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Latent Inhibition Is Unaffected by Direct Dopamine Agonists

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FELDON, J , A SHOFEL AND I WEINER *Latent inhibition is unaffected by direct dopamine agonists* PHARMACOL BIOCHEM BEHAV **38**(2) 309–314, 1991 —Latent inhibition (LI) refers to the finding that nonreinforced preexposure to a stimulus retards subsequent conditioning to that stimulus when it is paired with reinforcement The development of LI reflects a process of learning not to attend, or ignore, irrelevant stimuli Previous experiments showed that LI was disrupted by low but not high doses of amphetamine, and facilitated by neuroleptic drugs The present experiments sought to investigate the role of dopamine D1 and D2 receptors in LI disruption Experiments 1 and 2 showed that the selective D1 agonist, SKF-38393 (1, 5, 10 mg/kg) and the selective D2 agonist, quinpirole (0 1, 0 3, 1 0 mg/kg), did not affect LI. Experiment 3 showed that both low (0 3 mg/kg) and high (1 5 mg/kg) doses of the mixed D1-D2 agonist, apomorphine, failed to affect LI These results show that LI is not disrupted by direct stimulation of DA receptors and suggest that the differential effect exerted on this phenomenon by apomorphine (and possibly SKF-38393 and quinpirole) and amphetamine is related to the direct versus the indirect agonist action of these drugs In addition, apomorphine at the dose of 0 03 mg/kg, which is believed to activate preferentially DA autoreceptors, did not produce neuroleptic-like facilitation of LI The implications of the results for the involvement of DA mechanisms in LI are discussed

Apomorphine Quinpirole SKF-38393 Latent inhibition Conditioned suppression Rat

THE behavioral effects of the dopamine (DA) releasing drug amphetamine (AMPH) in animals constitute the most prominent animal model of schizophrenia [e.g., (44,48)]. The model is based on the fact that AMPH administration to humans induces psychotic symptoms and exacerbates such symptoms in schizophrenics. The most frequently studied behavioral effects of AMPH in animals are hyperactivity produced by relatively low doses of the drug and stereotypy produced by high doses. Several studies have tested the effects of AMPH on attentional processes, using the paradigm of latent inhibition (LI). In the LI paradigm, nonreinforced preexposure to a stimulus retards subsequent conditioning to that stimulus when it is paired with reinforcement (31). For example, if an animal is preexposed to a series of tones, these tones lose their capability to enter into associations with other stimuli, such as shock, or responses such as shuttle avoidance. This decremental process is considered to reflect a processes of learning not to attend to, ignore, or tune out, irrelevant stimuli (33–36, 40).

Since one of the central characteristics of schizophrenia is an attentional deficit, most often described as an inability to ignore irrelevant, or unimportant stimuli [for a recent review, see (2)], Solomon et al. (49) and Weiner et al. (58–60) suggested that the LI paradigm may be uniquely suitable for demonstrating a schizophrenic-like attentional deficit in AMPH-treated animals. More specifically, AMPH was expected to disrupt LI Indeed, these authors demonstrated that AMPH-treated animals failed to develop LI. In other words, AMPH disrupted animals' capacity to ignore irrelevant stimuli. A series of subsequent studies has provided evidence that the development of LI is mediated by DA mechanisms First, AMPH-induced disruption of LI is antagonized following DA-receptor blockade by neuroleptic drugs [(49), Feldon and Weiner, in preparation]. Second, neuroleptics on their own markedly enhance the LI effect (8, 17, 55, 56). This facilitation is obtained with both typical (haloperidol) and atypical (sulpiride) neuroleptics (16). These data demonstrate that enhancement of DA transmission disrupts LI, whereas blockade of DA transmission facilitates the development of this phenomenon In addition, there is evidence that AMPH-induced disruption of LI is mediated by the mesolimbic DA system. Solomon and Staton (50) showed that microinjections of AMPH into the nucleus accumbens (NAcc), but not into the cuadate nucleus, eliminated LI. In further support of the differential involvement of the mesolimbic and mesostriatal systems in LI we showed (57) that LI is disrupted by low doses of AMPH, which produce locomotor stimulation and which are considered to act primarily via the NAcc, or the ventral striatum, but not by high doses which produce intense stereotypy and which are believed to act primarily via the caudate-putamen, or the dorsal striatum [e.g., (10, 26, 37, 61)].

The above results suggested that the development of LI taps a DA-dependent attentional process which may be relevant to the pathogenesis of schizophrenia [see (16,18)]. In a direct support of this suggestion, the extension of LI studies to the clinic revealed that LI is present in medicated schizophrenics, but is absent in acute schizophrenics tested within the first week of the beginning of a schizophrenic episode (5,32).

