EFFECT OF CHLORPROMAZINE ON GROWTH AND DEVELOPMENT OF YOUNG RATS

V. D. Rozanova

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Prolonged administration of chlorpromazine to young rats during the first month of life reduced the rate of growth and the level of activity of the respiratory and cardiovascular systems and increased the role of cholinergic factors of regulation; the larger the dose of chlorpromazine given the more marked these changes were. When the compound was given in doses of 2.5 and 5 mg/kg daily the gain in weight of the experimental rats by the 30th day after birth was retarded by 16%, while if it was given in a dose of 10 mg/kg, it was retarded by about 44% compared with the control. The respiration and heart rates and the blood cholinesterase activity of the experimental rats were reduced by 28, 19, and 28.4%, respectively, compared with the control values.

Previous investigation in the writer's laboratory showed that a high level of oxygen consumption and of activity of the respiratory and cardiovascular systems, as well as a high growth constant in young animals are maintained by predominance of the sympathico-adrenergic mechanisms regulating homeostasis at rest [1-4, 6, 9, 10, 13]. Prolonged administration of reserpine to young rats and puppies aged 1-30 days reduced the catecholamine concentration in the brain stem and adrenals, the oxygen consumption, and the rate of growth [3, 8]. In this connection it was interesting to investigate the effect of chlopromazine on the growth and development of young rats aged 1-30 days, having regard to the contradictory information on the effect of phenothiazine derivatives on young animals [5, 11, 14, 15].

EXPERIMENTAL METHOD AND RESULTS

Experiments were carried out on rats aged between 6-12 and 30-40 days. Half of the rats in each litter received chlorpromazine by daily subcutaneous injection in doses of 2.5, 5, or 10 mg/kg, while the other half received the same volume of physiological saline. The rats were weighed at the beginning of the experiment and at the ages of 15, 20, 30, and 40 days. The growth constant (k) was calculated by Shmal'gauzen's equation [12]:

$$k = \frac{\lg v_2 - \lg v_1}{\lg t_2 - \lg t_1},$$

where v_1 and v_2 are the body weight (in g) and t_1 and t_2 the age at the beginning and end of the period of investigation (in days). The body temperature, respiration rate, and heart rate were noted and the ECG was recorded after a single injection of chlorpromazine and at the end of the experiment, when the blood acetylcholinesterase activity also was determined by Pokrovskii's method [7].

A single injection of chlorpromazine in doses of 2.5 and 5 mg/kg led to a decrease in mobility of the young rats aged 6-10 days, a fall of body temperature (from 33-34°C under normal conditions to 30-31.5°C), and a decrease in the respiration rate from 120-128 to 60-72/min and in the heart rate from 400-410 to

Laboratory of Age Physiology and Pathology, Institute of Normal and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. [Presented by Academician V. V. Parin (deceased)].
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250-270/min. This effect lasted for 30-60 min. An increase in the dose to 10 mg/kg caused the rats to lie down on their sides for 5-20 min and depressed the physiological indices more sharply still.

After repeated injections of chlorpromazine growth was delayed. In the series of experiments in which chlorpromazine was injected in doses of 2.5 and 5 mg/kg, the body weight of the experimental rats at the age of 15 days was 17.8 ± 0.04 and 19.3 ± 0.08 g (k = 0.08) while the weight of the control rats was 20.7 ± 0.05 and 23.53 ± 0.06 g (k = 0.6) respectively ($P < 0.001$). By the age of 30 days the weight of the experimental animals receiving chlorpromazine in a dose of 2.5 mg/kg was 73.6 ± 0.7 g, and the weight of the animals receiving chlorpromazine in a dose of 5 mg/kg was 75.3 ± 0.5 g (k = 1.5); the weight of the control rats was 85.4 ± 0.5 and 87.7 ± 0.7 g respectively (k = 1.7). In the series of experiments in which the largest dose of chlorpromazine was given (10 mg/kg) the retardation in weight of the experimental rats was more marked still: by the age of 30 they weighed 45.37 ± 1.2 g (k = 1.55). The control animals weighed 80.1 ± 0.4 g (k = 2.0; $P < 0.001$), which was 79% more than the experimental animals, whereas in the series in which the smaller doses of chlorpromazine were given the difference was only 16-17%. The heart and respiration rates of the experimental rats receiving chlorpromazine in doses of 10 mg/kg were 19 and 28% respectively (340.0 ± 1.75 and 108 ± 4.3/min) lower than in the control (420 ± 2.0 and 150 ± 1.0/min; $P < 0.001$).

The decrease in the level of activity of the autonomic systems and in the intensity of growth was due not only to blocking of the sympathico-adrenergic system, but also to potential of the cholinergic background of regulation. In the experimental rats which received chlorpromazine in a dose of 2.5 mg/kg, the blood acetylcholinesterase level was 1.09 ± 0.2 μmole, in the rats receiving 5 mg/kg chlorpromazine it was 1.19 ± 0.04 μmole, and in the rats receiving 10 mg/kg it was 1.02 ± 0.07 μmole; in the control rats this index was 1.29 ± 0.06, 1.35 ± 0.05, and 1.41 ± 0.04 μmole respectively.

The decrease in the rate of growth during the first month of life of the rats receiving chlorpromazine is thus an index which reflects the global effect of this compound on several different systems of the body which, under normal conditions, contribute to maintain high indices of homeostasis at rest through predominance of the sympathico-adrenergic mechanisms of regulation.

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