EFFECT OF CHLORPROMAZINE ON THE OXYGEN CONSUMPTION OF PUPPIES

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The effect of phenothiazine preparations is usually associated with their depressant action on the metabolic processes of all the cells and tissues, and especially those in the central nervous system, due largely to a decrease in the activity of many enzymes, notably dehydrogenases and cytochrome oxidase [6, 10-14, 15, 18, 19, 23]. However, reports of the action of chlorpromazine on the oxygen consumption of adult animals are contradictory. According to some investigations, the oxygen consumption in man [21], dogs, and rabbits [16] falls after administration of chlorpromazine. Meanwhile, experiments on rats showed that a decrease in the oxygen consumption to levels lower than in basal metabolic conditions takes place when the body temperature is below 31°. A slight fall of body temperature by 1-2°, on the other hand, may cause an increase in the oxygen consumption [17-22, 24]. Some authors [17] consider that in these circumstances the metabolic rate is lowered only if it was increased before the experiment.

No information concerning changes in metabolism of young animals as a result of the action of chlorpromazine could be found in the literature. Investigations in the author's laboratory [1, 2] have shown that the high level of energy expenditure characteristic of the young animal is associated with adrenergic features of homeostasis.

To investigate the significance of this relationship more closely, the action of the adrenolytic drug chlorpromazine on oxygen consumption was studied in young puppies.

EXPERIMENTAL METHOD

Two series of experiments were carried out on puppies of two age groups: group 1 — aged 2 to 11 days, group 2 — aged from 20 to 29 days. The choice of these age groups was made on the basis of observations in the author's laboratory establishing the oxygen consumption in normal conditions in a state of rest. In the puppies aged from 2 to 11 days, the highest level of oxygen consumption was observed at rest (from 18 to 23 ml/kg/min), reaching a maximum at the age of 4-5 days. After 18-20 days, when the standing posture had been adopted and locomotion was possible, the resting oxygen consumption fell (to 14.3-15.6 ml/kg/min). These age groups also differed in the character of their thermoregulation and the activity of their respiratory and cardiovascular systems [2].

The oxygen consumption was determined by a modification of Grad's method [24] in a room temperature of 19-21°. Measurements were made twice or three times before and 30-60 min after intramuscular injection of chlorpromazine in a dose of 20 mg/kg. This does is $^2/_5$ of the maximal dose tolerated by ycung puppies. The choice of such a high dose of chlorpromazine was based on observations showing that only doses of this order produced a marked fall of body temperature and of oxygen consumption [17-22]. For control purposes, in the third group of experiments the oxygen consumption was determined after administration of smaller doses of chlorpromazine (5-10 mg/kg) to the puppies of the first age group. The body temperature was measured at a depth of 1 cm in the rectum and the respiratory rate was determined. In the course of the experiment observations were made on changes in the respiration rate and muscle tone.

EXPERIMENTAL RESULTS

In the puppies aged from 2 to 11 days, 30-60 min after intramuscular injection of chlorpromazine (20 mg/kg) the respiration rate fell by 12-56 per min (on the average by 23.5 per min) and the muscle tone fell sharply so that in some experiments the puppies lay on their side. Their body temperature fell by

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3.0-8.5° (on the average by 4.7°), from 35-36° to 30-32°. In adult dogs this dose caused much less marked changes: the body temperature fell by 1° (to 37°); the respiration rate at first increased and only later began to decrease; a slight decrease in muscle tone was observed; expressed by general sluggishness. The results obtained in the experiments on adults dogs agreed with those described by M. D. Mashkovskii and co-workers [6]. The oxygen consumption in the puppies aged from 2 to 11 days fell 30-60 min after injection of chlorpromazine from 18.7±0.35 to 13.6±1.3 ml/kg/min, i.e., by 30% ($P < 0.001$).

In the second series of experiments the injection of chlorpromazine (20 mg/kg) into puppies aged from 20 to 29 days caused a slowing of respiration after 30-60 min by 4-32 per min (mean 17.7) and a fall of body temperature by 2.36°. The puppies did not lay on their side and the decrease in muscle tone did not affect all the muscles but was particularly marked in those of the forelimb.

The oxygen consumption fell from 16.36±1.2 to 10.67±1.04 ml/kg/min, i.e., by 34.8% ($P < 0.01$). Hence, despite the less marked fall of body temperature, respiration rate, and muscle tone after administration of chlorpromazine, the oxygen consumption in the puppies aged from 20 to 29 days fell by approximately the same degree as in the puppies aged from 2 to 11 days.

For this reason, the third series of experiments was carried out, in which the puppies of the first age group received chlorpromazine in doses of 5-10 mg/kg, which produced a smaller decrease of body temperature and muscle tone. A dose of 5 mg/kg is at the threshold level and lowered the body temperature by 3.0-3.5° (to 32-33°), and also produced slight muscle atony.

In puppies aged from 4 to 6 days, chlorpromazine in doses of 5-10 mg/kg reduced the oxygen consumption from 21.7±0.97 to 15.58±1.37 ml/kg/min, i.e., by 28.9% ($P < 0.02$). The higher initial value may be explained by the fact that all the animals were aged between 4 and 6 days, with maximal oxygen consumption at rest [1, 2]. It may be concluded from the results of the first series of experiments that, despite the less marked fall of body temperature and muscle tone the degree of decrease in oxygen consumption following injection of chlorpromazine in a dose of 5-10 mg/kg was almost the same as in the puppies of the same age group receiving chlorpromazine in a dose of 20 mg/kg (series 1).

