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EFFECTS OF α-METHYL DERIVATIVES OF NORADRENALINE, PHENETHYLAMINE AND TRYPTAMINE ON OPERANT CONDITIONING IN CHICKENS

BY

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The young chicken is extremely useful for studying the central actions of sympathomimetic amines, since the effects of and mode of action of the catecholamines can be differentiated from those of the amphetamine-like amines. The catecholamines produce drowsiness or sleep accompanied by large amplitude electrocortical potentials and diminished or absent cheeping ; in contrast, amphetamine-like amines elicit excitement accompanied by electrocortical alerting and increased amounts of cheeping (Key & Marley, 1962 ; Dewhurst & Marley, 1965a, b). Vane (1960) suggested that amphetamine might act on the central nervous system through its tryptamine-like properties, and indeed some tryptamines have identical central effects to amphetamine in mice (Vane, Collier, Corne, Marley & Bradley, 1961) and in chickens (Dewhurst & Marley, 1965a, b).

A multiple schedule of reinforcement was used in the present experiments to produce a stable baseline of operant responding. This consisted of a Fixed Interval, which generates a complex pattern of behaviour and is sensitive to drugs, alternating with a Fixed Ratio, which generates a simpler pattern of responding more refractory to drugs (Morse & Herrnstein, 1956). A short Fixed Ratio is useful to include, since if it is abolished it suggests that the drug doses used are too large and are producing incoordination. The patterns of conditioned behaviour produced by schedules of reinforcement are modified in a characteristic way by drugs (Morse & Herrnstein, 1956 ; Dews, 1958 ; Wurtman, Frank, Morse & Dews, 1959 ; Smith, 1964). In general, responding is decreased by catecholamines and, depending on the schedule, increased by amphetamine-like amines.

The α-methyl derivatives of noradrenaline, phenethylamine (dexamphetamine) and tryptamine were chosen for testing, since their effects were qualitatively similar to those produced by the parent molecules, but the changes were much longer-lasting and therefore the more easily observed in detail. The effects of these amines, which have not been previously studied on operant behaviour in very young animals or in the chicken, are given in this paper. Tests were also made to ensure that changes in behaviour were not an outcome of changes in blood pressure.

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METHODS

Apparatus

The chamber and procedure for the conditioning experiments have been described (Marley & Morse, 1966). Essential features included a transilluminated response key that closed an electrical contact when pecked; a food dispenser that occasionally permitted 4 sec access to a standard commercial chicken food; a mirror behind the feeding aperture and adjacent to the lighted response key which enabled young chickens to be studied singly without their behaviour being disrupted due to isolation from other chickens. Cheeping was recorded as the integral of the voltage output from a crystal microphone in the chamber (Dewhurst & Marley, 1965c). Noise recorded from within the chamber was limited to 1,500–6,000 cps, the frequency range of cheeping, by a band pass filter between the microphone and the amplifier. Noise from the chicken scratching the floor was reduced by a rubber mat, and noise from the chicken's beak pecking the lighted response key was diminished by covering the plastic key with a layer of crepe rubber; the operation of the food-dispenser was made as silent as possible. With these precautions essentially only cheeping was recorded. Implantation of cortical electrodes and recording of electrocortical activity with an 8-channel Kaiser electroencephalograph was as described by Key & Marley (1962). Electromyograms were recorded similarly from electrodes implanted in the dorsal neck muscles.

Subjects

Subjects were 10 Rhode Island Red chickens obtained about 24 hr after hatching and maintained on a regimen of partial food deprivation.

Procedure

The chickens were trained on a multiple fixed-ratio (FR) fixed-interval (FI) schedule as previously described (Marley & Morse, 1966). In the presence of a white light the presentation of the reinforcer followed 25 pecks on the key (FR); in the presence of a red light the reinforcer followed the first peck after a fixed time interval (FI). In the majority of experiments the FI value was 3 min in tests with α-methyl noradrenaline and 7 min in those with dexamphetamine or α-methyltryptamine; in a few experiments the FI value was 7 min in tests with α-methyl noradrenaline and 3 min in those with dexamphetamine. The FR and FI schedule components alternated throughout the session of approximately 50 food presentations.

A fixed sequence was followed in sessions in which drug observations were made. The trained chicken was exposed to the multiple schedule until the performance was relatively stable (usually 6 to 10 components). Then a control injection of saline was given immediately after the food cycle ending a fixed ratio component. After 10 schedule components (5 FI and 5 FR), the drug was injected after the food cycle ending the fifth FR component. Observations were continued over 30 more schedule components (occasionally only 20). Doses were given in random order with a lapse of at least 1 day between injections. For chickens in which electrocortical activity was recorded the cortical recording electrodes were implanted after the bird had been trained and control patterns of responding had been established. Experiments were not recommenced until 3 days after the operation. A total of 189 drug experiments were made on the 10 chickens.

Treatment of drug results

Cheeping was recorded as 1 min integrals throughout each experiment (Dewhurst & Marley, 1965c). Drug control activity ratios for key-pecking were obtained from the number of responses during successive series of 5 FI components, responses for the FRs being omitted. The total number of responses during the 5 FI components following the saline injection constituted the control observation. The total number of responses during the 5 FI components immediately following the drug injection constituted the primary drug observation. Subsequent responses were arbitrarily grouped into a second and third series of 5 FI components; when compared with the control observation these activity ratios indicate the magnitude and duration of the drug effect. A different treatment was required when responding was completely suppressed for longer than 3 FI components. In such instances the primary drug observation was taken to be the number of responses occurring in a period

equal to that of the control 5 FI observations. The significance of the difference between the number of responses made after saline and after the drug was obtained from the formula:

$$t = \frac{(\bar{x}_1 - \bar{x}_2)\sqrt{\frac{1}{N^1}}}{\sqrt{\left\{S\left(x_1^2\right) - \frac{[S.x_1)]^2}{N_1} + S\left(x_2^2\right) - \frac{[S.x_2]^2}{N_2}\right.}}$$

Postural changes

These are produced by amphetamine-like amines and have been described (Selle, 1940; Clymer & Seifter, 1947; Dewhurst & Marley, 1965a).

Grade 0 applied to normal posture.

Grade 1 referred to chickens able to walk but unable to extend fully the lower limbs, so that the animal waddled with bent limbs and horizontal back; wing extension was also present.

In *Grade 2* impairment of lower limb extension was more severe and the animal was unable to elevate the trunk from the ground, although still able to move on its belly.

In *Grade 3* the chest remained on the ground but the tail was elevated above the rest of the trunk. The beak was agape, there was head retraction and the bird was unable to move.

Vocalization

In the young chicken this was classified into: "distress calls" which are loud cheeps, repeated at about 1/sec or less, and commonly elicited by isolation, by cold or by hunger (Collias & Joos, 1953); twittering, which is a succession of high-pitched low-intensity calls repeated at 4 to 5/sec and originally described by Selle (1940) in young chickens given amphetamine; and other types of calling (referred to as cheeping).

Blood pressure

Since the blood pressure response to the amines is similar in young and in adult chickens, and as the tests are easier to make in older fowls, these experiments were made in fowls of about 1 kg weight. The chickens were anaesthetized with halothane (1.5% v/v) or phenobarbitone sodium (200 mg/kg intravenously). In the case of halothane the fowl was intubated before induction of anaesthesia, whereas with phenobarbitone the endotracheal tube was introduced into the trachea after induction. The fowl was artificially ventilated through the cannula with a pump. Arterial blood pressure was recorded from the carotid or ischiadic arteries either with a Condon manometer writing on smoked paper or with a transducer, the signals being amplified and displayed on a D.E. potentiometric recorder (Cambridge Instruments). Intravenous injections were made through a cannula tied into the ischiadic vein.

Drugs

The drugs used (molecular weights in parentheses) included the hydrochlorides of (±) α-methyl noradrenaline (220), chlorpromazine (355), (−)-dichloroisoprenaline (283), (±)-mebanazine (170), phenoxybenzamine (340), (±)-pronethalol (265) and (+) α-methyltryptamine (210). Also used were dexamphetamine sulphate (368), methysergide (470) and 6-hydroxytryptamine creatinine sulphate (397). Signs of optical activity are not given subsequently. All injections were made intraperitoneally unless otherwise stated. Doses are given as μ-mole/kg.

