Pharmacology Biochemistry & Behavior, Vol. 22, pp. 209–214, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

Behavioral Response to Apomorphine and its Interaction With Opiates in Domestic Pigeons

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Received 19 April 1984

DEVICHE, P. *Behavioral response to apomorphine and its interaction with opiates in domestic pigeons.* PHARMACOL BIOCHEM BEHAV 22(2) 209–214, 1985.—Domestic pigeons received peripheral injections of saline or the dopamine agonist apomorphine (AM) at doses of 0.025, 0.05, 0.1, 0.25, 0.5 or 1 mg and their behavior was studied for 30 min after these treatments. Given at a dose of 0.025 mg, AM decreased pecking, whereas doses ranging from 0.1 to 1 mg strongly stimulated this behavior. The frequency of headshaking was enhanced by the administration of each dose of AM; at the 3 higher doses, the drug also attenuated the frequency of preening. In another experiment, AM was administered 40 min after the injection of either naloxone (0.5, 1 or 4 mg), the opiate agonist levorphanol (0.25, 0.5 or 1 mg) or its dextroisomer, dextrorphan (0.25, 0.5 or 1 mg), while the birds were observed as before. No interaction between AM and either naloxone or dextrorphan was detected. By contrast, injection of each dose of levorphanol attenuated preening, and completely antagonized the stimulating effect of AM treatment on headshaking. At a dose of 1 mg, levorphanol also slightly decreased the frequency and increased the latency of occurrence of pecking. It is concluded that in pigeons, opiates modulate the behavioral response to apomorphine in a complex fashion.

Apomorphine Dopamine Naloxone Opiates Pecking Pigeons

A number of studies show that in laboratory animals, the administration of apomorphine (AM), a direct dopamine (DA) agonist [3,14], produces marked behavioral changes. In rats, for example, injection of this drug elicits stereotyped behavior such as gnawing [14,35] while in birds, it induces a bout of pecking [5, 7, 10, 28, 32] accompanied by a stimulation of other behavioral patterns such as mandibulating, swallowing and headshaking [16].

Numerous studies performed in mammals also indicate the existence of complex relationships between the dopaminergic and the opiate system [5, 19, 25, 42]. For example, opiate substances and opioid peptides alter the DA turnover [8, 23, 27] and the activity of DA neurons [15,31]. Morphine can attenuate the stereotypy and the emetic responses which are produced by AM treatment [9], an effect which probably results from a blockade of dopaminergic receptor-activity [35]; inversely, injection of the relatively specific opiate antagonist naloxone (NAL; [38]) in some cases potentiated the behavioral response to AM and to amphetamine [1, 18, 36], though in other cases no interaction or an antagonism between these drugs was observed [11, 20, 21, 30].

The present investigation aimed at identifying such relationships in domestic pigeons, for which virtually no information on this subject is presently available. For this, we first studied the behavioral response of this species to various doses of AM. We then examined the behavioral influence of the concomitant administration of AM and of either NAL, the opiate agonist levorphanol, or its inactive isomer, dextrorphan. The results show that in pigeons, opiates can affect the behavioral response to AM in a complex manner.

METHOD

Birds

Subjects (n=9) were adult domestic pigeons (*Columba livia*) of undetermined sex, weighing 430–570 g and obtained from various local breeders. During the experiments, artificial light was provided from 0700 to 2200 hr and the birds were kept in individual wire mesh cages (40×45×35 cm). Except during the behavioral observations, standard food (mixed grain) and grit were continuously available. Tap water was also given ad lib. About one month before the present study, the pigeons had been used in an experiment involving systemic injection of NAL (maximal dose: 5 mg/subject) but after that, they were not subjected to any further experimental treatment until this study began.

