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Differential Attenuation of Water Intake and Water-Rewarded Operant Responding by Repeated Administration of Haloperidol and SCH 23390 in the Rat

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LJUNGBERG, T. *Differential attenuation of water intake and water-rewarded operant responding by repeated administration of haloperidol and SCH 23390 in the rat.* PHARMACOL BIOCHEM BEHAV **35**(1) 111–115, 1990.—It has previously been described that water intake in thirsty rats require higher doses of dopamine (DA) D-1 and D-2 antagonists to be attenuated than operant lever-pressing with water as reward. In the present study, effects of repeated administration of the DA D-1 antagonist SCH 23390 and the DA D-2 antagonist haloperidol were investigated in the same experimental paradigm. In agreement with previous reports, attenuation of operant responding increased progressively by haloperidol (0.05 mg/kg) given for four consecutive days. However, this attenuation was not accompanied by decreased water intake, tested for in parallel experiments. After haloperidol (0.2 mg/kg), in contrast, a progressively decreasing attenuation of water intake was found. After SCH 23390, both the initial attenuation of lever-pressing (0.02 mg/kg) and consummatory water intake (0.1 mg/kg) became less pronounced over time. The results thus show that: 1) the previously reported progressively increasing attentuation of operant responding caused by repeated administration of D-2 antagonists is not mimicked by the D-1 antagonist SCH 23390, and 2) attenuation of water intake caused by higher doses of neuroleptics is, in direct opposition, less pronounced after repeated administrations. The results also show that attenuation of operant responding by neuroleptics cannot solely be dependent upon a blunting of the impact of the reward.

Dopamine Operant responding Water intake Neuroleptics Haloperidol SCH 23390 Repeated administrations

ANTIPSYCHOTIC drugs are thought to exert their therapeutic effect via blockade of dopamine (DA) receptors in the brain (3,27). Apart from their beneficial antipsychotic effect, DA receptor-blocking drugs also cause unwanted extrapyramidal side-effects, like acute dystonia and parkinsonism (3,7). The clinical effects of DA receptor-blocking drugs were previously considered to be related to blockade of DA receptors not stimulating production of cAMP, i.e., the DA D-2 receptor (9, 24, 25, 28). However, with the development of a selective DA D-1 antagonist—SCH 23390 (17)—this notion has been questioned. SCH 23390 has, for example, been found to 1) produce catalepsy and to 2) antagonise stereotyped behavior induced by DA agonist in rodents, two animal models believed to reflect extrapyramidal side-effects in the clinic (9,17). SCH 23390 has, furthermore, been found to induce acute dystonia in primates (9, 13, 15).

In laboratory animals, it is well known that dopamine D-2 antagonists attenuate various learned responses, like the conditioned avoidance response (CAR), operant lever-pressing with food or water as rewards or intracranial self-stimulation (1, 4, 30). The exact mechanism behind this effect is, however, not known and several theories have been put forward as explanations [see (4, 12, 30)]. Supporting the "anhedonia hypothesis" (30), are findings showing that animals tested with repeated administrations of D-2 antagonists in operant settings show a pattern of decreased responding from trial to trial that have been considered to resemble extinction (4,30).

In recent papers (20–22) the development of a new behavioral-pharmacological paradigm has been described in which effects of DA antagonists on water-rewarded operant lever-pressing and on the corresponding consummatory act, i.e., nonconditioned water intake, can be studied in parallel. We have found that operant lever-pressing is more potently attenuated both by DA D-1 and D-2 antagonists than water intake itself (20,22). This is in the same fashion as the conditioned avoidance response is more potently antagonised than the escape reaction by both DA D-1 and D-2 antagonists (1, 9, 17).

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In the present study we have investigated the effects of repeated administration of the DA D-1 antagonist SCH 23390 (9,17) and the D-2 antagonist haloperidol (24) in the same experimental paradigm. The doses tested of SCH 23390 and haloperidol were selected from our previous studies (20,22). Of special interest was 1) to compare the effects of repeated administrations on the operant responding and the consummatory water intake, and 2) to compare the effects of D-1 and D-2 antagonists.