RESULTS

Effects of α-methyl noradrenaline

Pecking

Three chickens were tested, two at various times between 8 and 19 days and one adult. The drug produced a dose-dependent decrease in schedule-controlled key-pecking which

was not preceded by any increase in pecking. The minimal effective dose was 2.5 μ-mole/kg and near maximal reduction of pecking occurred with the 10 μ-mole/kg dose (Figs. 1 and 2). Figure 1 (A and B) shows the progressively greater decrement in pecking with doses of 2.5 and 5 μ-mole/kg. The records are for chicken 4, aged 11 and 8 days

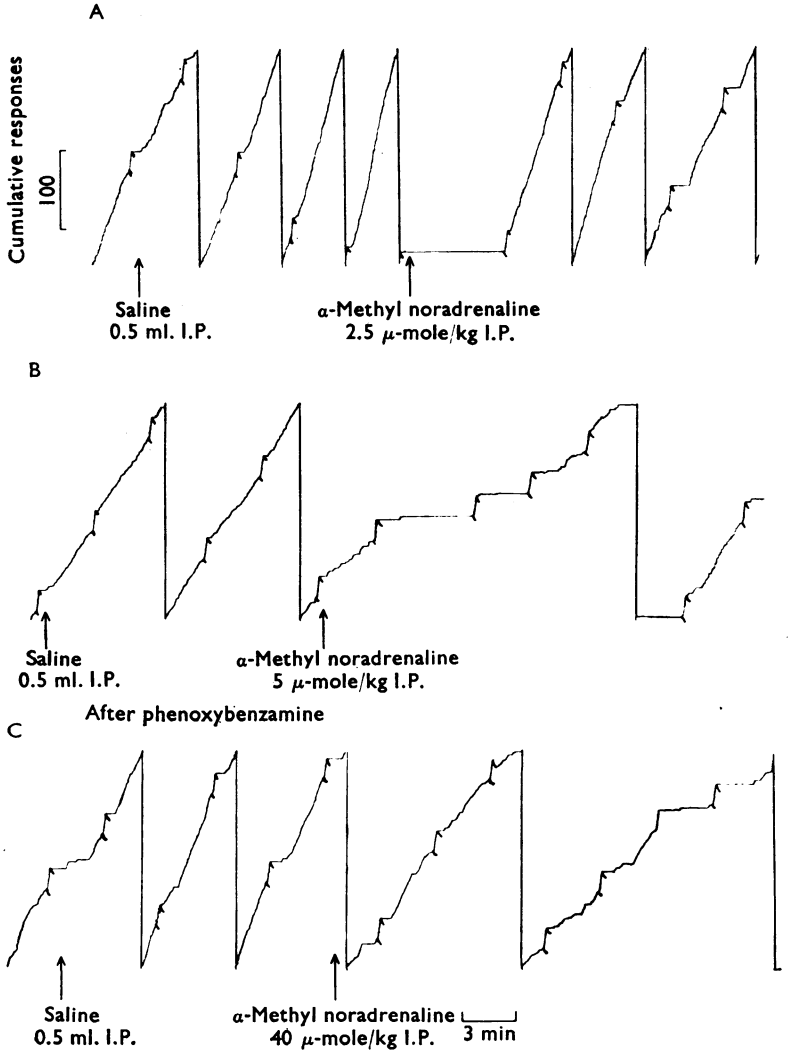

Fig. 1. Cumulative pecking records showing the effects of α-methyl noradrenaline in chicken 4 on a multiple FR25, FI 3 min schedule. Ordinate: cumulative pecks. Abscissa: time. The fixed ratio (FR 25) and fixed-interval (FI 3) components alternated. The short diagonal lines on the records indicate presentations of the food reinforcer. Each record shows a portion of the performance in separate sessions following injections of saline and of α-methyl noradrenaline Pecking was reduced in the FI component by α-methyl noradrenaline 2.5 μ-mole/kg and 5 μ-mole/kg (A and B). A dose of 40 μ-mole/kg α-methyl noradrenaline in the chicken pretreated with phenoxybenzamine (120 μ-mole/kg 3 days previously) was less effective (C) than the 5 μ-mole/kg dose in the untreated chicken.

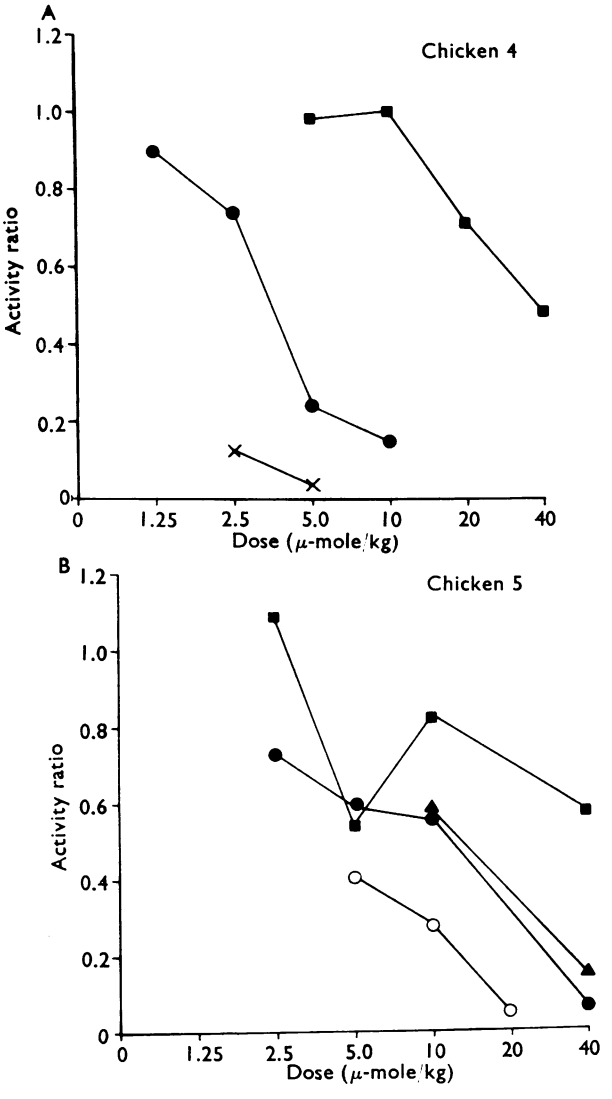

Fig. 2. Graphs for the effect on pecking of α-methyl noradrenaline given either alone or following various pharmacological antagonists in two chickens. In A and B ordinate is the activity ratio for pecking and abscissa is the dose of α-methylnoradrenaline. Pecking schedule FR25, FI 3 min. *Chicken 4.* In A the suppressant effect of α-methyl noradrenaline was antagonized by phenoxybenzamine (120 μ-mole/kg given 3 days before first dose of α-methyl noradrenaline) but enhanced by methysergide (0.1 μ-mole/kg given with control saline). *Chicken 5.* In B the suppressant effect of α-methyl noradrenaline (except for the 5 μ-mole/kg dose) antagonized by phenoxybenzamine (80 μ-mole/kg 3 days before first dose), but unaffected by chlorpromazine (40 μ-mole/kg) and enhanced by pronethalol (20 μ-mole/kg). Chlorpromazine and pronethalol injected with control saline (α-methyl noradrenaline in untreated chicken, ●——●; after phenoxybenzamine, ■——■; after methysergide, ×——×; after chlorpromazine, ▲---▲; after pronethalol, ○——○).

respectively; they show portions of the cumulative response records under the multiple schedule following injections of saline and of α-methyl noradrenaline. The 2.5 μ-mole/kg dose abolished pecking during the first fixed interval (FI) component following the injection. When a reinforced peck occurred after 6 min, recovery appeared complete in the subsequent ratio and interval components. The onset of the drug effect was more gradual with the 5 μ-mole/kg dose, some pecks being made in the first FI component after injection, and virtually ceasing in the second and third FI components; pecking then began to return, recovery being complete in 50 min. As shown in Fig. 1 (A and B), the fixed ratio (FR) performance was not affected by doses of 2.5 and 5 μ-mole/kg. A dose of 10 μ-mole/kg (not shown in Fig. 1) did disrupt the FR performance but recovery was more rapid than for the FI performance. The progressive decrement in pecking during the FI component with progressive increase in dose is given in terms of the activity ratio in Fig. 2 (A and B). An approximately linear descending slope was obtained by plotting the dose in geometric progression against the activity ratio plotted arithmetically. The activity ratios for the chicken shown in Fig. 2A (filled circles) declined from the control of 1 to 0.9, 0.74, 0.24 and 0.15 with doses of 1.25, 2.5, 5 and 10 μ-mole/kg respectively; the reduction was significant for the 5 μ-mole/kg ($t=6.34$; $P<0.001$) and 10 μ-mole/kg doses ($t=4.75$; $P<0.01$). The activity ratios for the chicken shown in Fig. 2B (filled circles) declined from the control of 1 to 0.72, 0.59, 0.56 and 0.06 with doses of 2.5, 5, 10 and 40 μ-mole/kg respectively. The reduction with the 40 μ-mole/kg dose ($t=9.01$; $P<0.001$) was statistically significant; those with the 2.5, 5 and 10 μ-mole/kg doses were not.

