Antidepressants are functional antagonists at the serotonin type 3 (5-HT3) receptor.

Abstract:
Antidepressants are commonly supposed to enhance serotonergic and/or noradrenergic neurotransmission by inhibition of neurotransmitter reuptake through binding to the respective neurotransmitter transporters or through inhibition of the monoamine oxidase. Using the concentration-clamp technique and measurements of intracellular Ca2+, we demonstrate that different classes of antidepressants act as functional antagonists at the human 5-HT3A receptor stably expressed in HEK 293 cells and at endogenous 5-HT3 receptors of rat hippocampal neurons and N1E-115 neuroblastoma cells. The tricyclic antidepressants desipramine, imipramine, and trimipramine, the serotonin reuptake inhibitor fluoxetine, the norepinephrine reuptake inhibitor reboxetine, and the noradrenergic and specific serotonergic antidepressant mirtazapine effectively reduced the serotonin-induced Na(+)- and Ca2+(+)-currents in a dose-dependent fashion. This effect was voltage-independent and, with the exception of mirtazapine, noncompetitive. Desipramine, imipramine, trimipramine, and fluoxetine also accelerated receptor desensitization. Moclobemide and carbamazepine had no effect on the serotonin-induced cation current. By analyzing analogues of desipramine
and carbamazepine, we found that a basic propylamine side chain increases the antagonistic potency of tricyclic compounds, whereas it is abolished by an uncharged carboxamide group. The antagonistic effects of antidepressants at the 5-HT3 receptor did not correlate with their effects on membrane fluidity. In conclusion, structurally different types of antidepressants modulate the function of this ligand-gated ion channel. This may represent a yet unrecognized pharmacological principle of antidepressants.

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