EFFECT OF CHLORPROMAZINE ON EXPERIMENTAL ARRHYTHMIAS OF CENTRAL ORIGIN

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The reticular formation of the brain stem not only exerts an ascending, activating influence on the cerebral cortex, but also regulates various autonomic functions, notably the rhythm of the heart. Because of this, local stimulation of the structures composing the reticular formation of the brain stem may give rise to pathological disturbances of the cardiac rhythm. This provides a suitable model for investigating the suppression of arrhythmias by the use of neurotropic drugs with a depressant type of action.

We have studied the effect of chlorpromazine on experimental arrhythmias of central origin by stimulation of various morphological structures in the floor of the fourth ventricle.

Effect of Chlorpromazine on Experimental Arrhythmias of Central Origin

Site of electrode	Type of arrhythmia	Dose of chlorpromazine (in mg/kg), causing	
		Diminution of arrhythmias	Total abolition of cardiac arrhythmias
Reticulotegmental nucleus	Extrasystoles (ventricular)	0.05	0.1
	Interference with dissociation	0.05	0.25
Nuclei of vestibular complex	Idioventricular rhythm	0.2	0.35
	Dissociation of sinus and heterotrophic ventricular rhythm	0.2	0.5
Nuclei of vagus complex	Disturbance of coronary circulation with extrasystolic arrhythmia	1.25	1.8
	Dissociation of sinus and ventricular rhythm	0.5 -1.0	1.0 -1.5
	Disturbance of coronary circulation with groups of extrasystoles	0.5 -1.5	2.25
	Ventricular paroxysmal tachycardia	0.5	1.0

EXPERIMENTAL METHOD

Experiments were conducted on cats anesthetized with urethane (1 mg/kg, intraperitoneally) and maintained on artificial respiration. The body temperature of the animals was maintained by external heating. After removal of the cerebellum, various zones of the medulla and pons were stimulated by means of a unipolar electrode, with rectangular pulses (1 millisec, 60 cps, 1-10 V) for periods of 5-10 sec at intervals of 10 min. At the end of the experiment the position of the electrode was verified by electrolytic destruction of the area of stimulation and subsequent histological examination of the specimen [2].

The electrocardiogram (ECG) of the animals was recorded during stimulation and after its cessation, in leads 1, 2, 3, and CR_4. Chlorpromazine was injected into the jugular vein in doses of between 0.005 and 2.5 mg/kg. Altogether 12 experiments were performed.