The activity ratios in Fig. 2 compare the first 5 FI components after the drug with the 5 FI components before it and following the control saline injection. But the effect of α-methyl noradrenaline, particularly the larger doses, extended to the second and third series of FI components. The number of pecks from a set of experiments with α-methyl noradrenaline in chicken 5 are shown in Table 1, giving both an idea of the quantitative effect on pecking and the duration of effect over three consecutive series of 5 FI components following drug injection. Thus, by the third of the series pecking had recovered with the 2.5 μ-mole/kg dose, but with the 10 and the 40 μ-mole/kg dose, the suppression of pecking continued longer and was statistically significant. An idea of both the quantitative effect of α-methyl noradrenaline and the rate of recovery, can also be obtained from Fig. 3A, in this case for chicken 4. The activity ratios for the four series of successive FI components in the 75 min after the injection of α-methyl noradrenaline (5 μ-mole/kg) were 0.21, 0.42, 0.89 and 0.91. The reduction in the first and second series are statistically significant, those in the third and fourth series are not.

The suppressant effects of α-methyl noradrenaline were obtained with fast and slow rates of pecking in chickens on identical schedules (FR 25, FI 3 min). The mean pecking scores for the control 5 FI preceding the four experiments with α-methyl noradrenaline were in chicken 4, 119.8, 115.2, 87.6 and 170.2 respectively, and 149, 228, 148.2 and 130 for chicken 5. In chicken 2, the mean pecking scores for the control 5 FI were lower—48.8, 76.4, 64.8 and 50.6 respectively, yet the dose-response slope for α-methyl noradrenaline was similar to those plotted in Fig. 2 for chickens 4 and 5. In a further experiment with chicken 2 on FR25, FI 7 min, a schedule that engendered a slow rate of pecking, α-methyl noradrenaline 5 μ-mole/kg reduced pecking.

TABLE 1

SCORES FOR PECKING AND CHEEPING OVER A CONTROL AND THREE SUBSEQUENT SERIES OF 5 FI AND 5 FR FOLLOWING THE INJECTION OF α-METHYL NORADRENALINE OR OF DEXAMPHETAMINE

The schedule with α-methyl noradrenaline was multiple FR25, F13 min and with dexamphetamine, multiple FR 25, FI 7 min. Activity ratios for pecking given in parentheses. Significance values given for cheeping.

Dose (μ-mole/kg I.P.)	CONTROL FI/FR series		1st FI/FR series		AFTER DRUG 2nd FI/FR series		3rd FI/FR series	
	Pecking	Cheeping	Pecking	Cheeping	Pecking	Cheeping	Pecking	Cheeping
α-Methyl noradrenaline (chicken 5)	Duration of each FI/FR series = 16 min							
2·5	745 (1)	1044	536 (0·73)	1401	637 (0·85)	2452 $t=2\cdot28$, $p<0\cdot05$	781 (1·05)	2638
5·0	1140 (1)	1137	656 (0·59)	3115 $t=3\cdot09$, $p<0\cdot01$				
10·0	741 (1)	403	419 (0·56)	1341 $t=2\cdot32$, $P<0\cdot05$	391 (0·53)	4776 $t=7\cdot57$, $P<0\cdot001$	141 (0·2)	7306
40·0	650 (1)	2120	37 (0·06)	1402	20 (0·03)	427 $t=6\cdot86$, $p<0\cdot001$	15 (0·02)	207
Dexamphetamine (chicken 1)	Duration of each FI/FR series = 36 min							
10·0	266 (1)	1437	692 (2·6)	3137 $t=4\cdot22$, $P<0\cdot001$	448 (1·68)	6545	284 (1·1)	5845
20·0	311 (1)	2351	844 (2·8)	6266	952 (3·1)	5843 $t=5\cdot89$, $P<0\cdot001$	805 (2·6)	8645
40·0	233 (1)	443	425 (1·8)	8190 $t=17\cdot2$, $P<0\cdot001$	513 (2·2)	5680	480 (2·1)	2570 $t=8\cdot03$, $p<0\cdot001$

In the young chickens, depression of pecking by α-methyl noradrenaline was accompanied by drowsiness or sleep. In the older fowl this soporific action was not observed although pecking was reduced.

Cheeping

In the operant experiments, cheeping was not reduced in the same way as in a non-operant situation in which cheeping was diminished or abolished by α-methyl noradrenaline (Dewhurst & Marley, 1965a). This difference is evident from Table 1 since, except with the 40 μ-mole/kg dose which significantly reduced cheeping, a

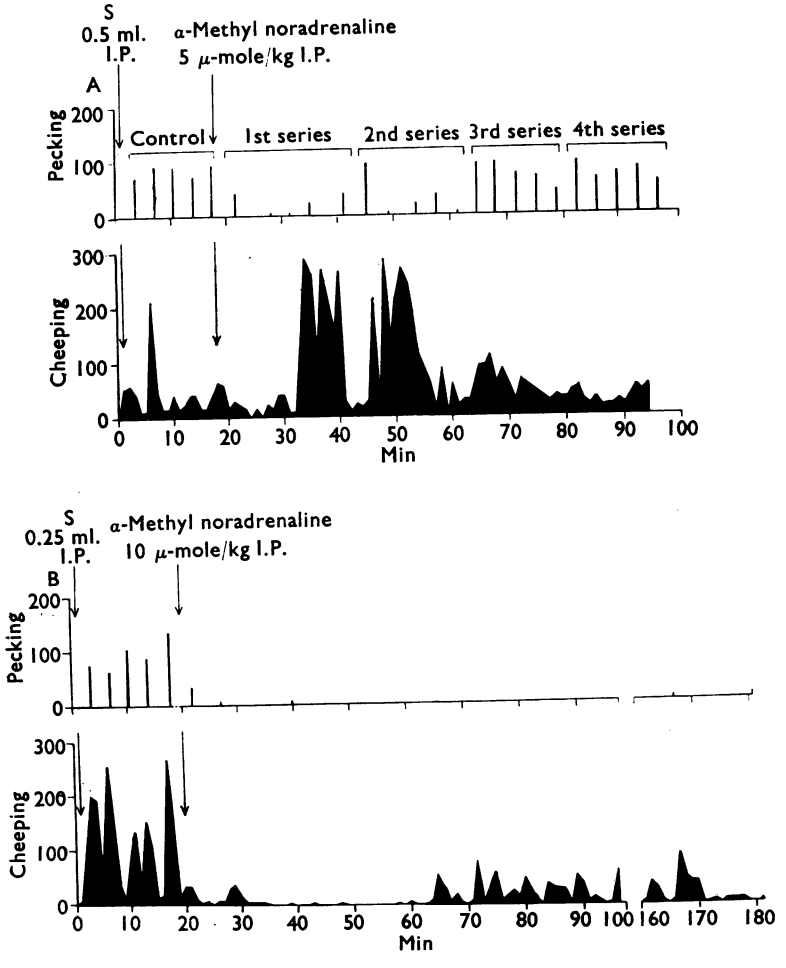

Fig. 3. Graphs of the effect of α-methyl noradrenaline on pecking in chicken 4, plotted as the number of pecks in each FI component shown by the vertical bars, and on cheeping plotted as integrals recorded in successive minutes. Pecking schedules FR25, FI 3 min. In A and B pecking was depressed by α-methyl noradrenaline as shown by the reduction in height of the vertical bars, with subsequent recovery shown for the 5 μ-mole/kg dose. In A cheeping was considerably increased when pecking reduced. In B both pecking and cheeping were diminished.

significant increase in cheeping accompanied the decline in pecking produced by α-methyl noradrenaline. This relation is also shown in Fig. 3A. After the 5 μ-mole/kg dose pecking was much diminished, but some cheeping continued although the chicken was drowsy. During the fourth FI component of the first series following the drug injection and before pecking recovered, cheeping (loud distress calls) suddenly increased giving integrals of almost 300/min as compared with those of 20 to 50/min during the control period. As pecking increased during the first FI component of the second series, cheeping declined giving integrals of less than 20/min, but with the reduction in pecking for the subsequent FI components of that series, cheeping was again substantially increased. As pecking recovered after the first FI component of the third series, cheeping returned to about the same amount as that recorded before injecting α-methyl noradrenaline.

