

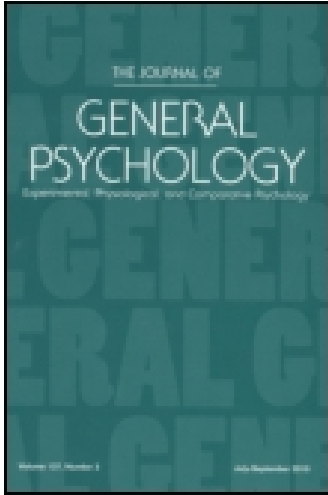
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CONDITIONED EMOTIONAL RESPONSE IN THE RAT: III.
DRUG ANTAGONISM*

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A. PROBLEM

A rat tends to crouch, urinate, and even defecate in the presence of a stimulus (CS) which has previously been associated with a painful shock. These behavioural reactions define a "conditioned emotional response" (CER). The CER can be quantified in terms of its depressant effect upon operant behaviour such as lever-pressing in a Skinner box for a water reward (4). In a previous experiment (9), some of the constitutional and situational determinants of the CER formation were examined, and in another (10), the nature of the response was investigated by observing the effect on it of selected drugs. The drugs used were amylobarbitone, pipradrol, chlorpromazine, and ephedrine. The two former drugs are best known for their effects on the central nervous system, and the latter two for their effects on the autonomic nervous system. The results indicated a greater effect of the centrally-acting drugs on the CER. The inference drawn was that the cortical excitation-inhibition balance (5) may be a crucial factor in the conditioning of the response. In order to investigate further the role of the postulated cortical excitation-inhibition balance, the present experiment was designed to show how the CER reflects the antagonising effects of the two centrally-acting drugs.

In particular, the use of a graded series of doses of the stimulant to antagonize the effect on the CER of a constant dose of the depressant, and vice versa, will permit a more precise evaluation of the action of both of the drugs by allowing a greater range in the effect on the excitation-inhibition balance than might be expected to result from the use of either drug alone.

In the previous study (10) it was also observed that emotionally reactive and non-reactive rats, so defined by virtue of their open-field defecation

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scores (2), differ in their reactions to drugs. It was, therefore, thought important to know whether or not the possible antagonism of drugs is affected by the innate emotional reactivity of the subjects.

In summary, the present experiment was designed to answer two main questions: how does the CER conditioning reflect the possible antagonism of drugs? and; how is the antagonism of drugs affected by the emotional reactivity level of the subjects? The drugs selected for the purpose were pipradrol hydrochloride ("Meratran", Rikers), a central stimulant (3), and sodium amylobarbitone ("Sodium Amytal," Lilly), a central depressant.

B. METHOD

1. *Subjects*

A total of 48 male rats, 24 reactive and 24 non-reactive, were drawn from the eighth generation of the Maudsley Strains of Reactive and Non-reactive rats selectively-bred for high or low defecation in the modified open-field test (1). The animals were brought up under strictly standardised and uniform conditions as described elsewhere (2). Between 98 and 102 days of age the rats were given the open-field test on four successive days. Only animals dropping a total of 14 or more fecal boli were assigned to the reactive group (mean: 19.04; $SE = \pm .71$), and only animals not defecating at all during the test to the non-reactive group. At the beginning of the present experiment the subjects averaged 189.2 ($SE = \pm 2.77$) days of age. Two animals succumbed during the course of the experiment.

2. *Apparatus*

A description of the apparatus used is given elsewhere (9). In brief, it consisted of two different boxes: a Skinner box fitted with a lever which delivered .25 cc. of water to the rat each time it was depressed; and a conditioning box with a floor which could be electrified, thus delivering a shock of pre-determined intensity to the feet of a rat in it (7). Bulbs of 3.5 W. illuminated the boxes, and a timer in the circuit produced a flashing light which served as the conditioning stimulus (CS).

