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Sensitization to apomorphine in pigeons: unaffected by latent inhibition but still due to classical conditioning

Abstract When administered apomorphine, pigeons exhibit protracted bouts of pecking behavior. This response is subject to sensitization, as it initially increases with repeated drug injections. The hypothesis is examined that the sensitization is due to a Pavlovian conditioning of the drug-induced pecking to the environment in which it first takes effect. In a first experiment, we attempted to suppress this conditioning by extensively pre-exposing the birds to the test environment and saline injections (latent inhibition procedure). As the experiment yielded undiminished sensitization, it cast doubt on the conditioning hypothesis. However, while inhibitory pretraining also proved ineffective in a second experiment, a shortening of response latencies specific to the environment in which the animals had first experienced the apomorphine effect supported the conditioning hypothesis. It is suggested that the absence of latent inhibition may be due to the interference of a context-dependent conditioning effect. A third experiment that examined the hypothesis that the reinforcing properties of apomorphine might be attributable to its well known anorectic properties. The results provided some support for this notion. At the same time, they also confirmed that apomorphine-induced pecking conditions reliably to environmental cues. These cues are then by themselves capable of provoking conditioned pecking.

Key words Apomorphine · Pigeons · Pecking · Sensitization · Tolerance · Classical conditioning · Latent inhibition · Reinforcement mechanism · Hunger reduction

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Introduction

Although apomorphine, a potent dopamine (DA) agonist, is best known for being a clinically effective emetic when injected at high doses, it is also known to elicit a variety of feeding stereotypes in diverse animal species, including humans, when administered in lower dosages. In birds, for example, 1 mg apomorphine per kg body weight injected intramuscularly (IM) with a delay of a few minutes elicits a protracted bout of pecking involving several thousand pecks and lasting for more than 1 h (Brunelli et al. 1975; Machlis 1980). Control injections of saline yield at most a dozen pecks during the same period. However, the maximal behavioural response to a given dose of apomorphine only develops after several injections, meaning that an initial sensitization to the drug takes place (Brunelli et al. 1975; Delius 1985; see also Szechtman et al. 1987; Mattingley et al. 1988; Stewart and Badiani 1993). Lindenblatt and Delius (1987) demonstrated that the apomorphine-induced pecking response of pigeons would classically condition to salient environmental stimuli, namely cages with striking colored patterns. After pigeons had experienced the unconditioned drug effect (US, UR) several times in such a conditioning cage (CS), they reliably showed a conditioned pecking response (CR) when placed into it without having been administered any apomorphine. Burg et al. (1989) additionally showed that pigeons actively sought stimulus cages in which they had previously experienced the drug effect. This demonstrated that apomorphine has a reinforcing effect.

The same authors also reported the results of an experiment in which two groups of pigeons were either repeatedly injected with the same dose of apomorphine in the same distinctive cage or in different distinctive cages. While the former group revealed the drug sensitization mentioned above, the latter group developed some tolerance to apomorphine. These findings suggested that the sensitization usually observed with

repeated apomorphine injections might be mainly, or even exclusively, due to the development of a pecking CR to a particular cage CS adding to the unconditioned, purely pharmacological response to the drug. Although Burg et al. assumed that the tolerance effect observed in the variable cage group was of a pharmacological nature, they could not, because of the design of their experiment, properly exclude the possibility that it might have also been caused by a conditioning phenomenon, namely latent inhibition (LI).

The three experiments reported in this paper were carried out to gain further insights into the behavioral processes associated with repeated apomorphine administration in pigeons. Although they are concerned with a somewhat special experimental preparation, they have the advantage of involving a comparatively specific response. The issues involved, in any case, are of wider psychopharmacological interest, as learning effects of a similar kind have been found to influence the responses to apomorphine and other drugs in various contexts (see, for example, Siegel 1983; Baker and Tiffany 1985; O'Brien et al. 1986; Mattingley and Gotsick 1989; Carey 1991; Schnur 1992; Stewart and Badiani 1993; Killcross et al. 1994).