As shown in Fig. 3B, both cheeping and pecking were greatly reduced immediately following the injection of 10 μ-mole/kg α-methyl noradrenaline. Pecking then ceased and was still minimal 160 min after giving the drug. Cheeping began to return 40 min after the injection but recovery was far from complete after 160 min.

As the chicken matured it vocalized to a lesser extent. Thus cheeping became much less marked at about the third month and no longer increased when pecking paused or stopped (Marley & Morse, 1966). Consequently, although in the adult chicken 2 pecking was reduced by α-methyl noradrenaline, vocalization did not increase.

Blood pressure

Tests were made in four chickens. In each, α-methyl noradrenaline 2.5 μ-mole/kg injected intraperitoneally, the minimal dose that affected pecking, had no action on the blood pressure whereas rises of blood pressure were produced by 5 and 10 μ-mole/kg. These pressor responses varied from chicken to chicken and in one fowl after 5 μ-mole/kg the blood pressure rose from 60 to 150 mm Hg with return to the pre-injection value at 27 min, whereas in another a rise only from 70 to 80 mm Hg occurred. After 10 μ-mole/kg, the blood pressure changes were long-lasting and in a representative experiment the blood pressure rose from 75 to 145 mm Hg and had not returned to the pre-injection value 140 min later when the experiment was ended.

Pharmacological antagonism

Phenoxybenzamine, a potent antagonist at peripheral α-receptors (Nickerson, 1949), proved to be the only satisfactory antagonist. Since large doses of phenoxybenzamine were required for antagonism of the behavioural and electrocortical effects of α-methyl noradrenaline in chickens tested in a non-operant situation (Dewhurst & Marley, 1965a), in the present tests phenoxybenzamine was injected in doses of 80, 120 or 160 μ-mole/kg at least 2 or 3 days previously.

Pecking

As shown in Fig. 1C, α-methyl noradrenaline 40 μ-mole/kg given after phenoxybenzamine (120 μ-mole/kg) had a smaller depressant effect on pecking than 5 μ-mole/kg α-methyl noradrenaline in the same but untreated chicken (Fig. 1B). The onset of

effect was slower, the almost complete abolition of pecking observed in the second FI component after the 5 μ-mole/kg dose in the untreated chicken (Fig. 1B), not occurring until the seventh FI component after the 40 μ-mole/kg dose when the chicken had been given phenoxybenzamine (Fig. 1C). The dose response slopes in terms of activity ratio for experiments in two of the chickens given phenoxybenzamine (filled squares) are shown in Fig. 2A and B. The upper graph demonstrates that a 10-fold increase in dose of α-methyl noradrenaline was required to be equally effective after phenoxybenzamine 120 μ-mole/kg, compared with its effect before treatment with the antagonist (contrast the effect of the 2.5 and 20 μ-mole/kg doses). The lower graph shows that with a smaller dose of phenoxybenzamine (80 μ-mole/kg), only a four-fold increase in dose of α-methyl noradrenaline was required to be equieffective. The lower graph (Fig. 2B) illustrates an additional point: that antagonism was surmountable with the 5 μ-mole/kg dose given in 2 days after phenoxybenzamine. This observation was confirmed in chicken 2, as was the finding that antagonism appeared not to be complete until 3 days after phenoxybenzamine and lasted for about 7 days. In neither of the chickens were the reductions of key-pecking by α-methyl noradrenaline statistically significant after 3 days pretreatment with phenoxybenzamine.

Also tested were methysergide, a potent antagonist at tryptamine receptors (Doepfner & Cerletti, 1958); pronethalol, a potent antagonist at β-receptors (Black & Stephenson, 1962) and chlorpromazine. These drugs may affect pecking, so the doses given were limited to those without apparent effects on pecking and were injected together with the control saline. They were: for methysergide, 0.1 μ-mole/kg intraperitoneally; for pronethalol, 20 μ-mole/kg intraperitoneally and for chlorpromazine, 40 μ-mole/kg intraperitoneally. The depressant action of α-methyl noradrenaline (10 and 40 μ-mole/kg intraperitoneally) was unaffected by chlorpromazine, whereas the depressant effects of α-methyl noradrenaline (2.5 and 5 μ-mole/kg) were enhanced by methysergide and those of α-methyl noradrenaline (5, 10 and 20 μ-mole/kg) were increased by pronethalol.

Cheeping

In contrast to experiments without phenoxybenzamine, cheeping was unaffected in chickens 4 and 5 by up to 10 or 20 μ-mole/kg α-methyl noradrenaline; these doses did not lower the activity ratio for pecking below 0.7 (Fig. 2). However, with 40 μ-mole/kg α-methyl noradrenaline which reduced the activity ratio about 50% in both chickens, as the reduction in pecking occurred so the amount of cheeping increased. Thus, in chicken 4, cheeping rose from a mean count of 233/min for the control 5 FI, to 439/min for the 5 FI following drug injection.

Blood pressure

Two chickens were given phenoxybenzamine (10 μ-mole/kg) 3 days previously. Doses of up to 50 μ-mole/kg α-methyl noradrenaline given intraperitoneally were now ineffective on the blood pressure and given intravenously produced a rise of only 20 mm Hg with return to the control blood pressure 5 min after injection.

Effects of dexamphetamine

Pecking

Dexamphetamine was tested in 3 chickens (1, 2, 6) at various times between the ages of 1 to 4 months and 2 chickens (5, 7) less than 28 days old. With schedules generating a low rate of pecking (FR 25, FI 7 min) there was an increase in pecking during the FI components with doses of 10 and sometimes 20 and 40 μ-mole/kg dexamphetamine. With the larger doses, however, pecking tended to be decreased. The data taken from chicken 1 are given in Table 1. These give in quantitative terms the increase in pecking during the FI component with doses of 10, 20 and 40 μ-mole/kg dexamphetamine, and the duration of the effect over three consecutive series of 5 FI components after the injection. The maximal enhancement was observed after the 20 μ-mole/kg dose, with an increase from a total of 311 pecks in the control 5 FI components to totals of 844, 952 and 805 pecks respectively in the ensuing three series of 5 FI components. These increases in pecking after dexamphetamine were statistically significant, the activity ratios and significance values being respectively 2.8 ($t=5.05$, $P<0.001$), 3.1 ($t=5.70$, $P<0.001$) and 2.6 ($t=5.41$, $P<0.001$). As each series of 5 FI components lasted some 36 min, the effect persisted at least 108 min. Smaller increases in pecking were observed with the 10 and 40 μ-mole/kg doses. The effects were also shorter-lived and that of the 10 μ-mole/kg dose abated by the third of the series of the 5 FI, about 70 min after the injection. None of the increases with the 10 μ-mole and 40 μ-mole/kg doses were statistically significant except for that for the second FI/FR series after the 40 μ-mole/kg dose ($t=3.12$; $P<0.02$).

The effects of dexamphetamine on the cumulative pecking record are shown in Fig. 4. As in experiments with α-methyl noradrenaline the records show the performance under the multiple schedule after the control saline injection, followed by the first series after dexamphetamine. In Fig. 4A, B, the 20 μ-mole/kg dose increased pecking during the FI components. As previously noted by Dews (1958) and as shown in the Figure, the effect of dexamphetamine was not so much to increase the terminal rate of pecking as to increase pecking early in the interval so that the usual pause at the beginning of the fixed interval disappeared. Thus in Fig. 4B the pause at the beginning of the second FI after the drug was shortened and by the third FI it had disappeared and pecking continued throughout the interval.

The response to dexamphetamine, while constant in the same chicken, nevertheless varied from chicken to chicken and, as shown in Fig. 4C, D, the same dose of dexamphetamine that had enhanced pecking in the first chicken brought pecking to a halt for 17 min in another bird on the same schedule of reinforcement (FR 25, FI 7 min). The cessation of pecking was associated with the development of Grade 3 postural changes. In experiments with chicken 7, aged 16 days, and in which pecking was recorded together with electrocortical and electromyographic activity, a dose of dexamphetamine that enhanced pecking (20 μ-mole/kg) and one (40 μ-mole/kg) that stopped pecking were both associated with the development of a 10–40 μV 20–40 c/sec alert electrocortical pattern and large electromyographic potentials. The cessation of pecking differed therefore from that produced by α-methyl noradrenaline in chickens 4 and 5 which coincided with drowsiness or sleep produced by the drugs.

