The Selective $\alpha_2$-Adrenoceptor Antagonist Mirtazapine (Org 3770) Enhances Noradrenergic and 5-HT$_{1A}$-Mediated Serotonergic Neurotransmission

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Summary

Mirtazapine (Org 3770) is a selective antagonist at $\alpha_2$-adrenergic auto- and heteroreceptors, which are involved in regulation of neuronal noradrenaline (norepinephrine) and serotonin (5-hydroxytryptamine; 5-HT) release. It was identified as a potential antidepressant in rat sleep studies, showing characteristic REM sleep suppression, as well as activity in the bulbectomised rat and an operant behaviour model. However, mirtazapine does not inhibit monoamine reuptake and is inactive in classical tests predictive of antidepressant activity (antagonism of reserpine-induced hypothermia, Porsolt test, and muricidal behaviour). As an $\alpha_2$-antagonist, mirtazapine inhibits clonidine-induced mydriasis and resembles idazoxan in evoking conditioned taste aversion. In addition, mirtazapine induces lower lip retraction, a response characteristic of 5-HT$_{1A}$ receptor stimulation, and resembles the 5-HT$_{1A}$ agonist 8-hydroxy-dipropylaminotetraline (8-OH-DPAT) in producing conditioned taste aversion. Thus, mirtazapine may have indirect serotonin-enhancing effects, since its affinity for 5-HT$_{1A}$ receptors is low.

As a consequence of noradrenergic facilitation, mirtazapine increases the firing of serotonergic raphe neurons and antagonises the inhibitory effects of noradrenaline on serotonergic terminals. In combination, these effects offer a mechanistic basis for the drug’s observed stimulatory effect on hippocampal serotonin release. Because mirtazapine blocks 5-HT$_2$ and 5-HT$_3$ receptors, 5-HT$_{1A}$-mediated transmission is selectively enhanced, as reflected in its 5-HT$_{1A}$-like behavioural effects.

In conclusion, noradrenergic activation via $\alpha_2$-autoreceptor blockade and the consequent indirect enhancement of serotonergic transmission probably underlie the marked antidepressant activity of mirtazapine. Blockade of 5-HT$_2$ and 5-HT$_3$ receptors may account for the absence of those adverse effects associated with nonselective serotonergic activation and may also contribute to the anxiolytic and hypnotic properties of mirtazapine.
The tricyclic antidepressants (TCAs) remain unsurpassed in their clinical efficacy, a fact possibly related to their nonselective action on noradrenergic and serotonergic neurotransmission.\(^1\)\(^4\) However, the severe risk of adverse effects associated with the TCAs and their lack of safety on overdose place them at a disadvantage against the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) and the reversible monoamine oxidase inhibitors (RIMAs).\(^5\)\(^6\) While lacking anticholinergic, \(\alpha\)-adrenolytic or antihistaminergic properties and the adverse effects associated therewith, these newer compounds still produce numerous clinically undesirable central and peripheral effects. These adverse effects, which are observed in 10 to 20% of patients receiving these drugs,\(^7\)\(^9\) are mostly due to nonselective stimulation of 5-HT\(_2\) and 5-HT\(_3\) receptor subtypes.\(^10\)\(^11\) Furthermore, the development of agents (viz. SSRIs) selective for serotonergic rather than monoaminergic systems has not been accompanied by an improvement in the efficacy of antidepressant therapy.

A growing body of evidence underlines the importance of combined alterations in both noradrenergic and serotonergic pathways to the success of antidepressant treatment.\(^12\)\(^-\)\(^14\) Mirtazapine (Org 3770) is an antidepressant agent with a novel mechanism of action. It combines the favourable properties of the TCAs (interaction with both noradrenergic and serotonergic neurotransmission) with those of the new generation of antidepressants, showing a favourable profile with respect to anticholinergic, adrenolytic and serotonergic adverse effects, as well as safety on overdose. Mirtazapine is a mixture of

![Graph showing effects of mirtazapine](image)

Fig. 1. Effects of mirtazapine on electroencephalographic sleep patterns in the rat. Sleep-waking behaviour is automatically classified into 6 categories: active waking, quiet waking, quiet sleep, deep sleep, pre-REM sleep and REM sleep. Deep sleep and REM sleep were compared in 2 groups of rats after treatment with mirtazapine (n = 8) or placebo (n = 8); differences at baseline between groups were not significant. The upper panel of the figure depicts changes in deep sleep and REM sleep seen in one group of rats before treatment with mirtazapine compared with the control group of rats after treatment with placebo. The lower panel shows changes over placebo that occurred in rats after treatment with mirtazapine (from Ruigt & Van Proosdij\(^15\)). The increase in deep sleep (0-2h) and the prolonged decrease in REM sleep (0-6h) in rats treated with mirtazapine were statistically significant compared with placebo treatment (Wilcoxon rank test, p < 0.05).