Impact of lipid raft integrity on 5-HT3 receptor function and its modulation by antidepressants.

Because of the biochemical colocalization of the 5-HT(3) receptor and antidepressants within raft-like domains and their antagonistic effects at this ligand-gated ion channel, we investigated the impact of lipid raft integrity for 5-HT(3) receptor function and its modulation by antidepressants. Treatment with methyl-beta-cyclodextrine (MbetaCD) markedly reduced membrane cholesterol levels and caused a more diffuse membrane distribution of the lipid raft marker protein flotillin-1 indicating lipid raft impairment. Both amplitude and charge of serotonin evoked cation currents were diminished following cholesterol depletion by either MbetaCD or simvastatin (Sim), whereas the functional antagonistic properties of the antidepressants desipramine (DMI) and fluoxetine ( Fluox) at the 5-HT(3) receptor were retained. Although both the 5-HT(3) receptor and flotillin-1 were predominantly found in raft-like domains in western blots following sucrose density gradient centrifugation, immunocytochemistry revealed only a coincidental degree of colocalization of these two proteins. These findings and the persistence of the antagonistic effects of DMI and Fluox against 5-HT(3) receptors after lipid raft impairment indicate that their modulatory effects are likely mediated through non-raft 5-HT(3) receptors, which are not sufficiently detected by
means of sucrose density gradient centrifugation. In conclusion, lipid raft integrity appears to be important for 5-HT(3) receptor function in general, whereas it is not a prerequisite for the antagonistic properties of antidepressants such as DMI and Fluox at this ligand-gated ion channel.