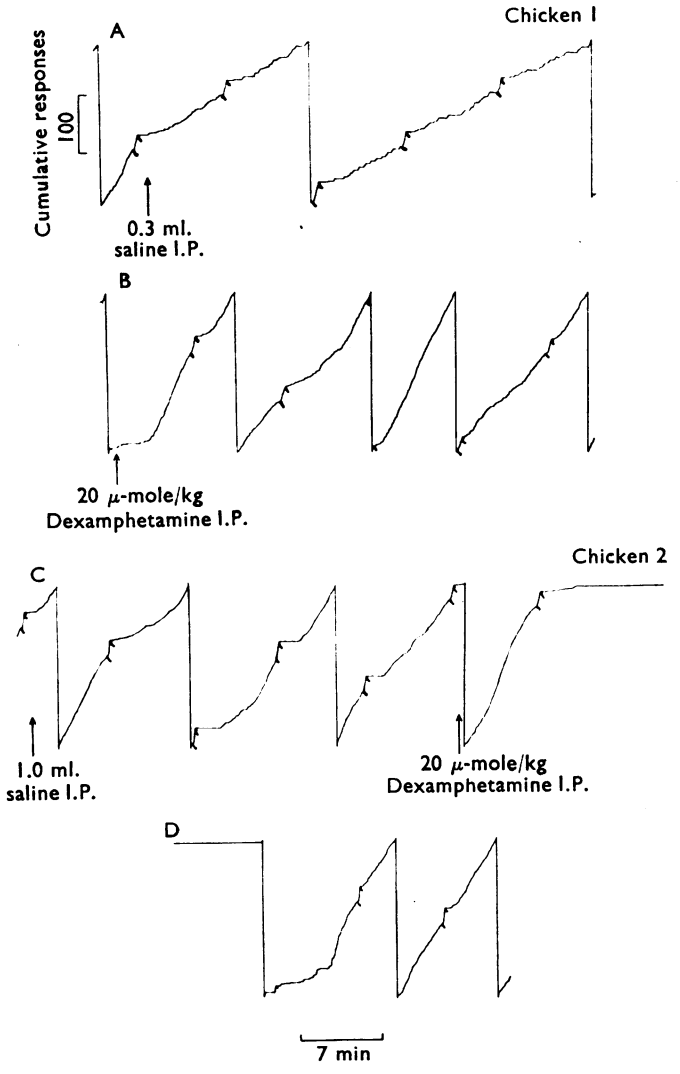

Fig. 4. Cumulative pecking records (as in Fig. 1) to show in chicken 1 (A, B) the increase in pecking by dexamphetamine (20 μ-mole/kg) and in chicken 2 (C, D) the abolition of pecking for 17 min with subsequent recovery and increased pecking following the same dose of dexamphetamine. Records A, B are in sequence for the first chicken, and C, D in sequence for the second chicken. The schedule for both was FR 25, FI 7 min.

The effect of dexamphetamine depended on the schedule in operation. Thus, in chicken 1 on a multiple FR 25, FI 7 min schedule, one which generated a slow rate of pecking, pecking was increased and the activity ratios for the first series of 5 FI after 20 and 40 μ-mole/kg dexamphetamine were 2.6 and 2.8 respectively. In contrast, in the same chicken on a multiple FR 25, FI 3 min schedule which generated a fast rate of pecking, dexamphetamine reduced pecking, and the activity ratios for the same doses of dexamphetamine were 0.91 and 0.2.

Cheeping

Cheeping and pecking were normally inversely related, cheeping being usually maximal during the pause in pecking at the beginning of the interval. The preponderance of cheeping at the beginning of each FI during the control series is shown in Fig. 5A and B. As also seen in the Figure, this inverse relation broke down after dexamphetamine and cheeping was sustained throughout the whole FI. Scores for cheeping before and after dexamphetamine 10, 20 and 40 μ-mole/kg are given in Table I for chicken 1. From these it can be seen that there were increases in cheeping of between 3- and 20-fold that persisted for at least 108 min after drug injection and were statistically significant. Figure 5A shows an additional feature—when marked postural changes (Grade 3) developed pecking and cheeping were in abeyance. With recovery from the postural changes, pecking and cheeping again increased but the reciprocal relation between cheeping and pecking was not restored for some hours. The cheeping elicited by dexamphetamine was of the high-pitched low-intensity variety termed twittering and different from the loud calls heard after α-methyl noradrenaline.

Blood pressure

Two fowls were tested. Doses of 5 μ-mole/kg or greater raised the blood pressure, the effect being dose-dependent. In one fowl a dose of 10 μ-mole/kg which would have increased pecking in the operant experiments raised the blood pressure from 95 to 135 mm Hg, the effect lasting 90 min. In another fowl, following a dose of 40 μ-mole/kg which generally suppressed pecking, the blood pressure rose from 70 to 100 mm Hg and was maintained there for 75 min, when the experiment was ended.

Pharmacological antagonism

Pecking

Methysergide, a specific tryptamine antagonist, was studied first, since in doses of 0.01 to 0.1 μ-mole/kg it antagonized the behavioural and electrocortical effects of dexamphetamine or of α-methyltryptamine in chickens tested in a non-operant situation (Dewhurst & Marley, 1964; 1965a).

In the present experiments, methysergide in doses of 0.01 and 0.1 μ-mole/kg intraperitoneally did not affect pecking. Consequently it was injected with the control saline about 35 min before injecting dexamphetamine. The effects of dexamphetamine (5, 10, 20 and 40 μ-mole/kg) on pecking or cheeping were not antagonized by these doses of methysergide in the two chickens in which it was tested (chickens 1 and 2). Larger doses were therefore given. Methysergide, 0.75 μ-mole/kg, depressed pecking completely, with recovery after 133 min. Dexamphetamine (10 μ-mole/kg) was then injected, but its actions on pecking and cheeping were not diminished. In another experiment, methysergide 5 μ-mole/kg was injected, followed by a similar dose 12 hr later. Pecking was again decreased but recovered 64 min after the last dose. Dexamphetamine (10 μ-mole/kg) was then given but its effects were not diminished.

Phenoxybenzamine was next tested. Doses of 100 or 160 μ-mole/kg were given 3 days previously in 2 chickens (No. 5, 6). These doses decreased pecking at the time of injection but pecking had recovered the following day. Dexamphetamine was injected

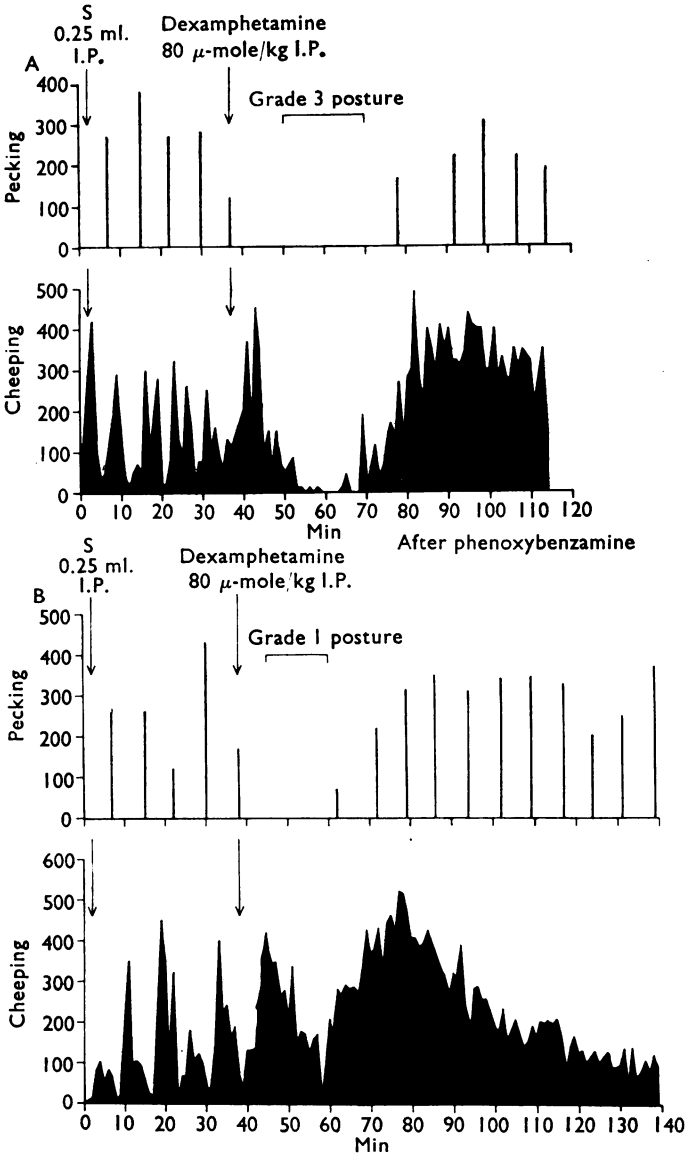

Fig. 5. Graphs of the effect of dexamphetamine in chicken 5 on pecking, plotted as the number of pecks in each FI shown by the vertical bars, and on cheeping plotted as integrals in successive minutes. Pecking schedule FR25, FI 7 min. In A the dose of dexamphetamine suppressed pecking and after an initial increase cheeping was also reduced. Recovery occurs about 40 min later, when cheeping but not pecking was increased. In B the chicken had been pretreated with phenoxybenzamine (100 μ-mole/kg 3 days previously). The suppression of pecking was now less marked and on recovery both pecking and cheeping were increased.

in doses of 5, 10, 20, 40 and 80 μ-mole/kg. In chicken 5, key-pecking was significantly increased by dexamphetamine 10 μ-mole/kg ($t=3.91$; $P<0.02$) and significantly diminished by the 40 μ-mole/kg ($t=3.98$; $P<0.01$) and 80 μ-mole/kg doses ($t=4.52$;

$P<0.01$). After pretreatment with phenoxybenzamine (100 μ-mole/kg) the increase of pecking with the 10 and 20 μ-mole/kg doses did not occur, and the reduction of pecking with the 40 and 80 μ-mole/kg doses was attenuated. None of the effects of dexamphetamine were now statistically significant. Similar results were obtained in chicken 6.