METHOD

Animals

The experiment was performed on 34 male Sprague-Dawley rats (ALAB, Sollentuna) which arrived at the animal colony at least 1 week prior to the start of the experiments. During the experiments, the animals were housed under conditions of controlled temperature and humidity on a 12-hr light/12-hr dark schedule (7 a.m.–7 p.m.) with lab chow ad lib. The weights of the animals were between 220–250 g and each animal was used in only one experiment.

Apparatus

Water intake and the ability to press the lever were tested in slightly modified Skinner boxes (length = 32 cm, width = 20 cm, height = 20 cm). All boxes were placed inside sound-protecting boxes equipped with one-way observation windows. Electric fans ventilated the boxes and provided a constant background noise.

In the boxes where water intake was tested, the levers and the dipper mechanisms were removed and water nipples, connected to a small water container, were mounted in place of the dipper cups. The animal thus only needed to lick the nipple to obtain water, not to perform or learn any operant response. The water consumed at 20 and 45 minutes after the start of the experiment was registered.

To test the ability to lever-press, a specially developed lever was used which was fitted beside the dipper cup. The lever resembled a "mill-wheel." Its four wings were 4 cm long and 3 cm wide and made out of 5 mm black plastic. One-quarter of a turn, which was signalled to the animal as a distinct click and as a sudden and transient drop in resistance, was defined as one lever press. The weight necessary to turn the lever was set to 20 g (23). A dipper of standard type, operated by a solenoid, delivered 0.05 ml every time it was activated (in this experiment after each lever-press). The accumulated number of lever-presses after 20 and 45 minutes was registered.

Experimental Procedure

The animals were kept individually in ordinary laboratory cages. Except for receiving water in the 45-min long daily experimental session, the animals also had access to water in the home cages for 15 minutes, 1 hour after the end of the test session. Each experiment extended over a two-week period and the animals were their own controls. After an initial day of learning to operate the lever, the animals were allowed 4 days of training. The total amount of water consumed and the total number of lever-presses performed in the last day of the training period (i.e., the results from day 5) were used as a control value for each animal (called "control end value"). During the following two days the animals had free access to water. The animals were allowed one day after the weekend to regain performance and the drugs were then administered from day 9 to day 12. The animals tested for water intake were run in parallel with the animals tested for lever-pressing.

Presentation of the Results and Statistics

To graphically present the drug effects, the change in response after each drug injection, expressed as a percentage of the "control end value," was calculated for every animal. The group mean and S.E.M. was then calculated for each day. To calculate significance, one-way analysis of variance for repeated measures followed by Dunnett's test was used. All comparisons were made against the control day and $p<0.01$ was considered as significant.

Drug Treatments

Haloperidol (Janssen Pharmaceutica, Belgium) was dissolved in 1% lactic acid and SCH 23390 (Schering Plough Co., USA) was dissolved in saline. The injection volume was 1 ml/kg and the injections were given subcutaneously in the flank 30 minutes before the start of the experiments. The doses refer to the above mentioned forms.

RESULTS

As control performance (shown as 100% in Figs. 1 and 2) the mean total number of lever-presses during a session was 312 ± 27 ($n = 7$) for the haloperidol group and 362 ± 22 ($n = 7$) for the SCH 23390 group ($p>0.05$, Student's t-test). The mean total amount of water consumed was 11.6 ± 0.6 ml ($n = 7$) for the haloperidol 0.2 mg/kg group, 12.7 ± 0.7 ml ($n = 6$) for the haloperidol 0.05; mg/kg group, and 13.6 ± 0.9 ($n = 7$) for the SCH 23390 group ($p>0.05$, one-way analysis of variance). Thus, no significant differences existed in the control performance between the different groups used.

Haloperidol

Overall treatment effects were found for haloperidol 0.05 mg/kg on the lever-pressing [0–20 min: $F(4,30) = 29.3$, $p<0.0001$ and 0–45 min: $F(4,30) = 13.1$, $p<0.0001$] and for haloperidol 0.2 mg/kg on the water intake [0–20 min: $F(4,30) = 12.0$, $p<0.0001$ and 0–45 min: $F(4,30) = 8.9$, $p<0.001$]. The lever-pressing response in animals treated repetitively with haloperidol 0.05 mg/kg ($n = 7$) was more attenuated at the end of the four-day treatment period than in the beginning. This was especially seen during the first parts of the sessions (see Fig. 1). The water intake in animals treated repetitively with haloperidol 0.2 mg/kg ($n = 7$) showed a somewhat different pattern. The main attenuation was found in the beginning of the four-day treatment period, with a reduced attenuation at the end.

