Sensitization to apomorphine, effects of dizocilpine NMDA receptor blockades

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Abstract

The dopamine agonist apomorphine (apo) elicits bouts of stereotyped pecking in pigeons, a response which increases with successive apo injections. This sensitization is strongly context-specific and has been suggested to arise through a Pavlovian conditioning to both external and internal cues. We hypothesized that this learning involves dopamino-glutamatergic interactions and investigated the issue by inducing NMDA glutamate receptor blockades with the antagonist dizocilpine (diz). A first experiment examined the effects that four different doses (ranging between 0.05 and 0.12 mg/kg) of diz co-administered with a standard dose of 0.5 mg/kg of apo had on the development of the incremented response and on the later expression of the conditioned pecking response. Both responses were impaired by doses of around 0.10 mg/kg diz. A second experiment assessed whether either a diz treatment or a diz plus apo co-treatment affected the development of a subsequent sensitization to apo. The first treatment had no effect on the latter sensitization. A part sensitization that arose with the second treatment did not transfer to the final sensitization. The last experiment examined whether the administration of diz had an immediate effect on the incremented responding to apo and on the conditioned response shown by already sensitized pigeons. No effect was apparent with the first treatment, but there was a marked response inhibition with the second treatment. It is concluded that NMDA glutamate receptors play an important role in apo-induced sensitization in pigeons which is compatible with the Pavlovian conditioning account of sensitization.

Keywords: Dizocilpine; MK-801; Apomorphine; Sensitization; Conditioning; Glutamate; Dopamine; Pigeons; Pecking

1. Introduction

A behavioral response increment that occurs in rodents upon repeated administration of psychostimulant drugs such as amphetamine and cocaine is widely suspected to be connected with their addictive potency in humans [47]. The sensitization phenomenon appears to be linked with the activation of dopaminoreceptive mechanisms which these drugs are known to trigger [13,21,31,53,54]. Non-addictive, more specific, and more direct dopamine agonists than the two previously mentioned drugs, such as apomorphine (apo) and quinpirole are, however, also capable of producing a sensitization effect of comparable nature [6,42,44,51,57]. This may be due to the mes-telencephalic reward-signalling system of vertebrates which is well known to largely rely on dopaminergic transmission [14,40,49]. This fact may also be responsible for the finding that the sensitization to dopamine agonists in rodents is often at least partly

context-specific. It seems possible that this finding is due to a conditioning to the environmental cues that happen to be contingent with the drug experience [4,8,11,16,38].

We have proposed that the behavioral sensitization which pigeons show in response to repeated administration of apo is largely, if not exclusively, due to a Pavlovian conditioning process. When a dose of about 0.5 mg/kg apo is administered for the first time to pigeons it occasions a bout of several hundred pecks that lasts somewhat less than 1 h, an unconditioned response (UR). When the same dose is repeatedly injected, an incremented response (IR) develops and the pecking in the experimental cage increases to an asymptotic level of several thousand pecks produced within approximately 1.5 h [17,60]. If later challenged with saline (sal) in the same cage, the pigeons exhibit a conditioned pecking response (CR) of about a hundred pecks within about 30 min, a response that gradually extinguishes with sal-treatment repetitions [12,28,39]. Both the IR and the CR are markedly context-specific in the sense that they are only evident when the pigeons are exposed to the same experimental cage in which they were sensitized. If the pigeons are placed in a sufficiently different cage so as to avoid a simple stimulus