Cheeping

An antagonistic action of phenoxybenzamine was also observed for the effects of dexamphetamine on cheeping. In the control experiment shown in Fig. 5A, dexamphetamine (80 μ-mole/kg) decreased pecking for 40 min and cheeping for 20 min. Postural changes (Grade 3) developed. On recovery, pecking was not increased in the subsequent series of 5 FI. After injecting the same chicken with phenoxybenzamine (100 μ-mole/kg 3 days previously), the same dose of dexamphetamine decreased pecking for 20 min but cheeping not at all, and only Grade 1 postural changes developed. Moreover, pecking was increased once the postural effects abated.

Blood pressure

Four fowls were tested. The effects of dexamphetamine on blood pressure were no more than slightly reduced by pretreatment with phenoxybenzamine. One fowl was given phenoxybenzamine (20 μ-mole/kg) 3 days previously. Dexamphetamine (10 μ-mole/kg) raised blood pressure from 90 to 100 mm Hg, the effect lasting 50 min ; blood pressure rose from 80 to 105 mm Hg for 43 min in the same fowl following dexamphetamine (20 μ-mole/kg). In another fowl given phenoxybenzamine (20 μ-mole/kg) 3 days previously, dexamphetamine (10 μ-mole/kg) produced an increase from 75 to 95 mm Hg lasting 65 min ; a dose of 20 μ-mole/kg dexamphetamine raised the blood pressure from 75 to 100 mm Hg but the effect abated after 35 min. The pressor effects of dexamphetamine (2 and 4 μ-mole/kg intravenously) in two fowls pretreated with phenoxybenzamine (20 μ-mole/kg 3 days previously) were substantially antagonized by methysergide (0.1 and 0.5 μ-mole/kg intravenously).

Effects of α-methyltryptamine

Pecking

Experiments were made in 4 chickens (4, 5, 9, 10) between 1 and 2 months old and in 1 chicken (8) under 28 days old. Reduction in the amount of key-pecking was the most marked feature with α-methyltryptamine. As shown in Fig. 6B, the effect of α-methyltryptamine (5 μ-mole/kg) was evident by the end of the second and beginning of the third interval component after its injection. The number of pecks decreased progressively during the ensuing two interval components shown in the Figure, although the FR was unaffected. This reduction in pecking was followed by the development of the postural changes already noted with dexamphetamine. The 10 μ-mole/kg dose of α-methyltryptamine completely and rapidly suppressed pecking during both the FI and the FR (Fig. 6D), recovery only beginning 2 to 3 hr later. In spite of the suppression of pecking the bird was alert. The activity ratio for the 5 consecutive FI shown in Fig. 7B following the injection of the 5 μ-mole/kg dose was 0.67, and that for the 5 consecutive FI after the 10 μ-mole/kg dose was 0.03. The reduction of key-pecking with the 5 μ-mole dose was not statistically significant ($t=1.4$; $P>0.1$), whereas that due to the 10μ-mole/kg

was obviously so. These activity ratios for the first 5FI following the drug are plotted in Fig. 7. The activity ratios fell further over the ensuing 5FI, that for the second series of 5FI following the 5 μ-mole/kg dose being 0.35. In this case the reduction in pecking was statistically significant ($t=6.53$; $P<0.001$). Figure 7 also shows that with a smaller dose of α-methyltryptamine, in this case 1.25 μ-mole/kg, a small increase in pecking can occur.

In an experiment with chicken 8, aged 18 days, in which pecking was recorded together with electrocortical and electromyographic activity, doses of α-methyltryptamine (5 or 10

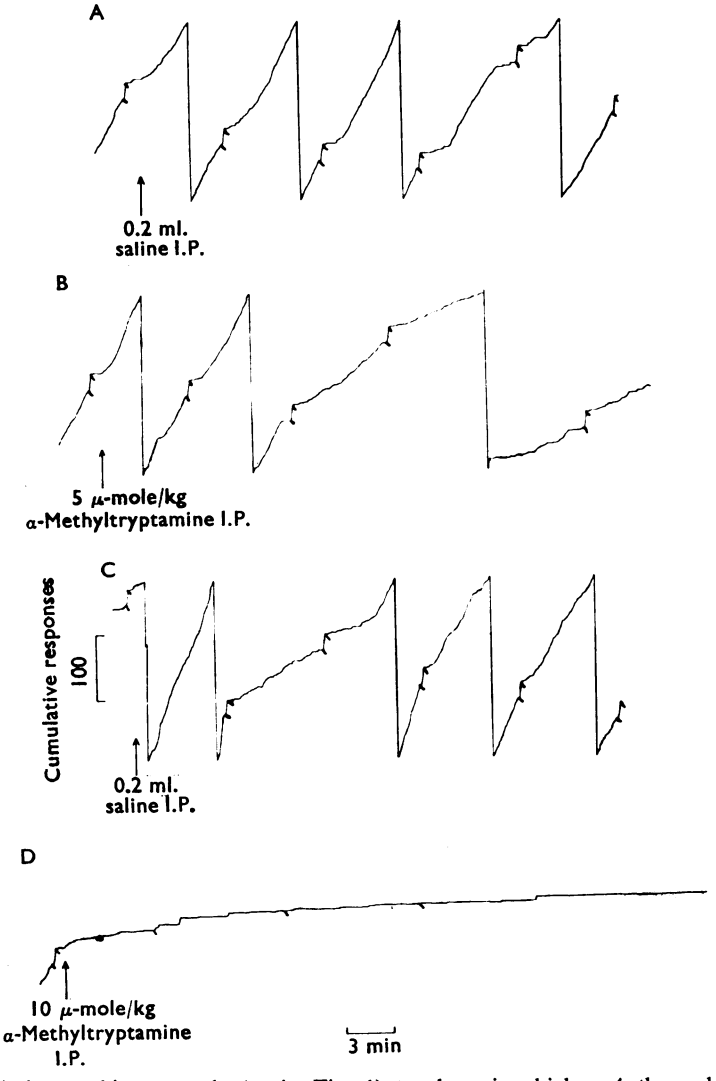

Fig. 6. Cumulative pecking records (as in Fig. 1) to show in chicken 4 the reduction (B) and suppression (D) of pecking by α-methyltryptamine. Records A, B are in sequence for one experiment as are C, D for the other. The schedule for both was FR 25, FI 7 min.