The original purpose of the present experiments was to elucidate further the role of DA mechanisms in the disruption of LI by testing the involvement of the two DA receptor subtypes, D1 and D2, in this phenomenon. The D1 receptor is defined as a receptor at which DA stimulates adenylate cyclase to increase cyclic AMP formation, whereas the D2 receptor is either uncoupled to

adenylate cyclase or may inhibit this enzyme and reduce cyclic AMP formation (47,51). Following the discovery of these two receptor subtypes, extensive efforts have been directed towards determining their behavioral functions [e.g., (9,53)]. Since DA released by AMPH apparently binds to both D1 and D2 receptors (45), and since the stimulation of either D1 or D2 receptors within the NAcc produces increase in locomotor activity (13), we sought to determine the relative involvement of each receptor subtype in mediating AMPH-induced disruption of LI

Experiments 1 and 2 revealed that both the selective D1 agonist SKF-38393, and the selective D2 agonist quinpirole, did not disrupt LI. In view of the substantial evidence that the combined stimulation of D1 and D2 receptors is necessary for the full expression of several physiological and behavioral phenomena associated with the stimulation of postsynaptic DA receptors [e.g., (4, 6, 12, 19, 63)], Experiment 3 investigated the effects of the direct, mixed D1-D2 agonist apomorphine (APO) on LI. Since our experiments with AMPH revealed a differential effect of low and high doses of this drug on LI, we used a low (0.3 mg/kg) and a high (1.5 mg/kg) dose of APO which are comparable in terms of their behavioral effects to the doses we used in our AMPH studies In addition, we tested the effects of an "autoreceptor" dose of APO (0.03 mg/kg) which is believed to stimulate preferentially DA autoreceptors, resulting in diminished DA function (7,46). Since such a reduction caused by neuroleptics enhances the LI effect (8, 17, 55, 56), we sought to test whether a low dose of APO would produce a similar enhancement of LI

The potential effects of apomorphine on LI were of interest to us for an additional reason. In contrast to AMPH, administration of APO has not been associated with the development of schizophrenic-form psychosis, even after prolonged treatment at high doses (1, 28, 29, 39). This differential effect of the indirect and direct DA agonists may have important implications for understanding the etiology of schizophrenia (39). A demonstration of a similar dissociation between the action of AMPH and APO on LI would considerably strengthen the parallel between the animal LI model and the human disease state.

EXPERIMENT 1

Subjects

Fifty male Wistar rats (Tel-Aviv University Medical School, Israel), approximately 4 months old, were housed one to a cage under reversed cycle lighting for the duration of the experiment Upon delivery, subjects were maintained on freely available food and water for three weeks. On the 22nd day all animals were weighed and placed on a 23-hour water deprivation schedule which continued throughout the experiment.

Apparatus

The apparatus consisted of four Campden Instruments Rodent Test Chambers (Model 410), each set in a ventilated sound-attenuated Campden Instruments Chest (Model 412). A drinking bottle could be inserted into the chamber through a 0.5 cm diameter hole which was at the center of the left wall of the chamber, 2.5 cm above the grid floor. When the bottle was not present, the hole was covered with a metal lid. Licks were detected by a drinkometer circuit (Campden Instruments drinkometer model 453). The preexposed to-be-conditioned stimulus was a 10-s, 2.8-kHz tone produced by a Sonalert module (Model SC 628) Shock was supplied by a Campden Instruments shock generator (Model 521/C) and a shock scrambler (Model 521/S) set at 0.5 mA, 1-s duration Equipment programming and data recording were controlled by an IBM-compatible personal computer (Amigo-MX).

Procedure

LI was assessed in the conditioned emotional response (CER) procedure which included the following stages:

Baseline. On each of five days, each subject was placed into the experimental chamber and allowed to drink for 20 min. The subjects were then returned to their home cages and an hour later allowed access to water for 30 min.

Preexposure (PE). With the water bottle removed, each animal was placed into the experimental chamber. The preexposed (PE) animals received 40 tone presentations with a variable interstimulus interval (ISI) of 30 s. The nonpreexposed (NPE) animals were confined to the chamber for an identical period of time but did not receive the tone

Conditioning With the water bottle removed, each animal was given two tone-shock pairings Tone parameters were identical to those used in preexposure The 0.5-mA, 1-s shock immediately followed tone termination. The first tone-shock pairing was given 5 min after the start of the session. Five minutes later the second pairing was administered. After the second pairing, animals were left in the experimental chamber for an additional 5 min

Rebaseline. Each animal was given a drinking session identical to sessions of the baseline period. This stage was introduced in view of pilot studies which indicated that a rebaseline day following conditioning decreased response variability on the test day.

Test. Each subject was individually placed in the chamber and allowed to drink from the bottle. When the subject completed 75 licks, the tone was presented, and continued for 5 min. The following times were recorded Time to first lick, time to complete licks 1–50, time to complete licks 51–75 (A period, no-tone) and time to complete licks 76–100 (B period, tone-on) In addition, the total number of licks during the 5 min of tone presentation were recorded. The amount of suppression of licking was measured using a suppression ratio $A/A+B$, where A is the time to complete licks 51–75 (pretone period) and B is the time to complete licks 76–100 with the tone on. A suppression ratio of 0.00 indicates complete suppression, i e , no LI, and a ratio of 0.50 indicates no difference between the times to complete licks 51–75 (pretone period) and the time to complete licks 76–100 (tone on), i.e , LI

The stages of preexposure, conditioning, rebaseline and test were given 24 hours apart. Each subject was run throughout the experiment in the same chamber.