Treatments

The birds were used for two consecutive experiments, which were separated by a 4 day interval. In the first experiment, each pigeon received a 0.5 ml control injection of normal saline (S) or an injection of apomorphine hydrochloride

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(Woelm Pharma, FRG) at doses of 0.025, 0.05, 0.1, 0.25, 0.5 and 1 mg. The second experiment examined the interaction between the administration of AM and of either NAL, or the opiate agonist levorphanol or its dextroisomer dextrorphan. In this case, each bird received 2 injections separated by a 40 min interval, on opposite sides, as follows: S, then S; either S, NAL (0.5, 1 or 4 mg), levorphanol tartrate (0.25, 0.5 or 1 mg) or dextrorphan tartrate (0.25, 0.5 or 1 mg), then AM. The quantity of AM which was administered remained constant for a given bird, but it varied from one pigeon to another, as explained below.

All treatments were given in an individually randomized order and into the pectoral muscles. The drugs were dissolved in saline to reach a final volume of 0.5 ml/injection. A minimum delay of 2 (Experiment 1) or 3 (Experiment 2) days separated consecutive injections to each subject. Each bird received all treatments and therefore served as its own control. No long-term behavioral adaptation to the treatments was observed.

Procedure

The behavioral response of the birds to the treatments was studied as described previously [12]. At least 3 hr before receiving an injection, the birds were taken from their home cage and released in a testing cage of the same size, but 3 lateral walls of which were covered with black paper sheets with yellow dots on them (average of 5.5 dots/dm^2); this environment was chosen on the basis of previous research showing that it elicits a strong pecking response to AM injection [5]. The cages were artificially lit and visually isolated from each other. Observations started within one min after the birds received AM; they were all viewed through a one-way mirror by a single experimenter situated in a separate room, thus minimizing disturbance of the pigeons.

The occurrence of 8 easily identified behavioral patterns was recorded at the end of each 30 sec period for 30 consecutive minutes after the injection; the highest possible score for each pattern was thus 60 per session. These patterns were: pecking at the floor or side walls; pecking at their own plumage or toes; preening; drinking; wing-flapping; stretching one or both wings; body- or headshaking; yawning. These names are sufficiently descriptive as to make detailed description unnecessary. Out of these, 3 appeared with a frequency sufficient for statistical analyses. These behaviors were pecking at side walls or the floor, preening, and headshaking. Only these patterns are therefore considered below. The latency of the onset of the pecking response was also measured to the nearest 30 sec.

Data were submitted to Friedman two-way analyses of variance (ANOVA) and to Wilcoxon tests [40]. Results were considered significant when they correspond to a two-tailed probability <0.05.

RESULTS

Dose-Response to Apomorphine Injection

Results obtained for pecking behavior are depicted in Fig. 1.

The upper panel of the figure shows the median frequency of the pecking response following the various treatments and (in brackets) the proportion of birds which pecked following the injection of AM at the different doses. Any bird was considered to display a significant pecking activity in response to the treatment when it pecked at least twice its control value during the whole session, and, moreover, when