If haloperidol 0.05 mg/kg ($n = 6$) was given repetitively to animals tested for only water intake, no significant effects on the water intake were seen [0–20 min: $F(4,25) = 1.64$, n.s. and 0–45 min: $F(4,25) = 1.54$, n.s.].

SCH 23390

Overall treatment effects were found for SCH 23390 0.02 mg/kg on the lever-pressing 0–20 min, $F(4,30) = 4.6$, $p<0.01$, and for SCH 23390 0.1 mg/kg on the water intake [0–20 min: $F(4,30) = 11.8$, $p<0.0001$ and 0–45 min: $F(4,30) = 11.5$, $p<0.0001$]. No overall treatment effect was found for SCH 23390 0.02 mg/kg on the lever-pressing 0–45 min, $F(4,30) = 2.2$, n.s. The pattern was different from that of haloperidol. For both the lever-pressing and the water intake the most pronounced attenuation was seen in the beginning of the four-days treatment period (see Fig. 2).

DISCUSSION

In agreement with previous reports [see (4,30)], it was found that a DA D-2 antagonist (in this case haloperidol 0.05 mg/kg) can

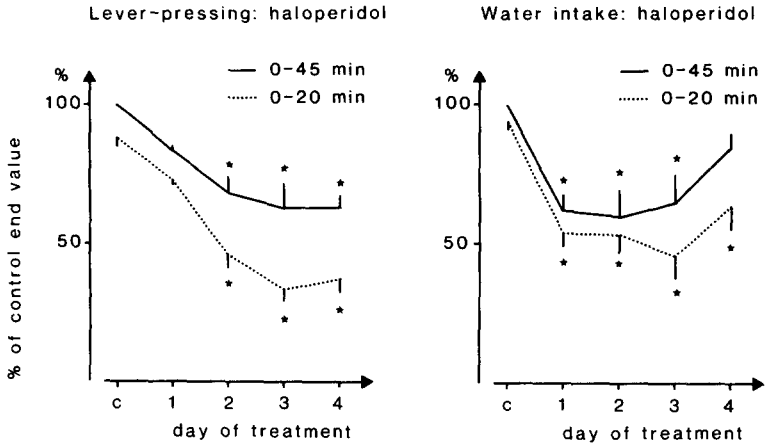

FIG. 1. Effects of repetitive haloperidol on lever-pressing (0.05 mg/kg; n = 7) and water intake (0.2 mg/kg; n = 7). The animals are their own controls and the data is presented as mean ± S.E.M. (*$p<0.01$; Dunnett's test). Haloperidol was administered 30 minutes before the start of the experiments.

cause a more pronounced attenuation of operant responding after repetitive administrations. However, the attenuation of drinking itself, caused by a higher dose of haloperidol (0.2 mg/kg), was not more pronounced by repetitive administrations. On the contrary, it was less pronounced (see Fig. 1).

We further found that repetitive administration of haloperidol 0.05 mg/kg to animals only drinking did not cause any significant change in water consumption. This result argues against the notion that the more pronounced attenuation of lever-pressing obtained by repetitive administration of haloperidol 0.05 mg/kg is only caused by an accumulation of haloperidol. If this was the case, a decreased water intake would have been expected [c.f. (20)]. The more pronounced attenuation of operant responding over days is, therefore, not paralleled by a simple blunting of the reactivity of the animals towards the water. After the same treatment of haloperidol, they still drank normal amounts of water and perfectly compensated for their water losses.

Our interpretation of this finding is that the more pronounced attenuation of operant responding seen after repeated administration of DA D-2 antagonists cannot primarily be seen as an extinction due to a diminished ability to react towards the reward. Instead, we see the increased attenuation as being caused by some other form of successively developing type of disturbance (see below). The finding that the response was more severely attenuated in the beginning of the sessions (not in the end as would be hypothesised if extinction was the case) further supports this view [see Fig. 1 and c.f. (20)].

