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Computational simulations of dopaminergic varicosities suggest two sources of DOPAC rather than two populations of dopamine storage vesicles

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Results from several different experimental paradigms have been interpreted as supporting the concept that two populations of dopamine storage vesicles exist in the nerve terminals of dopaminergic neurons. The goal of this work is to develop a computer simulation model of a dopaminergic varicosity that provides a plausible quantitative description of these populations and a possible set of rules for dopamine movement between two populations of vesicles. We first looked at how well a one compartment model provides accurate simulations of published experimental data. The model allocates dopamine among three compartments: vesicles, cytosol, and extracellular. Dopamine moves from vesicles to extracellular (exocytosis), extracellular to cytosol (dopamine transporter), and from cytosol to vesicles (vesicular monoamine transporter). Synthesis of new dopamine molecules occurs in the cytosolic compartment, with new dopamine entering that compartment. Metabolism of dopamine also occurs in the cytosolic compartment, with a fraction of the dopamine in that compartment being metabolized to DOPAC. With appropriate values for all rate constants, this model successfully explains all data purportedly supporting two populations of storage vesicles in paradigms that stimulate dopaminergic neurons at rates much faster than physiological. However, this model does not explain other data that support the two populations of vesicles concept. Models with two storage vesicle compartments were evaluated for ability to explain these data; however, none were successful. An alternate model was developed from the one storage compartment model but with the addition that the dopamine synthetic process has a branch point where newly synthesized dopamine is either secreted to the extracellular space or converted to DOPAC, which is deposited into the cytosolic compartment. This model successfully explains data regarding the specific activity of dopamine and metabolites after injection of labeled tyrosine into the varicosity, dopamine metabolite kinetics after inhibition of dopamine synthesis, and preferential secretion of newly synthesized dopamine. Thus, our model suggests that dopaminergic varicosities have two sources of DOPAC, one likely associated with mitochondria and the other associated with the dopamine synthetic complex.