THE CENTRAL AND PERIPHERAL ACTION OF CHLORPROMAZINE

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The sympatheticolytic properties of chlorpromazine and its effect on the central nervous system, especially on the reticular formation of the brain stem, have now been proved beyond doubt [1, 5, 8, 11, and many others]. Several writers consider that chlorpromazine also has a direct action on the cells of the cerebral cortex [7]. Convincing evidence has also been obtained that the site of action of chlorpromazine may vary depending on the dose, the species of animal, and certain other conditions [4].

The especially high sensitivity to chlorpromazine of the adrenergic structures of the brain, which are blocked by administration of this drug, suggests that chlorpromazine is an adrenalin antagonist in its action on the reticular formation of the brain [3, 13, and others]. If, however, the action of chlorpromazine is based on its adrenolytic property, this may be exhibited equally well at any level of the central nervous system and also at the periphery, for adrenergic elements are also represented there. For instance, the opinion is held, although controversially, that chlorpromazine blocks adrenergic transmission at the level of the sympathetic ganglia [2, 9].

In order to ascertain what effect, if any, chlorpromazine has on the various divisions of the central nervous system and on the periphery, we carried out experiments on cats and rabbits in which the central nervous system was partially or completely destroyed. Attention was paid to the arterial pressure, the pulse rate, and the respiration.

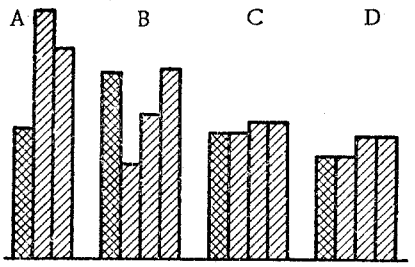

Fig. 1. The effect of chlorpromazine on the heart rate of intact (A), decerebrate (B), and spinal (C) cats and of cats in which the central nervous system was totally destroyed (D). Cross shaded columns—initial heart rate; obliquely shaded columns—changes in the heart rate immediately and 30 and 60 minutes after injection of chlorpromazine in a dose of 2 mg/kg body weight.

EXPERIMENTAL METHOD

Chronic and acute experiments were conducted on cats and rabbits, anesthetized with urethane and ether and immobilized with ditilin. A series of experiments was carried out on animals after partial (decerebrate or spinal animals) or complete destruction of the central nervous system. The total number of experiments was 78.

The pulse and respiratory movements were recorded by means of a 4-channel ink-recording oscillograph. The arterial pressure was measured by a mercury manometer and recorded on the drum of a kymograph. Chlorpromazine was dissolved in physiological saline and injected intravenously in a dose of 2 mg/kg body weight for cats and 5-10 mg/kg body weight for rabbits.

EXPERIMENTAL RESULTS

Effect of chlorpromazine on the heart rate, the arterial pressure, and the respiration of cats and rabbits. Following the intravenous injection of chlorpromazine in a dose of 2 mg/kg body weight, the heart rate of the anesthetized cats rose sharply from 140-150 to 200-280 beats per minute. Immediately after the injection of chlorpromazine the arterial pressure fell by 24-45%. Subsequent injections of the drug caused a smaller fall in the arterial pressure and a very slight increase in the heart rate. As a rule the heart rate regained its initial value after 40-60 minutes.

The intramuscular injection of chlorpromazine into unanesthetized cats, accustomed to the experimental environment, also led to an increase in the heart rate from 100-120 to 150-200 beats per minute, starting on the 7th to 10th minute after injection; the increased heart rate persisted for 50-60 minutes.

The changes in the heart rate following intravenous injection of chlorpromazine into cats immobilized with ditilin were of the same character.

The intravenous injection of chlorpromazine into unanesthetized rabbits led to a sharp rise of the heart rate (from 220-230 to 300-330 beats per minute), which appeared during the first minutes after injection of the drug and persisted for 40-60 minutes (Fig. 1).

No consistent changes in respiration were observed after injection of chlorpromazine into the cats and rabbits: in a few experiments a slowing of the respiratory movements was observed, and in others the rate increased. Frequently there was no change in the character of the respiratory movements, but sometimes the relationship between their phases was disturbed and their amplitude modified.

