Amphetamine-induced disruptions of latent inhibition are reinforcer mediated: implications for animal models of schizophrenic attentional dysfunction

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Abstract. Latent inhibition (LI) is a phenomenon observed when repeated, non-reinforced presentation of a stimulus results in a retardation of subsequent conditioning to that stimulus. Several recent experiments have suggested that LI is abolished in conditioned suppression paradigms following acute, low doses of amphetamine given during pre-exposure and conditioning. Experiment 1 sought to increase the generality of this finding in an appetitive LI paradigm, using a dose of amphetamine previously shown to disrupt the LI effect in an aversive paradigm (Killcross and Robbins 1993). However, no evidence for any disruption of LI was found. Experiment 2 extended this investigation to additional, higher doses of d-amphetamine, and also examined the role of reinforcer magnitude in the effect. A non-significant trend towards an attenuated LI effect was found, which was reversed by decreases in the concentration of the sucrose reinforcer. Experiments 3 and 4 investigated the influence of systemic amphetamine in aversive paradigms, with specific attention to the increased response to the aversive footshock reinforcer found in amphetamine-treated animals. These experiments revealed that the influence of amphetamine on the LI effect in conditioned suppression paradigms could be reversed by reducing the intensity of footshock used in conditioning, thereby paralleling the effect found in the appetitive paradigm. Therefore it is unlikely that a simple attentional account of the abolition of the LI effect in previous experiments can be sustained.

Key words: Dopamine – Latent inhibition – Schizophrenia – Amphetamine – Conditioning – Context – Attention

Recently, there has been substantial interest in animal models designed to reflect attentional impairments observed in acute schizophrenia. One model is that based on latent inhibition (LI), a phenomenon which is manifest when repeated, non-reinforced pre-exposure to a stimulus retards conditioning to that stimulus when it is subsequently paired with reinforcement (Lubow 1973). This effect has been interpreted by some as reflecting processes of selective attention by which irrelevant stimuli come to be ignored (Mackintosh 1975, 1983; Lubow et al. 1976; Lubow 1989), although this is by no means the only explanation (Pearce and Hall 1980; Wagner 1981; Bouton 1991). The rationale for this model lies in a possible parallel between the effects of dopaminergic drugs on LI and the deficits in selective attention seen in acute schizophrenia (Joseph et al. 1979; Lubow et al. 1987; Baruch et al. 1988; Gray et al. 1991, 1992).

The neural locus of these effects on LI has often been attributed to the dopaminergic innervation of the nucleus accumbens (NAc; Weiner 1990; Gray et al. 1991). More specifically, the abolition of the LI effect by amphetamine is claimed to result from the potentiating effect of amphetamine on dopaminergic transmission in the mesolimbic DA projections which innervate the NAc and related areas of the ventral striatum. However, recent results have provided some evidence against this hypothesis. Killcross and Robbins (1993) demonstrated that whereas systemic injections of amphetamine can abolish the LI effect in a within-subject conditioned suppression paradigm, no such influence is seen in the same paradigm following intra-accumbens infusions of either 3μg/μl or...
10 μg/μl d-amphetamine (1μl infused bilaterally). Further evidence comes from the failure to abolish the LI effect in animals reared in isolation following weaning, with dialysis of these same animals revealing enhanced levels of extracellular DA in the NAc, and an enhanced response of the mesolimbic DA system to systemic administration of low doses of d-amphetamine (Wilkinson et al. 1994).

These recent findings from our laboratory contradict previous work by Solomon and co-workers who found that sub-chronic 10 μg/μl intra-accumbens amphetamine (Solomon and Staton 1982), as well as chronic systemic amphetamine (Solomon et al. 1981; Solomon and Crider 1988) could abolish the LI effect in an active avoidance paradigm. The reason for this may lie in the differences in drug regime between these experiments, or may be due to the fact that increases in locomotor activity following amphetamine manipulations are highly compatible with the shuttle response required in the active avoidance paradigm (Bianchi and Marazzi-Uberti 1969; Evangelista and Izquierdo 1971; Barrett et al. 1972,1973), and may thus act to mask any LI effect.