From clinical experience it is known that parkinsonism induced by DA D-2 antagonists does not appear as an immediate extrapyramidal side-effect. Usually it takes several days or weeks to develop, a considerable time after receptor blockade has been established (3,7). It has also been found that in monkeys treated repetitively with the DA D-2 antagonists haloperidol more pronounced extrapyramidal, parkinsonian-like, motor disturbances

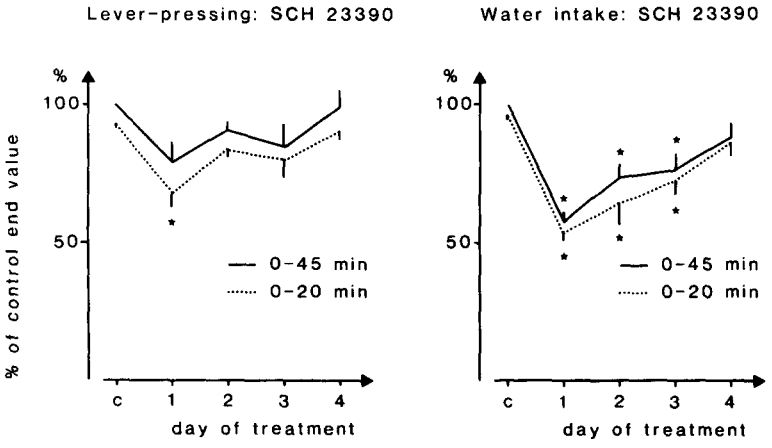

FIG. 2. Effects of repetitive SCH 23390 on lever-pressing (0.02 mg/kg; n = 7) and water intake (0.1 mg/kg; n = 7). The animals are their own controls and the data is presented as mean ± S.E.M. (*$p<0.01$; Dunnett's test). SCH 23390 was administered 30 minutes before the start of the experiments.

are developed over time (6). Thus, a similar phenomenon, with an increasing degree of disability over time, can also be found in other situations where D-2 antagonists are given repetitively.

It has previously been reported that the selective DA D-1 antagonist SCH 23390 attenuates conditioned avoidance responding and operant lever-pressing with positive reinforcers. In higher doses, SCH 23390 also attenuates the escape reaction and the nonconditioned food and water intake (9, 17, 19, 22). This profile of acute effects is, therefore, very similar to that of the DA D-2 antagonist haloperidol [see, e.g., (1, 9, 20, 22)].

However, after repeated administration, haloperidol and SCH 23390 produced very different results. Instead of a more pronounced attenuation of lever-pressing over time, as with haloperidol, SCH 23390 produced a less pronounced attenuation over days (see Fig. 2). This finding is surprising and shows that the effects of repeated administrations of neuroleptics on operant responding is dependent upon which of the DA receptor being blocked. The attenuation of water intake caused by SCH 23390 was less pronounced over days, in this case, the same as with haloperidol (c.f. Figs. 1 and 2). Acute administration of SCH 23390 to monkeys has been found to induce acute extrapyramidal motor disturbances (9, 13, 15). In agreement with our results, these effects have been reported to be diminished after repetitive administration (13,15).

It has previously been found that chronic administration of SCH 23390 and haloperidol cause a selective upregulation of DA D-1 and D-2 receptors respectively [see, e.g., (2)]. Such compensatory changes might underly our behavioral findings with less pronounced attentuation after repeated administration. However, the increased attenuation of the operant responding caused by repeated administration of haloperidol is difficult to explain with such a mechanism.

It has also previously been found that chronic administration of DA D-2 antagonists can reduce the number of spontaneously active DA cells due to development of depolarisation block (8,29). It has, furthermore, been suggested that development of depolarisation block in DA cells might be related to the more long-term clinical effects of DA antagonists (5). One possible mechanism for the progressively increasing attenuation of operant responding after repeated haloperidol could therefore be a developing depolarisation block. If so, one would hypothesise on the basis of our results, that the selective D-1 antagonist SCH 23390 should have a lesser tendency to induce a depolarisation block.