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generalization, the two responses are virtually absent. This is even so when the pigeons were pre-familiarized with the different cage while being sal-treated [3,34]. Furthermore, when thus-treated pigeons are later given the choice, their IR and CR pecking is nearly exclusively directed at visual features characteristic of the cage which they experienced while apo injected rather than at visual features typical of the cage which they experienced while sal was injected [33]. All this suggests that the cage in which the pigeons repeatedly experienced the effects of apo comes to act as a $CS_{\text{cage} \times \text{apo}}$ to which a pecking CR develops. The fact that this CR seen in the relevant cage upon a sal challenge is of a markedly lesser magnitude than the IR obtained when the pigeons are challenged with apo in that same cage, is explained by the circumstance that the drug, besides acting as a US eliciting a UR, also induces an internal state that has demonstrable CS_{apo} properties [19,20,30]. The large IR that arises during the sensitization to apo is apparently driven by an approximately multiplicative stimulus compound $CS_{\text{cage} \times \text{apo}}$. The CS_{apo} component is naturally absent when a sal challenge in the CS_{cage} yields the weak pecking CR. A similarly weak, partial CR due to the CS_{apo} component alone can sometimes be obtained when the pigeons are apo-challenged in a cage different from that in which they were sensitized [33]. However, this response is often obscured by the strong, though somewhat variable, pecking UR directly elicited by the drug [3,9,18].

Classical conditioning learning is commonly ascribed to a neurophysiological long-term potentiation (LTP) processes known to occur in many glutamatergic synapses in vertebrates. The apo-induced conditioning that we hypothesize is likely to involve a dopamine-enhanced LTP variant [7,35]. The changes in synaptic efficacy underlying this variant are nevertheless attributed to a lasting increase in glutamatergic rather than dopaminergic synaptic transmission. The longer term modifications associated with LTP are thought to be principally due to an increase in AMPA receptor density in the post-synaptic membrane, an increase that can be facilitated by the co-activation of dopamine receptors [15]. In the present study we examine whether NMDA receptors actually play a role in the sensitization to apo shown by pigeons. If so, that would constitute further evidence that the sensitization is based on a conditioning process. The matter was examined by administering the NMDA receptor blocker dizocilpine (diz), also known as MK-801, during successive phases of the sensitization process. Diz binds in a non-competitive manner to the ionotropic NMDA receptors and near-permanently blocks their normal response to glutamate. This blockage, however, only affects already glutamate-activated, open channel receptors. In mammalian brain tissue diz reaches its maximum concentration some 30 min after it has been intramuscularly administered and persists there with a half-life of about 2 h [55]. The receptors blocked by diz are displaced to the periphery of the post-synaptic membrane and replaced within about 10 min by viable NMDA receptors [48,52]. The overall pool of vi-

able NMDA receptors probably becomes exhausted when both glutamate and diz are present for some length of time. As diz vanishes, the pool is replenished by a slow unblocking of receptors and by a slow synthesis of new NMDA receptors, a process that may take some 18 h (G. Westbrook, personal communication). Apo, incidentally, is a potent, competitive agonist at D1- and D2-type dopamine receptors, acting within a few minutes after having been injected intramuscularly. It has a half-life of about 20 min in mammalian neural tissue [41,50].

The results of three experiments are reported. The first experiment dealt with the effects that four different doses of diz co-administered with the standard dose of apo had on the development of the IR and the subsequent expression of the CR. The second experiment assessed whether either a diz alone or a diz plus apo pretreatment affected the development of a subsequent sensitization IR to apo. The last experiment examined whether the administration of diz had an immediate effect on the expression of the IR and the CR in previously apo-sensitized pigeons.

2. Methods

2.1. Subjects and procedures

Drug naive adult pigeons (*Columba livia*), bred from local homing stock and weighing between 450 and 550 g were used. A week before the experiments began they were moved from an outside aviary to individual 40 cm × 40 cm × 45 cm stainless steel grid cages. These home cages were located in a well-ventilated and brightly lit (12 h on and 12 h off) room. Animal maintenance and treatments complied with the standards and rules specified by the German animal welfare law. It should be mentioned that at one point we discovered that we had accidentally used some pigeons that descended from inadvertently inbred pairs. These pairs had produced a high proportion of abnormally apo unresponsive offspring which were most probably homozygous for a recessive insensitivity mutant. The relevant birds ($n = 5$) were excluded and replaced by an equal number of identically treated, normally outbred pigeons.