Drug Treatment

SKF-38393 was dissolved in distilled water and injected subcutaneously (SC) in the back of the neck, 20 min prior to preexposure and prior to conditioning. The appropriate dose, 1.0, 5.0 or 10 0 mg/kg, was injected in a volume of 2 ml.

Experimental Design

The subjects were divided randomly into eight experimental groups in a 4×2 factorial design consisting of dose (0.0, 1.0, 5 0, 10.0 mg/kg) and level of preexposure (0, 40) Except for the 5 0 and 10.0 mg/kg PE groups, which included 7 Ss each, all other groups included 6 Ss each. The data of one subject (from the Vehicle-PE group) were lost due to apparatus failure. Thus the final analysis was carried out on the data of 49 Ss.

RESULTS

The eight experimental groups did not differ in their times to

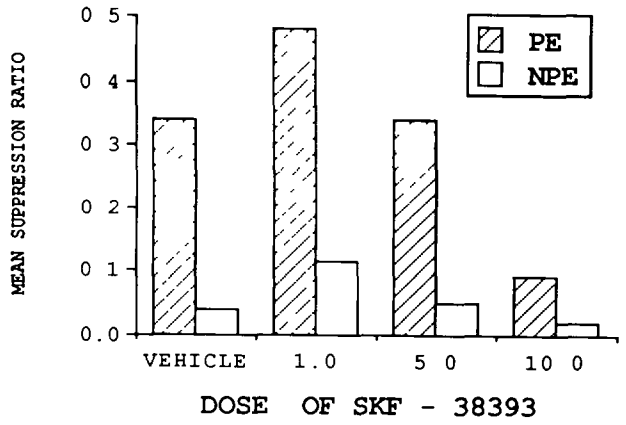

FIG 1 Mean suppression ratios of the preexposed (PE) and nonpreexposed (NPE) groups under four drug doses of SKF-38393 (administered during preexposure and conditioning) vehicle, 1 0, 5 0 and 10 0 mg/kg.

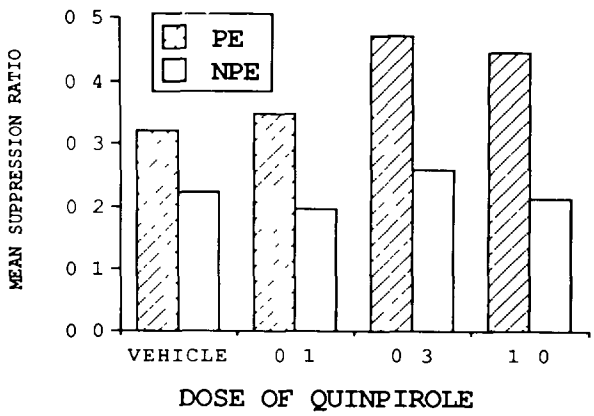

FIG 2 Mean suppression ratios of the preexposed (PE) and nonpreexposed (NPE) groups under four drug doses of quinpirole (administered during preexposure and conditioning) vehicle, 0 1, 0 3 and 1 0 mg/kg

complete licks 51–75 in the absence of the tone. A 4 × 2 ANOVA yielded no significant main effects or interactions (all F's<1). The means of the eight groups in seconds were: vehicle-PE = 4.35; vehicle-NPE = 4.02; 1.0 mg/kg-PE = 8.99, 1 0 mg/kg-NPE = 4.68; 5.0 mg/kg-PE = 11.38; 5.0 mg/kg-NPE = 7 20, 10.0 mg/kg-PE = 6.85; 10 0 mg/kg-NPE = 6.42

Figure 1 depicts the mean suppression ratios of the preexposed and nonpreexposed groups in each of the four drug conditions. As can be seen, in all four drug conditions, the preexposed groups exhibited less suppression of drinking during the presentation of the tone (higher suppression ratios) than the nonpreexposed groups, i e., LI was obtained The presence of LI was supported by a 4 × 2 ANOVA, with main factors of dose and preexposure performed on the mean suppression ratios, which yielded a significant main effect of preexposure, $F(1,41) = 32.67$, $p<0.001$. In addition, as can be seen in Fig. 1, the dose of 10.0 mg/kg led to a marked increase in suppression of licking in both the PE and the NPE groups, compared with the other three drug conditions. This outcome was supported by the significant main effect of drug, $F(3,41) = 5.13$, $p<0.005$. From the inspection of Fig. 1 it may appear that in the SKF-38393 10 mg/kg condition LI was attenuated. However, the pattern of results obtained in this condition merely reflects the fact that the long latencies to complete licks 76–100 exhibited by these animals yield very low values when transformed into suppression ratios LI is defined not in terms of absolute degree of suppression, but in terms of the difference in suppression between the PE and the NPE groups. This difference in the SKF-38393 10 mg/kg condition was of a similar magnitude to other conditions, as can be seen in the mean times (in seconds) to complete licks 76–100 in the PE and NPE groups in this condition (PE = 136; NPE = 265), as compared to the mean times of the remaining drug conditions (Vehicle, PE = 32; NPE = 118; 1 mg/kg, PE = 10; NPE = 88; 5 mg/kg, PE = 54, NPE = 150).