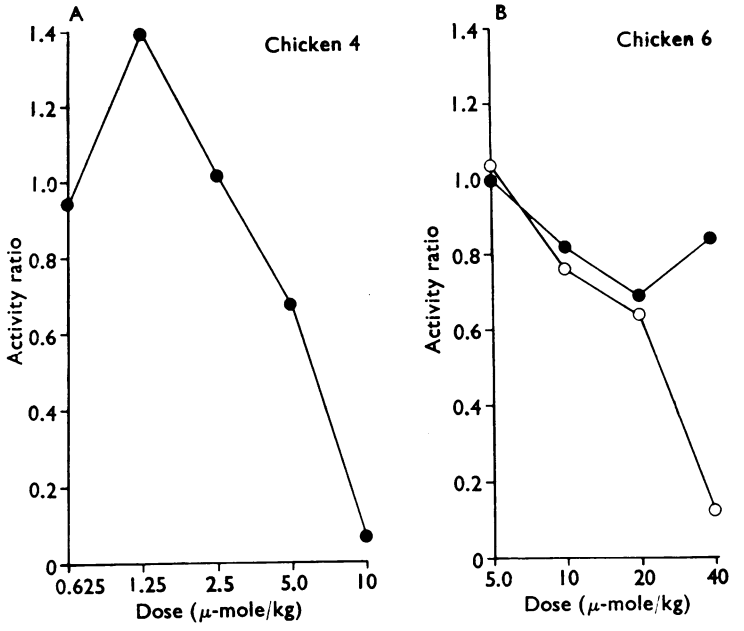

Fig. 7. Graphs for the effect on pecking (A) of α-methyltryptamine in chicken 4 and (B) of 6-hydroxytryptamine in chicken 6. In A and B, ordinate is the activity ratio for pecking and abscissa is the dose of drug. In A, the pecking schedule was FR 25, FI 7 min, in B, it was FR 25, FI 3 min. In A, small increase in activity ratio with 1.25 μ-mole/kg α-methyltryptamine, but progressive decrease in activity ratio with increase in dose. In B, greater suppression of pecking with 6-hydroxytryptamine injected after 100 μ-mole/kg mebanazine (○——○), than without pretreatment with the amine oxidase inhibitor (●——●).

μ-mole/kg) that reduced or abolished pecking were associated with development of the 10–40 μV 20–40 c/sec alert electrocortical pattern and large electromyographic potentials similar to those observed with dexamphetamine.

Indolealkylamines which are resistant to monoamine oxidase—for example, α-methyltryptamine—are inactivated by 6-hydroxylation (Szara, 1961; Jepson, Zaltzman & Udenfriend, 1962). Since 6-hydroxy-α-methyltryptamine was not available, the effect of 6-hydroxytryptamine was tested in a chicken (No. 6) before and after pretreatment with the amine oxidase inhibitor mebanazine (100 μ-mole/kg 90 min previously) to determine whether a 6-hydroxy derivative could suppress pecking. Pecking was little affected in the untreated chicken with doses of 5, 10, 20 and 40 μ-mole/kg 6-hydroxytryptamine (upper line in Fig. 7B) but was markedly decreased with the 40 μ-mole/kg dose after mebanazine (lower line in Fig. 7B). The effects of 6-hydroxytryptamine were otherwise unlike those of α-methyltryptamine, since the postural changes did not develop with any of the doses, and the bird was drowsy or asleep with the 40 μ-mole/kg dose while pecking was in abeyance.

Cheeping

The normal reciprocal relation between pecking and cheeping (Control 5 FI, Fig. 8) disappeared after α-methyltryptamine as it did after dexamphetamine, and as shown in

Fig. 8, following a dose of 5 μ-mole/kg, cheeping was increased throughout the whole FI. The increase during the 5FI following the drug had significantly increased compared to the control ($t=5.67$, $P<0.001$). The cheeping was of the high-pitched low-intensity variety, similar to that obtained with dexamphetamine. As with dexamphetamine, cheeping was reduced or abolished when there were marked postural changes.

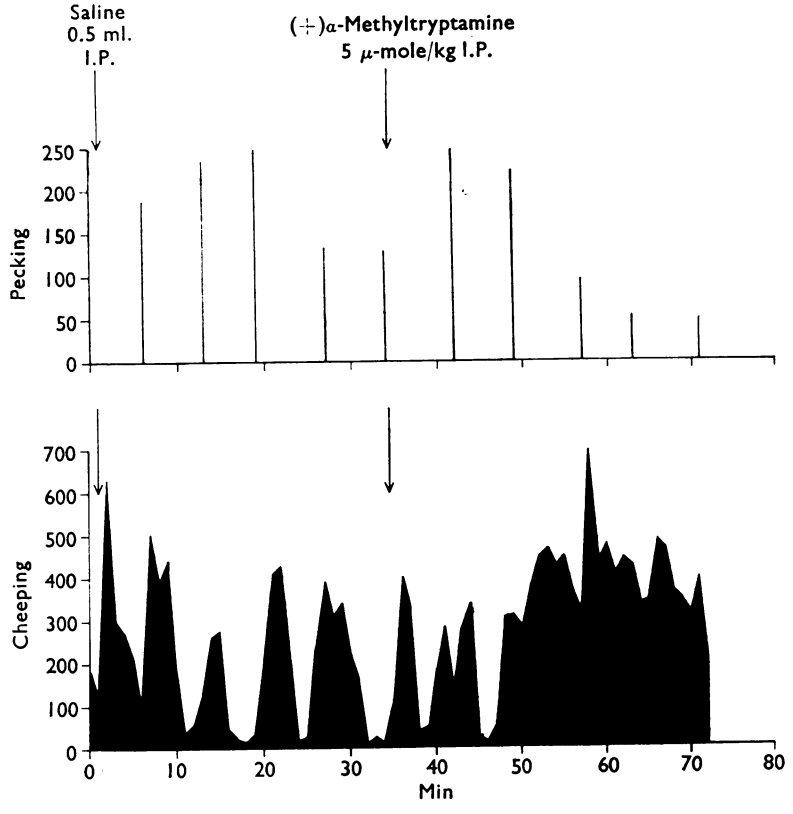

Fig. 8. Graphs for the effect of α-methyltryptamine on pecking in chicken 4, plotted as the number of pecks in each FI component shown by the vertical bars, and on cheeping plotted as integrals recorded in successive minutes. Pecking schedule FR 25, FI 7 min. Pecking was reduced by α-methyltryptamine (5 μ-mole/kg) as shown by the reduction in height of the vertical bars (upper trace) whereas cheeping (lower trace) was increased and sustained throughout the 5 FI.

Blood pressure

Tests were made in 4 fowls. In each, the first dose of α-methyltryptamine given intraperitoneally produced a virtually immediate fall of blood pressure. Subsequent injections either evoked small pressor responses or did not affect the blood pressure. The effect was dose-dependent. Thus, with 1.25 μ-mole/kg the blood pressure fell from 75 to 15 mm Hg with recovery in 3 min ; with 2.5 μ-mole/kg there was a decline from 90 to 25 mm Hg with recovery after 24 min. With 5 μ-mole/kg, the blood pressure fell from 95 to 47 mm Hg, and remained at this level for the ensuing 100 min when the experiment was

ended. Since considerable falls of blood pressure occurred even with the smaller doses of α-methyltryptamine which barely affected pecking, the effect on pecking appeared to be unrelated to that on blood pressure.

Pharmacological antagonism

Pecking and cheeping

A chicken (No. 2) given phenoxybenzamine (100 μ-mole/kg) 3 days previously, responded to α-methyltryptamine (1.25, 2.5, 5.0 and 10 μ-mole/kg) as it had done before phenoxybenzamine. In contrast, the suppressant effects of α-methyltryptamine (20 and 40 μ-mole/kg) on key-pecking in chickens 9 and 10 were antagonized by methysergide (1 μ-mole/kg). In these tests, saline control and drug injections were not injected until any effects of methysergide on pecking had abated.

DISCUSSION

In chickens, schedule-controlled key-pecking can be developed within a few days of hatching (Marley & Morse, 1966). The patterns established proved in the present experiments to be sufficiently sensitive and reproducible to be used in drug studies.

Since pecking was reduced by α-methyl noradrenaline but increased by dexamphetamine, the results are compatible with earlier findings (Key & Marley, 1962) that α-methyl noradrenaline was a central depressant in the young chicken but dexamphetamine a central excitant. The results also accord with observations that pecking in another avian species, the adult pigeon, was diminished by adrenaline or noradrenaline (Wurtman *et al.*, 1959) but enhanced by N-methyl amphetamine (Dews, 1958). The effects of dexamphetamine depended on the schedule in operation and in conformity with findings in the adult of a number of species (Dews & Morse, 1961), pecking was increased by dexamphetamine only if the control rate of pecking was slow. In contrast, reduction of pecking was obtained with α-methyl noradrenaline whether the control rate of pecking was fast or slow.

The effects of dexamphetamine and of α-methyltryptamine are indistinguishable in young chickens tested in a non-operant situation. They respond with behavioural and electrocortical alerting, increased cheeping and, after larger doses, by characteristic postural changes (Dewhurst & Marley, 1965a). Surprisingly, then, their effects on key-pecking differed, pecking being increased by the lower doses of dexamphetamine but rarely so by α-methyltryptamine which usually reduced responding. In a separate category was the suppression of pecking with the larger doses of α-methyltryptamine and of dexamphetamine that elicited marked postural changes and which were likely to interfere with movement and therefore of pecking. As the postural changes abated, pecking returned with dexamphetamine and was often greater than that before the injection, but continued diminished with α-methyltryptamine.