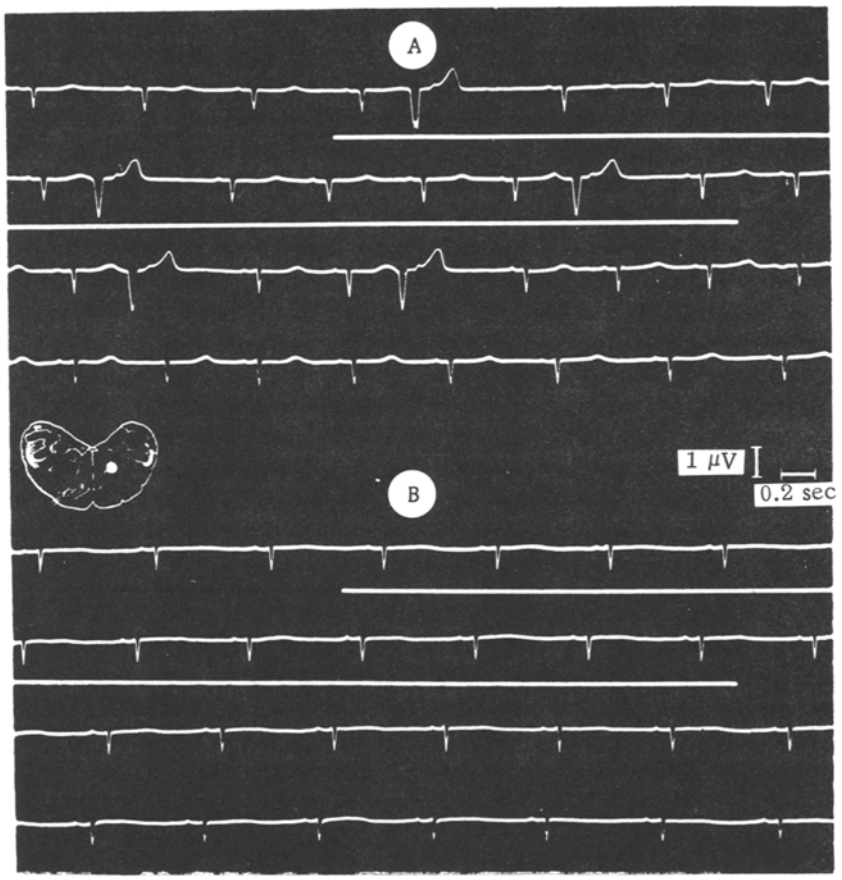

Fig. 1. Effect of chlorpromazine on arrhythmias arising during stimulation of the reticulotegmental nucleus. A) ECG (lead 2) before, during (straight line), and after stimulation. Each cut of the ECG is a direct continuation of the one above. During stimulation ventricular extrasystoles with full compensatory pauses appear; B) the same after injection of chlorpromazine in a dose of 0.1 mg/kg.

EXPERIMENTAL RESULTS

Stimulation of certain parts of the medulla causes different forms of disturbance of the cardiac activity, manifested by extrasystoles, interference with dissociation, dissociation of the sinus and ventricular rhythms, ventricular paroxysmal tachycardia and, in some experiments, disturbance of the coronary circulation with arrhythmias. Depending on the site of stimulation and the type of pathological manifestation of cardiac activity, different doses of chlorpromazine were required in order to abolish these disturbances (see the table).

The arrhythmias arising during stimulation of the zone of the reticulotegmental nucleus were most easily suppressed by chlorpromazine. According to Broadal [3], this zone corresponds to the region of the magnocellular and ventral reticular nuclei. Stimulation of this zone gave rise to interference with dissociation or to ventricular extrasystoles with full compensatory pauses.