The experimental cages used were modified standard cages. Their inner back- and side-wall surfaces were lined with white panels speckled with dark green dots (0.8 mm in diameter, about 10/100 cm²). These distinctive cages were located in a separate, brightly lit room equipped with a video-camera and -recorder. Drug treatments were administered on a once-a-day schedule. After having received these treatments (see the following for details) the pigeons were immediately and individually placed into the distinctive cages and videotaped for 20 min before they were returned to their home cages. The videotapes were later reviewed and the numbers of pecks per session were counted with a tally-counter. The pecks of pigeons involve a quite distinct, easy to recognize motion pattern [29] and permit quite

accurate counts that yield inter-observer agreement coefficients of $r_s > 0.85$. Nibbling and preening responses that sometimes occurred in lieu of pecking when the reaction to apo was partly suppressed by co-administered diz were disregarded. The experimental schedules to which the various groups of pigeons were subjected invariably consisted of two successive phases, mostly involving two different treatments. The abbreviated Xxx/Yyy-type names given to the groups allude to these sequential treatments. Daily mean scores and standard errors were calculated for each of the groups (see the following). Because the data were often not normally distributed, all statistical analyses were carried out with non-parametric Mann-Whitney *U* (between-group comparisons) and Wilcoxon *T* (within-group comparisons) tests.

2.2. Drug treatments

Apo obtained from Teclapharm as a ready clinical solution (10 mg/ml) was diluted with saline to a 1 mg/ml solution prior to injection. Throughout this study we used a standard 0.5 mg/kg dose of apo. In earlier studies it had been established that doses between 0.2 and 2 mg/kg apo yield an orderly increasing set of dose-dependent sensitization curves [5,27]. Dizocilpine(+)-maleate (MK-801), that is (5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5*H*-debenzo[*a*,*d*]cyclohepten-5,10-imine, was obtained from Tocris Cookson and dissolved in sal to yield a 0.2 mg/ml solution. Preliminary trials showed that doses of more than 0.20 mg/kg had a strong sedating effect, often accompanied by some postural tottering, whereas doses of 0.12 mg/kg or less yielded at most a slight sedation. Furthermore, in a pilot experiment doses up to 0.12 mg/kg had no inhibitory effect whatsoever on the normal forage pecking of hungry pigeons. Based on these findings we began by employing doses ranging between 0.05 and 0.12 mg/kg diz. After diz injections the pigeons spent 30 min (20 min in one instance: see the following) in their home cages to allow for the drug-taking effect before the next treatment step. Equivolume doses of sal were administered for control purposes. All injections were given intramuscularly (pectoral muscles).

2.3. Sensitization acquisition

We first examined whether the co-administration of diz during the sensitization acquisition phase would interfere with the development of a pecking IR to apo and subsequently result in a diminished pecking CR in response to sal. Pigeons ($n = 10$) constituting an Apo/Sal baseline group were injected with apo and videotaped for 6 days and then injected with sal for another 3 days ($n = 6$) or 6 days ($n = 4$) and videotaped in the distinct cages. The pigeons of groups Diz5 + Apo/Sal ($n = 5$), Diz8 + Apo/Sal ($n = 5$), Diz10 + Apo/Sal ($n = 6$), and Diz12 + Apo/Sal ($n = 5$) were first injected with 0.05, 0.08, 0.10, and 0.12 mg/kg diz, respectively, and returned to their home cages. Thirty minutes

later all of these groups, which will sometimes be referred to as Diz*X* + Apo/Sal groups, were additionally injected with apo and videotaped. During the second phase all the pigeons of these groups were injected with sal and videotaped for 3 days except for the Apo-Diz10/Sal pigeons which were so treated for 6 days. Pigeons ($n = 10$) belonging to a Sal/Sal control group were injected with sal and videotaped for 9 days ($n = 5$) or 10 days ($n = 5$).

