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Effects of \(d\)-amphetamine and haloperidol on latent inhibition in healthy male volunteers

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Latent inhibition (LI) refers to a retardation of learning about the consequences of a stimulus when that stimulus has been passively presented a number of times without reinforcement. Acute positive-symptom schizophrenics, normal volunteers who score high on questionnaire measures of schizotypy and non-patients or animals treated with dopamine agonists show reduced LI. Neuroleptic drugs, such as haloperidol, administered at low doses, potentiate LI and effectively reverse disruption of LI induced by dopamine agonists in animals. However, a high dose of haloperidol, administered on its own, has been found to reduce LI. We examined the effects on LI of acute oral administration of an indirect dopamine-agonist, \(d\)-amphetamine (5 mg), and a nonselective dopamine receptor antagonist, haloperidol (5 mg), in normal male volunteers, using an associative learning task. Replicating previous reports, we found that \(d\)-amphetamine reduced LI; haloperidol also reduced LI, but only in subjects who scored low on the Psychoticism scale of the Eysenck Personality Questionnaire. In a subsequent study, no effect was found of 2 mg oral haloperidol administration on LI. The effect of 5 mg haloperidol on LI is interpreted as similar to that observed with a high dose of haloperidol in rats.

Key words: \(d\)-amphetamine; dopamine; haloperidol; latent inhibition; psychoticism; schizophrenia

Introduction

Latent inhibition (LI) refers to retarded learning about the consequences of a stimulus when that stimulus has been inconsequential in the past (Lubow, 1973). This phenomenon has been robustly demonstrated in a number of species, employing a range of classical and instrumental conditioning paradigms (Lubow, 1989; Lubow and Gewirtz, 1995). LI is generally considered to reflect the processes of selective attention by which an organism screens out irrelevant stimuli (Lubow et al., 1976, 1987; Lubow, 1989), although the exact processes underlying this phenomenon, particularly in human beings, remain to be clarified (Hall, 1991; Schmajuk et al., 1996).

There have been several attempts to investigate the pharmacology of LI in experimental animals as well as in human beings. Of considerable importance are those studies investigating dopaminergic manipulations, since these provide a potential link between dopaminergic overactivity and cognitive dysfunction in schizophrenia (Gray et al., 1991). In the rat, the indirect dopamine receptor agonist amphetamine, which has psychotomimetic properties, has been found to disrupt LI when short duration (5–30 s) conditioned stimuli (CS) are used (Solomon et al., 1981; Solomon and Staton, 1982; Weiner et al., 1981, 1984, 1988; De la Casa et al., 1993a; McAllister, 1997), but has no effect if CS are of relatively longer duration (150 s) (De la Casa et al., 1993a). The effects on LI of a second compound that causes dopamine release, nicotine, also appear to be dependent upon CS parameters. Joseph et al. (1993) observed that nicotine impaired LI after forty 5-s CS exposures. Rochford et al. (1996) replicated Joseph et al.’s findings but, in addition, observed that nicotine enhanced LI after sixty 60-s CS pre-exposures and that this effect was reversed by the nicotinic antagonists hexamethonium and mecamylamine. The dopamine receptor antagonist haloperidol, which is a neuroleptic drug, has been found to antagonize the disruption of LI produced by amphetamine (Weiner et al., 1990; Warburton et al., 1994) and nicotine (Joseph et al., 1993). Administered on their own, neuroleptics, including haloperidol (Weiner and Feldon, 1987; Weiner et al., 1987; Christison et al., 1988; Trimble et al., 1997) and sulpiride (Feldon and Weiner, 1991), potentiate LI. The effect of haloperidol on LI appears to be dose-dependent: doses of 0.3–0.03 mg/kg have been found to enhance LI, doses of 0.003 mg/kg to have no effect, and doses of 3.0 mg/kg to abolish it (Dunn et al., 1993). There is evidence in support of the hypothesis (Solomon and Staton, 1982) that the effects on LI of the manipulations of dopaminergic transmission reflect actions of both indirect dopamine agonists and dopamine receptor antagonists, specifically in the nucleus accumbens...
Clear, the existing literature does not allow a definite interpretation of neuroleptic effects on LI in human beings. We therefore conducted two experiments to further investigate the effects of haloperidol on LI in normal volunteers, and also to re-examine the effects of amphetamine. Since normal volunteers who score high on psychometric measures of schizotypy have been found to show reduced LI compared with low scorers (Baruch et al., 1988b; Lubow et al., 1992; Lipp and Vaitl, 1992; De la Casa et al., 1993b; Lipp et al., 1994), subjects were required to complete two such questionnaires: the Psychotism (P) scale of the Eysenck Personality Questionnaire (EPQ; Eysenck and Eysenck, 1975) and the Schizotypal Personality Scale (STA; Claridge and Broks, 1984). The P scale of the EPQ was included as the main measure of schizotypy in this study because our previous studies (Baruch et al., 1988b; Thornton et al., 1996) have shown schizophrenic-like performance on the auditory LI task by healthy volunteers scoring high on this scale. Inclusion of these measures allowed us to investigate whether schizotypy would interact with haloperidol administration, as reported for the H-Mask task by Williams et al. (1997b).

