RESEARCH PAPERS

THE SECONDARY CONDITIONED RESPONSE OF RATS AND THE EFFECTS OF SOME PSYCHOPHARMACOLOGICAL AGENTS

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The secondary conditioned response has been studied in rats in an experimental avoidance situation. The activity of seventeen drugs has been tested upon the secondary conditioned response developed on a stable basis after an appropriate period of training. Chlorpromazine, promazine, reserpine and morphine block the secondary avoidance conditioned response as well as the usual avoidance conditioned response, in doses not affecting the motor function. Meprobamate, hydroxyzine, azacyclonol, phenaglycodol and phenobarbitone sodium have no specific inhibitory action on the avoidance conditioned response, but suppress the secondary conditioned response. A specific depression of conditioned behaviour is also produced by mescaline and iproniazid. Barbitone sodium, glutethimide, L1458 and mephenesin inhibit the conditioned responses only at neurotoxic doses. On the basis of these findings a new classification of "tranquillising agents" is proposed. It is also suggested that the systematic study of the secondary conditioned avoidance response of rats, may provide a useful experimental approach for studying the specific behavioural action of drugs.

CONDITIONED responses in rats have been used to evaluate the effects of central nervous system (CNS)-active drugs[1,2].

The conditioned avoidance response is a fear-motivated behaviour easily reproduced and widely used to investigate the effect of drugs. A noxious stimulus occurring contiguously with a warning stimulus can elicit anticipation of the noxious stimulus. In avoidance conditioning techniques a conditioning stimulus (buzzer) is associated with a "punishment" (electric shock) commonly defined as an unconditioned stimulus. The animal can avoid the shock by making a fixed response.

Rats are trained with repeated exposures to the experimental situation until the avoidance response is stable, when it is assumed that a conditioned avoidance behaviour has been established. This response is defined as the conditioned response (C.R.). With further training, some rats take up the position to avoid the unconditioned stimulus *before* the presentation of the conditioned stimulus.

Here it is assumed that the animals have developed a secondary conditioned reponse (S.C.R.) induced by environment, and its occurrence in rats has been described by others. It is usually regarded as a disturbing factor which is overcome either by excluding affected animals from further tests[1], or by prevention. In the latter instance rats are exposed to the experimental situation by placing them in a box containing the grid at the same time as they receive the conditioned stimulus. In

some circumstances the S.C.R. may be reinforced by allowing the buzzer to become a secondary negative stimulus that the animal can avoid or remove by making the correct response.

The present work is a study of the S.C.R. in the rat as well as the effects of many CNS-active drugs upon this conditioned behaviour in rats.

Experimental

Method

Male rats of the Carworth strain, weighing from 180 to 250 g. were used.

The experimental techniques were basically those of Cook and colleagues[3]. The animals were first conditioned to avoid an electric shock by placing them in a box the floor of which is a grid of steel rods. Shocks may be delivered to the grid from a stimulator. In all the experiments a shock of 45 ma, 250 V. was employed. The box is in a soundproof enclosure, which contains a buzzer. A wooden pole in the centre of the box provides the safety area. Rats escape the shock by climbing the pole (unconditioned response or U.R.) and by climbing the pole in response to the buzzer alone (conditioned avoidance response or C.R.). Long-trained rats climb the pole "before" the buzzer is activated and when this response becomes stable, the rat is considered to have developed a secondary conditioned response (S.C.R.). To assist this development and to stabilise the S.C.R., the conditioned stimulus was omitted when the rats made the correct response.

To provide enough conditioned rats, groups of 100–150 animals were trained. About twenty conditioning trials were given within five days to elicit a stable C.R. Ten to fifteen further trials were necessary to establish the S.C.R., in 85–90 per cent of the animals. For each experiment, rats showing a correct S.C.R. in ten consecutive trials were used.

