A Method for Simulating Dopamine Agonist Self-Administration with a Receptor-Based Mechanism

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**Objectives:** Rats trained to self-administer dopamine receptor agonists do so with a regularity predicted by

\[ T = \ln \left( 1 + \frac{D_U}{D_{ST}} \right)/k \]

where \( T \) is the inter-injection interval, \( D_U \) is the agonist unit dose, \( k \) is the first-order agonist elimination rate constant, and \( D_{ST} \) is the minimum level of agonist maintained in the body[1]. Herein is detailed a method for simulating self-administration behavior with a PK/PD model, as well as simulations that better reproduce self-administration behavior qualitatively and quantitatively[2].

**Methods:** MATLAB Simbiology was used to construct a two-compartment PK/PD model, where the brain compartment contains a steady-state receptor population that mediates a response in the form of an agonist dosing event. If the concentration of agonist-receptor complexes is above a concentration corresponding to priming threshold—the minimum concentration required to induce agonist self-administration events—and below a concentration corresponding to \( D_{ST} \), then agonist self-administration events will occur at short and defined intervals. Agonist-receptor binding proceeds according to the law of mass action, elimination and inter-compartmental distribution are assumed to conform to first-order kinetics, and the model can be exported as a set of ordinary differential equations.

**Results:** The model reproduced observations made with rats self-administering dopamine receptor agonists including a proportional (but non-linear) relationship between the dose and inter-event intervals. \( D_{ST} \) and \( T \) are now quantitatively similar to data from rats. Antagonist-induced acceleration of self-administration results from an increase in \( D_{ST} \) and the consequent increase in the rate of agonist elimination.

**Conclusions:** Several fundamental features of drug self-administration behavior can be explained by PK/PD interactions, which provides opportunities for pharmacometrics to advance the understanding of addictive behavior. This *in silico* approach provides a useful tool for exploring the contributions of specific pharmacological parameters to addictive behavior.

**References:**