In the first experiment, we examined the effects of 5 mg haloperidol on LI. The choice of this dose was dictated by clinical and ethical reasons: it is a clinically relevant dose and has been successfully used in normal subjects without causing excessive side-effects (Dawe et al., 1995). The dose of haloperidol was lowered from 5 mg to 2 mg in the second experiment in order to examine the dose-response relationship between LI and haloperidol administration.

**Experiment 1**

One hundred and twenty right-handed (age-range 18–45 years) male subjects were recruited by advertisements and referrals by other healthy subjects. All potential subjects underwent a semi-structured medical screening for thyroid dysfunction, glaucoma, heart disease, hypo- or hypertension, a history of severe mental illness, anorexia, violent or rapid mood changes, regular medical prescription, alcohol dependency and drug abuse (ascertained by urine analysis), before being accepted as subjects. All subjects completed the EPQ at the time of medical screening (5–15 days before testing) and the STA on the day of testing (but before drug administration, in order to control for the influence of d-amphetamine on schizotypy scores; Gray et al., 1996).

The protocol of the study was approved by the Ethical Committee at the Institute of Psychiatry, London. All subjects who participated in the study signed a written consent form. Subjects were paid £50 each for their participation.

**Experimental design**

A 2×2×3 [P: low and high groups×Experimental Condition: pre-exposed (PE) and non pre-exposed (NPE)×Drug: placebo, d-amphetamine and haloperidol] factorial design was employed. Subjects scoring 4 and below on the P scale of the EPQ were classified as low P scorers and those scoring 5 and above as high P: this criterion was based upon unpublished data obtained in our previous pharmacological studies (Kumari et al., 1996a,b; Thornton et al., 1996).
Subjects of the low and the high P groups were randomly assigned in equal numbers (n = 10) to each of the experimental conditions. Table 1 presents subjects’ ages, weights and P scores, classified by experimental condition.

### Drug dose and administration

Placebo (empty capsule), d-amphetamine (5 mg) and haloperidol (5 mg), were all administered orally in identical appearing capsules. The study was run double-blind. The interval between drug administration and commencement of the LI task was determined on the basis of previous studies; in the case of d-amphetamine it was 90 min (Wan et al., 1978) and in the case of haloperidol it was 3 h (Nordström et al., 1992). In order to be able to run the study double-blind, all subjects were given two capsules, one at 0 min and the other 90 min after the first capsule. The placebo group had two placebo capsules while the d-amphetamine and haloperidol groups had one placebo capsule and the other containing 5 mg d-amphetamine and 5 mg haloperidol, respectively. The schedule of drug administration is shown in Table 2.

Two of the first 14 subjects experienced severe side-effects (one had blurred vision and the other extreme restlessness), which required us to change the protocol so that all subjects who were given haloperidol could be administered orphenadrine routinely before leaving the hospital ward. To counteract any possible extrapyramidal reactions to haloperidol, all but the first 14 subjects who received haloperidol were routinely given a single oral dose of orphenadrine (50 mg) after the completion of the experimental testing by one of the co-authors (PAC or OFM); the experimenter (VK) had no knowledge which subjects were given orphenadrine until after the study had been completed. Medical cover was made available to subjects on a 24-h basis.