On the day of the experiments the rats, in groups of ten, were tested to check the S.C.R. The drug to be studied was then administered either orally or intraperitoneally. One group received only saline to provide controls. Every thirty minutes each animal was placed in the experimental box. No stimulation was given during the first 15 seconds, when secondary conditioned animals react by climbing the pole usually within five-ten seconds. When this occurred the operator returned the rat to the floor grid. The animals responding for the second time were considered to have retained their S.C.R. unaltered.

Any rat not making the correct response within the 15 seconds received the buzzer for 30 seconds. The C.R. by normally conditioned rats occurred within two seconds of the sounding of the buzzer. If the animal did not respond within the 30 seconds, shocks were delivered by the grid floor.

In this experimental design the deconditioning effect of a drug may be shown by: (i) the loss of the S.C.R. only (C.R. is retained); (ii) the loss of the S.C.R. and C.R. (U.R. is retained); (iii) the loss of the S.C.R., C.R. and U.R., usually as a result of a marked impairment of motor function.

For the evaluation of the activity of a drug, the maximal effect was always considered. As the experiment consisted usually of many trials (every 30 minutes for four hours or more) in which the negative reinforcement was not given regularly, a group of controls was always tested concurrently to insure that the S.C.R. would not be extinguished spontaneously for lack of reinforcement. Of 207 control rats, only six showed a loss of the S.C.R. in one or more of the eight half-hourly trials.

We used 630 rats, all of which were rested for at least two weeks before being used again.

TABLE I

THE DEVELOPMENT AND EXTINCTION OF THE SECONDARY AVOIDANCE RESPONSE PERCENTAGES OF RATS SHOWING A S.C.R. AT DIFFERENT STAGES OF THE CONDITIONING SCHEDULE (TOTAL RATS USED 70)

Day	Cumulative number of		Responding rats per cent (S.C.R.)
	trials	reinforcements	
1	4	4	0
5	18	14	83
10	33	19	92
15	48	21	94
25	78	21	89
35	83	21	85
65	89	21	78

Development and Extinction of S.C.R.

From Table I it may be seen that over 90 per cent of rats develop and retain a S.C.R. after about 33 conditioning trials, 94 per cent being reached after 48 trials. A significant decrease of this percentage does not occur after five weeks. The same rats develop a stable C.R. within the first 15 trials, which is retained for a longer period than the S.C.R., on cessation of reinforcement.

The duration of the conditioning and of the extinction is perhaps one of the most important features and allows a quantitative differentiation of the two phenomena of secondary—and normal—conditioning.

RESULTS

Effect of Drugs on C.R. and S.C.R.

As the effects of many CNS-active drugs on avoidance C.R. are well known, their effectiveness on C.R. and S.C.R. has been compared. For this purpose, we determined for each drug the ED50 blocking the S.C.R. as well as the C.R. and the U.R. These ED50 estimates were made by plotting on probability paper the percentages of respondent rats for every log dose, and fitting the straight line according to the method of Litchfield and Wilcoxon[4]. The ED50's for S.C.R. block, C.R. block and U.R. block were then compared and tested for the significance of differences. By this procedure the quantitative evaluation of the specificity of drug activity upon the conditioned avoidance behaviour was made possible. Seventeen drugs were tested and the ED50 and confidence limits are given in Table II.

Chlorpromazine was given orally to groups of previously conditioned rats in twelve different doses—from 0·5 to 45 mg./kg. The S.C.R.

TABLE II

EFFECTIVENESS OF VARIOUS DRUGS IN SUPPRESSING AVOIDANCE CONDITIONED RESPONSES IN RATS
ED50 ACCORDING TO THE METHOD OF LITCHFIELD AND WILCOXON[4] IN mg./kg.

