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Effects of the Atypical Antipsychotic Remoxipride on Alcohol Self-Administration

FORREST J. FILES, CHARLES E. DENNING AND HERMAN H. SAMSON

Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC 27157-1083

FILES, F. J., C. E. DENNING AND H. H. SAMSON. *Effects of the atypical antipsychotic remoxipride on alcohol self-administration*. PHARMACOL BIOCHEM BEHAV **59**(2) 281–285, 1998.—Remoxipride is a dopamine (DA) D_2 antagonist that produces fewer of the side effects normally associated with chronic DA antagonist administration. It has been demonstrated that DA antagonists can reduce the desire for a second drink in alcoholics. However, because of the usual side effects associated with DA antagonist administration, chronic use as an adjunct to alcoholism treatment has not been considered. Because the DA D_2 antagonist haloperidol reduces ethanol self-administration in an operant animal model of ethanol self-administration, this study was designed to determine whether remoxipride would produce similar results. Six Long–Evans rats were initiated to self-administer ethanol in daily 30-min operant sessions using a sucrose-substitution procedure. Following establishment of ethanol-reinforced lever pressing, remoxipride (0.5, 1.0, 5.0, or 10.0 mg/kg) or haloperidol (0.01, 0.05, or 0.1 mg/kg) were injected 30 min prior to the sessions. Remoxipride produced an approximate 50% reduction in the number of ethanol presentations per session at the highest dose tested (10.0 mg/kg) and did so by terminating the ethanol-drinking bout earlier in the session. Haloperidol also decreased ethanol presentations with the highest dose tested (0.1 mg/kg) producing the largest effect. These data indicate that remoxipride produces reductions in ethanol-reinforced responding similar to those observed with another DA antagonist. Because remoxipride produces fewer of the side effects commonly observed with chronic DA antagonist administration, it could prove to be a useful adjunct in the treatment of excessive alcohol consumption. © 1998 Elsevier Science Inc.

Alcohol self-administration Dopamine antagonists Remoxipride Rats

RESEARCH continues towards the development of new pharmacological adjuncts for alcoholism treatment despite the recently reported success of the use of the opiate antagonist naltrexone (13). This continued exploration of potential pharmacotherapies is required because naltrexone treatment appears to be maximally effective with only a subset of alcoholics (23). Therefore, although there are extensive preclinical studies using opiate antagonists to support the clinical use of naltrexone [see (21) for a review], drugs that interact with other neurotransmitter systems known to be involved in ethanol self-administration remain of interest. Serotonin reuptake inhibitors (e.g., fluoxetine) have been shown to reduce alcohol intake in rats and to reduce desire to drink and liking for alcohol in alcoholics [see (11) for a review]. Neuroleptic dopaminergic drugs have also been shown to alter both ethanol (18) and cocaine self-administration (5). Modell et al. (9) reported that the dopamine (DA) D_2 antagonist haloperidol, given acutely, decreased craving for alcohol significantly in patients characterized as alcohol dependent or as alcohol abusers. However, because of problems associated with prolonged, chronic treatment with DA antagonists (i.e., extrapyramidal side effects), the use of these drugs for alcohol abuse treatment has not been considered practical.

The effects of dopaminergic drugs on oral ethanol consumption by laboratory animals have been investigated by a number of researchers. Pfeffer and Samson (14,15) found that the systemic administration of DA D_2 antagonist pimozide reduced home-cage ethanol drinking (10% v/v) dose dependently and reduced lever pressing maintained by presentation of a 10% (v/v) ethanol solution in animals that were not food restricted. Likewise, haloperidol, also a DA D_2 antagonist, has been shown to reduce ethanol-reinforced responding (16). Related findings have been reported using the DA D_2 agonist bromocriptine (10,22). Some investigators have failed to find an effect on ethanol consumption by DA antagonists, however (2,7). Although it is unclear as to the nature of these inconsistent findings, differences in the methodologies employed to test the effectiveness of DA antagonists on ethanol self-administration are likely a main source of variability.

