Cholesterol and fate of drug targets of depression

Cells in our body communicate with their surroundings through tiny nanomachines called G protein-coupled receptors (GPCRs) that are embedded in the outermost membrane which wraps the cell. Owing to their crucial role in maintaining key cellular processes, these receptors have emerged as major drug targets in almost all clinical areas.

The serotonin$_{1A}$ receptor is one such important GPCR that is involved in neurotransmission and is an important drug target in neuropsychiatric disorders such as anxiety and depression. The function of GPCRs such as the serotonin$_{1A}$ receptor is regulated by their internalization into the inside of a cell through a process called endocytosis - a key event in the therapeutic action of several drugs that act *via* GPCRs. Prof. Amitabha Chattopadhyay's group from the CSIR-Centre for Cellular and Molecular Biology (CCMB), Hyderabadhad previously shown that the serotonin$_{1A}$ receptor internalizes into cells through specialized regions of the cell membrane, called clathrin-coated pits, and thereafter recycles back to the cell membrane.

In a follow-up discovery published in the American Chemical Society journal, *ACS Chemical Neuroscience*, Prof. Chattopadhyay's group has now shown that modulating the levels of cholesterol, an important lipid in the cell membrane, could modulate the mechanism of endocytosis of the serotonin$_{1A}$ receptor. When the researchers from CCMB treated cells with statin, the best-selling cholesterol lowering drug in the market, they observed that the serotonin$_{1A}$ receptor, instead of using clathrin-coated pits, internalized through alternate regions called caveolae, which are cave-like structures on the cell membrane. "We observed that this switch in the mechanism of internalization again reverted back to clathrin-coated pits when we put back cholesterol in cells that was lost upon statin treatment", said G. Aditya Kumar, a Ph.D. student who is the first author of the paper.

Interestingly, experiments from the team also revealed that receptors that usually recycle back to the cell membrane in normal conditions started getting degraded inside cells when they were treated with statin. "We believe that our findings arecrucial in understanding how cholesterol in cell membranes modulatesthe endocytosis of GPCRs", explains Prof. Chattopadhyay. An important class of anti-depressant drugs, termed selective serotonin reuptake inhibitors (SSRIs), target the endocytosis of the serotonin$_{1A}$ receptor as their mechanism of action. "From a biomedical standpoint, these results could provide novel insights into the mechanism underlying recent reports on the improved therapeutic activity of antidepressant drugs when administered in combination with statins", Prof. Chattopadhyay added. These studies from CCMB are especially relevant in the Indian context since the National Mental Health Survey (2015-16) reported that more than 5% of the adult Indian population suffers from depression.

Reference

Kumar, G.A., and Chattopadhyay, A. (2020) "Statin-Induced Chronic Cholesterol Depletion Switches GPCREndocytosis and Trafficking: Insights from the Serotonin$_{1A}$ Receptor" *ACS Chem. Neurosci.* 11: 453-465 (DOI: 10.1021/acschemneuro.9b00659).