EXPERIMENT 2

Subjects

Subjects were forty-six male Wister rats as in Experiment 1.

Apparatus and Procedure

Same as in Experiment 1

Drug Treatment

Quinpirole HCl was dissolved in saline and injected SC in the back of the neck, 30 min prior to preexposure and prior to conditioning. The appropriate dose, 0 1, 0.3 or 1 0 mg/kg, was injected in a volume of 1 ml.

Experimental Design

The subjects were divided randomly into eight experimental groups in a 4 × 2 factorial design consisting of dose (0.0, 0.1, 0.3, 1.0 mg/kg) and level of preexposure (0, 40). Except for the two 0.0 dose groups which included 5 Ss each, all other groups included 6 Ss each The data of two Ss were lost due to apparatus failure (one from Vehicle-PE and one from quinpirole 0.1-NPE). Thus the final analysis was performed on the data of 44 Ss.

RESULTS

The eight experimental groups did not differ in their times to complete licks 51–75 in the absence of the tone. A 4 × 2 ANOVA yielded no significant main effects or interactions (all F's<1). The means of the eight groups in seconds were vehicle-PE = 3.98, vehicle-NPE = 6.38; 0.1 mg/kg-PE = 4.60; 0.1 mg/kg-NPE = 5.54, 0.3 mg/kg-PE = 9.20; 0.3 mg/kg-NPE = 7 02, 1.0 mg/kg-PE = 8 49; 1.0 mg/kg-NPE = 8.26.

Figure 2 depicts the mean suppression ratios of the preexposed and nonpreexposed groups in each of the four drug conditions. As can be seen, in all four conditions, the preexposed groups exhibited less suppression of drinking during the presentation of the tone (higher suppression ratios) than the nonpreexposed groups, i e., LI was obtained. The presence of LI was supported by a 4 × 2 ANOVA with main factors of dose and preexposure, performed on the suppression ratios, which yielded a significant main effect of preexposure, $F(1,36) = 8.81$, $p = 0$ 005 Although inspection of Fig. 2 suggests that animals in the 0.3 mg/kg condition tended to show lower suppression (and possibly also in the 1.0 mg/kg condition), this trend was not supported by the statistical analysis.

EXPERIMENT 3

Subjects

Subjects were forty male Wistar rats as in Experiment 1.

Apparatus and Procedure

Same as in Experiment 1.

Drug Treatment

Apomorphine hydrochloride was dissolved in saline (contain-

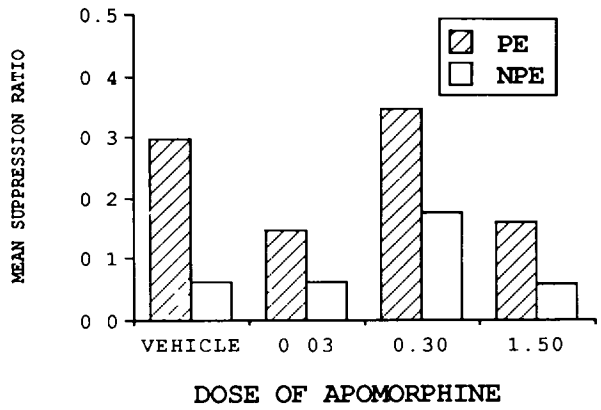

FIG 3 Mean suppression ratios of the preexposed (PE) and nonpreexposed (NPE) groups under four drug doses of apomorphine (administered during preexposure and conditioning) vehicle, 0 03, 0.3 and 1 5 mg/kg

ing 0 1 mg/ml ascorbic acid) and injected SC in the back of the neck, 15 min prior to preexposure and prior to conditioning The appropriate dose, 0.03, 0.3 or 1 5 mg/kg, was injected in a volume of 1 ml.

Experimental Design

The animals were divided randomly to eight experimental groups in a 4×2 factorial design consisting of dose (0.0, 0.03, 0.3, 1.5 mg/kg) and level of preexposure (0, 40). The data of four animals were lost due to apparatus failure (one APO 0.03-NPE, one APO 1.5-NPE, one APO 0.03-PE, and one APO 1.5-PE). Thus the final analysis was performed on 36 animals

RESULTS

The eight experimental groups differed in their times to complete licks 75–100 in the absence of the tone (A periods). The means of the eight groups in seconds were· vehicle PE—5.51, vehicle NPE—7.37; 0.03 APO PE—6.06, 0.03 APO NPE—4.28; 0.3 APO PE—25.24; 0.03 APO NPE—27.57; 1.5 APO PE—10.20; 1.5 APO NPE—7.75. Thus the two 0.3 mg/kg apomorphine groups, preexposed and nonpreexposed, were slower to complete the 25 licks prior to the presentation of the tone, compared with the other six groups which did not differ significantly from each other (the standard error derived from the analysis = 8.52). A 4×2 ANOVA with main factors of drug dose (0, 0 03, 0 3 and 1.5) and preexposure (PE, NPE) yielded only a significant main effect of drug, $F(1,28)=5.19$, $p<0.006$.

