

S01-01 - 5-HT₄ AGONISTS: A PUTATIVE NEW CLASS OF ANTIDEPRESSANTS, WITH A FASTER ONSET OF ACTION

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Objectives: Current antidepressants are clinically effective only after several weeks of administration. Because our previous studies indicated that both acute and sustained stimulation of serotonin₄ (5-HT₄) receptors facilitate central 5-HT activity, we assessed the ability of 5-HT₄ agonists to induce antidepressant-like effects in the rat brain within a short (3 days) time-frame.

Methods and results: We found that 5-HT₄ agonists reduce immobility in the Forced Swimming Test, displaying an antidepressant potential. Moreover, a 3-day regimen with such compounds modify rat brain parameters considered as key markers of antidepressant action, but observed only after 2-3 week treatments with classical molecules: desensitization of 5-HT_{1A} autoreceptors, increased tonus on hippocampal postsynaptic 5-HT_{1A} receptors, enhanced phosphorylation of the CREB protein and neurogenesis in the hippocampus. A 3-day regimen with the 5-HT₄ agonist RS 67333 was also sufficient to reduce both the hyperlocomotion induced by olfactory bulbectomy, and the diminution of sucrose intake consecutive to a chronic mild stress. Moreover, the concomitant administration of a 5-HT₄ receptor agonists with a classical antidepressant (SSRI) potentiated the amplitude of these effects, without altering the rapidity of action of the former.

Conclusions: These findings point out 5-HT₄ receptor agonists as a putative new class of antidepressants, with a rapid onset of action.