The present study was designed to investigate the effects of the atypical antipsychotic drug remoxipride on ethanol self-administration in animals that were neither food nor water re-

Requests for reprints should be addressed to Forrest J. Files, Ph.D., Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157-1083.

stricted. Remoxipride is a DA D_2 antagonist with a high affinity for DA receptors in mesolimbic regions of the brain and lower affinity for DA receptors in striatial areas (25). It has a low affinity for D_1, D_3, and D_4 receptors. However, remoxipride shows reduced occupancy of D_2 receptors compared to haloperidol and raclopride, suggesting that it acts primarily on a subpopulation of D_2 receptors (12). As a consequence, this drug has been found to result in fewer side effects produced by chronic administration in psychiatric patients (3,6). Also, it has been suggested that this drug could be beneficial in the treatment of cocaine addition (1). If remoxipride can reduce ethanol self-administration in animals, given the lower risk of producing side effects during chronic administration, it may prove to be a beneficial adjunct in the treatment of some types of alcohol abuse and alcoholism.

METHOD

Animals

Six experimentally naive, male Long–Evans rats were used. The animals weighed between 203 and 238 g upon arrival in the laboratory and were housed individually in stainless steel hanging cages with ad lib food and water except as noted below. The animal colony was maintained on a 12 h on/12 h off light/dark cycle. All animals were treated in accordance with the guidelines set forth by the NIH.

Apparatus

Experimental sessions were conducted in Plexiglas and stainless steel operant conditioning chambers, each containing two response levers and two liquid delivery systems (dippers). Each chamber was housed in a sound-attenuating cubicle that had a ventilation fan that also provided masking noise. Sessions were controlled and monitored by a microcomputer operating under MED Associates software (MED Associates, St. Albans, VT).

Drugs

Remoxipride hydrochloride (Astra) was dissolved in 0.9% saline and administered IP 30 min before experimental sessions. Haloperidol was dissolved in 1–2 drops of concentrated hydrochloric acid and diluted in 3.0% phosphate buffer solution (PBS; pH = 7.2) to a total volume of 6 ml. Solutions were made just prior to daily sessions. All injections were administered by the IP route.

Procedure

Following adaptation to individual housing, a two-bottle home-cage preference test was conducted. This procedure has been described in detail previously (17). The animals were next restricted to 30-min access to tap water per day in their home cages and trained to approach and drink a 20% (w/v) sucrose solution from the dipper in the operant chambers. Next, the animals were placed in the operant chamber overnight with 20% sucrose in the dipper and the dipper was programed to operate following one lever press (Fixed Ratio or FR1). Following three overnight sessions, all animals were reliably pressing the lever and consuming the sucrose solution from the dipper. Daily 30 min sessions were then begun. During these sessions, responses were reinforced under the FR1 contingency with the 20% sucrose solution for one session. The sucrose solution was then reduced to 10%. Water restriction was discontinued following six 30-min sessions. The sucrose-substitution initiation procedure (17) was begun by adding 2% (v/v) ethanol to the 10% sucrose solution. For the next 12 sessions, ethanol was gradually increased in concentration as sucrose was reduced in concentration until 10% ethanol alone functioned as the reinforcer for lever pressing. The response requirement for ethanol reinforcement was then increased over five sessions to FR4. Following five sessions of 10% ethanol reinforcement under the FR4 reinforcement schedule, the concentration of ethanol presented was increased to 15, 20, and 30% for five sessions each. The ethanol solution was then returned to 10% for 16 sessions. Sessions were 30 min long and conducted once per day, 5 days per week. This initiation procedure has been described in detail elsewhere (17). All drug testing was conducted using 10% ethanol as the reinforcement solution.