Figure 3 depicts the mean suppression ratios of the preexposed and nonpreexposed groups in each of the four drug conditions. As can be seen, in all four conditions, the preexposed groups exhibited less suppression of drinking during the presentation of the tone (higher suppression ratios) than the nonpreexposed groups, i.e., LI was obtained. The presence of LI was supported by a 4×2 ANOVA with main factors of drug dose and preexposure performed on the suppression ratios, which yielded a significant main effect of preexposure, $F(1,28)=4.68$, $p<0$ 04

DISCUSSION

Given the previous findings that the indirect DA agonist, AMPH, disrupted LI, the purpose of Experiments 1 and 2 was to determine whether preferential stimulation of either the D1 or the D2 receptor subtype would result in a similar effect. Results with both SKF-38393 and quinpirole showed that these drugs did not disrupt LI. The failure of direct stimulation of either receptor to mimic the effects of AMPH on LI, could stem from at least two reasons First, it will be recalled that LI is disrupted only by low, hyperactivity-producing dose of AMPH (1 mg/kg), but not by high, stereotypy-producing dose (5 mg/kg). Possibly, none of the doses of SKF-38393 and quinpirole used was equivalent, in functional terms, to low AMPH dose, although intra-accumbal injection of either drug produces hyperactivity (13), and systemically administered quinpirole at comparable doses produces hyperactivity without intense components of stereotypy [e g., (12, 14, 62)] which is probably subserved by the action of this drug on the NAcc, as cells in this structure are significantly more sensitive to D2 than D1 receptor agonist (24,63) Second, since the expression of various DA-mediated behavioral effects has been shown to depend on the stimulation of both receptor subtypes [e g., (4, 6, 12, 19, 63)], the present results with selective DA agonists could imply that concurrent stimulation of D1 and D2 receptors is necessary for the abolition of LI. Both possibilities were ruled out by the finding that APO, which stimulates both receptors, failed to disrupt LI, when given in doses comparable to either the low (hyperactivity-inducing) or the high (stereotypy-producing) AMPH dose (0.3 and 1 5 mg/kg). This result demonstrates conclusively that direct stimulation of DA receptors does not disrupt LI. In addition, it suggests that the differential effect exerted on LI by APO and AMPH is related to the direct agonist action of APO on DA receptors, in contrast to AMPH which increases DA release [e.g., (27)]. However, this suggestion raises the question as to why only low doses of the two drugs exert different effects on LI, whereas high doses produce the same effect (leave LI intact)

A possible answer is provided by a recent hypothesis of Geyer et al. (20) regarding the differing modes of action of low and high doses of AMPH and APO on striatal DA systems. According to these authors, at low doses of AMPH, the drug-induced release of DA is coupled to impulse flow, resulting in enhanced DA output in the presence of a relatively normal pattern of neuronal activity in striatal DA neurons. At high doses of AMPH, DA release becomes uncoupled from impulse flow, and the activation of DA receptors becomes independent of presynaptic neuronal activity This gives rise to perseverative and restricted behavioral output With direct-acting DA agonists like APO, the activation of DA receptors is uncoupled to DA impulse flow *at all doses* The distinct pattern of effects exerted by AMPH and APO on LI as a function of dose is consistent with this hypothesis. Whereas low and high doses of AMPH exert a differential effect on LI, the former disrupting the development of LI and the latter leaving it intact, no such differentiation is evident with low and high doses of APO, both of which act like a high dose of AMPH, i.e., do not affect LI. It should be noted that low doses of the two stimulants were reported to exert different behavioral effects in several additional paradigms, e.g., on response switching in an operant chamber (between two levers) (15, 25, 41, 42), responding for intracranial stimulation (11,21), responding for a conditioned reinforcer (38,43), and conditioned place preference (23,52) These differences were considered by the researchers to reflect the direct vs. indirect agonist properties of the two drugs (11, 21, 23, 38, 43) In regard to conditioned place preference, quinpirole was also found to exert a weak effect in comparison to AMPH (22,23).

Returning to the original question raised by this study regarding the DA mechanisms governing low AMPH-induced LI disruption, it can be concluded that the neural mechanism underlying such disruption is the enhancement of DA release in the NAcc [bearing in mind that intra-accumbens but not intra-caudate AMPH injection disrupts LI, for a detailed account of behavioral and neural mechanisms whereby NAcc activation disrupts LI, see (54)]. In addition, the present results have three more general

implications for the involvement of DA mechanisms in LI. First, the failure of the "autoreceptor" dose (0.03 mg/kg) to produce a neuroleptic-like facilitation of LI indicates that in this paradigm, autoreceptor activation does not produce behavioral effects identical to those produced by postsynaptic receptor blockade. This outcome is consistent with additional reports that autoreceptor agonists fail to mimic the behavioral effects of neuroleptics and potentiate effects of neuroleptics in combination experiments (3) One possible explanation for this difference is that autoreceptor stimulation merely diminishes DA tone, whereas blockade of postsynaptic receptors presumably results in a complete and abrupt shut-off of DA transmission (64) Possibly, the latter, but not the former, effect is necessary for LI facilitation.

