Computational Model Evaluation of DOPAC Secretion

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DOPAC (3,4-Dihydroxyphenylacetic acid) is a metabolite of the neurotransmitter dopamine. DOPAC has traditionally been considered to be a waste product with no biological function. However, microdialysis experiments report average extracellular DOPAC concentration is approximately 250 times higher than extracellular dopamine. Such observations suggest DOPAC may have a signaling function. DOPAC is generally considered to be made in nerve terminals and, because it is a charged molecule, would not be expected to diffuse through membranes into extracellular space. Understanding the mechanisms by which extracellular DOPAC is produced and regulated can shed light on a potential new signaling mechanism for dopamine neurons. The goal of this project is to determine and evaluate potential processes that may contribute to extracellular DOPAC. Three potential mechanisms were identified: a dedicated secretory complex, facilitated diffusion from cytosol to extracellular space, and metabolism of dopamine in extracellular space. A computational simulation model was used to evaluate how pharmacological interventions alter DOPAC levels and distribution. Simulation output was compared to published data with the hopes that one mechanism would be a good match for all drug effects. The secretory complex and diffusional mechanisms both matched experimental data well for some but not all of the conditions studied. The extracellular metabolism mechanism provided a very poor match for all conditions. These data suggest that DOPAC is synthesized inside the nerve terminal and secreted into extracellular space. However, regulatory mechanisms in addition to those considered here are required to explain all published data. Identification of these additional mechanisms is expected to provide new information on the function of dopamine neurons and their role in learning behaviors.