Antidepressants and antipsychotic drugs colocalize with 5-HT3 receptors in raft-like domains.

Abstract:

Despite different chemical structure and pharmacodynamic signaling pathways, a variety of antidepressants and antipsychotics inhibit ion fluxes through 5-HT3 receptors in a noncompetitive manner with the exception of the known competitive antagonists mirtazapine and clozapine. To further investigate the mechanisms underlying the noncompetitive inhibition of the serotonin-evoked cation current, we quantified the concentrations of different types of antidepressants and antipsychotics in fractions of sucrose flotation gradients isolated from HEK293 (human embryonic kidney 293) cells stably transfected with the 5-HT3A receptor and of N1E-115 neuroblastoma cells in relation to the localization of the 5-HT3 receptor protein within the cell membrane. Western blots revealed a localization of the 5-HT3 receptor protein exclusively in the low buoyant density (LBD) fractions compatible with a localization within raft-like domains. Also, the antidepressants desipramine, fluoxetine, and reboxetine and the antipsychotics fluphenazine, haloperidol, and clozapine were markedly enriched in LBD fractions, whereas no accumulation occurs for mirtazapine, carbamazepine, moclobemide, and risperidone. The concentrations of psychopharmacological drugs within LBD fractions was strongly associated with their inhibitory potency against
serotonin-induced cation currents. The noncompetitive antagonism of antidepressants at the 5-HT3 receptor was not conferred by an enhancement of receptor internalization as shown by immunofluorescence studies, assessment of receptor density in clathrin-coated vesicles, and electrophysiological recordings after coexpression of a dominant-negative mutant of dynamin I, which inhibits receptor internalization. In conclusion, enrichment of antidepressants and antipsychotics in raft-like domains within the cell membrane appears to be crucial for their antagonistic effects at ligand-gated ion channels such as 5-HT3 receptors.