Second, the fact that low doses of AMPH disrupt LI, whereas APO and selective agonists, as well as high AMPH, produce normal LI, raises an intriguing possibility that the latter treatments may restore LI in low AMPH-treated animals. This possibility is of particular interest in view of the therapeutic effect of APO in schizophrenia (28,30) Although such effects have been most often attributed to the stimulation of autoreceptors, doses of APO which preferentially activate these receptors in man are unknown, and in fact, it appears that higher APO doses may be preferable (30). Thus the possibility that the therapeutic effects of APO are mediated via postsynaptic mechnaisms cannot be ruled out.

Third, our results imply, quite paradoxically, that DA overactivation produced by APO and high AMPH does not alter the development of a normal LI effect. We suggest that normal LI is obtained only under conditions in which control animals show LI, and that the abnormality in LI development produced by high AMPH and APO would be revealed under conditions in which normal animals cease to show the LI effect. More specifically, since DA stimulation by APO and high AMPH produces behavioral perseveration (20), we suggest that such stimulation also leads to perseveration in ignoring irrelevant stimuli One way to demonstrate such "super LI" is to increase the number of stimulus-reinforcement pairings in the conditioning stage to a level at which normal animals switch to respond according to the new stimulus-reinforcement contingency, i.e., fail to show LI. We predict that under such conditions, animals treated with high AMPH or APO will persevere in ignoring the stimulus, and continue to display LI. Another interesting possibility which can be tested using the above procedure is that LI obtained following low APO is qualitatively different from the "super-LI" produced following high APO and high AMPH. Thus it is possible that animals treated with low APO, in contrast to those treated with high APO and high AMPH, will behave like normal animals, i.e , will not show LI.

Finally, as was pointed out in the introduction, APO, in contrast to AMPH, does not produce psychotic symptoms in humans. The finding that APO does not disrupt LI is consistent with this distinction, and provides additional support for the proposition that AMPH-induced disruption of LI constitutes a valid animal model of schizophrenic attention deficit.

ACKNOWLEDGEMENTS

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REFERENCES

1 Angrist, B , Rotrosen, J , Gershon, S Responses to apomorphine, amphetamine and neuroleptics in schizophrenic subjects Psychopharmacology (Berlin) 67 31–38, 1980
2 Anscombe, R The disorder of consciousness in schizophrenia Schizophr Bull 13 241–260, 1987
3 Arnt, J Behavioral studies of dopamine receptors Evidence for regional selectivity and receptor multiplicity In Creese, I , Fraser, C , eds Structure and function of dopamine receptor New York Alan R Liss, 1987 199–231
4 Arnt, J , Bogeso, K P , Hyttel, J , Meier, E Relative dopamine D1 and D2 receptor affinity and efficacy determine whether dopamine agonists induce hyperactivity or oral stereotypy in rats Pharmacol Toxicol 62 121–130, 1988
5 Baruch, I , Hemsley, D , Gray, J A Differential performance of acute and chronic schizophrenics in a latent inhibition task J Nerv Ment Dis 176 598–606, 1988
6 Carlson, J H , Bergstrom, D A , Demo, S D , Walters, J R Acute reduction of dopamine levels alters responses of basal ganglia neurons to selective D-1 and D-2 dopamine receptor stimulation Eur J Pharmacol 152 289–300, 1988
7 Carlsson, A Dopaminergic autoreceptors In Almgren, O , Carlsson, A , Engel, J , eds Chemical tools in catecholamine research II Regulation of catecholamine turnover Amsterdam North-Holland Publishing Co , 1975 219–225
8 Christison, G W , Atwater, G. E , Dunn, L A , Kilts, C D Haloperidol enhancement of latent inhibition Relation to therapeutic action? Biol Psychiatry 23 746–749, 1988
9 Clark, D , White, F J Review D1 dopamine receptor—The search for a function· A critical evaluation of the D1/D2 dopamine receptor classification and its functional implications Synapse 1 347–388, 1987
10 Clarke, P B S , Jakubovic, A , Fibiger, H C Anatomical analysis of the involvement of mesolimbocortical dopamine in the locomotor stimulant actions of d-amphetamine and apomorphine Psychopharmacology (Berlin) 96 511–520, 1988
11 Crow, T J Specific monoamine systems as reward pathways Evidence for the hypotheses that activation of the ventral mesencephalic dopaminergic neurons and noradrenergic neurons of the locus coeruleus complex will support self-stimulation responding In Wauquier, A , Rolls, E T , eds Brain stimulation reward Amsterdam North Holland-Elsevier, 1976 211–235
12 Dall'Olio, R , Gandolfi, O , Vaccheri, A , Roncada, P , Montanero, N Changes in behavioural responses to the combined administration of D1 and D2 dopamine agonists in normosensitive and D1 supersensitive rats Psychopharmacology (Berlin) 95 381–385, 1988
13 Dreher, J K , Jackson, D M Role of D1 and D2 dopamine receptors in mediating locomotor activity elicited from the nucleus accumbens of rats Brain Res 478 267–277, 1989
14 Eilam, D , Szechtman, H Biphasic effect of D-2 agonist quinpirole on locomotion and movement Eur J Pharmacol 161 151–157, 1989
15 Evenden, J L , Doggett, S J A comparison of the effects of amphetamine and white noise on response switching in the rat Psychopharmacology (Berlin) 97 238–242, 1989
16 Feldon, J , Weiner, I The latent inhibition model of schizophrenic attention disorder Haloperidol and sulpiride enhance rat's ability to ignore irrelevant stimuli Biol Psychiatry, in press
17 Feldon, J , Weiner, I Long-term attentional deficit in nonhandled males Possible involvement of the dopaminergic system Psychopharmacology (Berlin) 95 231–326, 1988.
18 Feldon, J , Weiner, I An animal model of attention deficit In Boulton, A A , Baker, G B , Martin-Iversen, M T , eds Neuromethods, vol 20 Animal models in psychiatry New York Humana Press, in press
19 Gershanik, O , Heikkila, R E , Duvoisin, R C Behavioral correlations of dopamine receptor activation Neurology 33 1489–1492, 1983
20 Geyer, M A , Russo, P V , Segal, D S , Kuczenski, R Effects of apomorphine and amphetamine on patterns of locomotor and investigatory behavior in rats Pharmacol Biochem Behav 28 393–399, 1987
21 Herberg, L J , Stephens, D N , Franklin, K B J Catecholamines and self-stimulation Evidence suggesting a reinforcing role for noradrenaline and motivating role for dopamine Pharmacol Biochem Behav 4 575–582, 1976