3. *Procedure*

After having been gradually accustomed to being deprived of water for 23 hrs. each day the subjects were trained in lever pressing for the water reward. Each subject was placed in the Skinner box for 4 min. per day, and the number of its lever pressing responses was recorded. This continued until the animal had pressed the lever 50 times altogether, the animal being

taken out of the Skinner box immediately after it had made the 50th response. On the next three trials the lever responses were recorded daily for only the 3-min. period elapsing between 30 sec. after the animal was put into, and 30 sec. before it was taken out of, the box. The mean score from these three trials was regarded as the normal rate of responding of the animal.

Each subject then had four conditioning trials, at the rate of one trial per day. The animal was placed in the conditioning box, and after 2 min. the flashing light (CS) was presented which, after 3 min., contiguously terminated with an electric shock of .25 ma., AC, for 2 sec. One minute later, the animal was taken out and returned to its home cage.

Approximately 30 min. prior to each conditioning trial, each rat had received two successive intraperitoneal injections of drugs and/or placebo, in accordance with its random assignment to one or other of the groups shown in Table 1. The dose levels shown were determined by two main considerations: the need to have, firstly, as wide a range of levels, and, secondly, as large intervals between them, as was possible within the technical limitations of the experiment. This was achieved by progressively halving a level somewhat below the LD50. The random assignment of subjects to the 12 groups shown in Table 1 was carried out within the two groups of 24 reactive and 24 non-reactive subjects, that is to say, there were two replications of the 12×2 factorial design.

In order to let the drug effects wear off completely and to avoid their interaction with lever pressing, one day was allowed between the last conditioning trial and the first of the six daily trials, given to test the CER, that is, to establish the degree of fear which had become associated with the CS in the conditioning trials. For this purpose, the animal was placed in the Skinner box, its lever pressing performance was observed for 3 min. as usual, but this time in the presence of the CS—the flashing light. Any variation in an animal's normal rate of lever responses was then evaluated in terms of the *inflection ratio* (6), which expresses this variation as a proportion of the normal rate of lever pressing. (Inflection ratio = $\frac{B-A}{A}$, where A = mean of the scores in the last three training trials (see above) which represents the normal rate of responding, and B = the score in the test trial. A negative ratio expresses a decrease in normal rate of responding and an increase in the CER, while a positive one means the opposite.)

TABLE 1
DESIGN OF EXPERIMENT AND DOSAGE LEVELS

Antagonism groups		Control groups	
Amylobarbitone (A) vs. pipradrol (P)	Pipradrol vs. amylobarbitone	Placebo (PL)**	Placebo (PL)
A1 (3.75)* + P3 (10)	P1 (2.5) + A3 (15)	A3 (15)	Placebo (PL)
A2 (7.5) + P3 (10)	P2 (5) + A3 (15)	P3 (10)	Placebo (PL)
A4 (30) + P3 (10)	P4 (20) + A3 (15)		
A5 (60) + P3 (10)	P5 (40) + A3 (15)		
	Standard doses: A3 (15) + P3 (10)		

* Figures in brackets indicate dosages in mg./kg. body weight.

** Body weight 5 c.c./kg. of distilled water. All drugs were given in this vehicle.

C. RESULTS

To ascertain the overall significance of the effects due to the various treatments used and their interactions, an analysis of variance was performed. The scores for the two groups A3P5, and P3A1, were omitted from this analysis because the death of one non-reactive rat in each of them had reduced the group total to three, thus causing an inequality with the other groups all of which totaled four. The results are given in Table 2. The

TABLE 2
RESULTS OF ANALYSIS OF VARIANCE

Source	<i>df</i>	MS	<i>F</i>
Treatment (T)	9	1.5722	26.19*
Reactivity (R)	1	.6532	10.87*
Trials (Tr)	5	1.6610	27.64*
T x R	9	.3293	5.01*
T x Tr	45	.0484	.74
R x Tr	5	.0749	1.14
T x R x Tr	45	.0551	.84
Residual variance	120	.0658	
Residual variance†	215	.0601	
Total	239		

* Significant at the .001 level.