The first experiment sought to determine whether latent inhibition (LI) effectively plays a role in apomorphine conditioning. LI refers to the fact that repeated pre-exposures to a prospective CS in the absence of an effective US reliably weakens, delays or even prevents the subsequent development of a CR when the same stimulus is paired with an effective US (Weiner 1990; Killcross et al. 1994). If sensitization to apomorphine in pigeons is mainly due to Pavlovian conditioning as suggested above, it should in principle be attenuated if the environmental CSs in which the birds experience the apomorphine effect are their familiar home cages, which previously have been largely associated with innocuous saline injections.

Since the above experiment eventually did not reveal any LI effect, the second experiment was designed to test whether a corresponding pretreatment would be effective within a classical conditioning procedure. The LI pretreatment was planned to interfere with the subsequent conditioning to apomorphine of one group of subjects but not with that of another group. The response measure this time was the promptness of the CS/US-induced pecking responses, rather than their magnitude. In many Pavlovian conditioning preparations, the reduction in response latency that develops with successive training pair repetitions is a proven measure of successful conditioning that does not require any intermittent CS-only presentations (Davey 1981; Hudson et al. 1994). We expected that this early indicator of conditioning might be more sensitive to the effect of LI than the overall response strength measure used in the first experiment.

The last experiment returned to a conventional classical conditioning paradigm not including any inhibitory preconditioning. It was primarily intended to reconfirm the emergence of a pure CR in response to a CS unaccompanied by a US, but it was also designed to explore the mechanism through which apomorphine might be exerting its reinforcing effect. Although the apomorphine pecking of pigeons is in some ways similar to their forage pecking (Brunelli et al. 1975; Delius 1985; Siemann and Delius 1992), it is mostly directed at non-edible items and very rarely leads to actual ingestion (Lindenblatt 1986). In fact, quite small doses of apomorphine suppress feeding in pigeons (Deviche 1984; see also Duterte-Boucher et al. 1989). The mechanism through which food rewards are thought to have a reinforcing effect in the course of common appetitive conditioning is hunger reduction (Davey 1981; Wise and Rompre 1989). Apomorphine could conceivably be acting through the same mechanism. If this idea was correct, food-deprived pigeons injected with apomorphine could be expected to experience a larger hunger reduction and condition more readily than equally treated satiated pigeons.

Materials and methods

The experimental subjects were adult pigeons (*Columba livia*) bred from local homing stock. A week before the experiments started, they were moved from an outside aviary to individual 40 × 40 × 45 cm stainless-steel wire-netting cages. These home cages were located in a well ventilated and brightly lit (12 h on/12 h off) room. Animal maintenance and experiments conformed to the standards and rules laid down by German animal protection laws and regulations.

Latent inhibition

Twelve pigeons were used in the LI experiment. For the first 5 days of the experiment all 12 subjects were injected IM (breast) with 0.5 ml saline once in the morning and once in the afternoon. For injection, the animals were briefly removed from their cage, but were then immediately returned to it and left undisturbed. This treatment was meant to associate an LI with the home cage and the injection procedure. To keep the design simple, no control groups were included, as the development of apomorphine sensitization without any inhibitory pretreatment had been determined in another study (Wynne and Delius in preparation), and also in the response conditioning experiment to be described below.

The subjects were then randomly divided into groups L (lower dose) and H (higher dose), each comprising six animals. The saline injection routine described above continued (to maintain inhibition) for a further 30 days except that now, on every second day either in the morning or in the afternoon (alternating quasi-randomly), the subjects were instead administered either 0.2 mg/kg (group L) or 0.5 mg/kg (group H) apomorphine. Comparatively low doses were chosen because of the fear that the sensitization induced by a more potent dose might overcome the LI that we wanted to demonstrate. The pigeons were observed beginning 5 min after each apomorphine injection through a one-way screen from a cubicle located 3 m away from the cage rack. Pecks emitted in the following 15 min were counted.

