Chen Institute Retreat 2023

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Poster title: Selective serotonin reuptake inhibitors within and near cells: Resolution at the compartmental and temporal levels via genetically encoded biosensors

Abstract: Selective serotonin reuptake inhibitors (SSRIs) are the most prescribed treatment for individuals experiencing major depressive disorder (MDD). Despite their widespread use, the mechanism that relieves MDD after SSRIs bind the serotonin transporter (SERT) is still not understood, partially because no method has existed to directly examine the cellular and subcellular pharmacokinetic properties of these compounds in living cells. Here, we studied movements of escitalopram and fluoxetine using several tools: new intensity-based drug sensing fluorescent reporters ("iDrugSnFRs"), targeted to the plasma membrane (PM), cytoplasm, and endoplasmic reticulum (ER); impermeant quaternary amine derivatives of these same SSRIs; and ~ 1 second solution changes, with cultured neurons and HeLa cells. For purified solutions of iDrugSnFRs and SSRIs, fluorescence signals are uncomplicated and reach completion within a few seconds; but the cellular measurements on the SSRIs and their iDrugSnFRs yield a rich set of kinetic phenomena, on time scales from a few seconds to ~10 min. In contrast, the membrane-impermeant quaternary derivatives showed simpler, faster signals; but they interact with SERT > 10-fold less strongly than the SSRIs. We interpret these data in light of previous reports that SSRIs both sequester within and perturb some membrane compartments and may reach SERT from the membrane phase. Although the time scale of our experiments is orders of magnitude slower than the "therapeutic lag" of SSRIs, the novel measurements presented here emphasize that pharmacokinetic properties of SSRIs, including their anomalously high volume of distribution, may play roles in both the therapeutic lag and the equally puzzling "antidepressant discontinuation syndrome".