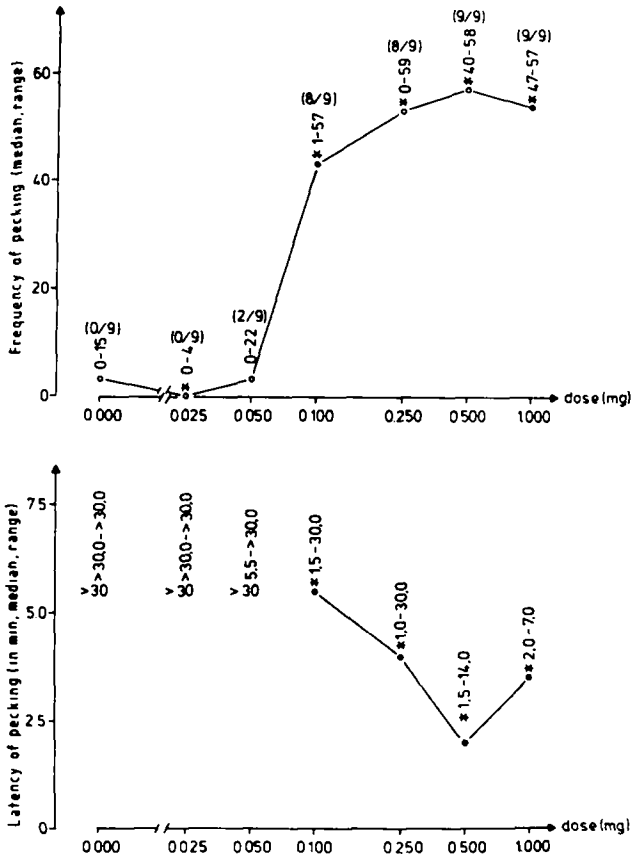

FIG. 1. Frequency (upper panel) and latency (lower panel) of the pecking response elicited by peripheral administration of either apomorphine at various doses or a control solution to domestic pigeons (n=9). The figure indicates the median and extreme values (ranges, listed vertically) which were observed. In the upper panel, numbers in brackets refer to the proportion of birds showing a consistent pecking response (see text for additional explanations) during the period of observation (30 min post-injection). *=2-tailed probability <0.05 for the comparison with control values (Wilcoxon test).

this behavior appeared during at least 4 consecutive 30 sec intervals.

The frequency of pecking varied markedly following the various treatments (ANOVA, $p<0.001$). It was very low in the control condition, and still lower ($p<0.01$) when the birds were administered 0.025 mg of AM. No difference with respect to the control values was observed following the injection of 0.05 mg of AM, whereas higher doses of the drug all induced a strong pecking activity (comparison with control values: $p<0.01$ in each case). It should be pointed out that large individual differences were observed with regard to the threshold dose of AM which produced pecking behavior. For example, 2 out of 9 pigeons displayed this behavior in response to 0.05 mg of AM. However, a dose of the drug ten times higher (0.5 mg, see Fig. 1) was required in order to elicit pecking from *all* the birds.

The lower panel of Fig. 1 presents the latency of the pecking response which was also affected by the various treatments (ANOVA, $p<0.001$). When the birds received either the control solution, or 0.025 mg or 0.05 mg of AM, the

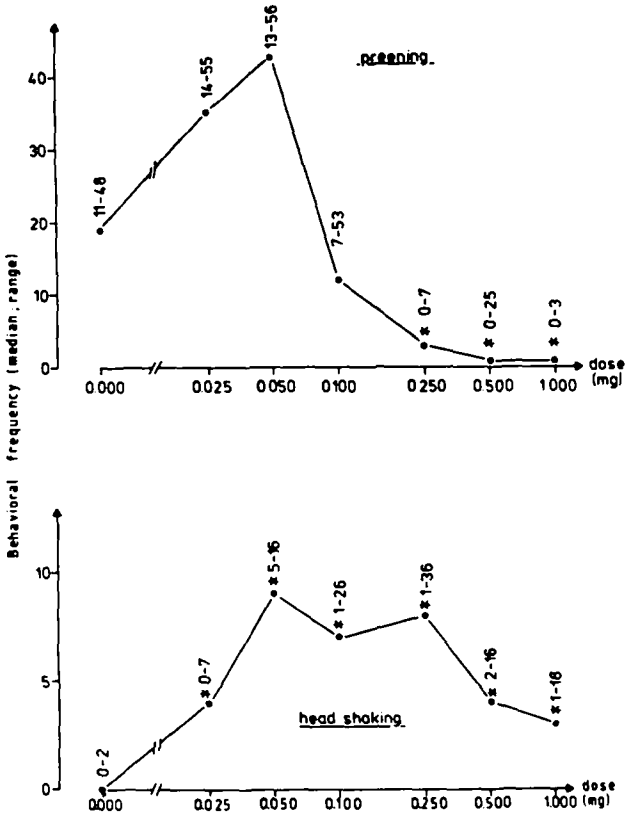

FIG. 2. Frequency of preening and headshaking following the peripheral administration of either a control solution or apomorphine at various doses to domestic pigeons (n=9). *=2-tailed probability <0.05 for the comparison with control values (Wilcoxon test). See Fig. 1 for additional comments.