2.4. Pretreatment effects

It seemed possible that the second phase results obtained in the preceding experiment (see Section 3.2) might have been due to an after-effect of the diz treatments during the first phase. To check this, pigeons of a Diz/Apo group ($n = 8$) received 0.10 mg/kg diz injections and were videotaped 30 min later for 6 days. Pigeons of a Sal/Apo control group ($n = 6$) were pre-treated with sal injections instead of diz injections. An additional Diz + Apo/Apo group ($n = 6$) of pigeons was first administered 0.12 mg/kg diz and 20 min afterwards administered apo and then videotaped. The shorter than usual delay and the compensating higher dose used with this latter group was occasioned by a logistic constraint. During the second phase all the pigeons received apo only injections for a further 6 days, again being videotaped.

2.5. Response retrieval

In this experiment we examined whether diz would have an immediate effect on the expression the IR and the CR in pigeons that had previously been sensitized to apo. Pigeons belonging to an Apo/Diz + Apo group ($n = 8$), an Apo/Diz + Sal group ($n = 7$), and an Apo/Apo control group ($n = 6$) were all injected with apo and videotaped for 6 days. During the second phase the Apo/Diz + Apo group received 0.10 mg/kg diz and 30 min later the standard dose of apo for 4 days. The Apo/Diz + Sal group received 0.10 mg/kg diz before receiving sal for 3 days. The Apo/Apo group continued to receive apo as before for a further 4 days. After the sal or apo injections the pigeons were videotaped.

3. Results

3.1. Sensitization acquisition

During the first phase of the experiment the co-administration of all four doses of diz reduced the pecking induced by 0.5 mg/kg apo in an approximately dose-dependent manner. The lesser pecking of the Diz5 + Apo/Sal group compared with the Apo/Sal group, however, did not reach significance. All the other Diz + Apo/Sal groups exhibited significantly less pecking than the Apo/Sal group throughout days 1–6 ($P_s < 0.05$). However, the pecking score differences between the Diz8 + Apo/Sal and Diz10 + Apo/Sal groups were not significant. Fig. 1 accordingly presents

Fig. 1. Sensitization acquisition, mean pecking scores $\pm$ S.E. Left: days 1–6 of Apo/Sal (●), Diz10 + Apo/Sal (■) and Diz12 + Apo/Sal (▲) groups while injected with 0, 0.10, or 0.12 mg/kg diz, respectively, and with apo. The Sal/Sal group (◆) was injected throughout with sal. Right: days 7–10 while all groups were injected with sal. The Diz12 + Apo/Sal group was not tested on session 10. Note that two differing response scales are valid for the right and left sections of the graph.

the results of only the Apo/Sal, Diz10 + Apo/Sal, and Diz12 + Apo/Sal groups. Of the latter two groups, the pecking scores pertaining to sessions 2–6 and 4–6, respectively, were nevertheless significantly higher (P s < 0.05) than those of the Sal/Sal group, also shown in Fig. 1.

During the second phase of the experiment when all groups were treated with sal the Apo/Sal group yielded a sizeable pecking response during day 7 compared with the Sal/Sal group (P < 0.01), a response which, however, declined over the next two days. This decrease (extinction) from days 7 to 9 was significant (P < 0.01). All four DizX + Apo/Sal groups yielded lesser pecking scores than the Apo/Sal group on day 7. This was significant in the case of the Diz8 + Apo/Sal, Diz10 + Apo/Sal, and Diz12 + Apo/Sal groups (P s < 0.05). The responding of all the DizX + Apo/Sal groups tended to increase slightly after day 7 but not significantly so. In any case, the difference between their scores and those of the Apo/Sal group were no longer significant on day 8 and all subsequent days. However, from day 8 onwards the pecking scores of the DizX + Apo/Sal groups were all significantly higher than those of the Sal/Sal group (P s < 0.05). The co-administration of diz during the sensitization phase thus lead to a development of a diminished IR and later also to the expression of a reduced CR.