All subjects were given the first drug/placebo capsule between 09.30 and 11.00 hours to control for possible differential time of day effects on drug metabolism. Similarly, the study sample was restricted to males only to reduce another potential source of variance.

### General procedure

Subjects were told that the study was concerned with the psychological effects of a stimulant drug d-amphetamine and a neuroleptic drug haloperidol. They were requested to have a light breakfast on the day of testing and to abstain from alcohol for at least 12 h prior to their appointment. No specific instructions were given to subjects as to whether or not to smoke before or after the drug/placebo administration. After the LI experiment, the experimenter requested subjects to provide information about their smoking status and, in the case of smoker subjects, noted down their smoking intake on the morning of testing and after the drug/placebo administration. The experimenter had no knowledge of subjects’ smoking status/smoking intake at the time of LI testing.

A research nurse assessed the degree of akathisia in all subjects using the rating scale for drug-induced akathisia (Barnes, 1989). This scale measures objective (i.e. restless movements observed by the rater) as well as subjective (reported by the subject) akathisia. The subjective akathisia scale has two items: (1) awareness of restlessness and (2) distress related to restlessness. All three items (one objective and two subjective) are scored on a four-point scale (0–3).

### Task and equipment details

These were identical to those used by Thornton et al. (1996). Briefly stated, there were two phases in the task: pre-exposure and test, each lasting approximately 5 min.

#### Pre-exposure

Subjects assigned to the non pre-exposed (NPE) group listened to a tape recording consisting of five repeated presentations of a series of 25 nonsense syllables, presented binaurally. For those assigned to the pre-exposed (PE) group, 25 white noise bursts were superimposed at random intervals (presented to the left ear only) onto the same tape recording of nonsense syllables as used for the subjects of the NPE group. All subjects were asked to choose any one syllable from the first five they heard, and to count the number of times it was repeated. They were asked by the experimenter immediately after the tape ended which syllable they had chosen and how many times they had heard it. No subject in any drug group reported less than four or more than six counts.

#### Test

This phase followed immediately the pre-exposure phase. White noise bursts were now present on the recordings for both NPE and PE groups.
Subjects were told that this was a new task; that they would be required to listen to the tape recording again; that the number of points on the digital scoreboard (which was placed in front of them) would increase according to some signal on the tape recording of the nonsense syllables; and that this time their job was to work out the signal associated with the increment in the number displayed on the scoreboard and to press a button each time they expected the number of points on the scoreboard to increase. The number on the digital scoreboard was increased automatically upon termination of each noise-burst. The experiment ended after the subject correctly predicted five consecutive scoreboard increments without any errors of omission or commission or after 25 noise-burst presentations.

Scoring
Each subject was assigned a learning score, which represented the number of noise-bursts up to the time when the subject correctly predicted five scoreboard increments. The learning scores ranged from 6 to 25. Subjects who did not learn the CS–UCS association by the end of the test were also given a score of 25, but were entered in the analysis as non-learner cases and are presented as having a learning score of 30, in order to differentiate such subjects from those who learnt the association at the very end.

Statistical analysis
All analyses were performed using the Statistical Package for Social Sciences (SPSS Version 6, SPSS Inc, Chicago, IL, USA). The data were subjected to survival analysis, using a Cox Proportional Hazards Regression (CPHR) model. This model takes into account both the learning score (5–25) and whether or not (1 or 0) the subject learned the white noise (CS)-scoreboard increment (UCS) association by the end of the experiment (Thornton et al., 1996). First, the three-way interaction (Drug × P × Experimental Condition), then two-way interactions (excluding the three-way interaction term from the model) and lastly the main effects of Experimental Condition in the three drug groups, separately for the low and the high P subjects, were examined by post hoc one-way comparisons using CPHR models.

Similar analyses to those reported above for P were carried out to examine the effects of STA scores (group median = 10; subjects scoring 10 or below included in the low STA group and those scoring 11 or above in the high STA group) and also of smoking status (nonsmoker, smoker). The relationships between the degree of akathisia in subjects given haloperidol and the PE/NPE learning scores and P scores were examined using Spearman rank correlations.

Results
Neither STA scores nor smoking status had any main or interactive influence on LI; these factors therefore are not reported further.