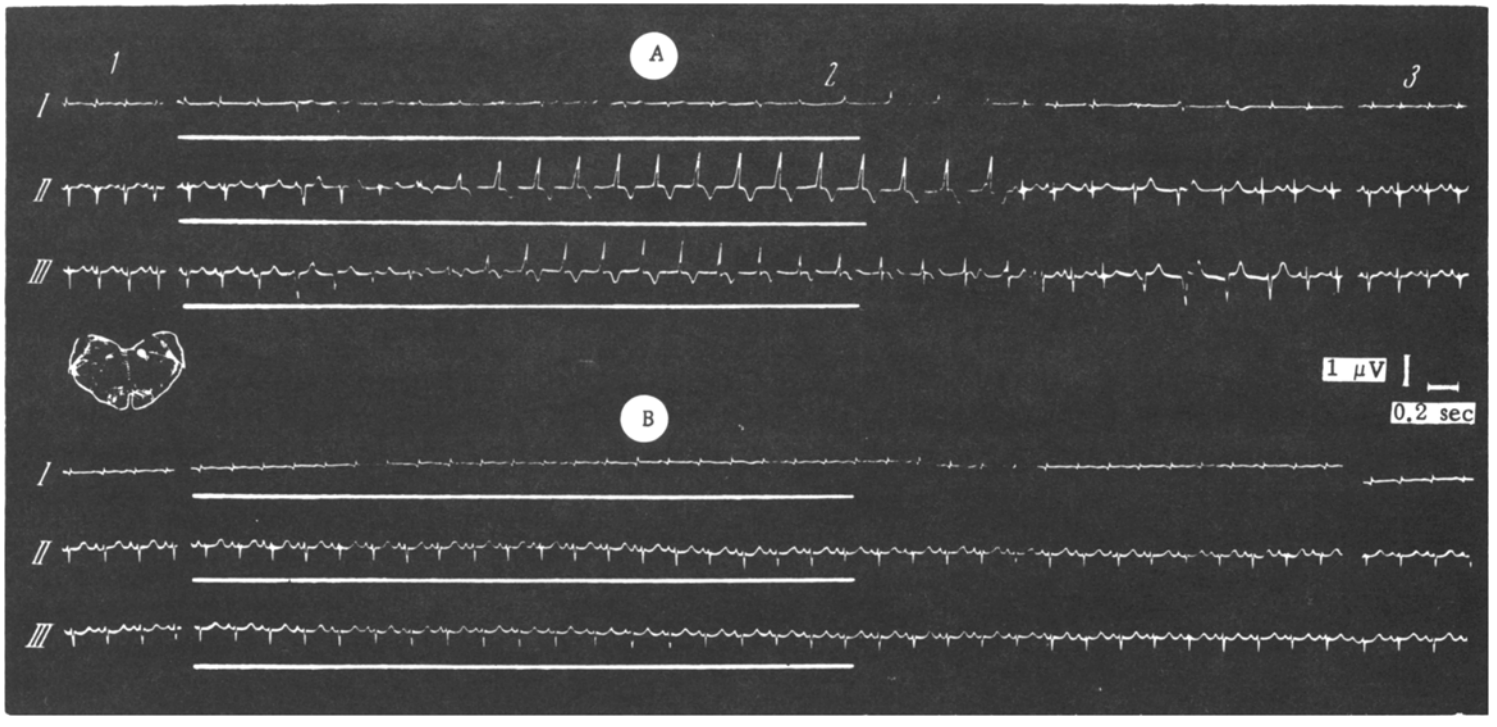

Fig. 2. Effect of chlorpromazine on disturbances of cardiac activity arising during stimulation of nuclei of the vestibular complex. A) ECG (leads 1, 2, and 3): 1) before stimulation, sinus rhythm 230/min; 2) during (straight line) and after stimulation, slowing of rhythm by 60/min. Dissociation between sinus and heterotropic ventricular rhythms. P wave merges with QRS complex; 3) 15 sec after stimulation; B) the same after injection of chlorpromazine in a dose of 0.5 mg/kg.

As is clear from Fig. 1, chlorpromazine in a dose of 0.1 mg/kg totally prevented the development of extrasystoles. Interference with dissociation was abolished by chlorpromazine in a dose of 0.25 mg/kg. The duration of action of the drug when given in these doses varied between 40 and 60 min. To abolish the arrhythmias and prevent changes in the morphology of the ECG waves for longer periods required larger doses of chlorpromazine.

During stimulation of the region of the vestibular nuclei (the medial nucleus of Schwalbe) depression of the function of the sinus node developed and was accompanied by an increase in the excitability of the subjacent nodes—atrioventricular and ventricular. Alternation of the sinus and heterotrophic ventricular rhythms both during stimulation and after its end may be seen in Fig. 2. To suppress these types of cardiac arrhythmia the dose of chlorpromazine had to be raised to 0.5 mg/kg.