Latency conditioning

Twelve new pigeons were used for the experiment that combined classical conditioning with LI. For the first 5 days of the experiment, each subject was injected IM with 0.5 ml saline each morning and immediately returned to their plain home cages. This represented the renewed effort to induce LI with reference to the home cage and the injection procedure.

The training phase followed. The subjects were randomly divided in two equally sized groups D (distinctive CS^+) and P (plain CS^+). Over the next 10 mornings on alternate days, the D group subjects were injected IM either with 0.5 ml saline and placed into their home cage (CS^-, previously inhibited) or with 0.5 mg/kg apomorphine and immediately placed in a distinctive cage with three walls lined with black foil peppered with yellow dots (8 mm diameter, 10 per dm^2; CS^+). This cage was initially novel to the birds and thus not associated with any inhibitory pretreatment. The P group subjects were similarly but conversely treated being placed in the plain home cage (CS^+, inhibited) when injected with apomorphine and in the distinctive cage (CS^-, non-inhibited) when injected with saline. When placed in the distinctive cage all subjects remained there for 2 h before being returned to their plain home cage.

Six days of tests followed. The 12 subjects were injected with 0.2 mg/kg apomorphine each day. On alternate days they were then placed either in the CS^+ cage or in the CS^- cage. The lesser dose used during these tests was meant to elicit a weaker direct UR to the drug, thus permitting any CR due to the cage environments to come to the fore. Whenever the subjects had been injected with apomorphine, they were immediately afterwards observed in the corresponding cage from the one-way screen cubicle until they had issued the first few pecks. The latency from the end of the drug injection to their first and fifth peck was recorded with a stopwatch.

Response conditioning

Twenty-four new pigeons were used in this experiment meant to confirm the occurrence of a pecking CR in response of a CS alone and to investigate the mechanisms of apomorphine reinforcement. Eight pigeons were deprived to 80% of their ad libitum weight through rationed feeding (group F, food deprived). Eight were maintained 2-days water deprived through rationed watering (group W, water deprived). This latter group was included as control for any general activation effects that deprivation as such might have on conditioning. Apomorphine has no appreciable effect on the intake of water (Deviche 1984; compare Dourish and Cooper 1981). Eight pigeons were maintained fully fed and watered (group N, non-deprived). On every second day each animal received a 1-mg/kg apomorphine IM injection and was placed in the distinctive cage described above (black lining, yellow dots; CS^+). Their pecking was recorded for 15 min but they remained in that cage until pecking ceased. Each animal received six drug injections. On intervening days they were injected with 0.5 ml saline and placed for an equivalent duration in an analogously distinct cage with white lining and green dots (CS^-). In an earlier experiment, this cage had proved to be an as effective CS as the above-mentioned black/yellow cage (Lindenblatt and Delius 1987; Burg et al. 1989). After completion of the training phase the deprived animals (groups F and W) were put back on ad libitum food and water.

The test phase began 3 days later. The animals were injected with 0.5 ml saline and placed on alternate days in the CS^+ cage and the CS^- cage, pecks being recorded as described above. Over 6 days, they were tested three times in each kind of cage. The F and W groups were then deprived again and all animals were retrained as described above for 6 days. With groups F and W subjects still deprived, they were then tested again as above for 4 days, that is twice in each cage. This additional testing under deprivation was motivated by the expectation that it might yield stronger differential CRs. As a control for investigator bias, the observer recording the subjects' pecking activity was uninformed as to which group the various animals belonged to.

Results

Latent inhibition

The peck scores recorded during the 15 sessions after apomorphine administration were averaged separately for each of the two dosage groups (L, 0.2 mg/kg; H, 0.5 mg/kg). They are shown in Fig. 1. Both groups, within the expected dose effect differences, exhibited a clear sensitization effect. In the case of the low dose group L, the response increase from the first to the fourth session was significant; in that of the high dose group H, the response increase from the first to the third session were significant (Wilcoxon tests, $T_6 = 19$ and $T_6 = 21$, $Ps < 0.05$; combined $T_{12} = 76$, $P < 0.005$). Beyond the fourth session the curves oscillate around two dose-dependent asymptote pecking rates. There is no evidence of any longer term sensitization.

