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Editorial

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Paradoxical results are very important in science, because they often pave the way to new truths concerning underlying mechanisms of normal function and disease. A long-standing dogma in neuropharmacology has been that increasing synaptic availability of the monoamines, noradrenaline and serotonin, is the primary way to treat depressive illness. Many compounds have been developed that effectively block noradrenaline and/or serotonin reuptake and which have antidepressant properties. Tianeptine is a new compound with the paradoxical effect of facilitating serotonin reuptake and decreasing synaptic availability; yet, it is also a clinically effective antidepressant with good tolerance and lacking in cholinergic side effects, as indicated by evidence summarized in this volume. This symposium is a progress report on the clinical properties of the drug as well as its effects on neurochemistry and neuroendocrine function that underlie its mechanism of action.

One of the most striking features discovered for tianeptine is its ability to reduce ACTH and glucocorticoid secretion in response to stress, while leaving basal secretion of these hormones at or only slightly lower than normal. Tianeptine has also been found to reduce the effects of stress in causing atrophy of neurons in the hippocampal formation, a brain region involved in learning and memory. Both of these effects appear to be related to the ability of tianeptine to reduce synaptic availability of serotonin, but it remains to be seen whether these effects are unique to tianeptine as opposed to other antidepressant drugs. Behavioral actions of tianeptine in experimental animals include antidepressant effects in tests involving immobilization-induced deficits in open field activity, as well as antagonism of the anxiogenic effects of benzodiazepine withdrawal. Tianeptine has also been found to prevent abnormal loss of memory in aging mice and to alleviate memory deficits resulting from long-term alcohol intoxication. Thus, the actions of tianeptine in animal models suggest interesting potential applications from a therapeutic standpoint as well as pointing to important brain processes in which serotonin may be involved.

The main message of this symposium is that it is necessary to re-examine the biochemical hypothesis that decreased serotonin neurotransmission is a sole or even primary mechanism of depression. In the concluding chapter, M Ansseau outlines experimental strategies to resolve the paradox of antidepressant drug action. He notes that, on the one hand, there may be subtypes of depressive illness involving different abnormalities of serotonergic function; and he proposes that the subtype responding therapeutically to tianeptine might be resistant to serotonin reuptake blocking drugs. On the other hand, he notes that there might be a final common effect of serotonin reuptake blockers and enhancers that could be dissected in terms of different time courses of therapeutic effect and might result in serotonin reuptake blockers having improved efficacy when given concurrently with tianeptine. Further clinical studies are needed to distinguish between these two possibilities, and they must be accompanied by further investigations of the mechanism of action of all classes of antidepressant drugs.

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