† Combining non-significant interactions.

effects due to treatments, to reactivity, to the interaction of these two, and also to trials were found to be statistically significant at the .001 level. The significant *F* for trials is due merely to the expected decline (extinction) of the CER on successive test trials. The overall difference in emotional reactivity between the two strains, the rats of the reactive strain acquiring greater CERs than those of the non-reactive strain, confirms the findings in the two previous studies (9, 10).

Figure 1 gives a clear picture of the significant treatment effects on the acquisition of the CER. It will be seen that, by and large, the order of the treatment groups is as might have been expected, in that the intensity of the CER decreases with the increasing dose level of amylobarbitone, as indicated by the progressively increasing height of the bars on the left, and increases in intensity with the increasing dose level of pipradrol, as indicated by the progressively decreasing height of the bars on the right. This effect may also be seen in Figure 2, which gives the dose response curves for the antagonism of the two drugs. The difference between the various treatment group means were analysed by *t* tests. Amylobarbitone significantly ($P < .01$) depressed the formation of the CER as compared

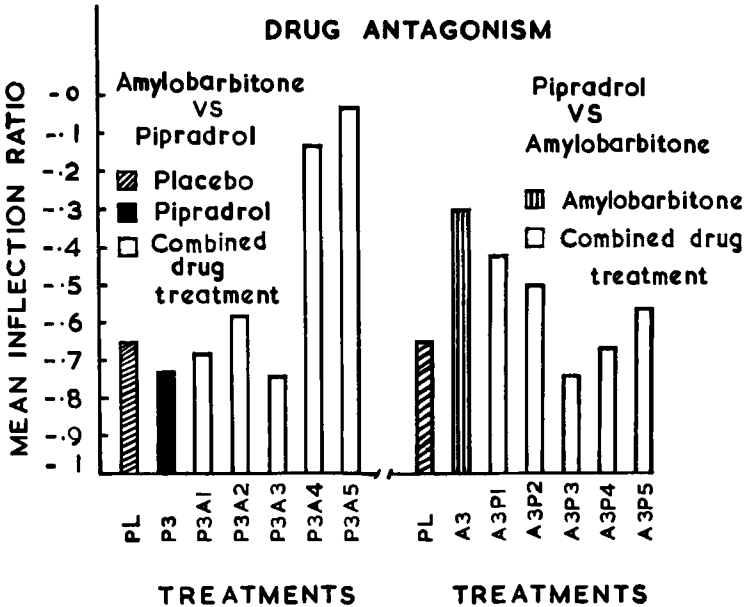


FIGURE 1

The height of the bars represents the mean CER (infection ratios) for the six test trials. Each was based on the results of four subjects, except for the P3A1 and A3P5 groups which contained only three. The bars are arranged in order of the increasing dose level of the variable drug in each antagonism (see Table 1 for actual dosages).

with the placebo group, and pipradrol facilitated it, though not significantly. However, the difference between the pipradrol and amylobarbitone group means was found to be highly significant ($P < .001$), a finding confirming previous work (10). As has been seen, the CER decreases, though not completely consistently, from Group P3 to Group P3A5, this overall decrease being highly significant ($P < .001$). On the other hand, the CER increases significantly from Group A3 to Group A3P3, but there is no further significant change despite the increasingly large doses of the stimulant given to Groups A3P4 and A3P5. It may, therefore, be concluded that the effect on pipradrol of the increasing doses of the antagonist, amylobarbitone, is expressed in a gradual decrease in the CER, and conversely, the effect on amylobarbitone of the increasing doses of pipradrol as antagonist is evident in a gradual increase in the CER.²

² A complete analysis would take account of other sources of variance. In particular, the variance between rats of the same strain could be distinguished

