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BRIEF COMMUNICATION

Remoxipride, a Specific D_2 Dopamine Antagonist: An Examination of Its Self-Administration Liability and Its Effects on d-Amphetamine Self-Administration

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AMIT, Z. AND B. R. SMITH. *Remoxipride, a specific D_2 dopamine antagonist: An examination of its self-administration liability and its effects on d-amphetamine self-administration.* PHARMACOL BIOCHEM BEHAV **41**(1) 259–261, 1992.—The self-administration liability of remoxipride, a specific dopamine D_2 antagonist, by laboratory rats was evaluated using an intravenous self-administration paradigm. It was observed that remoxipride failed to support self-administration behavior across the three doses tested. In addition, remoxipride pretreatment attenuated d-amphetamine self-administration. The findings of the present study provide support for the notion that remoxipride appears to have functional similarity in self-administration paradigms as other D_2 antagonists.

Remoxipride Self-administration Amphetamine D_2-receptors

THE dopamine (DA) system has been implicated in the mediation of positive reinforcement in general (7, 17, 21) and the reinforcing properties of a variety of drugs in particular (1, 7, 17, 22). While there has been less then general consensus about the interpretation of data in this field (6,15), various reports implicated dopamine in the mediation of electrical self-stimulation of the brain (8,9), food reinforcement (18) and the self-administration of drugs such as amphetamine in the rat (21).

The paradigms used to study the involvement of transmitter systems in reinforcement processes were, among others, drug self-administration (4), free feeding and drinking (23) and, more recently, place preference (11, 12, 16) and conditioned taste aversion paradigms (10). Of the above, self-administration has been the most valid, reliable and problem free. In general, it has been shown that DA agonists tend to be self-administered while DA antagonists are not (22). Furthermore, DA antagonists tend to block the self-administration of DA agonists (3, 5, 22), as well as other self-administered substances (e.g., food, fluids, electrical current) usually, in a dose-dependent fashion (14, 19, 20, 23).

When one examines the available literature it seems almost self-evident that the possibility that DA antagonists may in fact be self-administered by animals is extremely low. Indeed, since just about all of these compounds were shown to clearly block the self-administration of DA agonists, it would follow logically that DA antagonists would not, in themselves, be readily self-administered. However, given the fact that the specificity of any psychoactive compound is often a subject of controversy, if not immediately then later following the accumulation of data, one cannot therefore exclude the possibility that an antagonist will be self-administered without a direct examination of this notion.

The present study was therefore designed in an attempt to examine the self-administration liability of remoxipride, a specific dopamine D_2 antagonist (13) and to examine the effect of this agent on amphetamine self-administration.

EXPERIMENT 1A

METHOD

Subjects

Subjects were male Long-Evans rats (Charles River, Canada) weighing approximately 350 g at the start of the experiment. The animals were individually housed in stainless steel cages. Food and water were available ad lib except during the testing sessions. The animal colony was regulated for constant temperature, humidity and light (12-h on/off light cycle; 0800/2000 h).

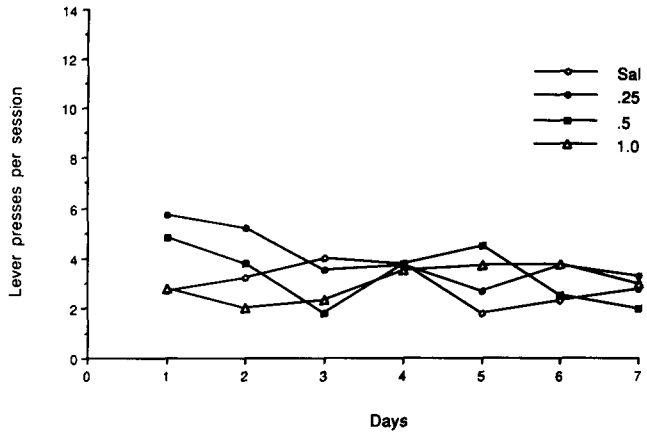

FIG. 1. The rate of lever pressing for IV infusions of remoxipride (0.25, 0.5 and 1.0 mg/infusion) and equal volumes of saline in laboratory rats in a self-administration paradigm (n = 6 per group).

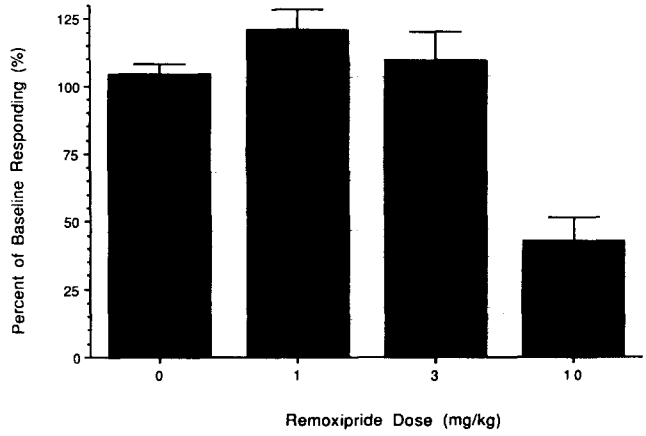

FIG. 2. The effects of remoxipride on the IV self-administration of amphetamine in laboratory rats (n = 7).