For comparison, Fig. 1 includes examples of sensitization curves obtained in experiments not involving LI treatments of any kind. One is that of the N group of pigeons from the response conditioning experiment reported in this study (H^+). The other two (L°, H°) are taken from the baseline phase of an experiment reported by Wynne and Delius (in preparation). In both these experiments, unlike the present one, the pigeons experienced the effects of repeated apomorphine administrations in a novel, distinctively colored cage, not associated with any saline preinjections. Even leaving aside the L° curve, evincing an admittedly uncommon absence of response increments, the sensitization courses obtained in the present experiment were at least as pronounced as those occurring in these other experiments.

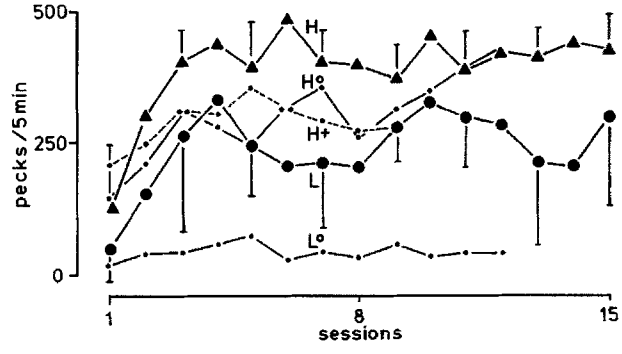

Fig. 1 Latent inhibition experiment. Average pecking rates (SD for alternate sessions) of pigeons upon repeated injections of two doses of apomorphine (L: 0.2 and H: 0.5 mg/kg) in their home cages in which they had been inhibitorily preconditioned with saline injections. For comparison, equivalent data from Wynne and Delius (in preparation), baseline phase, (L°: 0.2 mg/kg and H°: 0.5 mg/kg) and from exp. III, group N (H^+: 0.5 mg/kg) using novel, distinctive cages not associated with any LI treatment

Latency conditioning

The latency data pertaining to the first and fifth peck yielded virtually parallel results, those to the first peck being consistently only about a mean 50 s shorter. In the account that follows, for the sake of simplicity, we refer only to the fifth peck latencies. The training phase yielded a significant drop in peck latency occurring between the first and second apomorphine injections in both the D and P group (Fig. 2; Wilcoxon tests, $T_6 = 18$ and $T_6 = 21$, Ps < 0.05; combined $T_{12} = 71$, $P < 0.005$). Latency changes beyond the second training injection were minor and insignificant. It is reasonable to attribute these decreases in latency to the same sensitization process underlying the increases in response rate recorded in the previous experiment. As in this latter experiment, the pretreatment meant to generate a LI attaching to the home cages and the injection procedure again proved practically ineffective, as the latency decrements (sensitization) affecting the P group were not significantly less than those of the D group (Mann-Whitney test).

This conclusion is further supported by the fact that during the test sessions, the apomorphine-induced peck latencies produced by the P group in the plain, purportedly LI-affected CS^+ cages were not significantly longer than those generated by the D group in the distinctive, inhibition-free CS^+ cages (Mann-Whitney test). Also, the latencies of the D group in the plain, purportedly LI associated CS^- cages, were not significantly longer (they were actually somewhat shorter) than those of the P group in the distinctive, inhibition-free CS^- cages (Mann-Whitney test).