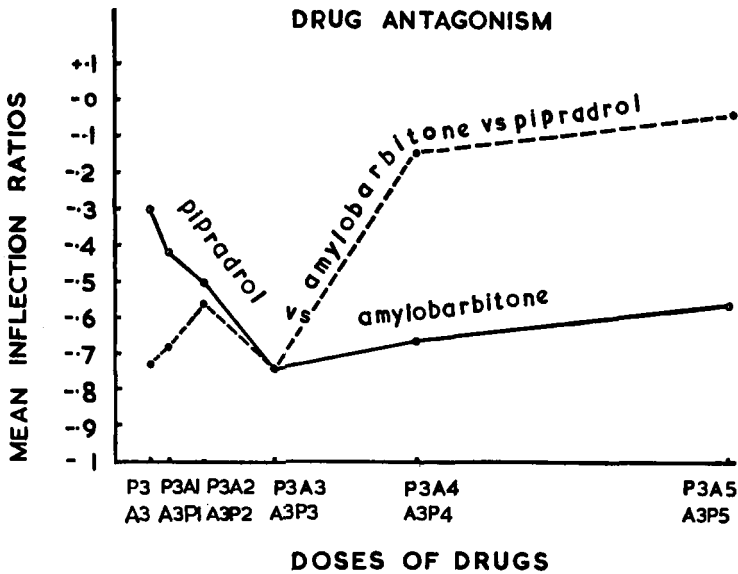


FIGURE 2

The graph shows the dose response relationship of the antagonising combinations of the drugs. The *ordinate* show the intensity of the CER in terms of the infection ratio averaged over the six test trials, and the linear scale on the *abscissa* represents the halving of the dose level employed for each antagonist. Each point on the curves represents the mean value for a group of four subjects, except for the P3A1 and A3P5 groups which contained only three.

Further *t* tests were applied to analyse the significant interaction between reactivity and treatments. Results are given in Table 3, and Figure 3 shows the nature of this interaction. It will be seen that the animals of the two strains responded differently to the drugs given alone, that the emotionally reactive rats were significantly more affected by the stimulant, pipradrol; and that the non-reactive rats were more affected by the depressant, amylobarbitone, though not significantly. Differential reactions also appear in the antagonisms of one drug by the other. The overall decrease in CER from Group P3 to Group P3A5 is significantly greater for the non-reactive than for the reactive subjects, and the increase in CER from Group A3 to Group A3P3 (only) is significantly greater for the reactives than the non-

from the variance due to rat: trial interactions (i.e., individual variations in the performances of a rat on different trials which depart from the general variance between trials due to the gradual extinction of the C. E. R.). But nothing would be gained: rats of the same strain resemble one another so closely as a result of in-breeding that the two sorts of variance are found to be of the same order of magnitude. Presenting all the interactions would complicate the table unduly.

TABLE 3
INTERACTION BETWEEN DRUG TREATMENTS AND EMOTIONAL REACTIVITY

	PL	P3	P3A1	P3A2	P3A3	P3A4	P3A5	Treatments					All
								A3	A3P1	A3P2	A3P4	A3P5	
Reactive	-.63	-.95	-.74	-.100	-.09	-.22	-.34	-.56	-.45	-.89	-.52	-.19	-.55
	N.S.	$P < .01$	N.S.	$P < .001$	N.S.	$P < .01$	N.S.	N.S.	N.S.	$P < .05$	N.S.	$P < .05$	$P < .01$
Non-reactive	-.67	-.50	-.63	-.35	-.17	+.14	-.26	-.27	-.53	-.62	-.81	-.75	-.42
$n = 2$ in each case, except in P3A3 and A3P5 (non-reactive) where it is one only.													

reactives. An apparent depressant effect of the two higher doses of pipradrol is seen among the reactive subjects only and reaches significance at the .05 level or beyond in both the P3-P4 and P4-P5 comparisons.

