Effect of haloperidol on (+)-amphetamine self-administration

To elucidate further the involvement of central neurohumoral systems in the pharmacologic reinforcement evoked by (+)-amphetamine, the role of brain noradrenaline was tested by using inhibitors of dopamine-β-hydroxylase which deplete the brain concentrations of noradrenaline, but not of dopamine (Davis, Smith & Khalsa, 1975). Results indicated that positive reinforcement associated with (+)-amphetamine fails if synthesis of noradrenaline is blocked. However, a possible joint involvement of dopaminergic and noradrenergic systems has not been excluded. The ability of haloperidol, a blocking agent at dopamine receptors, to affect (+)-amphetamine-induced reinforcement has therefore been tested.

Adult male Holtzman albino rats, 350 to 400 g were housed individually in a separate room from the experimental area. Both in the home cage and in the experimental apparatus, food and water were freely available. The rats under ether anaesthesia were implanted with a jugular cannula which could be connected to an infusion system (Davis & Smith, 1973; Smith & Davis, 1975). A volume of drug solution could be delivered either on an automatic schedule or as the consequence of an operant response, i.e., the depression of a bar which could be removed from the experimental chamber (a plexiglass cylinder with a wire mesh floor). At least 24 h elapsed after surgery before the animals were used.

In both experiments, rats were given 1 h to adapt to the chambers, then 6 h to record the operant level of responding (Day 1) when each bar-press resulted in a 0·2 s intravenous infusion of 0·018 ml of 0·9% saline solution coinciding with a 0·2 s buzzer presentation. In Experiment I, Day 2 consisted of a 6 h session for acquisition of responding for doses of (+)-amphetamine sulphate (each 15 μg kg^{-1}). Then on Day 3, a 6 h extinction session was given with all conditions of Day 1 reinstated. On Day 4, the capacity of haloperidol (5 mg kg^{-1}, i.p.) or saline, given 20 min before amphetamine, to block reacquisition of (+)-amphetamine self-administration behaviour was tested. The large dose of haloperidol was used to ensure that dopaminergic blockade should last the full session.

In Experiment II, either haloperidol (5 mg kg^{-1}) or an equal volume of saline was given on Day 2. Twenty minutes later the rats were placed in the chambers with response bars removed, and 50 pairings of buzzer and amphetamine infusion were given (see Davis & Smith, 1973) as in Experiment I. Four days after buzzer-amphetamine pairings, the rats were placed in the test chambers with Day 1 conditions reinstated. On the following (7th) day, a 6 h period was given in which bar-pressing caused presentation of the buzzer plus (+)-amphetamine. This was to discriminate any rat that would not respond to the amphetamine as a primary reinforcer, since such rats could not be expected to develop conditioned reinforcement. Data from both experiments were analysed via the Mann-Whitney U Test or the Wilcoxon Matched Pairs Test (Siegel, 1956).

The data of Experiment I show that baseline operant responding for the saline and haloperidol groups was almost identical (mean bar-presses, $\pm$ s.e., 38 $\pm$ 9 and 39 $\pm$ 14; n = 8), and that initial acquisition of self-administration behaviour on Day 2 did not differ for the 2 groups (89 $\pm$ 22; 75 $\pm$ 19). During reacquisition after extinction, bar-pressing by the haloperidol group was significantly less than by the saline group (232 $\pm$ 45; 8 $\pm$ 4; $P < 0{\cdot}001$). This difference might be taken to suggest that haloperidol blocked those actions of (+)-amphetamine essential to reacquisition of the bar-press behaviour. However, this dose of haloperidol also caused some motor impairment, as responding of the group under its influence during reacquisition was reduced significantly ($P < 0{\cdot}001$) from their operant level.

Because of this the conditioned reinforcement design, which allowed a 4-day post-drug interval before the drug-free test condition, was used to control for that factor in Experiment II. Operant levels again were similar (40 ± 7; 42 ± 10, $n = 12$), whereas the saline group responded over 3 times as often as the haloperidol group ($P < 0{\cdot}005$) in the test for conditioned reinforcement (128 ± 17 and 33 ± 9). This indicates blocking by haloperidol toward the reinforcing or motivational properties associated with (+)-amphetamine during the amphetamine-buzzer pairings. There was no difference between operant level and responding in the test of conditioned reinforcement for the haloperidol group ($P > 0{\cdot}05$), but the elevation in responding for the saline group was significant ($P < 0{\cdot}01$). Thus, the haloperidol group showed no residual motor depression and there were no conditioned motivational properties (reinforcement) for the buzzer; in contrast, the buzzer evidently provided strong conditioned reinforcement for the saline group.