Substance	Route	ED50* for blocking S.C.R.	ED50* for blocking C.R.	ED50* for blocking U.R.
Chlorpromazine	oral	1·75 (0·92–3·32)	11·6 (8·99–14·96)	33 (25·38–42·9)
Promazine	oral	16 (10·0–25·6)	84 (62–113)	163 (153–173)
Reserpine	i.p.	0·46 (0·33–0·63)	1·15 (0·93–1·41)	†2·16
Hydroxyzine	i.p.	24 (15–37)	76 (56–103)	†120
Azacyclonol	i.p.	25 (13–46)	†155	†192
Meprobamate	oral	163 (116–230)	475 (380–593)	475 (380–593)
	i.p.	32·5 (13·0–81·2)	170 (139–207)	170 (139–207)
Mephenesin	i.p.	70 (57–84)	108 (99–118)	108 (99–118)
Phenaglycodol	oral	86 (59–126)	220 (191–253)	305 (246–378)
Barbitone Na	oral	85 (53–137)	112 (83–151)	134 (102–175)
Pentobarbitone Na	oral	9·6 (8·1–11·4)	18·3 (16·6–20·1)	19·5 (18·1–20·9)
Phenobarbitone Na	oral	25 (18–34)	80 (49–130)	97 (81–115)
Glutethimide	oral	163 (102–261)	255 (161–403)	255 (161–403)
L1458	i.p.	28·2 (18·8–43·3)	48·5 (36·7–64·0)	65·0 (58·5–72·1)
Morphine	s.c.	0·94 (0·70–1·26)	4·3 (3·23–5·72)	15·2 (11·6–19·9)
Iproniazid	i.p.	84 (63–111)	>200	—
Mescaline	i.p.	32·5 (2·12–4·97)	>50	—

* and 19/20 confidence limits. † Approximately.

was blocked in 50 per cent of treated rats (ED50) after 1·75 mg./kg. No animal on this dose showed any effect on C.R. which was inhibited with 11·6 mg./kg. (ED50). The U.R. was affected by higher doses (ED50, 33 mg./kg.).

We can thus affirm that chlorpromazine specifically blocks the S.C.R. and at higher doses the C.R. The differences in ED50 as shown in Table II were very significant.

Promazine shows closely similar activity, specifically blocking the S.C.R. and the C.R. However, its effectiveness was found to be lower than that of chlorpromazine, as higher doses were necessary.

With both substances the slopes of S.C.R.-blocking activity curves (Table III, Fig. 1) were found to be greater than those of C.R. and U.R. blocking activity; however, the differences were significant only in the case of chlorpromazine.

TABLE III

SLOPES OF LOG DOSE/ACTIVITY CURVES

Substance	Route	Slope of dose/activity and 19/20 C.L.* for blocking S.C.R.	for blocking C.R.	for blocking U.R.
Chlorpromazine	oral	5·16 (4·37–6·08)	1·84 (1·64–2·06)	1·61 (1·13 2·30)
Promazine	oral	2·03 (1·70–2·41)	1·62 (1·36–1·92)	1·11 (0·99–1·24)
Reserpine	i.p.	1·64 (1·09–2·46)	1·48 (1·20–1·82)	1·38
Hydroxyzine	i.p.	2·53 (1·48–4·30)	1·66 (1·12–2·32)	—
Azacyclonol	i.p.	2·2 (1·01–4·84)	—	—
Meprobamate	oral	1·90 (1·11–3·23)	1·43 (1·06–1·91)	1·43 (1·06–1·91)
	i.p.	2·84 (1·18–6·81)	†1·26	†1·26
Mephenesin	i.p.	1·24 (1·01–1·51)	†1·10	†1·10
Phenaglycodol	oral	2·10 (1·39–2·17)	1·36 (1·07–1·72)	1·42 (1·10–1·81)
Barbitone Na	oral	1·54 (0·46–5·08)	1·82 (1·25–2·63)	1·71 (1·31–2·22)
Pentobarbitone Na	oral	1·21 (1·01–1·44)	1·17 (0·78–1·74)	1·12 (1·06–1·19)
Phenobarbitone Na	oral	2·35 (1·58–3·48)	1·47 (0·98–2·20)	1·49 (1·24–1·78)
Glutethimide	oral	1·47 (0·41–5·26)	1·45 (0·83–2·54)	1·45 (0·83–2·54)
Morphine	s.c.	2·13 (1·21–2·72)	1·82 (1·40–2·36)	1·34 (1·04–1·71)
L1458	oral	2·2 (1·18–3·47)	1·37 (1·12–1·67)	1·12 (0·79–1·58)
Iproniazid	i.p.	1·43 (1·15–1·77)	—	—
Mescaline	i.p.	2·18 (1·01–4·68)	—	—