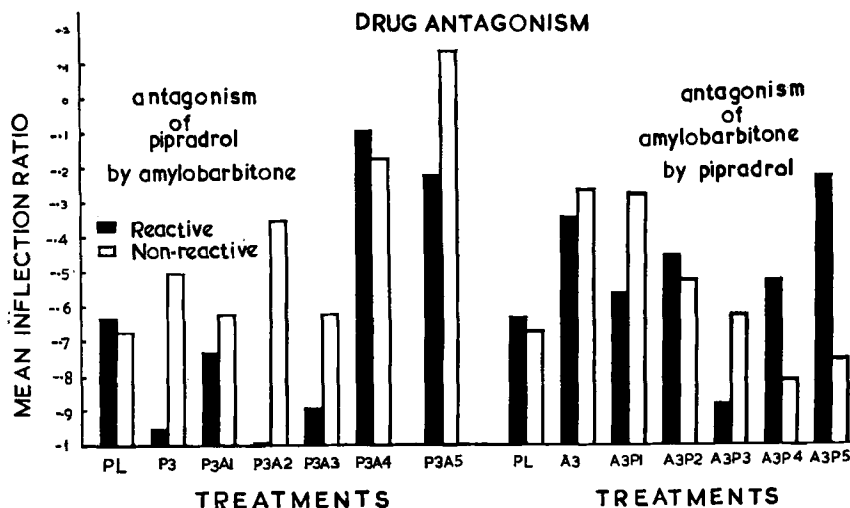


FIGURE 3

Figure 3 is drawn from the data shown in Fig 1, except that the means for the reactive and non-reactive subjects are now plotted separately.

D. DISCUSSION

Despite the rather small numbers in each treatment group in this experiment, the results clearly show that the conditioning of an emotional response can, within certain limits, be progressively increased or decreased by the antagonising effects of gradually increasing doses of a central stimulant or depressant drug on a fixed dose of the other drug. Indeed, the largest dose of amylobarbitone almost blocked the formation of the CER completely. These findings provide an additional support to the growing evidence that conditioning, in general, is a function of the postulated cortical excitation-inhibition balance (5) which can be, in turn, affected by drugs. Moreover, these results may be considered as suggestive of a linear relationship between the intensity of conditioning and the degree of the cortical excitation-inhibition imbalance.

The significant interaction between innate emotional reactivity and response to drugs confirms previous findings (10), and shows that the antagonism of drugs depends not only on the size of the antagonising dose, but also on individual differences in emotional reactivity. The suppression

of pipradrol by amylobarbitone seems to be more effective among the non-reactive subjects, while, up to a point, that of amylobarbitone by pipradrol is more effective among the reactive subjects, though, in this case, the overall effect is more consistent among the non-reactives. The depressant effect on the conditioning of the response among the reactive rats of the higher doses of the stimulant, pipradrol, is notable. This is perhaps the only aspect of the interaction which is sufficiently systematic to warrant an attempt at explanation. It may be analogous to Pavlov's "paradoxical effect" (8). He maintained that over-stimulation of the cortical processes elicits inhibition which is observed as a lowered response to intense conditioned stimuli. It seems possible that the higher doses of the stimulant may have so stimulated the cortical processes as to result in this "paradoxical effect," and hence weaker conditioning of the emotional response. The fact that this "paradoxical effect" is more marked in the reactive than in the non-reactive subjects signifies that constitutional factors are probably involved in its occurrence. Other inter-strain differences are probably suppressed by large individual differences among the subjects in our small groups. Nevertheless the overall significant effect points to physiological differences between the two strains of rats used.

E. SUMMARY

Twenty-four emotionally reactive, and 24 non-reactive rats were used to investigate the antagonism of two centrally acting drugs on the formation of a conditioned emotional response of the "anxiety" type. The response was defined in terms of a decrease in lever pressing in a Skinner box in the presence of a conditioned stimulus which had been previously associated with a shock.

The results showed that the suppression of the depressant drug (amylobarbitone) by increasing doses of the stimulant drug (pipradrol) is reflected in a corresponding increase in the CER, and that of the stimulant drug by increases in the depressant drug is reflected in a corresponding decrease. Emotional reactivity of the subjects had a significant interaction with the drug antagonism.

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