3.2. Pretreatment effects

Fig. 2 depicts the results of this experiment. As was expected both the Diz/Apo and the Sal/Apo pigeons pecked very little during the first phase. From day 3 onwards the Diz+Apo/Apo group pecked significantly more (P s < 0.01) than the formerly mentioned groups but significantly less

(P s < 0.05) than the Apo/Sal group of the previous experiment which is included in Fig. 2 for comparison. However, the present Diz + Apo/Apo group, although similarly treated with 0.12 mg/kg diz, pecked significantly more during days 3–6 (P s < 0.05), than the Diz12 + Apo/Sal group of Fig. 1. The pecking of the said Diz + Apo/Apo group was in fact not significantly different from that of the Diz10 + Apo/Sal group shown in Fig. 1. This might have been because, as explained in Section 2.4, the interval between the diz and apo injections employed with the present Diz + Apo/Apo group was shorter than that normally used. During the second phase the Diz/Apo, Diz + Apo/Apo, and the Sal/Apo groups all exhibited statistically indistinguishable sensitization courses. They were slightly but not significantly lower than the sensitization courses evinced by the Apo/Sal group during the first phase (compare also with Fig. 3, left). This establishes that the diz treatments experienced by the Diz/Apo and Diz + Apo/Apo groups during the first phase did not affect the IR development during a subsequent sensitization to apo phase. Concerning the Diz/Apo group, the outcome agrees with the circumstance that the NMDA receptor blocking effect of diz persists for only 18 h (see Section 1). It is worth noting, however, that the partial IR that the Diz + Apo/Apo group had developed during the first phase did not transfer to the second phase (day 6 to day 7 drop, P > 0.01). A tentative explanation of this finding is offered later in the Section 4.

3.3. Response expression

The results of this experiment are shown in Fig. 3. During the first phase all the groups responded in a very similar manner. In fact, the sensitization courses of groups Apo/Diz + Apo and Apo/Diz + Sal were nearly identical and

Fig. 2. Pretreatment effects, mean pecking scores $\pm$ S.E. Left: days 1–6 of groups Diz/Apo ($\blacklozenge$), Sal/Apo ($\blacktriangle$), Diz + Apo/Apo ($\blacksquare$), and Apo/Sal ($\bullet$) while they were injected with diz, sal, diz and apo, or apo, respectively. Right: days 7–12, scores while the three first groups were injected with apo and the last one with sal. Note that here the same response scale is valid for both the right and the left sections of the graph.

Fig. 3. Response expression. Mean pecking scores $\pm$ S.E. Right: days 1–6 of groups Apo/Apo ($\blacksquare$), Apo/Diz + Apo ($\blacktriangle, \blacktriangledown$), and Apo/Sal ($\bullet$) while all groups were treated with apo. The responses of groups Apo/Diz + Apo and Apo/Diz + Sal are shown pooled (see text). Right: days 7–10 of above groups while they were treated with apo, diz plus sal, diz plus apo, and sal, respectively. The Apo/Diz + Sal group was not tested on day 10. Note that an expanded scale is valid for the responses of the Apo/Sal and Apo/Diz + Sal groups during days 7–10.

are shown pooled for simplicity's sake. None of the sensitization courses differed significantly from that of the Apo/Sal group shown for comparison. The co-administration of diz which the Apo/Diz + Apo experienced during the second phase (days 7–10) did not affect the apo-sensitized pecking (compare with the Apo/Apo group). This indicates that once the IR is established, it can no longer be appreciably influenced by an NMDA receptor blockade. In contrast with that finding, the Apo/Diz + Sal group pecked very little during the second phase, significantly less in fact than the Apo/Sal group did during the same phase ($P_s < 0.05$). A comparable diz treatment could thus suppress the expression of the weak CR but could not appreciably inhibit the much stronger IR.

