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Cocaine and Apomorphine self-administration in rats used as a pharmacological bioassay system

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Cocaine self-administration in rats is a model of cocaine use disorder. A pharmacological theory of cocaine self-administration behavior in rats states that cocaine induces lever pressing behavior only when cocaine levels are below the satiety threshold and above the priming/remission threshold, a range termed the compulsion zone. It has been demonstrated that dopamine receptor antagonists increase the cocaine satiety threshold, resulting in an increased rate of cocaine self-administration. Antagonists increase equiactive agonist concentrations and the agonist concentration ratio is directly proportional to the antagonist concentration. Because the satiety threshold represents an equiactive cocaine level, the time course of the change in cocaine satiety threshold from baseline should reflect the change in antagonist concentrations in the brain. Therefore, cocaine self-administration in rats can be used as a bioassay system to measure the pharmacokinetics of dopamine receptor antagonists. The absorption rate differs for a drug when injected through different routes. The time-course of the effect of a D1-like or a D2-like dopamine receptor antagonist on cocaine and apomorphine self-administration were measured after injection via intravenous (IV), subcutaneous (SC) or intraperitoneal (IP) routes. Male Sprague Dawley rats (n = 8) were trained to self-administer cocaine. Next, they self-administered either apomorphine or cocaine (unit dose of 0.15 and 3 μmol/kg respectively) on an FR1 schedule in separate sessions. In the sessions, after 120 min of stable agonist self-administration, the rats were injected with a 0.02 μmol/kg dose (IV, SC or IP) of either dopamine receptor antagonists SCH23390 or (-)Eticlopride, after which the rate of agonist self-administration increased and then gradually decreased to baseline rate. The agonist levels in the body at the time of each self-administration were calculated. The agonist levels at the time of each self-administration first increased after antagonist injection and then gradually decreased to baseline levels. The agonist dose ratios were calculated by dividing the agonist levels at the time of each self-administration post-antagonist injection by the mean baseline agonist level. These were plotted against time for each session to determine the time to maximum effect (Tmax), the magnitude of maximum effect (Cmax) and the area under the curve (AUC), a measure of the bioavailability of the antagonist. An analysis of variance test was performed for each parameter to compare the three routes of administration. Tmax was shortest for IV and longest for IP while Cmax was highest for IV and lowest for IP. AUC was similar for IV and SC, and slightly lower for IP. Therefore, despite the differences in the time course and magnitude of antagonist effect, the bioavailability of the two antagonists were similar for each route of administration. Thus, cocaine self-administration behavior in rats is useful as a pharmacological bioassay system to measure the pharmacokinetics of dopamine receptor antagonists in the brain in real time.

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