types of serotoninergic agents (Boyer and Feighner, 1991), supporting 5-HT deficit as

the main origin of depression. Therefore, everything seemed clear: depression was caused by 5-HT deficit and treated by serotoninergic agents.

*Tianeptine*

Tianeptine is a dibenzothiazepine derivate which is clearly active in classical animal models predictive of antidepressant activity (Poignant, 1981; Mocaër *et al*, 1988). In rats, it inhibits the ptosis induced by reserpine and tetrabenazine, antagonizes apomorphine-induced hypothermia, and potentiates yohimbine toxicity; in cats, it decreases the pontogeniculo-occipital (PGO) waves induced by a tetrabenazine analogue, Ro-4 1284. Tianeptine is also active in behavioral screening tests at doses lower than 10 mg/kg, ip: it antagonizes isolation-induced aggression in mice and behavioral despair in rats undergoing the Porsolt's swim test. The antidepressant efficacy of tianeptine has been demonstrated in five controlled studies *vs* reference antidepressants such as amitriptyline, imipramine, and nomifensine (Ostaptzeff, 1981; Weiss *et al*, 1981; Lôo *et al*, 1988; Bersani *et al*, 1989; Guelfi *et al*, 1989) and this compound has been marketed with success in France since 1988.

Animal studies on the mechanism of action of tianeptine have revealed that in contrast to classical tricyclic antidepressants, tianeptine *stimulates* 5-HT reuptake *in vivo* in the rat brain (Mennini *et al*, 1987; Mocaër *et al*, 1988; Fattaccini *et al*, 1990). This somewhat surprising property was observed in the cortex and the hippocampus following both acute and chronic administrations. In the cortex, this increase reached about 30% after acute (1 h) and 30% after chronic (15 days) treatment at a dose of 10 mg/kg, ip and 70% at a dose of 20 mg/kg, ip (Mocaër *et al*, 1988). This increase in 5-HT uptake has also been confirmed in rat platelets after acute and chronic administrations (Mocaër *et al*, 1988). Moreover, in humans, a recent study in 10 depressed patients demonstrated that tianeptine significantly increased platelet 5-HT uptake after a single administration (+ 23%) as well as after 10 and 28 days of treatment(+ 14% and 13% respectively) (Chamba *et al*,1991).

This increase in 5-HT uptake was further supported by several reports of enhanced 5-hydroxyindol-acetic acid (5-HIAA) levels in various brain regions after acute tianeptine administration in the rat (Fattaccini *et al*, 1990; Ortiz *et al*, 1991). Such results were confirmed in an *in vivo* voltametric study showing that tianeptine induced a persistent increase in the extracellular levels of 5-HIAA in rat hippocampus whereas fluoxetine exhibited opposed activity (Fuller *et al*, 1974; De Simoni *et al*, 1992). Increased rat plasma 5-HIAA levels have also been reported under similar conditions (Ortiz *et al*, 1991). Moreover, the 5-HT depletion caused by 4-methyl-alpha-ethyl-metatyramine is markedly potentiated by tianeptine but opposed by 5-HT uptake inhibitors (Carlsson *et al*, 1969).

The activity of tianeptine appears to be selective for 5-HT since the drug does not influence dopamine or noradrenaline uptake (Mennini *et al*, 1987). Moreover, tianeptine does not bind to any of the receptors tested: 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_2$ and presynaptic 5-HT receptors, alpha1, alpha2 and beta-adreno receptors, dopamine D2 receptors, GABA, glutamate, benzodiazepine, muscarinic and histamine receptors, imipramine binding sites, or calcium channels (Mennini *et al*, 1987; Kato and Weitsch, 1988; Hamon *et al*, 1989). In total, all these findings confirm the unique property of tianeptine in activating 5-HT reuptake.

*Possible interpretations for the paradoxical activity of tianeptine*

The paradoxical finding that both tianeptine and selective 5-HT reuptake inhibitors exhibit antidepressant activity despite clearly antagonistic mechanisms is rather puzzling. Several interpretations could be elaborated in order to try to reconcile these data.