Hence, despite the difference in the doses of chlorpromazine, the degree of decrease in oxygen consumption was approximately the same (30 and 28.9%), if the puppies of the first age group (series 1 and 3) were considered. If the results for the first and second age groups (series 1 and 2) were compared, it could be concluded that the degree of lowering of the oxygen consumption after injection of the same dose of chlorpromazine (20 mg/kg) is independent of age. No significant influences likewise were found in relation to the degree of lowering of body temperature, muscle tone, or respiration. It must be pointed out that in all series of experiments a marked decrease in the oxygen consumption below the level of the resting metabolism was observed.

Chlorpromazine is known not to block the ascending activating influences in young puppies (under 18-20 days of age) [9]. The problem is to what extent can chlorpromazine block influences associated with the regulation of temperature, metabolism, and muscle tone in young puppies. Phenothiazine preparations are known to have a blocking effect on the function of the reticular formation of the brain stem and, in particular, on structures associated with the regulation of muscle tone [4, 5, 7] and of the hypothalamus, especially its posterior portion, a higher sympathetic center. Against the background of the action of chlorpromazine, electrical stimulation of the hypothalamus has no stimulant effects on several autonomic functions [27]. After administration of chlorpromazine, maximal accumulation of the drug takes place in the hypothalamus [26].

In newborn animals the total catecholamine level in the brain stem is twice or three times higher than that in adults. This high level in the newborn rabbits is sharply reduced if the mother received chlorpromazine in a dose of 5 mg/kg throughout the period from the 15th day of pregnancy until parturition [8]. In connection with these observations, the decrease found in the oxygen consumption, body temperature, muscle tone, and respiration rate of the young puppies after administration of chlorpromazine may be interpreted as the overall effect of the adrenolytic action of chlorpromazine on the adrenergic substance of the centers in the hypothalamus and brain stem. This effect is brought about by doses of not less than 5-10 mg/kg, and it is not increased with an increase in the dose. The central adrenolytic effect of chlorpromazine may also be intensified as a result of the depressant action of chlorpromazine on the secretion of catecholamines by the adrenals in young animals [8]. In the author's laboratory the great importance of the adrenergic factors of regulation of homeostasis at an early age has been demonstrated [1]. In this

connection, and because of the absence of several adaptive mechanisms in young puppies, homeostasis is disturbed sooner and to a more marked degree after the action of adrenolytic preparations such as chlorpromazine.

LITERATURE CITED

1. I. A. Arshavskii, in the book: Neurohumoral Regulation in Ontogenesis [in Russian], Kiev (1964), p. 6.
2. O. T. Vakhidova, Analysis of Correlative Relationships between Energy Metabolism, Natural Respiration Rate, and Cardiac Activity of Dogs at Different Age Periods, Author's abstract of candidate dissertation, Moscow (1964).
3. O. T. Vakhidova, Byull. Éksp. Biol., No. 2, 32 (1965).
4. N. A. Kruglov, Uchen. Zapiski Inst. Farmakol. Khimioter. AMN SSSR, 1, 59 (1958).
5. V. P. Lebedev, in the book: New Data on the Pharmacology of the Reticular Formation and Synaptic Transmission [in Russian], Leningrad (1958), p. 87.
6. M. D. Mashkovskii, S. S. Liberman, and A. I. Polezhaeva, Zh. Farmakol. Toksikol., No. 1, 14 (1955).
7. M. D. Mashkovskii and B. A. Medvedev, Byull. Éksp. Biol., No. 4, 50 (1956).
8. A. V. Nasedkin, Adrenergic Mechamisms of the Brain Structures of Rabbits in Ontogenesis and in Various Functional States, Author's abstract of candidate dissertation, Moscow (1962).
9. V. D. Rozanova, Byull. Éksp. Biol., No. 6, 62 (1959).
10. R. V. Chagovets, E. V. Lakhno, and A. A. Rybina, Zh. Farmakol. Toksikol., No. 1, 50 (1958).
11. I. N. Shchelovanova, Uchen. Zapiski Inst. Farmakol. Khimioter. AMN SSSR, 1, 161 (1958).
12. L. G. Abood, Proc. Soc. Exp. Biol., (New York), 88 (1955), p. 688.
13. A. Andrejew and A. J. Rosenberg, C. R. Soc. Biol., 150 (1956), p. 639.
14. J. Bernsohn, I. Namajuska, and L. S. G. Cochrane, Arch. Biochem., 62 (1956), p. 274.
15. J. Bernsohn, I. Namajuska, and B. Boshes, J. Neurochem., 1 (1956), p. 145.
16. M. Bourgeois-Gavardin, W. K. Nowill, G. Margolis, et al., Anesthesiology, 16 (1955), p. 829.
17. W. Brendel and H. L'Allemand, Arch. Exp. Path. Pharmak., Bd 225, S 87 (1955).
18. S. Courvoisier, et al., Arch. Int. Pharmacodyn., 92 (1953), p. 305.
19. Ph. Decourt, Therapie, 8 (1953), p. 846.
20. Ph. Decourt, Therapie, C. R. Acad. Sci. (Paris), 236 (1953), p. 1195.
21. J. Ducuing and J. Rieunau-Serra, Mém. Acad. Chir., 79 (1953), p. 414.
22. K. Feller, Arch. Exp. Path. Pharmak., Bd 225, S. 90 (1955).
23. M. Finkelstein, W. A. Spencer, and E. R. Ridway, Proc. Soc. Exp. Biol., New York, 87 (1954), p. 343.
24. B. Grad, Endocrinology, 50 (1952), p. 94.
25. L. Peruzzo, Presse Méd., 61 (1953), p. 1463.
26. A. W. Wase, J. Christensen, and E. H. Polley, Arch. Neurol. Psychiat., 75 (1956), p. 54.
27. G. Werner, Wien. Klin. Wschr., Bd. 66, S. 966 (1954).