This suggestion is supported by two previous reports showing that chronic SCH 23390 does not induce depolarisation block in DA cells (11,18). However, Skarsfeldt (26) reported a lower number of active DA cells after chronic SCH 23390 and Goldstein and Litwin (16) reported a development of depolarisation inactivation in A10, but not A9, DA cells after chronic SCH 23390. Future experiments, therefore, have to validate if a difference exists between the potential of D-1 and D-2 antagonists to induce depolarisation block, and if development of depolarisation block is the mechanism responsible for the progressively increasing attenuation of operant responding after repeated administration of D-2 antagonists.

We have previously suggested that the operant and consummatory phases observed in our paradigm are governed by different mechanisms in the CNS, differently controlled by the dopaminergic transmission (20,21). Our evidences for this view are: 1) that different doses of neuroleptics are needed to attenuate the two phases and 2) that the haloperidol attenuation of the operant phase, but not the consummatory phase, can be counteracted by scopolamine. This study adds another difference—the haloperidol attenuation of the lever-pressing is more pronounced by repetitive administrations, the haloperidol attenuation of water intake is less (see Fig. 1).

If our argumentation above is correct, it would mean that when giving D-2 antagonist, the operant responding should be more sensitive to the development of depolarisation block than to the development of compensation receptor supersensitivity, giving as a net result an increased behavioral attenuation over time. For the water intake, on the other hand, this should be reversed. The explanation for such a specificity could be that different CNS mechanisms are governing these two different behavioral functions, as was discussed above.

If this line of reasoning is continued in a more general sense, it would mean that if D-2 antagonists are administered chronically, one might be able to, on the functional level, find both aspects of progressively increasing effects, as well as progressively decreasing effects, caused by, for example, development of supersensitivity. In the clinic it has been found that parkinsonism can coexist with tardive dyskinesia (TD) in up to 70% of the patients showing TD (14), which has hitherto been an unexplained finding. If it is assumed that parkinsonism is in some sense more dependent upon the development of depolarisation block, while symptoms of TD is more dependent upon compensatory mechanisms, like receptor supersensitivity, such a coexistance can be understood. Such an explanation would be supported by our results.

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REFERENCES

1. Arnt, J. Pharmacological specificity of conditioned avoidance response inhibition in rats: inhibition by neuroleptics and correlation to dopamine receptor blockade. Acta Pharmacol. Toxicol. 51:321–329; 1982.
2. Baker, G. B.; Greenshaw, A. J. Effects of long-term administration of antidepressants and neuroleptics on receptors in the central nervous system. Cell. Mol. Neurobiol. 9(1): 1–44; 1989.
3. Baldessarini, R. J. Drugs and the treatment of psychiatric disorders. In: Goodman, Gilman, A.; Goodman, L. S.; Rall, T. W.; Murad, F., eds. The pharmacological basis of therapeutics. New York: Macmillan Publishing Company; 1985:387–445.
4. Beninger, R. J. The role of dopamine in locomotor activity and learning. Brain Res. Rev. 6:173–196; 1983.
5. Bunney, B. A. Antipsychotic drug effects on the electrical activity of dopaminergic neurons. Trends Neurosci. 7(6):212–215; 1984.
6. Casey, D. E. Neuroleptic-induced parkinsonism increases with repeated treatment in monkeys. In: Dahl, S. G.; Gram, L. F.; Paul, S. M.; Potter, W. Z., eds. Clinical pharmacology in psychiatry. Selectivity in psychotropic drug action—Promises or problems. Berlin: Springer Verlag; 1987:243–247.
7. Casey, D. E.; Keepers, G. A. Neuroleptic side effects: acute extrapyramidal syndromes and tardive dyskinesia. In: Casey, D. E.; Christensen, A. V., eds. Psychopharmacology: Current trends. Berlin: Springer Verlag; 1988:74–93.
8. Chiodo, L. A.; Bunney, B. S. Typical and atypical neuroleptics: differential effects of chronic administration on the activity of A9 and A10 midbrain dopaminergic neurons. J. Neurosci. 3:1607–1619; 1983.
9. Clark, D.; White, F. J. D1 dopamine receptor—The search for a function. Synapse 1:347–388; 1987.
10. Creese, I.; Burt, D. R.; Snyder, S. H. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic

drugs. Science 192:481–483; 1976.
11. Esposito, E.; Bunney, B. S. The effect of acute and chronic treatment with SCH 23390 on the spontaneous activity of midbrain dopamine neurons. Eur. J. Pharmacol. 162:109–113; 1989.
12. Fibiger, H. C.; Phillips, A. G. Reward, motivation, cognition: psychobiology of mesotelencephalic dopamine systems. In: Mountcastle, V. B.; Bloom, F. E.; Geiger, S. R., eds. Handbook of physiology: The nervous system. vol. 4. Bethesda, MD: American Physiological Society; 1986:647–675.
13. Gerlach, J. Future treatment of schizophrenia. In: Casey, D. E.; Christensen, A. V., eds. Psychopharmacology: Current trends. Berlin: Springer Verlag; 1988:94–104.
14. Gerlach, J.; Casey, D. E. Tardive dyskinesia. Acta Psychiatr. Scand. 77:369–378; 1988.
15. Gerlach, J.; Lublin, H. Dopamine D-1 vs. D-2 receptor antagonists in schizophrenia. Relation to therapeutic effect and acute/tardive dykinesia. Psychopharmacology (Berlin) 96(Suppl.):29; 1988.
16. Goldstein, J. M.; Litwin, L. C. Spontaneous activity of A9 and A10 dopamine neurons after acute and chronic administration of the selective dopamine D-1 receptor antagonist SCH 23390. Eur. J. Pharmacol. 155:175–180; 1988.
17. Iorio, L. C.; Barnett, A.; Leitz, F. H.; Houser, V. P.; Korduba, C. A. SCH 23390, a potential benzazepine antipsychotic with unique interactions on dopaminergic systems. J. Pharmacol. Exp. Ther. 226(2): 462–468; 1983.
18. Kabzinski, A. M.; Szewezak, M. R.; Cornfeldt, M. L.; Fielding, S. Differential effects of dopamine agonists and antagonists on the spontaneous electrical activity of A9 and A10 dopamine neurons. Soc. Neurosci. Abstr. 13:908; 1987.
19. Koechling, U.; Colle, L. M.; Wise, R. A. Effects of SCH 23390 on motivational aspects of deprivation-induced feeding. Psychobiology 16(3):207–212; 1988.
20. Ljungberg, T. Blockade by neuroleptics of water intake and operant responding in the rat: Anhedonia, motor deficit or both? Pharmacol. Biochem. Behav. 27:341–350; 1987.
21. Ljungberg, T. Scopolamine reverses haloperidol-attenuated lever-pressing for water but not haloperidol-attenuated water intake in the rat. Pharmacol. Biochem. Behav. 29:205–208; 1988.
22. Ljungberg, T. Effects of the dopamine D-1 antagonist SCH 23390 on water intake, water-rewarded operant responding and apomorphine induced decrease of water intake in rats. Pharmacol. Biochem. Behav. 33:709–712; 1989.
23. Ljungberg, T.; Enquist, M. Decision making by rats in an unpredictable laboratory environment: final decision rules. Anim. Behav. 34:1120–1128; 1986.
24. Seeman, P. Brain dopamine receptors. Pharmacol. Rev. 32(3): 229–313; 1981.
25. Seeman, P.; Lee, T.; Chau-Wong, M.; Wong, K. Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature 261:717–719; 1976.
26. Skarsfeldt, T.; Effect of chronic treatment with SCH 23390 and haloperidol on spontaneous activity of dopamine neurons in substantia nigra pars compacta (SNC) and ventral tegmental area (VTA) in rats. Eur. J. Pharmacol. 145:239–243; 1988.
27. Snyder, S. H. Neurotransmitters and CNS disease: schizophrenia. Lancet October 30:970–974; 1982.
28. Stoff, J. C.; Kebabian, J. W. Two dopamine receptors: biochemistry, physiology and pharmacology. Life Sci. 35:2281–2296; 1984.
29. White, F. J.; Wang, R. Y. Differential effects of classical and atypical antipsychotic drugs on A9 and A10 dopamine neurons. Science 221:1054–1057; 1983.
30. Wise, R. A. Neuroleptics and operant behaviour, the anhedonia hypothesis. Behav. Brain Sci. 5:39–87; 1982.