To adapt the animals to the injection procedure, saline was injected (IP) before daily sessions twice a week on successive days for 2 weeks. Saline was then administered the session before each drug-administration session for the remainder of the experiment. Remoxipride or haloperidol was administered once per week in the session following the vehicle injection session. Thus, on the sessions occurring on Monday, Tuesday, and Friday, the rats received no injections, while on Wednesday and Thursday they received the drug vehicle and the drug injection, respectively. The day before vehicle injections (i.e., Tuesday) was used for no-injection control comparisons. The dose range of remoxipride tested was 0.5, 1.0 , 5.0, and 10.0 mg/kg. The choice of these doses was based on the range of doses used in previous studies on the behavioral effects of remoxipride [e.g., (2,18)]. Each dose of remoxipride was tested twice except for 0.5 mg/kg, which was tested three times. The order of dose testing was 0.5 mg/kg three times, 1.0 mg/kg, 5.0 mg/kg, 10.0 mg/kg twice, 5.0 mg/kg, and finally 1.0 mg/kg. Haloperidol was administered in doses of 0.01, 0.05, and 0.1 mg/kg with the 0.01 and 0.1 mg/kg doses tested once each and the 0.05 mg/kg dose tested twice. The order of doses was 0.01 mg/kg, 0.05 mg/kg twice, and finally 0.1 mg/kg. All animals received all doses of both drugs.

RESULTS

Remoxipride had little effect on ethanol-reinforced responding except at the highest dose (10.0 mg/kg; Fig. 1, top). Two-way repeated-measures ANOVA between vehicle and drug sessions revealed that there were significant main effects of injection type [vehicle vs. drug; $F(1, 5) = 17.4$, $p = 0.0087$] and of dose, $F(8, 40) = 2.23$, $p = 0.045$. Multiple pairwise comparisons (Bonferonni t) showed that the 0.5 mg/kg dose differed significantly from the 10.0 mg/kg dose ($p < 0.05$). There was no significant interaction between injection and dose. There was also no significant difference between control and vehicle-injection sessions on number of responses.

Remoxipride also had little effect on alcohol intake (g/kg) except at the highest dose (Fig. 1, bottom). Two-way repeated-measures ANOVA showed that there was a main effect of injection type [vehicle vs. drug; $F(1, 5) = 13.89$, $p = 0.0136$]. There was no significant main effect of dose on alcohol intake, and there was no significant interaction between injection type and dose. There were no significant differences on alcohol intake between control sessions and vehicle-injection sessions.

Haloperidol produced decreases in responding at the 0.05 and 1.0 mg/kg doses (Fig. 1, top). Two-way repeated-measures ANOVA revealed that there was a significant main effect of injection type [vehicle vs. drug; $F(1, 5) = 23.01$, $p =$

0.0049] but not of dose. There was no significant interaction between injection type and dose, and there was no significant difference between control and vehicle-injection sessions.

Alcohol intake (g/kg) was reduced by haloperidol at the two higher doses (Fig. 1, bottom). Two-way repeated-measures ANOVA showed that there was a significant main effect of injection type [vehicle vs. drug; $F(1, 5) = 12.15$, $p = 0.0175$] but not of dose. There was no significant interaction between injection type and dose, and there was no significant difference between control and vehicle-injection sessions.