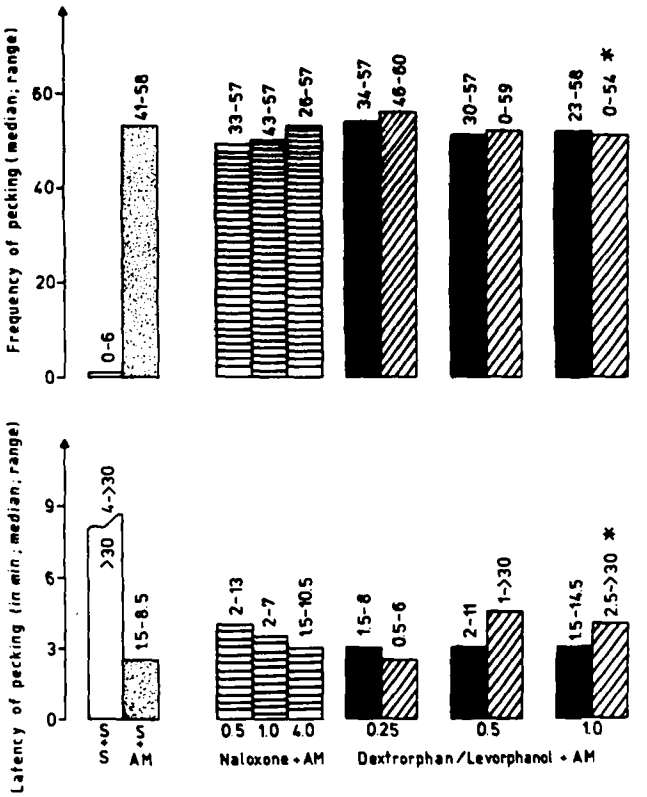

FIG. 3. Frequency (upper panel) and latency (lower panel) of the pecking response elicited by various treatments to domestic pigeons (n=9). Each bird received 2 injections separated by a 40 min delay: saline (S) then S (hollow bars); S then apomorphine (AM; dotted bars); either naloxone (horizontal striped bars), dextrorphan (black columns), or levorphanol (oblique striped bars) at various doses, then AM. Each subject was observed for 30 min after the 2nd injection. *=2-tailed probability <0.05 for the comparison with the S + AM values. Wilcoxon test. See Fig. 1 for additional comments.

frequency of their pecking behavior was very low, so that the median latency of this response was considered to be longer than the observation period (30 min). With higher doses, its value varied from 5.5 min (0.1 mg AM) to 2 min (0.5 mg AM) after the injection; these two values did not differ significantly from each other.

The frequency of two other behavioral patterns (preening, headshaking) markedly differed according to the experimental treatment (ANOVA, $p<0.001$ in each case; see Fig. 2).

The frequency of preening tended to show a biphasic response (increase, then decrease) to the injection of increasing doses of AM. Individual comparisons with control values revealed, however, that only the injection of 0.25, 0.5 and 1 mg of the drug produced a significant influence (decreased frequency) on this pattern. Finally, headshaking was very sensitive to AM treatment, since its frequency was increased by the administration of all doses of the agonist, including the smallest one (0.025 mg).

Effect of Opiate Treatment on AM-Induced Behavioral Effects

The first experiment showed that the threshold dose of AM that was required to elicit a significant pecking response varied markedly from one bird to another. In this experiment, therefore, different subjects were treated with varying drug amounts. The amount of AM which they received each time was that which in the first experiment had produced as nearly as possible 50% of the maximal pecking response.

Accordingly, 6 pigeons were administered each time 0.1 mg of AM, whereas the others were given 0.25 mg (n=2) or 0.5 mg (n=1) of the drug, respectively.

The results obtained for the frequency and the latency of pecking behavior are shown in Fig. 3. As in the first experiment, AM injection (S + AM data) induced an intense pecking response as compared to the control situation (S + S data; $p<0.01$). This effect was not altered at all when AM was administered together with NAL or dextrorphan. Injections of 0.25 mg or 0.5 mg of levorphanol did not influence the frequency or the latency of the AM-induced pecking either; given at a dose of 1 mg, however, levorphanol slightly but significantly ($p<0.05$) decreased the frequency of pecking, and increased the latency of occurrence of this behavior in response to AM treatment.

Figure 4 presents the results obtained for preening and for headshaking.