* According to Litchfield and Wilcoxon[4]. † Approximately.

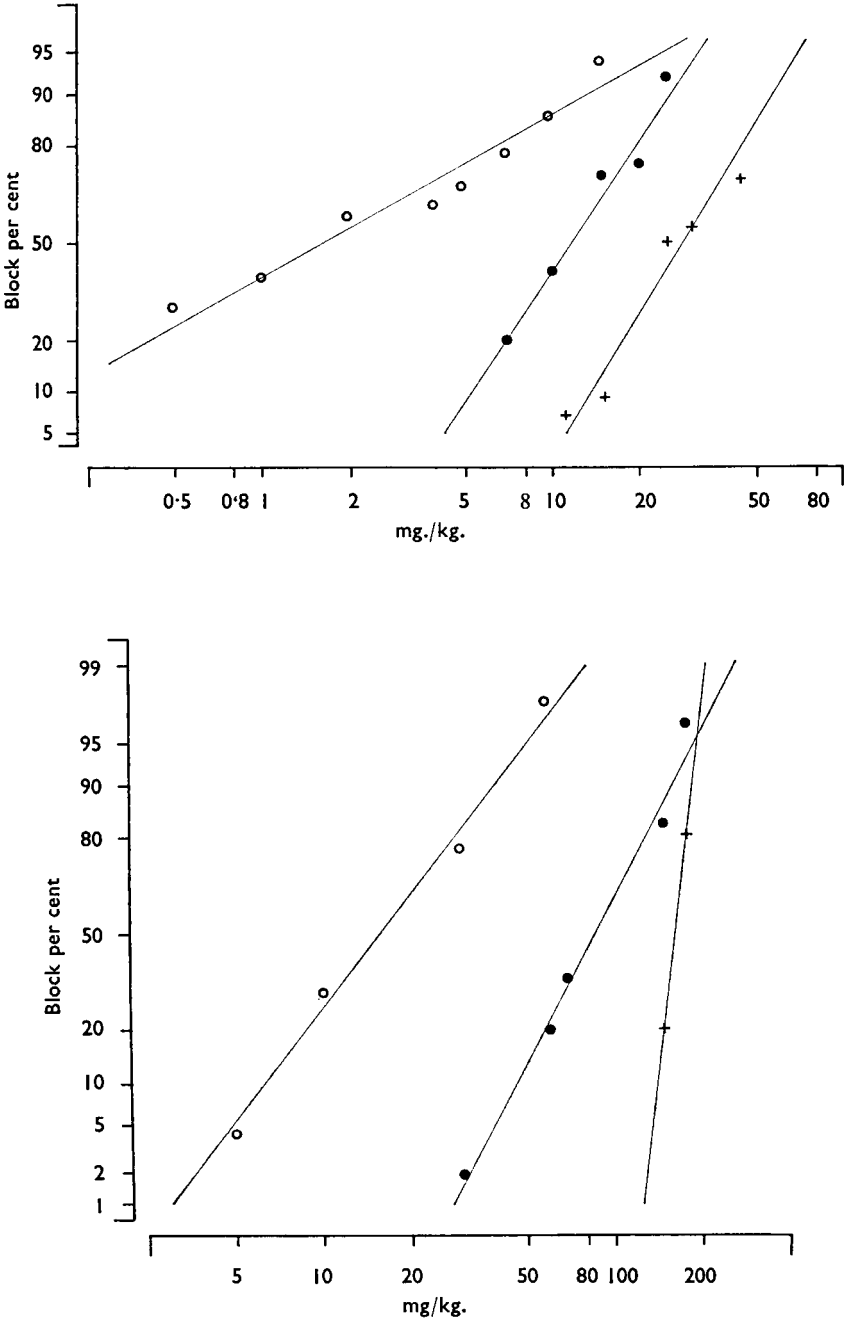

FIG 1. Block of secondary conditioned response (○), conditioned response (●) and unconditioned response (+) by different compounds. Upper graph—Chlorpromazine by oral route. Lower graph—Promazine by oral route

The duration of the effectiveness of both substances is shown in Table V.

Reserpine was given by intraperitoneal injection in doses from 0·3 to 2·5 mg./kg. A large variability was found particularly in the abolition of the U.R. Nevertheless, the results enable us to affirm that this substance specifically blocks both S.C.R. and C.R. (Table II). The ED50 for blocking the S.C.R. was 0·46 mg./kg. and 1·5 mg./kg. for the C.R. The U.R. was affected at doses higher than 2 mg./kg. As shown in Table V, the onset of reserpine activity has been observed 120 minutes after administration and lasted for more than 10 hours.

Hydroxyzine, like reserpine, was given intraperitoneally and was found to specifically suppress the S.C.R. From Table II, the ED50 for blocking the S.C.R. and particularly the C.R. can be seen to be close to the ED50 for blocking the U.R. as with chlorpromazine.

Azacyclonol, intraperitoneally, produces a specific block of S.C.R., but not of C.R. This means that the doses affecting the C.R. (Table II) also affect the motor function and block the U.R. in some animals. Such doses therefore approach the lethal dose.

Benactyzine, by the oral or intraperitoneal route, gave inconsistant results. The S.C.R. appears to be blocked by between 20 and 40 mg./kg. The C.R. was concurrently affected. However, a linear relationship of doses to effects was not found because of the great variability in the responses of different animals and even in the same animal on different days.

