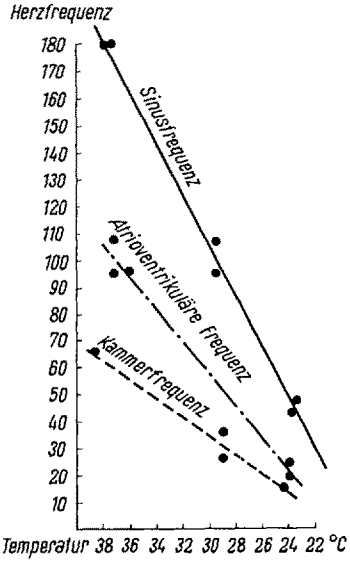
Reaktion der höheren und tieferen Reizbildungszentren des isolierten Herzens bei Durchströmung mit Lockelösung von 38°C bzw. 26°C

	n	Frequenz/min			t	p
		38°C	26°C	Frequenzabnahme		
Vorhof	20	151,35 ± 8,65	42,90 ± 4,00	108,45 ± 7,10	4,52	< 0,001
Atrioventrikularknoten	9	83,10 ± 6,11	25,80 ± 2,03	57,30 ± 5,61	7,14	< 0,001
Kammer	20	48,35 ± 4,01	19,35 ± 2,23	29,00 ± 2,49		



Ein Beispiel für die Änderungen der Vorhoffrequenz, der atrioventrikulären Frequenz und der Kammerfrequenz bei Abkühlung der Durchströmungsflüssigkeit.

Es soll hier noch erwähnt werden, dass an Langendorff-Herzen mit durchschnittenem Hisschem Bündel in einigen Fällen bei tiefer Temperatur die Vorhöfe sich langsamer kontrahierten als die Kammern. Manchmal konnte eine regelmässige Kammertätigkeit auch bei völligem Vorhofstillstand beobachtet werden. Durch diese höhere Empfindlichkeit der Sinusreizbildung ist die Möglichkeit einer Erklärung für die von GROSSE-BROCKHOFF und SCHOEDEL[3] am EKG des Hundeherzens *in situ* beobachtete Erscheinung gegeben, dass nämlich bei Senkung der Körpertemperatur unter 25°C die Führung der Herztätigkeit durch die atrioventrikuläre Reizbildung übernommen wird.

In unseren früheren Untersuchungen (SZEKERES, FALLER und LICHNER[2]) haben wir gezeigt, dass in Hypoxie wie auch in Hyperkapnie die «tertiäre» Kammerreizbildung am empfindlichsten reagiert, die atrioventrikuläre Reizbildung schwächer und die Sinusreizbildung am wenigsten beeinflusst wird. Hier liegen somit gerade umgekehrte Verhältnisse vor wie in den oben beschriebenen Versuchen. Es ist folglich nicht wahrscheinlich, dass die bei Temperatursenkung beobachteten Empfindlichkeitsunterschiede der einzelnen Reizbildungszentren auf einen etwaigen Sauerstoffmangel oder Kohlesäureüberschuss zurückzuführen sind.

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Summary

In the isolated rabbit heart perfused by the Langendorff method total heart block has been produced by section of the His bundle. The influence of cooling of the perfusion fluid upon higher and lower automatic centers was studied. The sinoauricular pacemaker responded to cooling with a much greater decrease of the heart rate than did the ventricular automatism. The responsiveness of the atrioventricular node to cooling lay between that of the two others.

[3] F. GROSSE-BROCKHOFF und W. SCHOEDEL, Arch. exp. Path. Pharmak. *201*, 417 (1942).

PRO LABORATORIO

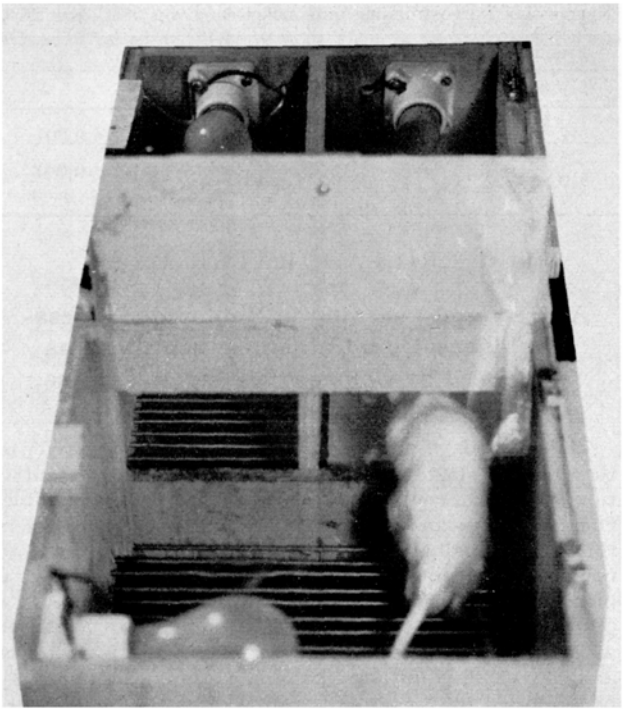
Anxiety and Learning in Rats under Stress-Avoidance-Discrimination Conditions as Influenced by Chlorpromazine, Reserpine, and Glutamate

The methods of measurements of the central activity of the ataraxics have been most diverse. A clear differentiation from other central depressants is not always possible. One popular means of measuring responses to tranquilizers is a shock-avoidance apparatus in which animals learn to react to a warning auditory or visual stimuli such as a buzzer or light. Failure to heed this warning results in a punishment by an electric shock. Animals learn to escape when this warning stimulus is applied. The fear and/or anxiety which is initiated by this warning stimulus may be abolished by the administration of various central depressants. An animal thus treated will not escape until it has received the shocking stimulus.