Firstly, depressive disorders could be characterized by excessive 5-HT neurotransmission rather than 5-HT deficit and therefore justify antidepressant compounds which decrease 5-HT levels, such as tianeptine. The fact that many antidepressants show some degree of blockade of 5-HT receptors, which may predominate over their 5-HT enhancing effects, has been advanced as suppport for the hypothesis that some depressions may be a reflection of hyperactive 5-HT mechanisms (Aprison *et al*, 1982). In fact, many tricyclic and atypical antidepressants markedly antagonize post-synaptic 5-$HT_2$ receptors. Therefore, in considering the net effect of antidepressants on 5-HT transmission, the blockade of post-synaptic 5-$HT_2$ receptors must be set against the increase in receptor bombardment brought about by uptake blockade. In the case of amitriptyline, for instance, moderate 5-HT uptake inhibition is combined with powerful blockade of 5-$HT_2$ receptors, resulting in a reduction in 5-HT neurotransmission. Acute amitriptyline administration has been reported to reduce electrophysiological and behavioral depression (Nagayama *et al*, 1980; Willner, 1985). Moreover, ritanserin, a selective 5-$HT_2$ receptor blocker, has been repor-

ted to exhibit antidepressant properties (Reyntjens *et al*, 1986). However, it is clearly not a general property of antidepressant drugs that they antagonize 5-HT receptors to an extent sufficient to predominate over the 5-HT increasing effect of 5-HT uptake inhibition.

Secondly, it has been suggested that uptake inhibition may not be the explanation for the clinical activity of 5-HT reuptake blockers: 5-HT uptake is inhibited from the first day of drug administration while at least 2-3 weeks is needed before the therapeutic effect of these antidepressants is manifested (Quitkin *et al*, 1984; Kato and Weitsch, 1988). Furthermore, it is known that while imipramine and desipramine inhibit 5-HT uptake *in vitro* and after acute administration, these compounds may enhance 5-HT uptake after chronic administration (Barbaccia *et al*, 1983). Similar changes over time in uptake activity have been reported for fluvoxamine, a selective 5-HT reuptake inhibitor (Brunello *et al*, 1987). These findings are interesting to relate to the phenomenology of clinical changes following antidepressant therapy, often characterized by a 1-2 week worsening in depressive symptoms followed by the clinical improvement (Ansseau, 1988). These biphasic clinical changes are particularly obvious for 5-HT reuptake blockers, such as fluvoxamine (Den Boer and Westenberg, 1988) and could reflect successively opposed biochemical mechanisms. According to this theory, tianeptine could represent the first antidepressant inducing final biochemical changes from the initiation of therapy. On a clinical level, this could be reflected by a lack of initial worsening of the symptomatology and a more rapid antidepressant onset.

Thirdly, tianeptine and 5-HT reuptake inhibitors could be effective in different types of depression, characterized by either excessive or diminished 5-HT neurotransmission (Willner, 1985).

Fourthly, instead of relative excess or deficit in 5-HT mechanisms, depression could result from an 'unstability' in 5-HT mechanisms (Willner and Montgomery, 1980). This unstability could eventually be corrected through opposed mechanisms.

## Methodologies to test these hypotheses

Several types of clinical trials could be designed in order to test the hypotheses concerning the differences in biochemical mechanisms between tianeptine and 5-HT reuptake blockers.

Firstly, tianeptine and 5-HT reuptake inhibitors could be administered concomitantly in order to verify if this association leads to an inhibition or to a potentiation of antidepressant efficacy. An anecdotal report of a patient concurrently treated by tianeptine and fluoxetine suggested excellent antidepressant response (Ganry, personal communication).

Secondly, a careful comparison of the antidepressant phenomenology following tianeptine and 5-HT blocker therapy could show if the two types of compounds can be differentiated according to uniphasic (continuous improvement) *vs* biphasic (initial worsening followed by improvement) changes over the first weeks of treatment.

Thirdly, tianeptine could be tested in depressive patients resistent to 5-HT reuptake blockers and *vice versa*, in order to test the hypothesis that the two types of drugs are effective in different subsamples of depressive patients.

Fourthly, the clinical and biochemical profile of patients who respond to tianeptine on the one hand and to 5-HT reuptake blockers on the other hand could be compared in order to establish whether differential profiles could be formed. In this regard, indirect probes of serotonergic systems, particularly of neuroendocrine and neurophysiological types, could be of major interest in order to classify the patients according to serotonergic disturbances (Ansseau, 1991).

