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An Overview of Maintained Dopamine Agonist Self-Administration Behaviour in Rats as a Pharmacological Assay System

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Dopamine receptors in the brain are targets for pharmacotherapies for a range of disorders. Extensive compound libraries and in vitro high throughput screening of activity has accelerated lead compound identification. However, in vivo screens of bioavailability, distribution and clearance remain a major rate-limiting step in identifying and advancing the development of lead candidates. We have developed a pharmacokinetic/pharmacodynamic (PK/PD) model of direct and indirect dopamine receptor agonist self-administration behaviour that can be used to rapidly measure the in vivo potency and pharmacokinetics of dopamine receptor agonists and antagonists. Herein, an overview of the uses of this assay is provided.

1) **Agonists:** Self-administration behaviour is described by the equation $T=\ln(1+Du/Dst)/k$, where T=time between self-administrations, Du= agonist dose administered per injection, Dst=agonist satiety threshold (minimum maintained concentration), and k=first order elimination rate constant of the agonist. The regularity of inter-injection intervals is because a quantal response (self-administration) is induced at a specific concentration of agonist (1). Dst represents an equiactive agonist concentration and is a measure of agonist potency and is constant for a particular agonist (1). Therefore, measuring the rate of behaviour as a function of the unit dose can be used to determine agonist potency and its pharmacokinetics in the brain.

2) **Competitive antagonists:** Competitive antagonists accelerate agonist self-administration by increasing the Dst. This is the result of a PK/PD interaction where the rate of cocaine elimination is faster at the higher concentrations, as dictated by first-order kinetics, so that agonist levels decline more rapidly to the elevated Dst. Antagonist induced increases in the agonist concentration ratios can be analysed according to the classical method of Schild. This pharmacological approach allows the measurement of key parameters including: a) The dose of antagonist producing a two-fold increase in the Dst, a measure of the pharmacodynamics potency of the antagonist (apparent pA_2) (2). b) Whether the antagonist is a substrate for p-glycoprotein or related drug transporters in the blood-brain barrier assessed by measuring the effects of a p-glycoprotein inhibitor, e.g. tamoxifen, on antagonist potency. c) The time-course of the effect on self-administration may measure antagonist pharmacokinetics. d) Absolute bioavailability via different routes of administration is measured by comparing the area under the time-effect curve with this area following i.v. administration of the antagonist. For example, the absolute bioavailability of eticlopride given intramuscularly (i.m), subcutaneously (s.c) and intraperitoneally (i.p) was found to be: $D_{IV} = 1.0$, $D_{SC} = 0.67$, $D_{IP} = 0.73$ respectively.

3) **Irreversible antagonists:** Irreversible antagonists also accelerate self-administration by increasing the concentration of agonist required to occupy the same

number of receptors. These can be differentiated from competitive antagonists by the recovery of the rate of self-administration to baseline. Following irreversible antagonist treatment, this will occur over many days, rather than the much shorter (hours) recovery after competitive antagonist treatment. Initially, the rate of self-administration was doubled. Then the rate of self-administration after irreversible antagonist treatment can also be used to study receptor activity recovery rates. Self-administration behaviour returned to baseline after approximately one week.

In conclusion, agonist self-administration represents a high-content screening bioassay system that can measure fundamental PK/PD parameters of important classes drugs.