These discrepant findings serve to question the generality of the effects of amphetamine on LI. Whilst there is clearly an effect of amphetamine administration during pre-exposure and conditioning in conditioned suppression paradigms, assessed either during acquisition of suppression of ongoing behaviour (on-baseline) or, following acquisition, in an extinction test (off-baseline), it is important for the validity of the model that the influence of dopaminergic agents on the supposed attentional mechanisms underlying the appearance of LI should not be restricted to aversively-motivated paradigms. Studies of LI in appetitive situations are less common than aversively motivated paradigms, but several examples exist (e.g. Baker and Mackintosh 1977). Typically, repeated pre-exposure to a stimulus is followed by pairings of the stimulus with food. Conditioning is assessed by examining the tendency to approach the food magazine during the conditioned stimulus (CS), relative to a similar period immediately prior to CS onset.

The main problem with the use of appetitive paradigms in assessing the effects of drug manipulations is that appetitive conditioning under conditions usually studied often proceeds much more slowly than aversively-motivated parallels. Asymptotic levels of conditioning are often only achieved following 40–50 pairings of the CS with reward, relative to the one or two pairings of CS with footshock required in aversive paradigms. As conditioning is typically even slower if conditioning trials occur too frequently, these CS-US pairings are usually spread over four or five sessions run on consecutive days, a procedure that is often incompatible with required regimes of drug administration.

However, the within-subject paradigm used by Killcross and Robbins (1993) demonstrated that repeated administrations of low doses of amphetamine are compatible with the drug’s ability to abolish the LI effect. Furthermore, pilot studies examining the rate of appetitive acquisition using high levels of reinforcement demonstrate that rapid appetitive conditioning can be obtained if large magnitudes of the positive reinforcer are used – rates which approximate to those seen in parallel aversive paradigms and thereby facilitate direct comparison. Therefore, experiment 1 sought to evaluate the generality of the abolition of LI effects following systemic amphetamine injections by extending the previous result (using the same dose of amphetamine (0.5 mg/kg) to an analogous appetitive task that was designed to produce rapid conditioning. Experiment 2 expanded these findings to further doses of amphetamine. As previous results of Killcross and Robbins (1993) indicated that amphetamine treatment in an aversively-motivated LI paradigm enhanced the functional severity of the footshock, experiment 2 included a condition to examine the influence of reinforcer magnitude in the parallel appetitive paradigm.

**Experiment 1: 0.5 mg/kg d-amphetamine and LI in appetitive conditioning**

**Method**

**Subjects.** Subjects were male, Lister-hooded rats (OLAC, Bicester, UK) which weighed 295–330 g at the time of the experiment. Animals were housed in cages of four in natural daylight, and maintained on a 22.5-h schedule of food deprivation.

**Apparatus.** Four standard operant chambers (26.5 × 22 × 20 cm, Campden Instruments) housed in light- and sound-attenuating boxes were used. These were modified to enable the delivery of a large quantity of sucrose solution as a reward. Each chamber contained a central, recessed magazine that provided access, via a hinged Plexiglas panel, to a liquid dispenser. Peristaltic pumps were fitted that delivered 2 ml of a sucrose solution, over a 0.5-s period, into this recessed magazine. The magazines were sealed with epoxy resin to prevent leaking. The floor of the chambers consisted of 16, 5 mm diameter, steel rods spaced 1.5 cm apart. The chambers were illuminated by a diffuse light source located above the translucent plastic ceiling. Two discrete auditory stimuli were available in each chamber, one a 3-kHz tone, produced by a Sonalert module (Model SC 628) and delivered through a wall-mounted speaker located opposite to the food magazine; the other 10-Hz clicks from a heavy-duty relay mounted behind the wall containing the lever. Each stimulus produced a sound level of 75 dB in the experimental chamber. A BBC Master-128 microcomputer, equipped with the SPIDER extension for on-line control (Paul Fray), controlled the equipment and recorded the data.

**Behavioural procedure.** LI was assessed using an appetitive conditioning paradigm closely modelled on the conditioned suppression paradigm used previously to demonstrate the abolition of LI by systemic injections of amphetamine (Killcross and Robbins 1993). All animals received ten magazine-training sessions in each of which 2 ml of 20% sucrose solution was delivered five times in 40 min, according to a random schedule with an average intertrial interval (ITI) of 6 min. The latency of the animals to enter the magazine following the delivery of reward was measured, together with their overall number of magazine entries and total duration spent in the magazine. This training phase ensured that all animals were taking the sucrose with an average latency of not more than 2.5 s.

After the initial training phase, the animals were randomly divided into four groups, two to receive drug treatment, and two to receive control treatment. One group in each of these two conditions was pre-exposed to the 3 kHz tone (AMP0.5, n = 4, control, n = 5), and the other to the 10 Hz clicks (AMP0.5, n = 4, control, n = 5). Pre-exposure consisted of three 40-min sessions during each