## Conclusion

Until the demonstration of the antidepressant activity of tianeptine, the biochemical hypothesis of a decreased serotonergic neurotransmission in depression appeared rather coherent, with serotonin reuptake blockers as therapeutic agents. Tianeptine, with its clearly opposite mechanism of action makes it necessary to re-evaluate the biochemical foundation of depressive disorders. The paradox of tianeptine demonstrates quite obviously that much progress is still needed for an actual understanding of the pathophysiology of depression and subsequently of its most effective therapy.

## References

Ansseau M (1988) Les antidépresseurs. *Méd et Hyg* 46, 2314–2321

Ansseau M (1991) Biological markers of depression: State of the art. *In: Biological Markers of Depression: State of the art* (Ansseau M, von Frenckell R, Franck G, eds). Excerpta Medica, Amsterdam, 1–10

Aprison MH, Hintgen JN, Nagayama H (1982) Testing a new theory of depression with an animal model: neurochemical-behavioral evidence for postsynaptic serotonergic receptor involvement. *In: New Vistas in Depression* (Langer SZ, Takahashi R, Segawa T, Briley M, eds). Pergamon, New York, 171–178

Barbaccia ML, Gandolfi O, Chuang DM, Costa E (1983) Modulation of neuronal serotonin uptake by a putative endogenous ligand of imipramine recognition sites. *Proc Natl Acad Sci USA* 80, 5134–5138

Bersani G, Pasini A, Brancato T, Valducci M, Ciani N (1989) Serotonina e depressione: studio multicentrico controllato tianeptina *versus* amitriptilina. XXXVII Congresso Nazionale della Societa Italiana di Psychiatria - Roma 6-11 febbraio 1989. CIC Edizioni Internazionali, 1243–1249

Boyer WF, Feighner JP (1991) The efficacy of selective serotonin re-uptake inhibitors in depression. *In: Selective Serotonin Re-uptake Inhibitors* (Feighner JP, Boyer WF, eds). Wiley, Chichester, 89–108

Bunney WE, Davis JM (1965) Norepinephrine in depressive reactions. *Arch Gen Psychiatry* 13, 483–494

Bunney WE Jr, Post RM, Andersen AE, Kopanda RTA (1977) A neuronal receptor sensitivity mechanism in affective illness (a review of evidence). *Commun Psychopharmacol* 1, 393–406

Carlsson A, Corrodi H, Fuxe K, Hökfelt T (1969) Effect of antidepressant drugs on the depletion of intraneuronal brain 5-hydroxytryptamine stores caused by 4-methyl-alpha-ethyl-metatyramine. *Eur J Pharmacol* 5, 357–366

Chamba G, Lemoine P, Flachaire E, Ferry N, Quincy C, Sassard J, Ferber C, Mocaër E, Kamoun A, Renaud B (1991) Increased serotonin platelet uptake after tianeptine administration in depressed patients. *Biol Psychiatry* 30, 609–617

Den Boer JA, Westenberg HGM (1988) Effect of a serotonin and noradrenaline uptake inhibitor in panic disorder: a double-blind comparative study with fluvoxamine and maprotiline. *Int Clin Psychopharmacol* 3, 59–74

De Simoni MG, De Luigi A, Clavenna A, Manfridi A (1992) *In vivo* studies on the enhancement of serotonin uptake by tianeptine. *Brain Res* 574, 93–97

Fattacini CM, Bolanos-Jimenez F, Gozlan H, Hamon M (1990) Tianeptine stimulates uptake of 5-hydroxytryptamine *in vivo* in the rat brain. *Neuropharmacology* 29, 1–8

Fuller RW, Perry KW, Molloy BB (1974) Effect of an uptake inhibitor on serotonin metabolism in rat brain: studies with 3-(p-trifluoromethylphenoxy)-N methyl-3-phenylpropylamine (Lilly 110140). *Life Sci* 14, 1161–1171

Guelfi JD, Pichot P, Dreyfus JF (1989) Efficacy of tianeptine in anxious-depressed patients. Results of a controlled multicenter trial *versus* amitriptyline. *Neuropsychobiology* 22, 41–48

Hamon M, Bourgoin S, Gozlan H (1989) Effets de la tianeptine sur la libération *in vitro* de [$^3$H] 5-HT et sur les divers types de récepteurs sérotoninergiques dans le système nerveux central chez le rat. *J Psychiatr Biol Thér* N° spécial mars, 48–51