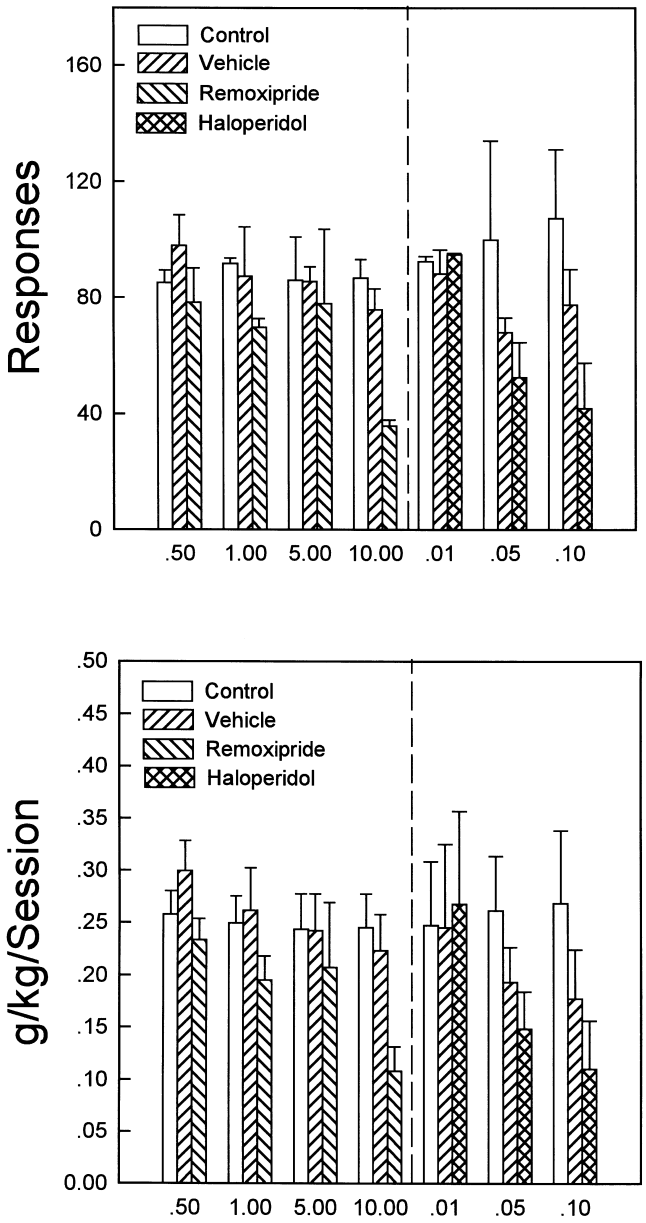

FIG. 1. Mean dose effects of remoxipride (left) and haloperidol (right) on responding maintained by alcohol reinforcement (top) and alcohol intake (g/kg, bottom). Data presented are means from all administrations of all doses. See text for procedural details. Bars represent SEM.

Representative cumulative response records show that patterns of responding following injection of the drug vehicle were similar to those observed under baseline conditions following sucrose-substitution initiation (Fig. 2, top). These cumulative records were taken from an animal whose session performance most closely resembled the group mean. All animals showed similar patterns of responding. Following injection of 10.0 mg/kg remoxipride, responding during the first minute of the session was unchanged (Fig. 2, bottom left). Responding then terminated and only a few responses occurred later in the session. When 0.05 mg/kg haloperidol was administered, responding was reduced during the first 3 min of the session and fewer responses occurred during the session (Fig. 2, bottom right).

DISCUSSION

Remoxipride reduced voluntary ethanol consumption to levels observed previously following administration of other DA antagonists (14–16). These data support other research implicating the involvement of the dopaminergic system in ethanol self-administration (8,24). The change in the patterns of responding observed following administration of remoxipride was similar to that occurring following administration of haloperidol (16) and other DA antagonists (14,15). This change consisted of a normal onset and rate of self-administration followed by termination of self-administration that occurred earlier than during vehicle sessions. Thus, remoxipride's primary action, like other DA antagonists, was to reduce the duration of ethanol self-administration with little apparent effect on initial responding.

This effect is consistent with data reported by Modell et al. (9) in that alcoholics, following the administration of haloperidol, reported less desire for a second alcoholic drink after having had a priming alcoholic beverage. It was hypothesized that haloperidol may have reduced the reinforcing effects of the initial drink (9). Given the changes in pattern of self-administration observed in the present study and the reported human data, it is possible that the decrease in the duration of self-administration could reflect a change in the reinforcing efficacy of ethanol following administration of remoxipride.

Neuroleptic drugs such as remoxipride and haloperidol have been shown previously to produce response decrements in operant performance of food-restricted rats. For example, Sanger and Perrault (19) compared the effects of nine antipsychotic drugs on responding under an FR10 schedule of reinforcement. They found that only remoxipride and haloperidol produced within-session response decrements. However, with remoxipride, Sanger and Perrault found that some responding continued to occur for the entire duration of the 15-min experimental session at all doses tested (0.5, 0.1, and 2.0 mg/kg). Furthermore, with haloperidol they found that the response decrement was first observed at 0.2 mg/kg and that responding ceased completely halfway through the session only after the highest dose was administered (0.3 mg/kg). In the present study, however, haloperidol produced the cessation of responding at 0.1 mg/kg, suggesting that the effect observed in the present study may not be due merely to a motor deficit but rather may be specific to the type of reinforcer used. Remoxipride, on the other hand, reduced responding only at a dose five times higher than the largest dose used by Sanger and Perrault (19). If the response decrement observed by Sanger and Perrault was due to a motor deficit, then a decrease in responding would have been expected at a lower dose in the present study. This, again, suggests that an interac-

tion between the type of reinforcer used and the drug may influence the extent to which response decrements are observed. However, it is important to note that with alcohol reinforcement, high rates of responding are usually observed only at the beginning of sessions under baseline conditions. These data suggest that the type of reinforcer used (drug vs. nondrug) and the presence or absence of food restriction are important considerations when studying the effects of neuroleptic drugs on operant responding.