There was a significant three-way Drug × P × Experimental Condition interaction (Wald = 6.59, d.f. = 2, p = 0.04). Figure 1 represents learning scores in all experimental conditions (i.e. learning score in the low and the high P subjects of the placebo and drug groups in the PE and NPE conditions).

Although the Drug (d-amphetamine, Placebo) × Experimental Condition interaction was not significant (Wald = 2.69, d.f. = 1, p = 0.10), in line with our expectations subjects assigned to the PE condition learnt the CS–UCS association faster if given d-amphetamine than those given placebo (Wald = 5.64, d.f. = 1, p < 0.02). No effect of d-amphetamine was found in subjects assigned to the NPE condition. There was no effect of P in this drug (d-amphetamine) group either in the PE or in the NPE condition.

Subjects assigned to the PE condition and given haloperidol learnt the CS–UCS association faster than subjects given placebo, but only if also scoring low on P (Wald = 3.99, d.f. = 1, p = 0.05); there was no effect of haloperidol compared with placebo in high P subjects (Wald < 1).

In subjects given placebo, the two-way Experimental Condition × P interaction did not reach an accepted level of significance (Wald = 1.96, d.f. = 1, p = 0.16). The learning score did not differ significantly as a function of P, either in those assigned to the PE or in those assigned to the NPE condition.

Out of 40 subjects given haloperidol, 19 had mild (score 1), one moderate (score 2) and four had severe (score 3) objective akathisia (restless movements) as observed by the research nurse. For the awareness of inner restlessness (subjective item), 13 subjects scored 1, six scored 2, and five scored 3. For the distress related to restlessness (subjective item), 13 subjects scored 1, four scored 2, and two scored 3. Taken together, these observations suggest that more than 50% of subjects who received haloperidol experienced akathisia to some degree. We therefore examined the relationships between the degree of akathisia 4 h after haloperidol administration and the NPE/PE learning scores. There was a significant negative relationship between the PE learning scores and ratings on the objective item of the akathisia scale (r = −0.62, p < 0.01), indicating that lower PE learning (i.e. improved learning or disrupted LI) was associated with akathisia. This relationship did not hold for the subjective akathisia items, awareness of restlessness (r = −0.16) or distress related to restlessness (r = −0.06).
There was no significant relationship between the NPE learning scores and the degree of akathisia (objective: $r=0.16$, awareness of restlessness: $r=-0.02$, distress related to restlessness: $r=-0.01$).

The finding of an association, on the one hand, between PE learning and the ratings on the objective item of the akathisia scale and, on the other hand, between the P scores and PE learning in subjects given haloperidol, prompted us to explore the relationship between the P scores and akathisia ratings. The scores on the P scale and the ratings on the subjective item, awareness of restlessness ($r=-0.18$) or distress related to restlessness ($r=-0.03$).

Experiment 2

This experiment was designed to follow-up the significant relationship between speed of learning and observed akathisia in the haloperidol group by using a smaller dose (2 mg) of haloperidol unlikely to produce severe akathisia (King et al., 1995). The same LI task and experimental procedures were used in this experiment as for Experiment 1 in order to study the dose-dependence of haloperidol-induced impairment in LI. Only those details are described which differed from Experiment 1.

Forty right-handed (age range 18–45 years; mean age in placebo group 24.10 years, SD = 7.03; mean age in haloperidol group 27.60 years, SD = 7.29) nonsmoker male volunteers served as subjects. Although we found no influence of the smoking habit on LI in Experiment 1, in view of the effects of cigarette smoking on prepulse inhibition of the startle reflex, another measure of sensory gating (Kumari et al., 1996b), and of haloperidol administration on smoking intake (Dawe et al., 1995), smoking volunteers were not accepted as subjects in this experiment. All accepted subjects completed the EPQ at the time of medical screening.

Experimental design

A $2 \times 2$ [Experimental Condition: pre-exposed (PE) and non-pre-exposed (NPE) $\times$ Drug: placebo, haloperidol] factorial design was employed.

Drug dose and administration

Placebo (empty capsule) and haloperidol (2 mg), were both administered orally in identical capsules following a double blind design. The interval between drug administration and LI testing was the same as in Experiment 1, i.e. 3 h. All subjects who received haloperidol were routinely given a single oral dose of orphenadrine (50 mg) after the completion of the experiment.