Meprobamate, both orally and intraperitoneally, failed to produce any specific block of C.R. Rats began to lose the C.R. at dose-levels that also block the U.R. because of ataxia and incapacitation of motor function. However, meprobamate was shown to have a specific blocking action of the S.C.R. The oral and intraperitoneal ED50 estimates are given in Table II.

Mephenesin, a drug similar in action to meprobamate, failed to produce any specific block of the S.C.R. as well as of the C.R.

Phenaglycodol, tested only by oral route, produces like meprobamate, a specific block of S.C.R. The C.R. was blocked only with doses that also affect the U.R. in different degrees.

Among the barbiturates, *barbitone sodium* does not produce any specific block either of S.C.R., or of the C.R. Also, *pentobarbitone*-induced inhibition of S.C.R. is caused by doses near the neurotoxic ones. On the contrary, *phenobarbitone* produces a moderate but significant degree of specific block of S.C.R. In this respect phenobarbitone was found to differ not only from other barbiturate derivatives but also from other hypnotics, such as *glutethimide*, which behaves like barbitone (Table II).

Morphine sulphate, by subcutaneous injection, produces minimal inhibitory effects on the S.C.R. after 0·5 mg./kg. The calculated ED50 for blocking of S.C.R. was 0·94 mg./kg. Morphine also produces a specific block of C.R. in doses much lower than those which suppress the U.R. Its action on conditioned behaviour of rats, very much resembles that of chlorpromazine.

2-*Thienyl*-5-*amino*-1 : 3 : 4-*thiadiazole* (L1458), a muscle relaxant recently described[5], and in some aspects of its pharmacological action resembling benzimidazole[6], blocks in a moderate degree only the S.C.R. and fails to affect the normal C.R.