Johnson AM (1991) The comparative pharmacological properties of selective serotonin re-uptake inhibitors in animals. *In: Selective Serotonin Re-uptake Inhibitors* (Feighner JP, Boyer WF, eds). Wiley, Chichester, 37–70

Kato G, Weitsch AF (1988) Neurochemical profile of tianeptine, a new antidepressant drug. *Clin Neuropharmacol* 11 (suppl 2), S43–S50

Lôo H, Malka R, Defrance R, Barrucand D, Benard JY, Niox-Riviere H, Raab A, Sarda A, Vachonfrance G, Kamoun A (1988) Tianeptine and amitriptyline: controlled double-blind trial in depressed alcoholic patients. *Neuropsychobiology* 19, 79–85

Maas JW, Fawcett J, Dekimenjian H (1968) 3-methoxy-4-hydroxy-phenylglycol (MHPG) excretion in depressive patients. *Arch Gen Psychiatry* 19, 129–134

Mennini T, Mocaër E, Garattini S (1987) Tianeptine, a selective enhancer of serotonin uptake in rat brain. *Naunyn Schmiedeberg's Arch Pharmacol* 336, 478–482

Mocaër E, Rettori MC, Kamoun A (1988) Pharmacological antidepressive effects and tianeptine-induced 5-HT uptake increase. *Clin Neuropharmacol* 11 (suppl 2), S32–S42

Nagayama H, Hinntgen JN, Aprison MH (1980) Pre- and postsynaptic serotonergic manipulations in an animal model of depression. *Pharmacol Biochem Behav* 13, 575–579

Ortiz J, Mocaër E, Artigas F (1991) Effects of the antidepressant drug tianeptine on plasma and platelet serotonin concentration in the rat. *Eur J Pharmacol* 199, 335–339

Ostaptzeff G (1981) Étude contrôlée à double insu *versus* imipramine de l'efficacité de la tianeptine dans les états dépressifs ou psychotiques (Perris C, Struwe G, Jansson B, eds). Biological Psychiatry. Elsevier/North-Holland Biomedical Press, Amsterdam New York Oxford. *Proceedings of the Third World Congress of Biological Psychiatry*, Stockholm, June 28/July 3, 1981, 597–600

Poignant JC (1981) Étude pharmacologique d'un nouvel antidépresseur: la tianeptine *In: Biological Psychiatry 1981. Proceedings of the IIIrd World Congress of Biological Psychiatry* June 28/July 3, 1981 Stockholm, Sweden. Elsevier/North-Holland, 573–578

Quitkin FM, Rabkin JG, Ross D, Mc Grath PJ (1984) Duration of antidepressant drug treatment. What is an adequate trial? *Arch Gen Psychiatry* 41, 238–245

Reyntjens A, Gelders YG, Hoppenbrouwers ML, Vanden Bussche G (1986) Thymosthenic effects of ritanserin (R55 667), a centrally acting serotonin $S_2$ receptor blocker. *Drug Dev Res* 8, 205–211

Schildkraut JJ (1965) The catecholamine hypothesis of affective disorder: a review of supporting evidence. *Am J Psychiatry* 122, 509–522

van Praag HM (1982a) The significance of biological factors in the diagnosis of depressions: I. Biochemical variables. *Comp Psychiatry* 23, 124–135

van Praag HM (1982b) Depression, suicide and metabo-

lism of serotonin in the brain. *J Affect Dis* 4, 275–290

Weiss C, Gorceix A, Kindynis S, Dimitriu M (1981) Étude contrôlée à double insu *versus* nomifensine de l'activité et du délai d'action d'un nouvel antidépresseur la tianeptine (Perris C, Struwe G, Jansson B, eds). Biological Psychiatry. Elsevier/North-Holland Biomedical Press, Amsterdam, New York, Oxford. *Proceedings of the Third World Congress of Biological Psychiatry*, Stockholm, June 28/July 3, 1981, 593–596

Willner P (1985) Depression. *A psychobiological synthesis*. Wiley, New York

Willner P, Montgomery T (1980) Neurotransmitters and depression: too much, too little, too unstable - or not unstable enough? *Trends Neurosci* 3, 201