No effect of AM injection on the frequency of preening was detected (compare S + AM with S + S data). This result was not unexpected, since in the first experiment, the frequency of this pattern decreased only when the birds re-

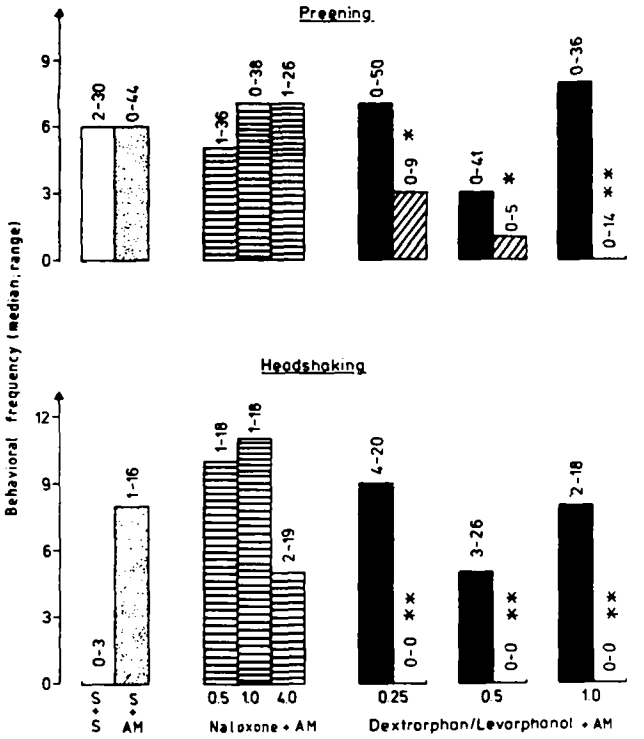

FIG. 4. Frequency of preening behavior and of headshaking following various treatments to domestic pigeons (n=9). * (or **)=$p<0.05$ (or <0.02) for comparison with AM + S values, Wilcoxon test. See Figs. 1 and 3 for additional comments.

ceived rather high doses of the drug. No influence of either NAL or dextrorphan treatments on preening was observed either. By contrast, injection of levorphanol markedly reduced the frequency of preening; given each dose of the opiate, the pigeons also performed this behavior with a lower frequency than following the control treatment (S + S data; $p<0.05$ each time).

As in the first experiment, AM injection strongly increased the frequency of headshaking ($p<0.01$); this stimulation was not altered by the administration of either NAL or dextrorphan, whereas it was completely counteracted by each dose of levorphanol.

DISCUSSION

Given peripherally to pigeons at doses ranging from 0.1 to 1 mg, AM produced a marked pecking response, as it was previously described by several authors [5, 7, 10]. Remarkably enough, a lower dose of the drug (0.025 mg) induced an effect in the opposite direction, that is, a reduction of pecking frequency as compared to control values. The simplest explanation for this observation probably consists in assuming that in some brain areas of pigeons, AM is able to bind itself to pre-(auto-) as well as to post-synaptic DA receptors, as it appears to be the case in the mammalian striatal complex [39,41]. Accordingly, low doses of AM would activate preferentially pre-synaptic DA receptors, thus reducing the release of DA from the nerve terminals, and hence attenuating the frequency of pecking; a similar proposition has previously been put forward to explain some behavioral effects of AM treatment in rats [2]. By contrast, higher doses of AM would stimulate post-synaptic DA receptors as well, leading to an enhancement of pecking.

At the present time, the brain region which is involved in the stimulation of pecking by AM administration has not been precisely identified. It seems that the paleostriatal complex plays an important role in this respect. On the one hand, indeed, this area contains high levels of DA [22]. On the other hand, paleostriatal injection of AM or electrical stimulation of this area elicits pecking, whereas pigeons with bilateral paleostriatal lesions exhibit a temporarily reduced pecking response to AM treatment [17].