The test phase results, however, agree well with the notion that the pecking response elicited by apomorphine was conditioned to the CS^+. For both the D and P groups, the test session latencies in the CS^+, apomorphine associated cages were significantly shorter than those in the CS^-, saline associated cages (Wilcoxon tests, each group $T_6 = 21$, $P < 0.05$; combined $T_{12} = 78$, $P < 0.001$). In other words, the sensitization reflected in the latency shortening that had occurred during the training phase was only maintained in the environment in which the apomorphine effect had been initially experienced. The fact that latencies of apomorphine-induced pecking evinced in the CS^- cages were somewhat longer than those evinced during early training in the CS^+ cages (Fig. 2) even suggests the incidence of some drug tolerance. However, the test data were obtained with a lower apomorphine dose (0.2 mg/kg) than the training data (0.5 mg/kg), and this alone could have yielded the tendency towards longer latencies. Nevertheless, the peculiar fact that the repeated injections of apomorphine in the CS^- cages during the tests did not lead to the same persistent shortening of latencies as during training (Fig. 2) is an additional sign that some environment-independent tolerance to apomorphine was interfering with renewed development of sensitization.

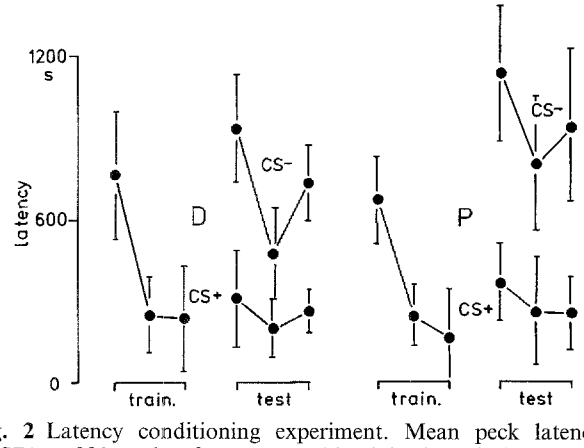

Fig. 2 Latency conditioning experiment. Mean peck latencies (± SD) to fifth pecks after apomorphine injections during training (0.5 mg/kg doses, CS^+ cages, first three sessions only) and test sessions (0.2 mg/kg doses, CS^+ and CS^- cages), separately for P (plain CS^+) and D (distinctive CS^+) pigeon groups

Response conditioning

The mean apomorphine-induced pecking observed during the training and retraining phase of this experiment is shown separately for each group in Fig. 3A. All show the usual sensitization course. During at least the retraining phase, the F group yielded the highest response rates, the W group the next highest and the N group the lowest. This could perhaps be seen as already supporting the hypothesis that food deprivation would potentiate the reinforcing effect of apomorphine but the differences do not quite reach significance (Jonckheere test).

Because there were no significant differences between the results of the first and second tests, the deprivation operating during the second having no enhancing effect (Wilcoxon test), the response rates were pooled. Disregarding the group divisions, the average number of pecks emitted in the CS^+ cage was very significantly higher than that produced in the CS^- cage ($T_{24} = 281$, $P < 0.001$). The result confirms that in the present preparation, after suitable training, a pecking CR to the a CS^+ environment obtains even in the complete absence of an apomorphine US (Lindenblatt and Delius 1987).

Each of the pigeon groups (Fig. 3B) produced on average more pecks in the CS^+ than in the CS^- cage. The differences were significant for the W and F groups (Wilcoxon tests, both $T_8 = 36$, $P < 0.005$) but did not quite reach significance for the N group. Notice, however, that in the above-mentioned study Lindenblatt and Delius, using more pigeons, had already demonstrated a significant discrimination for this latter undeprived condition. The different discriminatory performances here are best reflected by the percent pecks emitted in the CS^+ cage out of the total emitted