Thus haloperidol can inhibit both the self-administration of (+)-amphetamine and the establishment of a conditioned reinforcer based on (+)-amphetamine as primary reinforcer. While motor impairment might have contributed to the former effect, it could not have been a significant factor in the latter results because of the 4-day interval.

Other alternative explanations remain possible. Haloperidol might have so disturbed hearing that discrimination of the buzzer stimulus was modified; or it may have interfered with the learning process concerning the relationship between the buzzer and amphetamine. However, while employing an identical pairing procedure and the same or even much higher dosages of haloperidol, Smith & Davis (1973) found that haloperidol did not block the establishment of a morphine-based conditioned reinforcer. Clearly, if the action of haloperidol in the present study were based upon a general interference with either perceptual or associative processes, such action(s) should also have been apparent in the morphine study.

Yokel & Wise (1975) found pimozide (0·5 mg kg^{-1}), another dopaminergic blocking agent, to inhibit self-administration of (+)-amphetamine by rats, while lower doses increased responding. Smith & Davis (1973) found high doses of haloperidol to cause a motor deficit and a concommitant reduction in self-administration behaviour toward morphine, while a low dose increased self-administration. However, data from the conditioned reinforcement design proved that the reduction could not be attributed to antagonism of the pharmacological reinforcer. The report of Yokel & Wise and our present Experiment I do not as such constitute proof of dopaminergic involvement. However, both studies, when combined with our present Experiment II, clearly point to a dopaminergic involvement in the mechanism of positive reinforcement associated with intravenous injections of (+)-amphetamine.

From these data it may be suggested that haloperidol or similar drugs have potential value in treatment of drug dependence of the amphetamine type.

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The absorption and elimination of orally administered [^{14}C]hyoscine *N*-butylbromide (butylscopolamine)

The absorption of quaternary ammonium antiacetylcholine agents from the gastrointestinal tract has been much debated (Möller & Rosén, 1968; Hellström, Rosén & Söderlund, 1970; Beermann, Hellström & Rosén, 1971, 1972) and hyoscine *N*-butylbromide (butylscopolamine) has roused particular interest. While many authors hold that its absorption from the gut is insignificant (Herxheimer & Haefeli, 1966; Guignard, Herxheimer & Greenwood, 1968; Brömster, Carlberger & others, 1969; Hellström & others, 1970), its use clinically, even by mouth, has been found helpful in the treatment of various gastrointestinal disorders (Schmid, Bleichert & others, 1969).

In animal studies with the labelled drug an enterohepatic circulation was proved (Pentikäinen, Penttilä & others, 1973). It has been suggested that after oral administration, though only absorbed slightly, it accumulates in the intestinal wall and the bile, and thus has a local effect (Pomeroy & Rand, 1968). This suggestion is supported by our animal results (Pentikäinen & others, 1973). To throw more light on this question, the labelled drug has been given to two patients and the radioactivities of serum, bile and urine measured.

[^{14}C]Hyoscine butylbromide was synthesized (Pentikäinen & others, 1973). Two volunteer female patients with normal liver function, aged 24 and 46 years and weighing 54 and 60 kg, had a T-drain, kept under a constant suction by a pressure of 50 mm of water (see Kaltiala, Penttilä & others, 1974), inserted into the common bile duct after choledocholithotomy. On the morning after the operation one 10 mg tablet of the drug, containing 17·1 μCi ^{14}C, was taken with a glass of water on an empty stomach.

Blood samples were taken from the cubital vein 20, 40, 60 and 180 minutes later

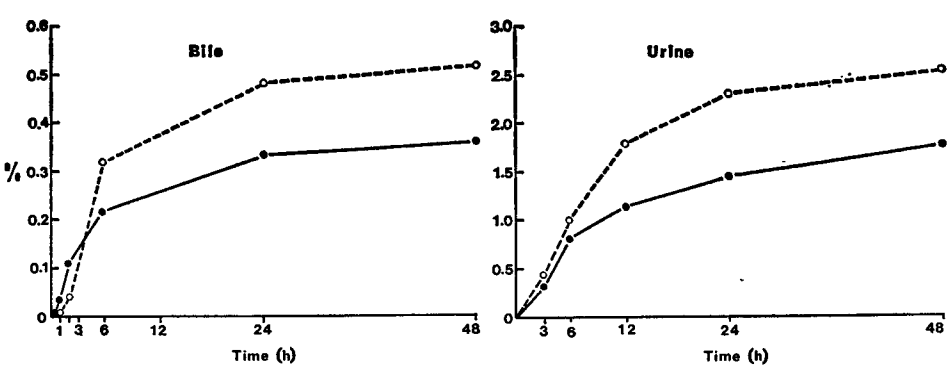

FIG. 1. Cumulative excretion of radioactivity in urine and bile in two volunteers after oral administration of 10 mg of [^{14}C] hyoscine butylbromide.