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EDITORIAL

Depression, 5-HT Deficit, SSRIs . . . and Tianeptine

The classical theory of the biochemical foundation of depression hypothesizes a decrease in central synaptic neurotransmission secondary to the deficiency in monoaminergic neurotransmitters, serotonin (5-HT) and/or noradrenaline. The main support for this theory was that all clinically effective antidepressants increase the amount of neurotransmitters available in the synaptic cleft, by inhibiting reuptake mechanism (tricyclics) or by inhibiting enzymatic catabolism (MAOI). The major role suggested for 5-HT deficiency in this theory led to the development of a large number of compounds intended to increase 5-HT neurotransmission, particularly by inhibiting 5-HT reuptake (SSRIs), such as zimeldine, indalpine, fluvoxamine, fluoxetine, citalopram, sertraline, paroxetine ... Numerous clinical trials have demonstrated the antidepressant efficacy of such type of serotonergic agents, supporting 5-HT deficit as the main origin or depression. Therefore, everything seemed clear: depression was caused by 5-HT deficit and treated by serotonergic agents ...

Tianeptine is a tricyclic derivative which is clearly active in classical and behavioral animal models predictive of antidepressant activity. Its antidepressant efficacy has been demonstrated in seven controlled studies as superior to placebo or equivalent to reference antidepressants such as amitriptyline, imipramine, and nomifensine (review in Ansseau, 1994) and tianeptine has been marketed with success in France since 1988. Biochemical studies however have clearly 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 (Mennini *et al.*, 1987; Fattaccini *et al.*, 1990). Therefore, as a 5-HT reuptake *enhancer*, tianeptine exhibits a mechanism of action totally opposite to SSRIs but, paradoxically, both mechanisms of action are associated with a therapeutic activity in depressive disorders.

Several interpretations to explain these paradoxical findings could be elaborated (Ansseau, 1993). First, 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 support for this hypothesis. Secondly, uptake inhibition may not be the explanation for the clinical activity of SSRIs: 5-HT uptake is inhibited from the first day of drug administration while at least 2–3 weeks are needed before the therapeutic effect of these antidepressants is manifested. 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 the SSRI fluvoxamine (Brunello *et al.*, 1987). Third, tianeptine and SSRIs could be effective in different types of depression, characterized by either excessive or diminished 5-HT neurotransmission. Fourthly, instead of relative excess or deficit in 5-HT mechanisms, depression could result from an 'unstability' in 5-HT mechanisms which could eventually be corrected through opposed mechanisms. Fifth, tianeptine could be effective through other mechanisms, particularly through its effect on the output of dopamine in the nucleus accumbens.

Several types of clinical trials could be designed in order to test the hypotheses concerning the differences in biochemical mechanisms between tianeptine and SSRIs.

First, tianeptine and SSRIs could be administered concomitantly in order to verify if this association leads to an inhibition or to a potentiation of antidepressant efficacy. Second, a careful comparison of the antidepressant phenomenology following tianeptine and SSRIs 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. Third, tianeptine could be tested in depressive patients

resistant to SSRIs and vice-versa, in order to test the hypothesis that the two types of drugs are effective in different subsamples of depressive patients. Fourth, the clinical and biochemical profile of patients who respond to tianeptine on the one hand and to SSRIs on the other hand could be compared in order to show if differential profiles could be established.

In total, the paradox of neurochemical and clinical properties of SSRIs and tianeptine demonstrates quite obviously that much progress is still needed for an actual understanding of the pathophysiology of depression.

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