22 Hoffman, D C , Beninger, R J Selective D1 and D2 dopamine agonists produce opposing effects in place conditioning but not in conditioned taste aversion learning Pharmacol Biochem Behav 31 1–8, 1988
23 Hoffman, D C , Dickson, P R , Beninger, R J The dopamine D2 receptor agonists, quinpirole and bromocriptine produce conditioned place preferences. Prog Neuropsychopharmacol Biol Psychiatry 12 315–322, 1988
24 Hu, X -T Wang, R Y Comparison of the effects of D-1 and D-2 dopamine receptor agonists on neurons in the rat caudate putamen An electrophysiological study J. Neurosci 8 4340–4348, 1988
25 Koek, W , Woods, J H Response repetition in pigeons pharmacological and behavioural specificity Psychopharmacology (Berlin) 90 475–481, 1986
26 Kolta, M. G , Shreve, P , Uretsky, N J. Effect of pretreatment with amphetamine on the interaction between amphetamine and dopamine neurons in the nucleus accumbens Neuropharmacology 28 9–14, 1989
27 Kuczenski, R. Biochemical actions of amphetamine and other stimulants In Creese, I , ed Stimulants Neurochemical, behavioral and clinical perspectives New York Raven Press, 1983 31–62
28 Lal, S Apomorphine in the evaluation of dopaminergic function in man. Prog Neuropsychopharmacol Biol Psychiatry 12 117–164, 1988.
29 Lal, S , De La Vega, C E Apomorphine and psychopathology J Neurol Neurosurg Psychiatry 38 722–726, 1975
30. Losocuzy, M F , Davidson, M , Davis, K. L The dopamine hypothesis of schizophrenia In Meltzer, H Y , ed Psychopharmacology The third generation of progress New York Raven Press, 1987 715–726
31 Lubow, R E Latent inhibition Psychol Bull 79 398–407, 1973
32 Lubow, R E , Weiner, I , Schlossberg, A , Baruch, I Latent inhibition and schizophrenia Bull Psychon Soc 25 464–467, 1987
33 Lubow, R E , Weiner, I , Schnur, P Conditioned attention theory In Bower, G H , ed The psychology of learning and motivation, vol 15 New York Academic Press, 1981 1–49
34 Mackintosh, N J Stimulus selection Learning to ignore stimuli that predict no change in reinforcement In Hinde, R A , Hinde, J S., eds. Constraints on learning Limitations and predispositions Cambridge Academic Press, 1973 79–100
35 Mackintosh, N J A theory of attention: Variations in the associability of stimuli with reinforcement Psychol Rev 82 276–298, 1975
36 Mackintosh, N J. Conditioning and associative learning New York Oxford University Press, 1983
37 Makanjuola, R O A , Ashcroft, G W Behavioural effects of electrolytic and 6-hydroxydopamine lesions of the accumbens and cuadate-putamen nuclei Psychopharmacology (Berlin) 76 333–340, 1982
38 Mazurski, E J , Beninger, R J The effects of (+)-amphetamine and apomorphine on responding for a conditioned reinforcer Psychopharmacology (Berlin) 90 239–243, 1986
39 Miller, R Major psychosis and dopamine controversial features and some suggestions Psychol Med 14 779–789, 1984
40 Moore, J W Brain processes and conditioning In Dickinson, A , Boakes, R A , eds Mechanisms of learning and motivation A memorial volume for Jerzy Konorski Hillsdale Erlbaum, 1979 111–142
41 Robbins, T W Behavioural determinants of drug action In Cooper, S J., ed Theory in psychopharmacology, vol 1 New York Academic Press, 1981 1–63
42 Robbins, T W , Watson, B J Effects of d-amphetamine on response repetition and win-stay behaviour in the rat In Bradshaw, C M , Szabadi, E , Lowe, C F , eds Quantification of steady state operant behaviour Amsterdam Elsevier/North Holland, 1981 441–444
43 Robbins, T W , Watson, B A , Gaskin, M , Ennis, C Contrasting interactions of pipradol, d-amphetamine, cocaine, cocaine analogues, apomorphine and other drugs with conditioned reinforcement Psychopharmacology (Berlin) 80 113–119, 1983