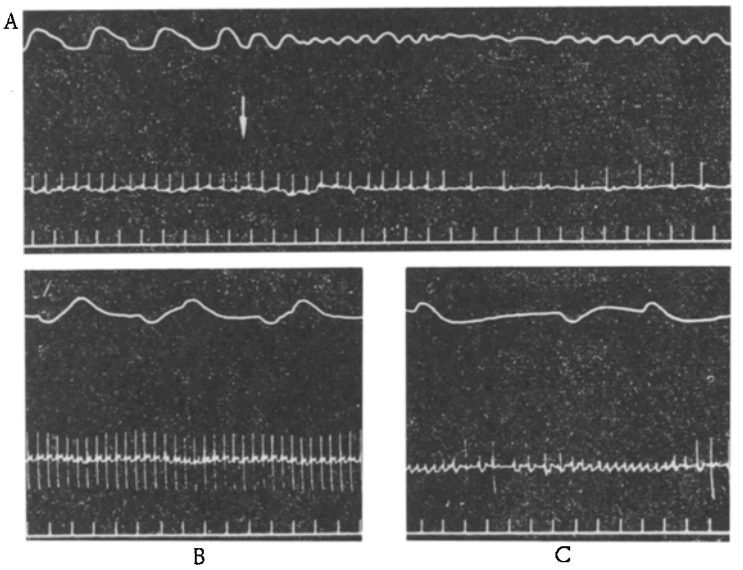

Fig. 2. The effect of chlorpromazine on the heart rate and respiration of a decerebrate cat. A) Intravenous injection of chlorpromazine in a dose of 2 mg/kg (the moment of injection is indicated by an arrow); B) 5 minutes, and C) 10 minutes after injection. Significance of the curves (from above down): pneumogram; EGG; time marker (in seconds).

Experiments on decerebrate animals. As a rule the intravenous injection of chlorpromazine into decerebrate cats in a dose of 2 mg/kg body weight led to a considerable slowing of the heart rate (from 130-150 to 70-80 beats per minutes), which was observed immediately after injection of the drug, and sometimes it led to arrhythmia (Fig. 2). Subsequently, either a small increase in the heart rate was observed, or it returned to its original value (Fig. 1B).

The sensitivity of the decerebrate animals to chlorpromazine was appreciably increased. The fall in the arterial pressure following injection of chlorpromazine reached 48-53%. Under the influence of the drug the rate of respiratory movements of the decerebrate cats was slowed. In a series of experiments injection of the drug led to respiratory arrest and to death of the animal soon after, but this was never observed in the animals with an intact nervous system after injection of the same doses of chlorpromazine. We must emphasize that application of artificial respiration in such cases saved the animals from death: cardiac arrest did not take place.

Experiments on spinal cats. When injected in the same doses into spinal animals, chlorpromazine had a less marked effect on the heart rate and arterial pressure than in intact animals. Occasionally the heart rate was unaltered, but usually a slight increase was observed (by 10-12%), which persisted for 20-30 minutes, after which the rate returned to its initial level (Fig. 1C). Under the influence of chlorpromazine the arterial pressure in the spinal cats fell by 20-25%.

Experiments on cats in which the central nervous system was destroyed. The reactions to injection of chlorpromazine of the cats after total destruction of the central nervous system showed no significant difference from those in the spinal animals so far as the heart rate (Fig. 1D) and level of the arterial pressure were concerned.

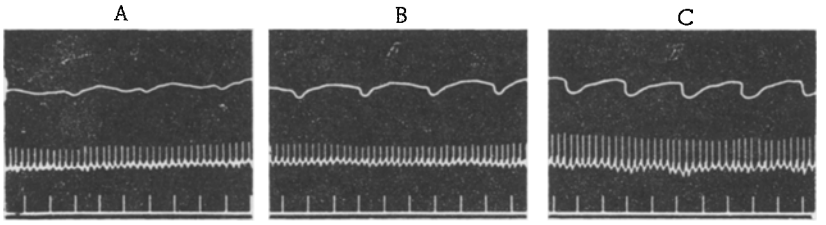

Fig. 3. The effect of chlorpromazine on the heart rate and respiration of a vagotomized cat. A) Before, and B) 45 minutes after intravenous injection of chlorpromazine in a dose of 2 mg/kg. Legend as in Fig. 2.

Experiments on vagotomized animals. To study the role of the vagus nerves in the reactions of the cardiovascular system to injection of chlorpromazine, the drug was given to vagotomized animals. The vagus nerves were divided in the neck on both sides. As a rule in these cases chlorpromazine had no appreciable effect on the heart or on respiration (Fig. 3). Stimulation of the central segment of the vagus nerve with an electric current (the opposite vagus nerve being intact) after injection of chlorpromazine had no effect on the heart rate. The reaction was restored only 30-40 minutes after the injection.