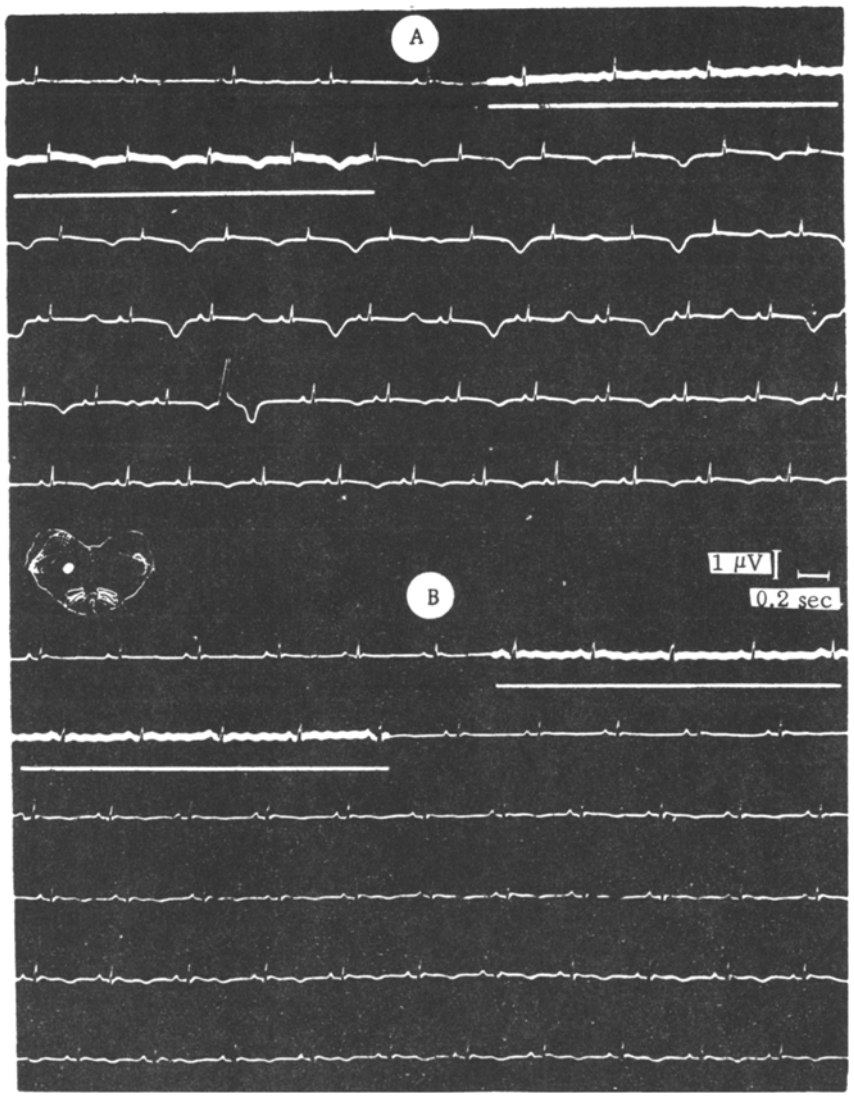

Fig. 3. Effect of chlorpromazine on disturbance of the coronary circulation and cardiac rhythm during stimulation of the nucleus ambiguus. A) ECG (lead 2) before, during (straight line), and after stimulation. Each cut of the ECG is a direct continuation of the one above. Before stimulation) sinus rhythm, rate 100/min. At the end of and after stimulation the rate increases on the average by 12/min; B) after injection of chlorpromazine in a dose of 1.8 mg/kg.

Still larger doses of chlorpromazine were required to abolish the disturbances of cardiac activity arising during stimulation of the nuclei of the vagus nerve. Some of these arrhythmias were like those which developed during stimulation of the nuclei of the vestibular complex. However, these disturbances of the cardiac rhythm were suppressed by administration of chlorpromazine in a dose of 1.5 mg/kg, i.e., twice as large as the dose given in the preceding case.

The cats proving most resistant to chlorpromazine were those in which the disturbances of the cardiac rhythm were accompanied by changes in the coronary blood flow. They developed during stimulation of the various nuclei of the vagus nerve (the dorsal motor nucleus, nucleus ambigums, etc.). To suppress these disturbances fully, doses of chlorpromazine of the order of 1.0-2.25 mg/kg were required (Fig. 3).

