Antipsychotic drugs antagonize human serotonin type 3 receptor currents in a noncompetitive manner.

The serotonin type 3 (5-HT(3)) receptor is the only ligand-gated ion channel receptor for serotonin (5-HT). 5-HT(3) receptors play an important role in modulating the inhibitory action of dopamine in mesocorticolimbic brain regions. Neuroleptic drugs are commonly thought to exert their psychopharmacological action mainly through dopamine and serotonin type 2 (5-HT(2)) receptors. Except for clozapine, a direct pharmacological interaction of neuroleptics with 5-HT(3) receptors has not yet been described. Using the concentration-clamp technique, we investigated the effects of flupentixol, various phenothiazines, haloperidol, clozapine and risperidone on Na(+) -inward currents through 5-HT(3) receptors stably expressed in human embryonic kidney 293 cells, and through endogenous 5-HT(3) receptors of murine N1E-115 neuroblastoma cells. In addition, we studied their effects on Ca(2+) influx, measured as a change in intracellular Ca(2+) concentrations ([Ca(2+)](i)). All neuroleptic drugs, but not risperidone, antagonized Na(+) - and Ca(2+) -inward currents evoked by 5-HT (10 microM for 2 s and 1 microM, respectively) in a voltage-independent manner. Only clozapine was a competitive antagonist, while all other compounds turned out to be noncompetitive. Fluphenazine and haloperidol affected
membrane anisotropy at concentrations below their IC(50) values, indicating that a change in membrane anisotropy might contribute to their antagonistic effect at the 5-HT(3) receptor. Only structure analogues of flupentixol and fluphenazine with a lipophilic side chain were potent antagonists against 5-HT-evoked Na(+) and Ca(2+) currents. Since 5-HT(3) receptors modulate mesolimbic and mesocortical dopaminergic activity, the functional antagonism of neuroleptics at 5-HT(3) receptors may contribute to their antipsychotic efficacy and may constitute a not yet recognized pharmacological principle of these drugs.