A specific block of S.C.R. is also produced by *iproniazid* but only in very high doses, the estimated intraperitoneal ED50 being 84 mg./kg. It was found that 200 mg./kg. produced a block of the C.R. only in 10 per cent of the tested rats (1/10).

Mescaline behaves very similarly to iproniazid, although at a lower dosage. The intraperitoneal ED50 for blocking the S.C.R. was found to be 33 mg./kg. Following 50 mg./kg. only 10 per cent of the tested rats showed a loss of C.R.

Observations on Dose : Activity Curves

By analysing log-dose : per cent blocking-activity curves it was found that the slopes of the curves for blocking the S.C.R. were almost always higher than those for blocking the C.R. but only in a few instances was this difference significant ($P = 0{\cdot}05$). Of the 14 substances considered in this respect, only three—chlorpromazine, meprobamate by i.p. route and phenobarbitone—show dose : activity curves for S.C.R. blocking, significantly different from those for C.R. blocking. The slopes of the curves for C.R. and U.R. block were always statistically equivalent for every product and route of administration. With few exceptions, the slopes obtained with different products are not significantly different.

Onset and Duration of Action

Remarkable differences were observed in the time of onset and in the duration of action of the tested drugs. As reported, the ED50 estimates have been calculated on the basis of the maximum effect, irrespectively of the time. In Table V the times of onset of the blocking-activity and its duration are given for each of the tested drugs. The effects of the respective ED50 doses on the three responses are shown.

With the exception of reserpine the onset of the S.C.R. block is very rapid for the drugs. The suppression of this response in 10 per cent of the animals is produced usually within 30 or 40 minutes after administration. The duration of maximal and minimal action is more variable.

By comparing the onset of S.C.R. block and the C.R. block produced by approximately equi-active doses of each drug, it appears that an equal or a more prolonged interval after administration is necessary for the suppression of C.R.

The maximal blocking effect on S.C.R. is more prolonged than the maximal blocking effect on C.R. with equi-active doses of chlorpromazine, reserpine, hydroxyzine, oral meprobamate and morphine. An approximately equal duration of inhibition on S.C.R. and C.R. has been observed following azacyclonol, i.p. meprobamate, phenaglycodol and phenobarbitone.

Of the drugs tested reserpine shows a unique behaviour, its action beginning two hours after administration and lasting for more than 10 hours.

DISCUSSION

The results show that the S.C.R. developed by rats in a simple experimental situation, may be made stable in a high percentage of animals. Examples of secondary avoidance conditioning may be found in literature[7–9]. However, we are unaware of any pharmacological application or systematic study of the effects of drugs on these S.C.R. responses.

Our results show that the avoidance S.C.R. may be suppressed by some drugs and that with these a linear relationship exists between log-doses and percentage blocking effect.

It first appeared that many depressive agents in suitable doses may suppress all three responses. To define the "specificity" of the effect on the conditioned behaviour the ED50 ratios have been chosen (Table IV). By analysing the specific activity of each drug, different degrees of potency were found.

TABLE IV

SPECIFICITY OF DRUGS ACTIVITY ON CONDITIONED BEHAVIOUR
ED50 RATIOS AND 19/20 CONFIDENCE LIMITS*

Substance	Route	ED50 ratio for block of U.R./ block of S.C.R.	ED50 ratio for block of U.R./ block of C.R.
Chlorpromazine	oral	18·85 (14·28–24·88)	2·84 (2·15–3·74)
Promazine	oral	5·25 (9·13–13·01)	1·94 (1·43–2·61)
Reserpine	i.p.	†4·70	†1·87
Hydroxyzine	i.p.	5·08	1·60 (N.S.)
Azacyclonol	i.p.	4·77	1·20 (N.S.)
Meprobamate	oral	2·91 (1·94–4·36)	1·00 (N.S.)
	i.p.	5·23 (2·17–12·55)	1·00 (N.S.)
Mephenesin	i.p.	1·54 (N.S.)	1·00 (N.S.)
Phenaglycodol	oral	3·54 (2·29–5·45)	1·20 (N.S.)
Barbitone Na	oral	1·57 (N.S.)	1·12 (N.S.)
Pentobarbitone Na	oral	2·03 (1·84–2·23)	1·06 (N.S.)
Phenobarbitone Na	oral	3·38 (2·77–5·47)	1·21 (N.S.)
Glutethimide	oral	1·56 (N.S.)	1·00 (N.S.)
L1458	i.p.	2·30 (1·52–3·47)	1·34 (N.S.)
Morphine	s.c.	16·17 (10·78–24·25)	3·53 (2·37–5·26)
Iproniazid	i.p.	>2·38	—
Mescaline	i.p.	>1·54	—