General procedure

Subjects were told that the study was concerned with the psychological effects of a neuroleptic drug, haloperidol.

Blood sampling

Plasma haloperidol levels were not measured in Experiment 1, as we have previously found the dose of 5 mg haloperidol to have clear behavioural effects (Dawe et al., 1995). We have not, however, previously examined the effects of the lower dose of 2 mg haloperidol and therefore, in Experiment 2, determined plasma drug levels. Blood samples were taken by venepuncture immediately after the LI task. The samples were centrifuged at 3000 g to separate blood plasma and then stored at $-20^\circ$C until analysed using Micro-Plate Haloperidol EIA (Cozart Bioscience Ltd, UK) with a detection limit of 0.1 ng/ml.

Task, equipment details and scoring

These were identical to those described for Experiment 1.

Statistical analysis

The LI data were analysed using two-way (Drug $\times$ Experimental Condition) CPHR models, followed-up by one-way analyses as reported for Experiment 1.

Results

For the haloperidol group, the mean plasma haloperidol concentration obtained after the LI task (approximately 3 h 15 min after haloperidol administration) was 0.41 ng/ml (SEM = 0.05). For the placebo group, all plasma haloperidol concentrations were zero.

The two-way (Drug $\times$ Experimental Condition) CPHR model showed an overall significant LI (Wald = 16.76, d.f. = 1, $p<0.001$), but no effect of Drug or the Drug $\times$ Experimental Condition interaction (Walds < 1). Post hoc examination of the data revealed that seven out of 10 subjects assigned to the haloperidol PE group could be classified as low P scorers (scoring 4 or below on the P scale). The effects of haloperidol on LI in these seven subjects were similar to those found for the whole sample. Figure 2 represents learning scores in all experimental conditions.

Only one subject reported mild restlessness and two others reported feelings of sleepiness approximately 3 h after the administration of 2 mg haloperidol. Two of these three subjects had been assigned to the NPE condition and one (feeling sleepy) to the PE condition. No other side-effects were noted.
Discussion

The finding (Experiment 1) with respect to the effect of the indirect dopamine agonist, d-amphetamine (5 mg oral), on LI was as expected and represents a replication of previous reports (Gray et al., 1992b; Thornton et al., 1996) in showing that pre-exposed subjects administered d-amphetamine at this dose learn the CS–UCS association faster than subjects given placebo. Surprisingly, the dopamine receptor antagonist haloperidol, also 5 mg oral (Experiment 1), had a similar direction of effect upon LI. This pattern of results contrasts with our previous findings (Kumari et al., 1997) on a procedural learning task obtained 3 h 35 min after 5 mg haloperidol administration. In that study, both response speed and procedural learning increased linearly from the haloperidol through the placebo to the amphetamine condition. It is unclear whether these different patterns of results reflect task differences or pharmacodynamic effects due to the differences in time between drug administration and behavioural testing. The former possibility, however, seems more likely, as the difference in timing (20 min) between the two studies is relatively slight.

Haloperidol had no effect on LI at the 2 mg dose but reduced LI at 5 mg (only in subjects low on EPQ P scores). The dose-dependence of the haloperidol-induced impairment in LI reported here is similar to that observed by Williams et al. (1996, 1997a,b) using the same LI task, but administering haloperidol by the i.v. route: these authors report that at 0.5 mg there was no change in LI, but at 1.0 mg LI was reduced. This pattern of dose effects suggests that, in both experiments, haloperidol may have been administered at a dose above the effective range to observe the expected potentiated LI. Consistent with this possibility, Dunn et al. (1993) found potentiated LI in rats over a range of doses of anti-psychotic drugs, but reduced LI at the highest dose of haloperidol tested, 3 mg/kg.