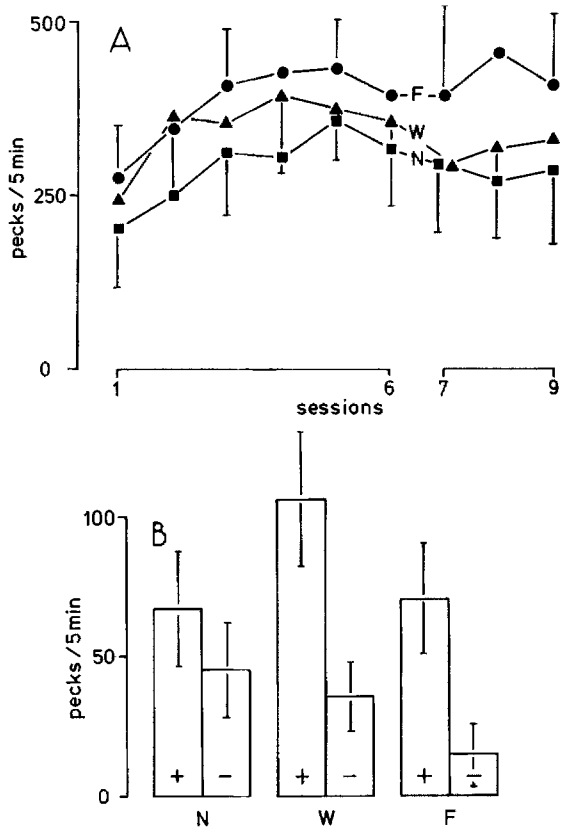

Fig. 3A, B Response conditioning experiment. **A** Mean pecking rates (SD for alternate sessions) of food-deprived (*F*), water-deprived (*W*), and non-deprived (*N*) pigeons upon repeated apomorphine injections. **B** Mean pecking responses (± SD) of N, W, and F pigeons in the CS^+ and CS^- cages after saline injections

in both the CS^+ and CS^- cages where the score 50% represents no discrimination. The highest mean percent score occurred with the F group (89.6%), followed by the W group (83.5%) and the N group (74.7%), the ordering being significant (Jonckheere test, $J_{8,8,8} = 127$, $P < 0.05$). This result is in line with the hypothesis that apomorphine would have a stronger conditioning effect in hungry animals by causing a larger hunger reduction. The fact that the thirsty pigeons exhibited better conditioning than the non-deprived ones suggests that a simple activation due to deprivation generally might also have played a role. However, it is worth keeping in mind that water deprivation automatically, through a concomitant restriction of food intake, is known to generate secondary hunger in pigeons (McFarland 1964). The hunger reduction argument could thus, in some measure, have also applied to our thirsty group.

Discussion

The first experiment confirmed again that repeated injections of apomorphine taking effect in the same environment lead to an initial increase in the pecking response induced by the drug (Brunelli et al. 1975; Delius 1985). What is remarkable, in this instance, is that the environment in which the sensitization developed was the familiar home cage where the pigeons had previously experienced multiple saline injections. In theory, these cages should have been associated with a thorough LI capable of preventing any substantial subsequent conditioning to them. The finding that the sensitization was, in fact, patently unaffected by the preexposure seems to argue against the hypothesis that the sensitization to apomorphine is due to a classical conditioning of the drug response to the cage environment.

However, the results of the second experiment showed that apomorphine pecking reliably conditions to cues associated with the environment in which pigeons initially experience the drug effect in such a manner that it effectively yields an environment-specific sensitization. This agrees with Burg et al.'s (1989) findings and interpretation, despite the fact that the present experiment employed a somewhat different design and response measure. At the same time, the results corroborated that a LI pretreatment analogous to that used in the first experiment could not impair the emergence of a CR to the corresponding environmental CS. This absence of a LI effect in turn strengthen Burg et al.'s assumption that the significant environment-independent tolerance that they observed in their experiment was not due to the incidence of LI.

The third experiment supported an expectation arising from the same study, namely that hunger may potentiate the rewarding effects of apomorphine. Its results indicated a stronger differential conditioning in food-deprived pigeons than in water- or non-deprived pigeons agreeing with the hypothesis that apomorphine may act reinforcingly through its anorectic properties. However, it has to be kept in mind that the neural reward-signalling system may be quite generally based on dopaminergic transmission (Wise and Rompre 1989). It is thus possible that circulating apomorphine also acted through direct stimulation of this system and not only indirectly through its hunger-reducing (anorexic) effects. The fact that the conditioning effects obtained with direct electrical activation of this reward system in pigeons are often also potentiated by hunger (Delius and Pellander 1982) may be relevant here.