In addition to its effect on pecking, AM administration markedly altered the frequency of two other behavioral patterns, which are headshaking and preening. The frequency of headshaking was increased by injection of each dose of AM, including those which either decreased (0.025 mg) or did not change (0.05 mg) the frequency of pecking. This observation suggests that AM treatment affected both patterns, at least in part, independently from each other. Such a conclusion is in line with the results of another study involving intracerebroventricular administration of AM [12], in which it was concluded that this drug affects headshaking and pecking by acting on different (so far not precisely localized) brain areas. As to preening, its frequency was attenuated only by the administration of rather high amounts of AM (0.25 mg and more). It is presently unclear whether this reduction arose from a primary influence of the drug of some brain area(s) involved in the control of this pattern, rather than from an indirect effect, that is, from a competition with pecking. It is, indeed, quite possible that as higher amounts of AM were given, pecking became the main activity performed by the birds, and since this behavior could not be performed simultaneously with preening, the latter was therefore eliminated.

The second part of this investigation aimed at researching possible behavioral interactions between the injection of AM and of opiate substances.

At each administered dose, levorphanol reduced preening and completely abolished AM-stimulated headshaking. Furthermore, 1 mg of the opiate slightly but significantly decreased the frequency and increased the latency of AM-induced pecking. The latter observation confirms and extends results obtained previously in pigeons with the same drug [13] and also with morphine [7]. It should be stressed that the effects of levorphanol were entirely stereoselective, since they did not occur following dextrorphan treatment at any dose; this strongly suggests that they arose from the specific binding of levorphanol to opiate receptors.

The mechanism of action of levorphanol on the behavior of pigeons remains partly speculative at present. One possibility is that the opiate agonist produced an overall behavioral depression. Support of this view comes from the results obtained for preening. The frequency of this pattern was, indeed, not altered when the birds were administered only AM, whereas it markedly decreased when levorphanol was given concurrently with AM. These results suggest that levorphanol itself may have inhibited preening. Examination of other results, however, makes it unlikely that all behavioral effects of levorphanol should be attributed only to a general decreased arousal. In the case of pecking, indeed, it was observed that the AM-induced stimulation of this pattern was not affected by the concurrent injection of either 0.25 or 0.5 mg of levorphanol, while 1 mg of the opiate induced a slight decrease. In light of this observation, it must therefore be recognized that the behavioral activity of levor-

phanol was at least partly selective, not all patterns being affected to a same extent by the drug. This conclusion is also in line with the results obtained for headshaking. Like pecking, this pattern was strongly enhanced by AM administration; contrarily to pecking, however, headshaking was completely suppressed by levorphanol treatment to AM-given pigeons. Together with other studies (see above), this difference brings additional support for the idea that though both pecking and headshaking are DA-dependent, they are controlled by different regions of the brain or/and by distinct mechanisms.

One area of the brain which is possibly involved in the attenuation of AM-induced behavioral changes by levorphanol is the paleostriatal complex. This region appears to play a direct role in the control of pecking (see above), and it contains high amounts of opioid peptides in chickens as well as in pigeons [4,29]. Furthermore, it seems to be homologous to the mammalian striatal complex [24], where opiate receptors are found [33,34] and where complex interactions between opiates and the dopaminergic system are well demonstrated [8, 26, 35, 42].

Finally, no behavioral interaction was observed between the injection of AM and of NAL. According to some authors, NAL treatment potentiates AM-induced stereotyped behavior [1, 36, 37]. By contrast, other reports show that NAL administration rather inhibits the behavioral response to either APO [30] or amphetamine [11]. These discrepancies cannot be explained uniquely by interspecies differences [21] or by differences in the amounts of drugs or methodology which were used, and they require additional research.

ACKNOWLEDGEMENTS

Naloxone hydrochloride was a gift from du Pont de Nemours and Co (Glenolden, PA, USA) whereas levorphanol and dextrorphan tartrate were kindly provided by Hoffman-La Roche (FRG). The work was carried out in collaboration with Dr. M. Binder (Institute of Physiological Chemistry, Ruhr-Universität Bochum, FRG); thanks are due to Prof. J. D. Delius for improving the original manuscript and to Mrs. A. Lohmann and Mr. H. Stankewitz for varied help. The author was Senior Research Assistant at the Belgian Fund for Scientific Research and received an A. von Humboldt fellowship (FRG) and a NATO grant. The research was supported by the Deutsche Forschungsgemeinschaft through its Sonderforschungsbereich 114.

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