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A computational model of dopamine and tyramine interactions in striatal storage vesicles

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Background

The vesicular monoamine transporter pumps dopamine, norepinephrine, and five-hydroxy tryptamine into synaptic storage vesicles. A variety of exogenous amines are also substrates for this transporter. Once stored, amines can be redistributed out of vesicles by compounds that inhibit the VMAT or by substrates for the VMAT. Recently, data were reported comparing uptake of dopamine and tyramine into vesicles and comparing ability of dopamine, tyramine, and a variety of amphetamine analogues to redistribute stored dopamine and tyramine out of vesicles [1]. The kinetics of dopamine and tyramine uptake are markedly different, and the maximum amount of stored amine that is redistributed out of vesicles differs substantially when comparing various displacers. A potential explanation is the presence of a storage compartment within each vesicle for which various amines have differing affinities.

Objective

The objective of this project is to explain why the maximum velocity of uptake varies between different amines and to provide a quantitative/kinetic description of the storage compartment within a vesicle.

Method

We developed a computational model for simulating dopamine and tyramine uptake into vesicles and their displacement by various types of compounds. The model parameters include transporter mediated uptake into vesicles, diffusion in and out of vesicles, on-rate for binding to a storage compartment, off-rate for unbinding from a storage compartment, and capacity of the storage compartment.

Results

Regarding uptake studies, the membrane diffusion rate constant controls the time to reach steady-state conditions and the magnitude of uptake. More diffusible compounds reach lower steady-state values than do less permeable compounds. The time to reach steady-state is also quicker for more permeable compounds. Therefore, the apparent maximum velocity, as measured by uptake studies, is lesser for the more permeable compounds. Regarding an intra-vesicular storage compartment, a satisfactory model uses a storage compartment with a capacity of 500 binding sites and a very fast on-rate which is held constant for all amines. Dopamine is tightly bound to this compartment because of a slow off-rate. Tyramine is loosely bound because of a fast off-rate. Amphetamine and analogues have intermediate off-rates. This model results in a maximum vesicular amine displacement of 100% when dopamine is displacing either dopamine or tyramine, of 86% when tyramine is displacing dopamine, of 60% when an inhibitor of the VMAT is displacing tyramine, and of 47% when an inhibitor of the VMAT is displacing dopamine.

References

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