* When the differences in ED50 estimates are not statistically significant ($P = 0·05$), the confidence limits are omitted and N.S. (non-significant) added.

† Approximately.

In the works of others on rats in conditioned avoidance situations, only the specific effects on C.R. of the drugs have been considered. We have found that the S.C.R. also is of considerable importance as a test for the activity of drugs.

We consider the tested drugs may be divided in three main groups, according to their activity on conditioned behaviour of rats.

(i) Group reducing a specific block of both the S.C.R. and C.R. This comprises chlorpromazine, promazine, reserpine and morphine. Some of these substances have been differentiated by Cook and Weidley[3] for their blocking activity on C.R. According to Berger[10], they are defined as "autonomic suppressants" because of their antagonism to acetylcholine, histamine and serotonin, which regulate certain functions of the autonomic nervous system. Some of these drugs are also called by Pfeiffer and colleagues[11] "ataractics" as they cause adrenergic blockade,

lower the electrical threshold for convulsions and inhibit conditioned avoidance responses of rat and monkey.

Chlorpromazine, reserpine and promazine also have been called "tranquillisers" by Alexander[12], on the basis of clinical implications, and by Delay and Deniker[13] "neuroleptiques".

Despite the autonomic "side effects" of these substances, it seems evident that they really possess a behavioural specificity in their action. The activity on S.C.R. is, in our opinion, a further confirmation of their specificity.

The high blocking activity of morphine on C.R. has been confirmed by our experiments and the specific behavioural effect of this substance is further shown by its great effectiveness in suppressing the S.C.R. Apparently the changes in conditioned avoidance behaviour of rats do not allow the differentiation of this drug from the tranquillisers, but other pharmacological tests[1,14] may be used to reveal the differences in the activity of morphine and that of other behaviour-affecting drugs.

(ii) A second group of substances were those which specifically block the S.C.R. with little, if any, effect on the C.R.

Different degrees of specificity were found in activity upon S.C.R. In order of decreasing specific potency the drugs are: meprobamate (i.p.), hydroxyzine (i.p.), azacyclonol (i.p.), phenobarbitone (oral), phenaglycodol (oral), meprobamate (oral).

Meprobamate is perhaps one of the most largely used agents for its tranquillising action, but according to others does not affect conditioned and avoidance reflexes[1,10,11,15]. This fact may be explained by a possible inadequacy of the usual techniques. The same may be said for other substances classified in this group such as *hydroxyzine*, *azacyclonal* and *phenaglycodol*. The major differences among the substances of this group have been found in the onset and duration of their activity, as can be seen from Table V.

The experimental results compel us to insert phenobarbitone in this group of substances. The specific block of S.C.R. produced by this drug clearly differentiates it from other barbiturates and hypnotics, an effect for which no ready explanation is available.

(iii) The third group of agents include barbitone, pentobarbitone, mephenesin, L1458 and glutethimide, i.e., hypnotics and centrally acting paralysing drugs. All these substances failed to produce any significant specific block of either S.C.R. or C.R.

We therefore conclude that the effect of drugs upon the secondary conditioned avoidance response permits the selection of substances with high behavioural specific activity. Two different classes of drugs among the agents depressing the behaviour of organisms are apparent. They are the "general deconditioning agents" (chlorpromazine, promazine, reserpine and morphine) and the "secondary deconditioning agents" (meprobamate, hydroxyzine, azacyclonol, phenaglycodol and phenobarbitone).