We wished to add the factor of discrimination to these responses. A shock-avoidance box was designed in such a manner so that discrimination is necessary for avoidance of shock (Figure). In this apparatus there is a main compartment the floor of which consisted of metal bars. By this design a shock (5 mA) was administered to the test animal 15 s after a warning light was turned on. At the same time as the compartment was lighted a guillotine type of door was raised, which offered to the animal two possible exits. One of the exit-compartments contained a low-voltage light and the other was darkened. The lighted escape compartment was unsafe as the floor of this 'room' was also covered with metal bars which continued the shock for 15 s if the rat chose to jump into it. The other compartment was a safe exit of escape since the floor was covered with a removable smooth insulating material. The position of the safe compartment was changed in random order every one to six trials. The total number of right and left escape routes were equal. If a rat failed to leave the main compartment during the 15 s in which the light was on, a shock of 5 mA was administered for 15 s. If this shocking stimulus was not effective the door was lowered and another 15 s of shock was administered. In this experiment the total number of trials per animal was 56, over a period of 29 days.

With this plan we have measured and recorded the following data: (1) The number of trials in which the animals did not respond to the stimulus or the light i.e. they took the shock (TS), (2) The responses to light that were correct (L +) and those that were incorrect (L −), (3) S + or the total correct responses to the shocking stimulus and the incorrect responses, S −. Correctness means the escape to the safe exit compartment. The total responses to the light would therefore be L + plus L −. L + plus S + will then give us a total measurement of the discriminatory reaction of the test animal.

Weanling untrained male rats were used. Reserpine, chlorpromazine, and monosodium glutamate were administered orally every day. The tranquilizers chosen have unrelated chemical structure and presumably different



sites of action. Many of the pharmacological effects of these drugs are also different. In a previous report we have found that glutamate increased the potentiating property of reserpine but not of the phenothiazine type of drug[1]. Each of the drugs was diluted with distilled water and given by mouth *per os* 1 h before testing. A 3 × 3 factorial design was used.

The factors were:

(a) ataraxics, 3 levels, 0,2 mg/kg reserpine, and 2 mg/kg chlorpromazine;

(b) monosodium glutamate, 3 levels, 0,1 g/kg, and 2 g/kg.

Nine rats were used per block, a total of 81 rats.

Results. Table I represents the six analyses of a variance that were made. There was no difference in the initial weight of the group.

Table II represents the performance of each group in percentage form. Reserpine depressed the number of responses to light, both discriminatorily correct (L+) and incorrect (L−). Since the time interval that the light is on preceeds the shock, it can be considered as a response to an indirect, or derived stress and has been considered to be a measure of anxiety. Thorazine and glutamate did not effect this. Reserpine also depressed the total number of correct responses both from indirect stress or light (L+) and from direct stress or shock (S+). This correctness in escape route *in toto* (L+ plus S+) we consider as a measure of discrimination.

[1] E. KOPMANN and F. W. HUGHES, Proc. Soc. exp. Biol. Med. *97*, 83 (1958).

Table I

P-values of Analysis of Variance for:				
Source-F-Ratios	L+	TS	L+ plus S+	L+ plus L−
MSG-1 g/kg .	n.s.	n.s.	n.s.	n.s.
MSG-2 g/kg .	n.s.	n.s.	n.s.	n.s.
Reserpine 2 mg/kg . . .	decrease $< 0{\cdot}02$	increase $< 0{\cdot}05$	decrease $< 0{\cdot}05$	decrease $< 0{\cdot}05$
Thorazine 2 mg/kg . . .	n.s.	n.s.	n.s.	n.s.

Reserpine decreased the number of total correct responses made to light and it increased the total number of times that the animals took shock (TS). These animals were all conscious and physically able to respond.

Experiments are in progress in which we will further measure changes in this discriminatory capacity of animals under the influence of various tranquilizers and other depressants. The extinction of this learned-descrimination response by various compounds may aid in the isolation of distinct activity of these ataraxics.

An interesting observation was that the mean weight gain in the groups treated with chlorpromazine was greater (106 g) than the control group (101 g). This was not of a significant nature in this series of animals. However the animals receiving reserpine showed a lesser weight gain (74 g) than the control group (101 g). This was highly significant ($P < 0{\cdot}001$).

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Department of Pharmacology, Indiana University School of Medicine, Indianapolis, May 23, 1958.

Zusammenfassung

Ein neuer Apparat wird beschrieben, in welchem die Wirkungen von Chlorpromazin, Reserpin und Natriumglutamat auf Furcht und Lernen in Ratten untersucht wurden.

Table II. Total responses of rats on % basis. Drugs administered daily via oral route

Treatment	Dosage	TS %	S− %	L− %	S+ %	L+ %
Water	2 cm³	14	4	27	8	47
Monosodium Glutamate (MSG)	1 g/kg	20	9	21	9	41
MSG	2 g/kg	21	10	19	8	42
Reserpine	2 mg/kg	25	9	23	9	34
Reserpine and MSG	2 mg/kg 1 g/kg	38	7	21	8	26
Reserpine and MSG	2 mg/kg 2 g/kg	28	7	23	7	35
Chlorpromazine	2 mg/kg	21	7	23	7	42
Chlorpromazine and MSG	2 mg/kg 1 g/kg	9	11	28	8	44
Chlorpromazine and MSG	2 mg/kg 2 g/kg	23	8	23	13	33

TS = Take shock; No attempt to escape upon shocking. S+ = Correct response to shock. S− = Incorrect response to shock. L+ = Correct response to light. L− = Incorrect response to light.