4. Discussion

Several of the results reported above show that a first administration of a medium dose of apo in pigeons elicits a sizeable bout of stereotyped pecking (UR) and that a repeated treatment with the same dose of apo treatment yields a progressively increasing pecking response (IR). Furthermore, the Apo/Sal group (Fig. 1) demonstrates that, when challenged with sal, pigeons previously sensitized with apo exhibit a pecking CR. This confirms findings of several earlier studies in which it was additionally shown that the expression of both the IR and CR is strongly dependent on the pigeons being tested in the same distinctive cage in which they experienced the original sensitization treatment

[3,28,33,34]. As explained in the Section 1 these and other studies [12,39,60] have led us to postulate that the IR is the complete learned response shown when the full $CS_{cage \times apo}$ compound is present while the much weaker CR is only a part-response exhibited when the CS_{cage} component is present. A complementary part-response is elicited by the CS_{apo} component when the pigeons are treated with apo in a cage different from that in which they were previously sensitized. This small pecking response is difficult to ascertain because it is often obscured by variations of the much stronger UR directly elicited by apo through its unquestionable US quality [19,33]. Regardless of this, the sensitization to apo in pigeons is well accounted for by a Pavlovian conditioning process. In as much as this kind of learning appears to be neurally based on modifications of glutamatergic synapses and the onset of these modifications, in turn, are dependent on the activation of synaptic NMDA receptors, the co-administration of diz (MK-801), an NMDA receptor blocker, should have inhibitory effects on the development and expression of pecking IRs and CRs.

The role usually ascribed to the ionotropic NMDA receptors in LTP conditioning is that their channel opens when presynaptically released glutamate binds to them while the post-synaptic membrane is depolarized as a result of simultaneous activation of non-NMDA glutamate receptors. The inflow of calcium ions that follows triggers a complex biochemical cascade [23,32]. In dopamine-facilitated LTP, another such biochemical cascade may be triggered by dopamine D1 receptor activation [35,46]. When the two cascades converge they lead to the phosphorylation of a nuclear CREB protein [10]. When so activated this protein probably promotes the gene-controlled synthesis of AMPA glutamate receptors. These receptors are thought to play a critical role in the establishment of long-term memory [43]. In any case, viable NMDA receptors are assumed not to be any longer involved when the synaptic enhancement phase is over [23,32]. However, this latter view has been occasionally upset when NMDA receptor antagonists have been found to also impair the retrieval of previously well-learned responses (e.g. [2,25,26]). The synaptic mechanisms responsible for these model-anomalous findings are not yet properly understood.

The results pertaining to the various DizX + Apo/Sal groups (Fig. 1) indicate that a co-administration of a suitable dose of diz inhibits the acquisition of the IR and curtails the magnitude of the CR expressed afterwards. This accords with predictions that follow from the above LTP model. However, the very low day 1 pecking shown by the Diz10 + Apo/Sal and Diz12 + Apo/Sal groups (see also the Diz + Apo/Apo group, Fig. 2) suggests that the pecking UR elicited by apo is already inhibited by diz co-administration. This is an effect not foreseen by the LTP model. It may be that this dopaminergically triggered pecking response involves an intervening glutamatergic transmission link. The CR impairment, in any case, is unlikely to be due to any lingering diz since the Diz/Apo group (Fig. 2) did not re-

veal any suppressive diz after-effect. But the reader should keep in mind that this latter remark does not invalidate the response strength and the diz state arguments forwarded in the following paragraphs.

As might be expected according to the standard LTP model, the second phase co-administration of diz and apo in the Apo/Diz + Apo group (Fig. 3) had no effect on the expression of the sensitization IR previously established through an apo-alone treatment. But in contrast to the standard model's predictions it was found with the Apo/Diz+Sal group (Fig. 3) that the administration of the same dose of diz inhibited the expression of a pecking CR in response to a sal challenge. It is possible that the difference in strength between the IR (more than 2000 pecks/20 min) and the CR (less than 100 pecks/20 min) is the source of the disparity. The diz administration, in agreement with the model-deviating findings mentioned earlier, might have impaired the retrieval of the weak CR but not have affected the much stronger IR.