General deconditioning agents can suppress both conditioned avoidance responses in doses that are not neurotoxic. Some have been found to

suppress also experimental "anxiety"[15,16]. The action of these drugs is characterised by high specificity in blocking the S.C.R. of rats, and usually a marked but minor specificity in blocking the C.R.

Secondary deconditioning agents do not suppress the C.R. of rats, but specifically affect the S.C.R. of rats.

TABLE V

DURATION OF EFFECTIVENESS OF DRUGS IN PRODUCING BLOCK OF THE THREE RESPONSES

Substance	Route	Dose mg./kg.	Response blocked	Time (minutes) after administration and blocking effect			
				Onset 10 per cent	Maximal from	Maximal to	End 10 per cent
Chlorpromazine ..	oral	2	S.C.R.	30	210	270	420
	"	10	C.R.	75	120	210	345
	"	30	U.R.	300	390	—	>390
Promazine ..	oral	10	S.C.R.	40	60	210	345
	"	80	C.R.	30	90	390	>390
	"	180	U.R.	60	300	360	>390
Reserpine	i.p.	0·5	S.C.R.	120	240	560	600
	"	1	C.R.	240	360	440	520
	"	2·5	U.R.	120	240	>360	—
Hydroxyzine ..	i.p.	20	S.C.R.	30	60	210	300
	"	60	C.R.	30	45	90	150
	"	100	U.R.	30	30	45	150
Azacyclonol ..	i.p.	25	S.C.R.	30	120	180	300
	"	150	C.R.	75	120	180	240
	"	200	U.R.	75	150	>390	—
Meprobamate ..	oral	200	S.C.R.	30	60	180	280
	"	500	C.R. and U.R.	<30	30	150	>420
	i.p.	50	S.C.R.	30	60	90	150
	"	200	C.R. and U.R.	<30	30	90	150
Mephenesin ..	i.p.	75	S.C.R.	<30	30	—	90
	"	100	C.R. and U.R.	<30	<30	—	<60
Phenaglycodol ..	oral	100	S.C.R.	<30	90	210	340
	"	200	C.R.	40	150	240	>340
	"	300	U.R.	60	210	>420	>420
Barbitone Na ..	oral	100	S.C.R.	40	180	360	>390
	"	100	C.R.	90	180	240	330
	"	150	U.R.	75	150	300	>390
Pentobarbitone Na	oral	10	S.C.R.	<30	60	100	180
	"	20	C.R.	<30	30	100	180
	"	20	U.R.	<30	30	100	170
Phenobarbitone Na	oral	20	S.C.R.	<30	60	210	300
	"	75	C.R.	45	90	240	360
	"	100	U.R.	30	150	270	>360
Glutethimide ..	oral	200	S.C.R.	45	60	150	360
	"	250	C.R. and U.R.	50	210	360	>360
L1458	i.p.	30	S.C.R.	30	60	150	180
	"	60	C.R.	<30	30	60	120
	"	60	U.R.	<30	30	60	120
Morphine	s.c.	1	S.C.R.	<30	60	120	190
	"	4	C.R.	30	60	90	120
	"	20	U.R.	60	90	150	180
Iproniazid	i.p.	100	S.C.R.	30	60	150	220
Mescaline	i.p.	25	S.C.R.	30	60	150	180

It is not the purpose of this paper to interpret, on the basis of these findings, the mechanism of action of the different drugs. However, one might suggest that although the secondary deconditioning agents, unlike the general deconditioning agents, do not block the behaviour depending upon a conditioned emotional disturbance, they nevertheless influence a process depending in some manner on emotional arousal.

We believe that the study of the S.C.R. will provide an easy experimental approach to the problem of revealing, testing, and classifying new tranquillising drugs.

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