44. Robinson, T E , Becker, J B Enduring changes in brain and behavior produced by chronic amphetamine administration A review and evaluation of animal models of amphetamine psychosis Brain Res Rev. 11 157–198, 1986
45 Ross, S B , Jackson, D M , Edwards, S R The involvement of dopamine D1 and D2 receptors in the locomotor stimulation produced by (+)-amphetamine in naive and dopamine-depleted mice Pharmacol Toxicol 64 72–77, 1989
46 Roth, R H Dopamine autoreceptors Pharmacology, function and comparison with post-synaptic dopamine receptors Commun Psychopharmacol 3 429–445, 1979.
47 Seeman, P , Niznik, H B Dopamine D1 receptor pharmacology ISI Atlas Pharm 2 161–170, 1988
48 Segal, D S , Schuckit, M A Animal models of stimulant-induced psychosis In Creese, I , ed Stimulants Neurochemical, behavioral and clinical perspectives New York Raven Press, 1983
49 Solomon, P R , Crider, A , Winkelman, J W , Turi, A , Kamer, R M , Kaplan, L J Disrupted latent inhibition in the rat with chronic amphetamine or haloperidol-induced supersensitivity Relationship to schizophrenic attention disorder. Biol Psychiatry 16 519–537, 1981
50 Solomon, P R , Staton, D M Differential effects of microinjections of d-amphetamine into the nucleus accumbens or the caudate putamen on the rat's ability to ignore an irrelevant stimulus Biol Psychiatry 17 743–756, 1982
51 Stoof, J C , Kebabian, J W Opposing roles of D1 and D2 dopamine receptors in efflux of cyclic AMP from rat neostriatum Nature 294 366–368, 1981
52 van der Kooy, D , Swerdlow, N R , Koob, G F Paradoxical reinforcing properties of apomorphine Effects of nucleus accumbens and area postrema lesions Brain Res 259 11–118, 1983
53 Waddington, J L Behavioural correlates of the action of selective D-1 dopamine receptor antagonists Impact of SCH 23390 and SKF 83556, and functionally interactive D-1 D-2 receptor systems Biochem Pharmacol 35 3661–3667, 1986
54 Weiner, I Neural substrates of latent inhibition The switching model Psychol Bull , in press
55 Weiner, I , Feldon, J Facilitation of latent inhibition by haloperidol Psychopharmacology (Berlin) 91 248–253, 1987
56 Weiner, I , Feldon, J , Katz, J Facilitation of the expression but not the acquisition of latent inhibition by haloperidol in rats Pharmacol Biochem. Behav 26 241–246, 1987
57. Weiner, I , Izraeli-Telerant, A , Feldon, J Latent inhibition is not affected by acute or chronic administration of 6 mg/kg dl-amphetamine Psychopharmacology (Berlin) 91 345–351, 1987
58 Weiner, I , Lubow, R E , Feldon, J Chronic amphetamine and latent inhibition Behav Brain Res 2 285–286, 1981
59 Weiner, I , Lubow, R E , Feldon, J Abolition of the expression but not the acquisition of latent inhibition by chronic amphetamine in rats Psychopharmacology (Berlin) 83 194–199, 1984
60 Weiner, I , Lubow, R E ; Feldon, J Disruption of latent inhibition by acute administration of low doses of amphetamine Pharmacol Biochem Behav 30 871–878, 1988
61 Weiss, F , Tanzer, D J , Ettenberg, A. Opposite actions of CCK-8 on amphetamine-induced hyperlocomotion and stereotypy following intracerebroventricular and intra-accumbens injections in rats Pharmacol Biochem Behav 30 309–317, 1988
62 White, F J , Bednarz, L M , Wachtel, S R , Hjorth, S , Brooderson, R J Is stimulation of both D1 and D2 receptors necessary for the expression of dopamine-mediated behaviors? Pharmacol Biochem Behav 30 189–193, 1988
63 White, J W , Wang, R Y Electrophysiological evidence for the existence of both D-1 and D-2 dopamine receptors in the rat nucleus accumbens J Neurosci 6 274–280, 1986
64 Wolf, M. E , Roth, R H Dopamine autoreceptors In Creese, I , Fraser, C , eds Structure and function of dopamine receptors New York Alan R Liss, 1987 45–96