In the operant situation there is generally a reciprocal relation between key-pecking and cheeping so that when pecking is maximal, as at the end of the FI or during the FR, cheeping is minimal and *vice versa* (Marley & Morse, 1966). The effects of α-methyl noradrenaline on cheeping appeared to be at least partly secondary to those on pecking. With doses up to 5 μ-mole/kg α-methyl noradrenaline, pecking was reduced and consequently cheeping was increased. With larger doses of α-methyl noradrenaline which

produced sleep, cheeping as well as pecking was suppressed. When pecking recovered, the reciprocal relation between pecking and cheeping was re-established. Cheeping was also increased by α-methyltryptamine which suppressed pecking. This inter-relation between cheeping and pecking was not observed after dexamphetamine since both pecking and cheeping were increased. Moreover, the reciprocal relation between pecking and cheeping broke down, so that cheeping was sustained throughout even fast pecking. The characteristics of the cheeping differed with the different amines. After dexamphetamine or α-methyltryptamine it consisted of fast-frequency low-intensity twittering, whereas after α-methyl noradrenaline cheeping consisted mainly of loud calls.

In the isolated chicken studied in a semi-sound-proof non-operant situation, cheeping was not always increased by dexamphetamine or α-methyltryptamine, but if in addition social (other chickens) or extraneous stimuli (noise) were present then cheeping or twittering invariably occurred (Dewhurst & Marley, 1965a). Presumably there was some kind of interaction between the effects of amphetamine and of sensory or social stimulation. Similarly, schedule-controlled key-pecking modified the effects of dexamphetamine on cheeping. Since appropriate doses of dexamphetamine increased cheeping even under relatively sound-proof operant conditions, then the combination of the drug and the pattern of responding could account for the increased and sustained cheeping, instead of diminished or absent cheeping normally to be expected when key-pecking was maximal.

The effects of the amines on pecking did not appear to be related to any particular change in blood pressure. For example, pecking was suppressed by doses of α-methyl noradrenaline which raised blood pressure, and also by doses of α-methyltryptamine which lowered it. Doses of dexamphetamine that increased pecking also raised the blood pressure to a similar degree to those of α-methyl noradrenaline which suppressed pecking.

The depressant effects of α-methyl noradrenaline on pecking were prevented by phenoxybenzamine suggesting an action mediated through α-receptors for catecholamines in the brain; the pressor effects of α-methyl noradrenaline were also prevented by phenoxybenzamine. The results accord with observations of Wurtman *et al.* (1959) that phenoxybenzamine prevented the suppression of pecking by adrenaline or noradrenaline in adult pigeons. The effect of α-methyl noradrenaline on behaviour and electrocortical activity of chickens in a non-operant situation was also prevented by phenoxybenzamine (Dewhurst & Marley, 1965a) as were its actions on temperature and oxygen consumption (Allen & Marley, 1966).

Vane (1960) and Gelder & Vane (1962) suggested that amphetamine might act on tryptamine receptors in the central nervous system. Experiments with chickens in a non-operant situation favoured this idea, since dexamphetamine and α-methyltryptamine had identical effects and both were antagonized by similar doses of the same pharmacological antagonist, methysergide (Dewhurst & Marley, 1964, 1965a). In the present operant experiments the amines differed in their effects, at least with the lower doses, key-pecking being enhanced by dexamphetamine and reduced or suppressed by α-methyltryptamine. However, α-methyltryptamine was more potent than dexamphetamine and had a steeper dose-response slope. Possibly because of this, the descending part of the dose-response slope (reduction of key-pecking) was more conspicuous than the ascending part of the slope (increased responding). More difficult to account for was the finding that phenoxybenzamine antagonized the effects of dexamphetamine on key-

pecking but not those of α-methyltryptamine, whereas methysergide antagonized the effects of α-methyltryptamine but not dexamphetamine.

These are by no means the only inconsistencies and there are differences, not as yet explained, between the effects of the amines in different species. Thus the behavioural effects of dexamphetamine and of α-methyltryptamine have many similarities in mice (Vane *et al.*, 1961) and in rats (Randrup, Munkvad & Udsen, 1963) but are dissimilar in cats (Bradley & Marley, 1965). In rats trained to deliver electrical stimuli to the brain, amphetamine enhanced responding whereas α-methyltryptamine had no effect (Stein, 1964). The results from the various species, including chickens, suggest that amphetamines have at least two central modes of action, one mediated through tryptamine receptors and the other determined *via* noradrenaline release.

Some of the effects of α-methyltryptamine have been ascribed to the formation of 6-hydroxylated indole derivatives. These derivatives have been thought to be more active than the parent compound (Szara, 1961); alternatively, 6-hydroxylation has been considered a detoxication mechanism giving compounds with less pharmacological activity (Jepson *et al.*, 1962). In non-operant situations, compounds such as α-methyl phenethylamine or α-methyltryptamine which lack substituents on the radical, induce arousal in chickens. In contrast, analogues with electronegative substituents on the radical such as tyramine, 5- or 6-hydroxytryptamine induce sleep in young chickens treated with monoamine oxidase inhibitors (Dewhurst & Marley, 1965b). These findings hold good for the present operant experiments, although both types of compound reduced key-pecking. The evidence was against the reduction of key-pecking with α-methyltryptamine being due to the formation of a 6-hydroxy derivative.

What general conclusions emerged from these and previous findings with chickens? The effects of the amines on posture, electrocortical and electromyographic activities were consistent and reproducible irrespective of whether chickens were tested in operant or non-operant situations. In contrast, the effects on behaviour differed in certain respects depending on the situation in which the chickens were studied. That they varied to such an extent in the same species indicated the need to take the on-going behaviour into account when specifying the behavioural effects of drugs and was a salutary pointer to the fallacy of extrapolating their behavioural effects from observations in only one situation. Clearly too, the over-all change produced by a drug was more important than a change in one aspect, be it cerebral electrical activity or behaviour like cheeping or pecking—a change in each by itself being insufficient to categorize a drug's actions. This proviso would be particularly apposite when one type of behaviour, such as key-pecking, is reinforced, since the effect of drugs on this behaviour may determine the effects on subsidiary items of behaviour. Accordingly, difficulties in interpretation may be resolved by a better understanding of the relations and interactions among the variables, behavioural and electrophysiological, likely to be affected by drugs.

SUMMARY

1. The effects of the ω-methyl derivatives of noradrenaline, phenethylamine and tryptamine were tested on key-pecking in young and in mature chickens maintained on multiple FI, FR schedules. The effects of the drugs were most marked on the Fixed

Interval component of the schedule and least marked on the Fixed Ratio component. The effects on cheeping and blood pressure were also recorded.

2. Pecking was suppressed by α-methyl noradrenaline, the effect being obtained with schedules generating slow or fast rates of pecking. With doses of 5 μ-mole/kg α-methyl noradrenaline as pecking was reduced, cheeping increased ; with larger doses, both pecking and cheeping were abolished. These effects of α-methyl noradrenaline were prevented by pretreating the chicken with phenoxybenzamine.

3. With schedules generating slow rates of pecking, dexamphetamine increased the amount of pecking. With schedules generating fast rates of pecking or with larger doses of dexamphetamine, pecking was reduced or suppressed. Cheeping was increased and its character altered by dexamphetamine and the normal reciprocal relation lost between cheeping and pecking, so that cheeping was sustained throughout pecking. Larger doses of dexamphetamine evoked characteristic postural changes which interfered both with cheeping and with pecking. Electrocortical alerting and increased electromyographic potentials occurred with doses of dexamphetamine that increased or decreased pecking. The effects of dexamphetamine on pecking and cheeping were prevented by pretreating the chicken with phenoxybenzamine ; in contrast, the effects on blood pressure were prevented by methysergide.

4. Pecking was suppressed by α-methyltryptamine ; this was invariable with the larger doses and usual with the smaller doses, although in 2 of the chickens tested, key-pecking was increased by one of the smaller doses of α-methyltryptamine. Cheeping was increased and its character altered by α-methyltryptamine and the normal reciprocal relation lost between cheeping and pecking, so that cheeping was sustained throughout pecking. Larger doses of α-methyltryptamine produced characteristic postural changes. Electrocortical alerting and increased electromyographic potentials occurred with α-methyltryptamine although pecking was decreased. The suppressant effect of α-methyltryptamine was antagonized by methysergide.

5. The effects on blood pressure did not appear to be related to changes in behaviour. Thus pecking was suppressed by α-methyl noradrenaline and α-methyltryptamine, although the one raised the blood pressure and the other lowered it. Blood pressure was raised by dexamphetamine in doses that increased or decreased pecking.

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