Design

After one week of habituation to the laboratory conditions, animals underwent surgery to implant a chronic indwelling catheter. The animals were first anesthetized with sodium pentobarbital (60 mg/kg). The catheter, which was constructed of sylastic tubing, was implanted in the jugular vein and threaded under the skin up to a point of exit at the top of the skull. The protruding end of the catheter was fitted with a metal tube which was secured to the skull by means of stainless steel screws and dental cement. Following a period of one week recovery from surgery, the experimental sessions began. Animals were randomly divided into one of three groups receiving remoxipride (dissolved in saline) and a saline vehicle control group. There were six animals placed into each group.

Procedure

During a period of seven days, the animals were taken daily from the colony, transported to the experimental room and placed in self-administration operant chambers (Ralph Gerbrands Co.) for a daily session of three hours. These daily sessions took place approximately between 1100–1400 h. The catheters of all animals were connected to a flow-through swivel by means of polyethylene tubing. The swivel, in turn, was connected to an infusion pump (Razel Co.) equipped with a syringe containing either one of three concentrations of remoxipride or a saline solution. Each depression of the operant lever in the self-administration chamber activated the pumps which delivered either remoxipride in a dose of 0.25 mg, 0.5 mg or 1.0 mg in a volume of 100 μl over 5 s, or saline in an equal volume. All three concentrations of remoxipride delivered a dose which was found to be within the range of DA receptor blockade in vivo (13). Each animal received one priming infusion delivered by the experimenter at the start of each session. The schedule of reinforcement was signalled continuous reinforcement with a light located in the wall above the operant lever serving as the signal. The lamp which was also activated by the depression of the lever, was illuminated only for the duration of the infusion.

Each depression of the lever was recorded on a chart recorder. The catheter assembly of each animal was flushed with saline before and after each daily session to ensure the patency of the catheter. At the end of each daily session the animals were returned to the colony room.

RESULTS

Figure 1 shows the number of lever presses per session for the three remoxipride groups and for the saline control group. There was no significant difference between the rate of lever pressing for any dose of remoxipride compared to the saline control group. A two-way ANOVA revealed no significant effect of dose, $F(3,20) = 0.239$, $p > 0.05$, no significant effect over days, $F(6,120) = 0.757$, $p > 0.05$, and there was no significant interaction of the the two main effects, $F(18,120) = 0.929$, $p > 0.05$.

EXPERIMENT 1B

METHOD

Subjects

Subjects were male Long-Evans rats (Charles River, Canada) weighing approximately 350 g at the start of the experiment. The animals were individually housed under the same conditions as above.

Design

Animals were prepared with indwelling intravenous catheters as described above. The experimental sessions began one week following recovery from surgery. Animals (n = 7) were placed in the operant chambers described above for a three-hour session once per day, every day during which they were presented with the opportunity to lever press for d-amphetamine (0.06 mg/kg/infusion).

Procedure

After the establishment of 4 days of stable amphetamine self-administration (within 8 days of initial testing), the animals were tested with remoxipride, administered 60 minutes prior to the start of each test session. Remoxipride was injected IP in increasing doses of 0 (saline vehicle), 1, 3 and 10 mg/kg. Following the administration of each individual remoxipride dose during the amphetamine self-administration session, the animals were placed in the operant chambers to self-administer amphetamine for two days without pretreatment. These intervening two days

served as the baseline of amphetamine responding for each subsequent remoxipride test session.

RESULTS

The results obtained in this experiment reveal that the animals receiving amphetamine pressed at rates significantly higher than saline controls. For the last 4 days prior to the commencement of the remoxipride test the mean rate for amphetamine responding was 37.7 ± 6.8 compared to 3.0 ± 1.5 for saline control animals.

Figure 2 shows the percent of baseline responding for animals treated with remoxipride (0, 1, 3, 10 mg/kg). There was a significant effect of remoxipride administration on responding for amphetamine, $F(3,18) = 21.89$, $p < 0.05$. Post hoc analysis (Tukey, $p < 0.05$) indicated that there was no effect of treatment with either 1.0 or 3.0 mg/kg of remoxipride on amphetamine self-administration. However, the highest dose of remoxipride (10 mg/kg) resulted in a significant decrease in responding for amphetamine.

GENERAL DISCUSSION

The results obtained in Experiment 1A are consistent with what would be expected on the basis of the available data in this field. The failure of remoxipride to support self-administration suggests that its behavioral effects appear to be similar to other known D_2 antagonists. Experiment 1B was conducted as a further check on the functional similarity between remoxipride and other D_2 antagonists. DA antagonists were repeatedly shown to block the self-administration of DA agonists (5, 6, 22). Furthermore, it has been suggested that this blocking action is mediated by the antagonism of D_2 receptors (2). The present findings indicate that remoxipride, a D_2 antagonist, has functional similarities when examined in a self-administration paradigm to other dopamine D_2 receptor antagonists.

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