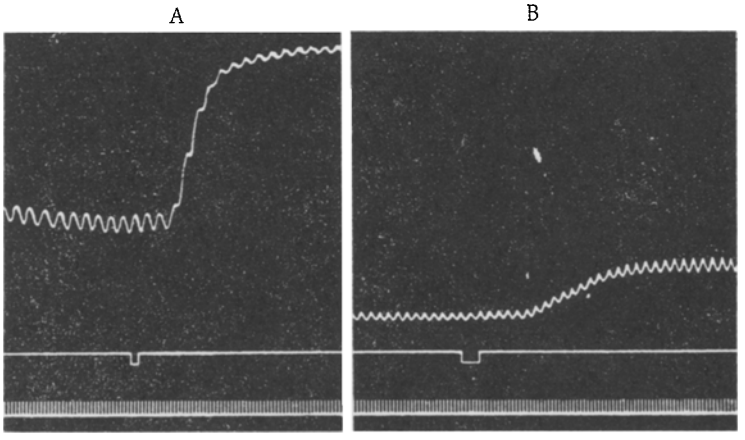

Fig. 4. The effect of adrenalin on the arterial pressure of a cat following total destruction of its central nervous system. A) Injection of 0.2 ml adrenalin (1 : 1000) intravenously; B) injection of 1 ml adrenalin (1 : 1000) after chlorpromazine (7 mg/kg body weight). Significance of the curves (from above down): arterial pressure; zero line with marker of injection of the drug; time marker (in seconds).

The effect of adrenalin, injected after chlorpromazine, on the arterial pressure in cats. Experiments on cats have yielded results showing antagonistic relationships between adrenalin and chlorpromazine in their effect on the arterial blood pressure. For instance, the injection of adrenalin in doses causing death of the intact animal as a result of a very marked elevation of the arterial pressure led to only a slight rise in the arterial pressure or sometimes had no effect on it whatever, if the animal had previously received an injection of chlorpromazine. Similar findings were obtained by I. P. Anokhina [2] and M. D. Mashkovskii [8].

A considerable decrease in the pressor effect of adrenalin, when administered after chlorpromazine, was also revealed in experiments on decerebrate and spinal cats and on cats in which the central nervous system was totally destroyed (Fig. 4).

The results published in the literature show that the effect of chlorpromazine on the cardiovascular system is the result of its action on the central and autonomic nervous system [2, 5, 6, 8, 12, and others].

The results of our experiments showing that chorpromazine changes the heart rate and the level of the arterial pressure in cats in which the central nervous system is completely destroyed give grounds for the assumption that this drug also possesses a peripheral action, and acts upon the adrenergic elements of the vascular wall. There is no doubt, however, that chlorpromazine exerts its action on the cardiovascular system mainly through the adrenergic systems of the reticular formation of the brain stem. This is shown by experiments in which equal doses of chlorpromazine were injected into spinal cats and into cats in which the central nervous system was totally destroyed; these experiments showed that the heart rate and arterial pressure in such animals were affected to a lesser degree than in decerebrate animals. It must be assumed that the action of chlorpromazine on the cardiac activity of the animals is largely brought about through the vagus nerve system. Bilateral vagotomy weakens the effect of chlorpromazine on the cardiovascular system.

The fact that the cardiovascular and respiratory systems of decerebrate animals are more sensitive to chlorpromazine than those of intact animals is presumably explained by the considerable disturbance of the compensatory powers of animals deprived of the telencephalon, mesencephalon, and diencephalon. The administration of chlorpromazine cannot therefore bring into play mechanisms directed towards the compensation of the respiratory changes, and cardiac arrest subsequently develops. These experiments show that the indeterminateness and often the absence of changes in respiration after injection of chlorpromazine into intact animals are due to the compensatory powers of the central apparatuses controlling respiration.

The reticular formation of the brain stem is the structure mainly responsible for development of the antagonistic relationships between chlorpromazine and adrenalin in their effect on the cardiovascular system. However, the decrease in the vascular effect from injection of adrenalin into cats after total destruction of the central nervous system, which have received a preliminary injection of chlorpromazine, indicates that the relationships between these drugs are also manifested at the level of the peripheral adrenergic structures.

SUMMARY

Cardiovascular and respiratory disturbances occuring in chlorpromazine administration are more pronounced in decerebrated animals than in the intact ones. Antagonistic relationships of chlorpromazine and adrenaline (according to the indices of arterial pressure and respiration) developed in decerebrated animals without significant differences from the animals with an intact central nervous system.

Intravenous injection of chlorpromazineto spinal animals and to those with a completely destroyed CNS caused a reduction of the arterial pressure and a change of the frequency of cardiac contractions; these changes however were less pronounced than in the animals with an intact central nervous system.

The interrelations of adrenaline and chlorpromazine in their effect on the arterial blood pressure level are antagonistic both in spinal animals and in those with a completely destroyed central nervous system. Bilateral vagotomy considerably decreases the effect of chlorpromazine on the cardiovascular system and respiration. The reticular formations of the brain stem is the main site of chlorpromazine application in its effect the cardiovascular system. However, aminazine had also a marked effect on the peripheral adrenaline structures.

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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.