More importantly, perhaps, the same experiment additionally confirmed the finding of Lindenblatt and Delius (1987) that pigeons, after suitable conditioning, evince a pure, though admittedly modest pecking CR to an environmental CS in the absence of the apomorphine US. In this respect, the apomorphine pecking of pigeons is similar to the apomorphine-conditioned locomotory turning shown by DA-system lesioned rats (Carey 1990; Hudson et al. 1994). It differs, however, from the conditioned locomotory activity exhibited by intact rats where, strikingly, only the CS/US combination, but not the CS alone is capable of eliciting a significant CR effect (Mattingly and Gotsick 1989; compare Stewart and Badiani 1993). We shall return to this issue later.

The fact that our two relevant experiments did not yield any evidence of an LI effect is remarkable. The inhibitory devaluation of prospective CSs has been a quite reliable phenomenon in many other Pavlovian preparations (Tranberg and Rilling 1978; Weiner 1990; Killcross et al. 1994). However, casual observations of apomorphine treated pigeons in their habitual home cages have suggested to us a reason why the LI treatments may not have been effective in our experiments. It is striking that such pigeons exhibit a renewed interest in many of the small features of their cages and inspect these thoroughly, much as if they were quite novel (compare Lanerolle and Millam 1980). Indeed, an autoradiographic metabolic labelling study reveals that among many other central-nervous structures, apomorphine also activates several of the pigeon's visual system nuclei (Delius and Scheich 1995; compare also Parkinson 1989). During sensitization or conditioning, apomorphine could modify the perception of a previously LI treated CS, converting it effectively into a differing and novel CS liberated from LI. This phenomenon would provide the basis for a state-dependent learning effect, in the sense that the LI acquired in the undrugged state could not be retrieved while under the influence of the drug (Mackintosh 1974; Overton 1991). This state-dependent retrieval can be considered as a special instance of the more general phenomenon that the ready recall of a given memory content is substantially dependant on the precise reinstatement of the corresponding conditioning context (Thomas and McKelvie 1982; Bouton 1993; McLaren et al. 1994).

An analogous conditional retrieval effect might also explain why in pigeons the CR pecking elicited by the CS alone is rather weak compared with the strong pecking increment accruing during the initial presentations CS/US combination (last experiment here; see also Lindenblatt and Delius 1987). The CS presented alone may simply lack the original drug-state context provided by the apomorphine US. Suitably extended, this type of argument could perhaps help to explain why Mattingly and Gotsick (1989) did not obtain a locomotor activity CR upon presentation of the environmental CS alone in their normal rats, whereas Carey (1990) and Hudson et al. (1994) did so with their unilaterally, nigrostriatal system lesioned rats. Conceivably, the lesions of the latter animals, without affecting much the US properties of apomorphine, significantly weakened its context-setting, CS-modifying potencies. Of course, only further experiments can decide whether context effects such as these really contribute to the ample variety of drug tolerance and sensitization courses already identified (Stewart and Badiani 1993). That drug-induced contexts can, however, play an important role in determining the outcome of psychopharmacological experiments has been established by Killcross et al. (1994) in studies on the amphetamine modulation of LI effects in rats.

In conclusion, none of the present experiments yielded any evidence for an environment-independent sensitization to apomorphine. Thus as far as the pigeons' pecking is concerned, the increased responsiveness to the drug does not appear to be due to any simple pharmacological process such as DA receptor multiplication or receptor tuning directly triggered by agonist stimulation. Except for the peculiar ineffectiveness of the LI pretreatment accounted for above, the present results agree instead with the hypothesis that the sensitization observed upon repeated injections of apomorphine in pigeons is caused primarily by a conditioning process involving the association of the drug effect with environmental stimuli (Burg et al. 1989). Whether these processes are still mediated by DA-related synaptic changes, or by unrelated synaptic modifications (compare Carey 1990) is an issue that clearly requires additional investigation .

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