Also consistent with the possibility that haloperidol-induced reduction in LI represents a high-dose effect is the fact that approximately 60% of our subjects given the 5 mg dose showed signs of akathisia, as also observed by other researchers (Nordström et al., 1992; Ramaekers et al., 1997) in normal subjects after oral administration of similar doses of haloperidol. The time course of dopamine D2 receptor occupancy, examined using positron emission tomography after single oral doses of haloperidol by Nordström et al. (1992), suggests that, in our subjects, dopamine receptor blockade during Experiment 1 was likely to be over 75%. These authors report that, 3 h after administration, single oral doses of 2 and 4 mg haloperidol (one subject per dose) produced 52% and 73% dopamine receptor occupancy, respectively, while a 7.5 mg dose produced 92% and 83% occupancy in two subjects, respectively. Since akathisia was not noted in any subject in Experiment 2 at the 2 mg dose of haloperidol, the occurrence of akathisia in Experiment 1 in a substantial proportion of subjects appears to be a high-dose related effect. Given also that the degree of haloperidol-induced akathisia correlated with speed of learning in the PE condition only (Experiment 1), and that haloperidol neither caused akathisia, nor influenced LI at the lower dose (Experiment 2), these observations strengthen the hypothesis that the reduction in LI observed after 5 mg oral haloperidol is due to the use of a relatively high dose of the drug. It should be noted, however, that in the study of Williams et al. (1997a) in which LI was also reduced after haloperidol, subjects did not show signs of akathisia. This discrepancy may be due to the different route of administration (i.v.) that they employed. If these arguments are correct, it should be possible to observe potentiated LI at doses of haloperidol below the 2 mg oral dose used here or the 0.5 mg i.v. dose used by Williams et al. (1997a), neither of which altered LI. Note that, given the observations by Williams et al. of task dependence in the effects of haloperidol on LI, these predictions can be regarded as strong only in relation to the specific task used here.

Although we did not measure dopamine receptor occupancy in this study, we postulate that LI blockade by haloperidol is due to a high degree of receptor occupancy. However, we saw LI reduction with haloperidol treatment in low P subjects only. If the receptor occupancy hypothesis is correct, this implies that receptor occupancy was lower in high P subjects, in which haloperidol did not affect LI. Consistent with this possibility, Gray et al. (1994) reported a negative correlation between scores on the P scale of the EPQ (Eysenck and Eysenck, 1975) and dopamine D2 binding in both left and right basal ganglia, a finding replicated (though with a different measure of schizotypy) by Farde et al. (1997). These observations suggest that P scores may reflect differences in dopamine receptor function. The significant negative correlation we observed between P scores and ratings on the objective item of the akathisia scale further supports the possibility that, on average, dopamine receptor occupancy after 5 mg haloperidol was lower in the high P group than in the low P group.

Note, however, that the observed relationships to reduced LI of akathisia and low P scores, respectively, coupled with the negative relationship between akathisia and P scores, raise the possibility that the enhanced learning seen in the pre-exposed subjects given 5 mg haloperidol is an artefact of drug-induced akathisia (greater in low P subjects). While it is difficult to see what form such an artefact might take, we cannot rule this out. It is also difficult at present to see how the ‘differential receptor occupancy’ hypothesis can be applied to the rather similar observations by Williams et al. (1997b) of enhanced LI in one of their two visual-CS tasks (the H-Mask task) after administration of haloperidol only at the higher (1.0 mg i.v.) of the two doses used by this group and only in high schizotypal subjects. However, the fact that we observed reduced LI in low schizotypal subjects and that Williams et al. observed enhanced LI in high schizotypals suggests that some resolution along these lines may be possible.

Similar to a previous report from this laboratory (Thornton et al., 1996), but in contrast to results reported by Allan et al. (1995), we found smoking to have no influence on LI (Experiment 1). However, unlike previous studies from both our laboratory and others (see Introduction), LI in the high P subjects of the placebo group in the present study was not significantly weaker than that observed in the low P subjects of this group. Moreover, there was no effect of schizotypy (STA) on LI. Our study sample, however, appears to be different from other studies regarding P and STA scores. The mean (and median) STA score observed for the present sample was much lower (mean = 10.58; median = 10) than that usually observed.
elimination of high P drug users who might have provided a
measures of schizotypy.

in undrugged normal subjects as a function of psychometric
finding too is consistent with data from animal experiments
dopamine receptor occupancy by the administered haloperidol
investigation, e.g. by measuring LI in matched groups of
1988b; Lubow

positive replication of the effects of P on LI (Baruch
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