The IR impairment observed in the Diz + Apo/Apo group (Fig. 2) during the first phase agrees, as already noted, with what was seen in the earlier discussed DizX + Apo/Sal groups (Fig. 1). However, the fact that at the beginning of the second phase (day 7) the pecking response of the Diz + Apo/Apo group was not different from that of the previously unsensitized Diz/Apo and Sal/Apo groups (Fig. 2) is puzzling. This means that the part-sensitization that the Diz + Apo/Apo group had shown at the end of the first phase did not transfer to the second phase. An explanation may be that diz, besides partially blocking the sensitization during the first phase, was also acting as a component CS_{diz} that made the part-sensitization to apo diz-state dependent (i.e. the controlling stimulus here was effectively a triple $CS_{cage \times apo \times diz}$ compound). When the CS_{diz} component was left out during the second phase the previously acquired part-IR went missing and a new IR controlled by the simpler $CS_{cage \times apo}$ began to build up. In rodents it has been demonstrated that in drug discrimination experiments diz has a CS-like effect [37]. Nevertheless, this complication does not detract in the least from the replicated finding that diz co-administration interferes with the development of a pecking IR in response to repeated apo doses. The question whether this effect came about through inhibition of a CS_{apo} -IR, or of a CS_{cage} -IR linkage formation, or even both, can not be properly decided. By the way, we can also not totally discount the possibility that the reduced CRs shown by the DizX + Apo/Sal groups (Fig. 1) might be also partly due to this hypothetical CS_{diz} dropout effect.

5. Conclusion

We have shown that the development of the IR and the later expression of a CR that are characteristic of the pecking response sensitization arising with repeated apo administrations is impaired by NMDA receptor blockades brought about by a co-administration of diz. These findings were ex-

pected on the basis that the sensitization to apo in pigeons depends on a dopamine-induced, LTP-like, classical conditioning process. But we also found that the retrieval of the CR elicited by the environmental context was similarly inhibited by diz blockades. This finding does not agree with the standard LTP model which assumes that the production of previously conditioned responses is independent of NMDA receptors. However, contrary to the theory, it is a frequent empirical finding that NMDA receptor antagonists can interfere with response retrieval. Our results in any case agree with the hypothesis that sensitization to apo in pigeons is based on a process leading to an alteration of glutamatergic transmission mechanisms. The results of two further studies involving the administration of dopamine D1 and D2 receptor antagonists in pigeons being sensitized or in pigeons already sensitized to apo [1,3] agree with the above conclusion in as much as they indicated that the sensitization to apo does not entail a major change in dopaminergic transmission.

Although a large number of studies have investigated whether the sensitization in rodents to amphetamine and cocaine is affected by diz treatments, only a smaller number has examined how the sensitization to apo is affected by diz treatments. These studies have fairly consistently shown that the expression of a CR after an apo-sensitization is largely prevented when diz is administered before the challenge with sal [6,22,24,56]. Opinions about whether diz has an analogous effect on the emergence of the IR in response to apo are not so unanimous. One study found that a pre-administration of diz did not prevent the emergence of an apo-induced locomotor rotation IR in unilaterally substantia nigra lesioned rats [24]. Another study found that co-administration of diz immediately before apo did not impair and perhaps even enhanced a locomotor activity and stereotyped behavior IR in a context-dependent manner [56]. Nevertheless, several other studies report that the administration of diz 30 min before the injection of either apo or amphetamine prevented the development of a locomotor IR in rodents [6,22,24,36,45]. The discrepancies could of course be due to the differing strains, procedures, and drugs that were employed. A review adduces that although a co-administration of diz often inhibits the sensitization to amphetamine and cocaine in rodents, it can sometimes induce a sensitized locomotor response on its own which then adds to that produced by the psychostimulants [58,59]. Nevertheless, the author's overall conclusion is that NMDA receptors play a central role in the development of sensitization to amphetamine and cocaine. Even though we have some qualms about equating too easily the sensitization of psychostimulant-induced locomotor activity in rodents with the sensitization of apo-induced pecking behavior in pigeons it would seem that with respect to the involvement of NMDA receptors there are some interesting parallels. The avian apo-sensitization/conditioning preparation may in any case be a useful model for the study of the dopaminergic-glutamatergic synaptic interactions thought to underlie most sensory-motor learning in vertebrates.

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