During stimulation of the nucleus ambiguus (ventral nucleus of the vagus and glossopharyngeal nerves) the changes in the T wave on the ECG were particularly characteristic. At the end of stimulation the positive T wave was changed into a deep negative or biphasic wave, and 10 sec after the end of stimulation alternation of positive and negative T waves took place during successive cardiac contractions with arrhythmias. The P wave was greatly reduced in amplitude after stimulation for 10 sec. The PQ interval was considerably shortened. Migration of the source of the rhythm towards the atrioventricular node was observed. With the appearance of a positive T wave the Q–T segment was shortened and the heart rate increased on the average by 27 beats per minute. These changes demonstrate a disturbance and a slowing of the process of repolarization of the T wave in association with the changes taking place in the myocardium of the ventricles. While these changes in the coronary T wave were going on, an arrhythmia with a single ventricular extrasystole was observed.

In some experiments disturbances of the coronary blood flow were accompanied by an extrasystolic arrhythmia or dissociaton of the sinus and ventricular rhythms. If increasing doses of chlorpromazine were given fractionally, these disturbances were suppressed by very small doses of the drug, much smaller than those required to control the disturbances of the coronary circulation.

Hence different doses of chlorpromazine were required to suppress the different types of cardiac arrhythmias of central origin produced by stimulation of certain zones of the medulla. The arrhythmias developing during stimulation of the reticulotegmental nucleus and the nuclei of the vestibular complex responded most easily to chlorpromazine (0.1-0.5 mg/kg). These observations are in agreement with reports in the literature. The vascular reactions evoked by stimulation of the reticulotegmental nucleus and the nuclei of the vestibular complex likewise were suppressed more easily by chlorpromazine [1] than the reactions to stimulation of other morphological structures. On the whole, however, the vascular reactions were more difficult to control by chlorpromazine than the disturbances of cardiac activity. The cardiac arrhythmias and disturbance of the coronary circulation with arrhythmias obtained by stimulation of the nuclei of the vagus complex proved most resistent to the action of chlorpromazine.

The action of chlorpromazine on the various types of cardiac arrhythmias evoked by stimulation of certain zones of the reticular formation was dependent on the localization of the stimulation. Stimulation of the nuclei of the vagus complex had a more prolonged effect on the function of excitability (changes in the T wave) than on the other functions of the heart, and at the same time it caused changes in the lumen of the coronary arteries. This was reflected in the blood supply to the heart which, in turn, caused changes in the ECG.

The effect of chlorpromazine was dependent, not only on the site of stimulation, but also on the type of the cardiac arrhythmia. This may account for the fact that in combined disturbances in the course of the same experiment, ventricular extrasystoles were abolished by chlorpromazine in a dose of 0.1 mg/kg, while abolition of the disturbances of the coronary circulation with arrhythmias required a dose of 1.8 mg/kg. The arrhythmias produced by stimulation of the reticulotegmental nucleus and the nuclei of the vestibular complex were depressed by smaller doses of chlorpromazine than those produced by stimulation of the nuclei of the vagus nerve. It is important to note that in nearly every experiment the extrasystoles and certain disturbances of conduction disappeared after the administration of comparatively small doses of chlorpromazine (0.1-0.5 mg/kg).

SUMMARY

Various types of cardiac arrhythmias were induced by local stimulation of the medulla. In studying the effect of chlorpromazine it was revealed that extrasystoles interference with dissociation, and dissociation of the sinus and (heterotropic) ventricular rhythms are arrested by low doses (0.1-0.5 mg/kg body weight). Ventricular paroxysmal tachycardia, dissociation of sinus and ventricular rhythm and disturbance of coronary circulation with an extrasystolic arrhythmia are depressed by high doses of chlorpromazine (1-2.25 mg/kg).

The effect of chlorpromazine depends on the localization of the stimulation. Disturbances of the cardiac rhythm caused by stimulation of reticulotegmental nucleus and of the nuclei of the vestibular complex were more easily depressed by chlorpromazine than those caused by stimulation of the vagus nerve nuclei.

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3. A. Brodal, The Reticular Formation of the Brain Stem [Russian translation], Moscow (1960).

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. ***Some or all of this periodical literature may well be available in English translation.*** **A complete list of the cover-to-cover English translations appears at the back of this issue.**