Data showing that dopamine antagonists produce patterns of responding consistent with a reduction in reward magnitude when motor confounds are controlled have been reported previously (4). Because responding at the beginning of remoxipride sessions was similar to that observed in the absence of the drug, the present data do not support the notion that remoxipride reduced "ethanol-seeking" behavior at the beginning of experimental sessions. Although defining "craving" for ethanol in an animal model is problematic, the lack of effect of DA antagonists on the onset of ethanol self-administration suggests that these drugs will not be effective in treatment of initial ethanol "seeking." Rather, these drugs may be potentially valuable for altering the number of drinks consumed once drinking is begun. If it is the case that haloperidol and remoxipride reduce the reinforcing efficacy of ethanol, then it is possible that over drinking episodes where less ethanol is consumed, "craving" might be reduced as well. Whether craving is in any way related to repeated exposure to the reinforcing effects of alcohol is a topic for future research. How-

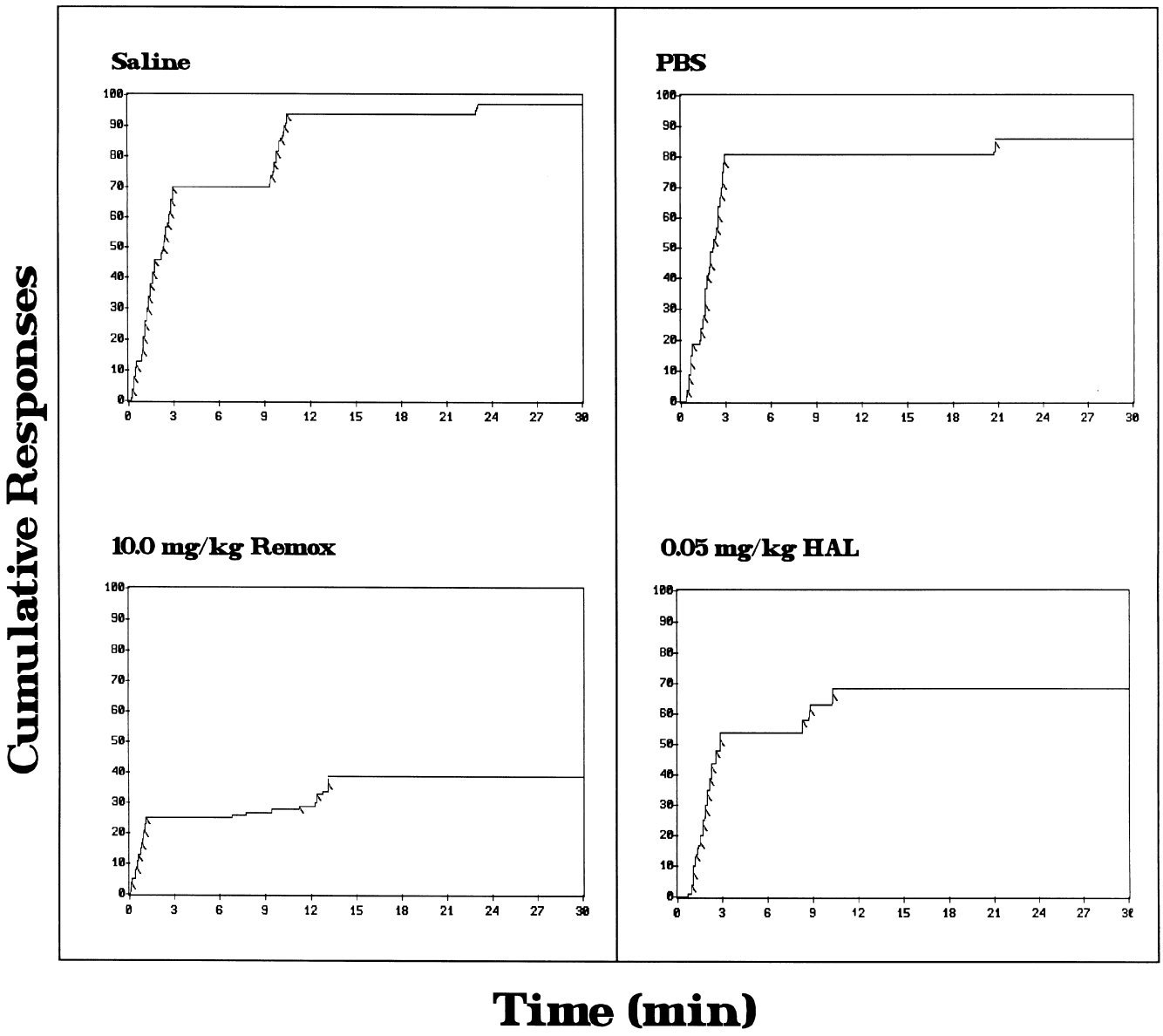

FIG. 2. Representative cumulative response records from sessions before which saline, 10.0 mg/kg remoxipride, PBS (phosphate buffer solution) or 0.05 mg/kg haloperidol were administered. Time (minutes) is on the x-axis and cumulative responses are on the y-axis. Cross marks on the records indicate reinforcement presentations.

ever, if they are related, then administration of a drug that reduces the reinforcing efficacy of ethanol might result in the "extinction" of craving.

The known involvement of other neurotransmitter systems (e.g., opioidergic and serotonergic systems) in the regulation of excessive alcohol consumption suggests that the administration of DA antagonists will not be the only effective adjunct for treatment of alcoholics. However, as the interactions between the opioidergic and dopaminergic systems become more fully understood (22), it is possible that a combination of drug treatments could prove to be of value in reducing excessive alcohol consumption in a larger subset of problem drinkers. Thus, DA antagonists, such as remoxipride, may add to the armamentarium of treatment options available.

In summary, 10.0 mg/kg remoxipride reduced alcohol intake by approximately 50% in this operant self-administration model. This model was also predictive of the treatment potential of naltrexone (20). Given the reduced level of side effects associated with chronic remoxipride administration in humans compared to haloperidol, it would appear that remoxipride might have clinical value in the treatment of alcoholism as an adjunct to those treatments currently in use.

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REFERENCES

1. Bourland, J. A.; French, E. D.: Effects of remoxipride, an atypical antipsychotic, on cocaine self-administration in the rat using fixed- and progressive-ratio schedules of reinforcement. Drug Alcohol Depend. 40:111–114; 1995.
2. Brown, Z. W.; Gill, K.; Abitbol, M.; Amit, Z.: Lack of effect of dopamine blockade on voluntary ethanol consumption in rats. Behav. Neurol. Biol. 36:291–294; 1982.
3. Eriksson, K.: Remoxipride in the treatment of psychosis. Prog. Neuropsychol. Biol. Psychiatry 18:619–623; 1994.
4. Ettenberg, A.: Dopamine, neuroleptics and reinforced behavior. Neurosci. Biobehav. Rev. 13:105–111; 1989.
5. Hubner, C. B.; Moreton, J. E.: Effects of selective D_1 and D_2 dopamine antagonists on cocaine self-administration in the rat. Psychopharmacology (Berlin) 105:151–156; 1991.
6. Keks, N.; McGrath, J.; Lambert, T.; Catts, S.; Vaddadi, K.; Burrows, G.; Varghese, F.; George, T.; Hustig, H.; Burnett P.; et al.: The Australian multicentre double-blind comparative study of remoxipride and thioridazine in schizophrenia. Acta Psychiatr. Scand. 90:358–365; 1994.
7. Linseman, M. A.: Effects of dopaminergic agents on alcohol consumption by rats in a limited access paradigm. Psychopharmacology (Berlin) 15:195–200; 1990.
8. McBride, W. J.; Murphy, J. M.; Lumeng, L.; Li, T.-K.: Serotonin, dopamine and GABA involvement in alcohol drinking of selectively bred rats. Alcohol 7:199–205; 1990.
9. Modell, J. G.; Mountz, J. M.; Glaser, F. B.; Lee, J. Y.: Effects of haloperidol on measures of craving and impaired control in alcoholic subjects. Alcohol. Clin. Exp. Res. 17:234–240; 1993.
10. Nadal, R.; Prat, G.; Pallares, M.; Hernandez-Torres, M.; Ferre, N.: Effects of bromocriptine on self-administration of sweetened ethanol solutions in rats. Psychopharmacology (Berlin) 128:45–53; 1996.
11. Naranjo, C. A.; Bremner, K. E.: Serotonin-altering medications and desire, consumption and effects of alcohol-treatment implications. EXS 71:209–219; 1994.
12. Ögren, S. O.; Rosén, L.; Fuxe, K.: The dopamine D_2 antagonist remoxipride acts in vivo on a subpopulation of dopamine D_2 receptors. Neuroscience 61:269–283, 1994.
13. O'Malley, S. S.; Jaffe, A. J.; Chang, G.; Schottenfeld, R. S.; Meyer, R. E.; Rounsaville, B.: Naltrexone and coping skills therapy for alcohol dependence: A controlled study. Arch. Gen. Psychiatry 49:881–887; 1992.
14. Pfeffer, A. O.; Samson, H. H.: Oral ethanol reinforcement: Interactive effects of amphetamine, pimozide and food-restriction. Alcohol Drug Res. 6:37–48; 1985.
15. Pfeffer, A. O.; Samson, H. H.: Effects of pimozide on home cage ethanol drinking in the rat: Dependence on drinking session length. Drug Alcohol Depend. 17:47–55; 1986.
16. Pfeffer, A. O.; Samson, H. H.: Haloperidol and apomorphine effects on ethanol reinforcement in free feeding rats. Pharmacol. Biochem. Behav. 29:343–350; 1988.
17. Samson, H. H.: Initiation of ethanol reinforcement using a sucrose-substitution procedure in food- and water-sated rats. Alcohol. Clin. Exp. Res. 10:436–442; 1986.
18. Samson, H. H.; Hodge, C. W.: Neurobehavioral regulation of ethanol intake. In: Dietrich, R. A.; Erwin, V. G., eds. Pharmacological effects of ethanol on the nervous system. New York: CRC Press; 1996:203–226.
19. Sanger, D. J.; Perrault, G.: Effects of typical and atypical antipsychotic drugs on response decrement patterns in rats. J. Pharmacol. Exp. Ther. 272:708–713.
20. Schwarz-Stevens, K. S.; Files, F. J.; Samson, H. H.: Effects of morphine and naloxone on ethanol- and sucrose-reinforced responding in nondeprived rats. Alcohol. Clin. Exp. Res. 16:822–832; 1992.
21. Sinclair, J. D.: The feasibility of effective psychopharmacological treatments for alcoholism. Br. J. Addict. 82:1213–1223; 1987.
22. Stinus, L.; Cador, M.; LeMoal, M.: Interaction between endogenous opioids and dopamine within the nucleus accumbens. Ann. NY. Acad Sci. 654:254–273; 1992.
23. Volpicelli, J. R.; Alterman, A. L.; Hayashida, M.; O'Brien, C. P.: Naltrexone in the treatment of alcohol dependence. Arch. Gen. Psychiatry 49:876–880; 1992.
24. Weiss, F.; Mitchiner, M.; Bloom, F. E.; Koob, G. F.: Free-choice responding for ethanol vs. water in alcohol preferring (P) and unselected Wistar rats is differentially modified by naloxone, bromocriptine, and methysergide. Psychopharmacology (Berlin) 101:178–186; 1990.
25. Westlind-Danielsson, A.; Gustafsson, K.; Andersson, I.: Remoxipride shows low propensity to block functional striatal dopamine D_2 receptors in vitro. Eur. J. Pharmacol. 288:89–95; 1994.