MECHANISMS OF EFFECT OF OROTIC ACID ON GROWTH AND DEVELOPMENT OF YOUNG RATS

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Chronic administration of potassium orotate to young rats in a dose of 75 mg/kg body weight from the 5th to the 14th day and 150 mg/kg from the 15th to the 30th day of life sharply accelerates growth and functional maturation of the animals. The rate of growth of the experimental animals between the 5th and 14th days and the 21st and 30th days was much greater than in the control rats, but between the 14th and 21st days there was no significant difference. The acceleration of growth from the 5th to the 14th day is accounted for by the greater activity of the autonomic systems (increased oxygen consumption, respiration rate, and heart rate at rest) than in the control. Between the 21st and 30th days the acceleration of growth in the experimental rats was connected with an earlier decrease in activity of the autonomic systems and sympathicoadrenal control mechanisms, as shown by a decrease in the catecholamine concentration in the adrenals and brain.

Key words: postnatal development, potassium orotate.

Acceleration of growth of rats under the influence of methylated dihydroxypurines (caffeine and theobromine), explained by the effect of these substances on nucleic acid synthesis [14-16], was demonstrated previously [3, 4, 15].

Orotic acid, a pyrimidine derivative, is widely used in clinical practice [1, 5, 6, 8, 10, 11]. Evidence of its stimulant effect on growth of adult animals, especially those receiving a deficient diet, has been obtained.

In this investigation the effect of chronic administration of orotic acid on the growth and development of young rats in the early postnatal period was studied.

EXPERIMENTAL METHOD

Experiments were carried out on 56 noninbred albino rats. In each litter eight rats remained after the first day of life, and some of them served as the control. From the 5th to the 14th day of life the experimental rats received potassium orotate by mouth daily in a dose of 75 mg/kg, and from the 15th to the 30th day in a dose of 150 mg/kg, in starch mucilage. The control rats received pure starch mucilage in the same volume. The animals were weighed and their body length measured at the age of 1, 7, 14, 21, and 30 days, always between 10 a.m. and noon. On the 14th, 21st, and 30th days of life, when the rats were in a resting state, the ECG was recorded in lead II and respiration was recorded by means of a carbon detector (Elcar electrocardiograph). The oxygen consumption was measured at the same time [7, 18]. The animals were killed on the 30th day of life. Catecholamines were determined fluorimetrically [9] in the brain and adrenals. Acetylcholinesterase (ACE) and butyrylcholinesterase (BCE) activity was determined in the blood and myocardium [12]; the absolute and relative weights of several organs were obtained.

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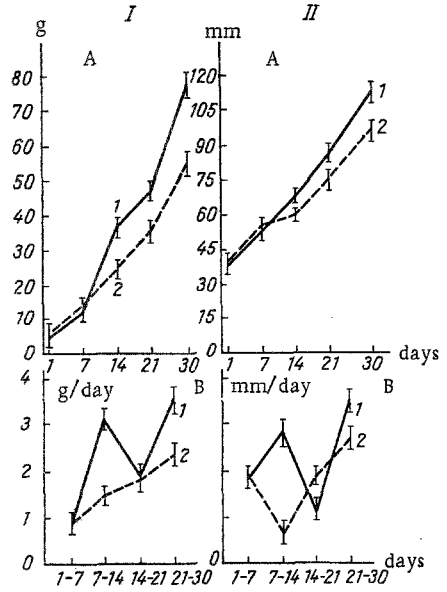

Fig. 1. Characteristics of growth of experimental (1) and control (2) rats: A) curves of growth; B) curves of rate of growth. Vertical lines show confidence limits of variations. Abscissa: days after birth; ordinate: I) weight (in g), II) body length (in mm), rate of increase of body length (mm/day), and rate of increase in body weight (in g/day).

EXPERIMENTAL RESULTS AND DISCUSSION

As Fig. 1 shows, starting with the 14th day of life, i.e., on the 10th day of administration of potassium orotate, the weight and body length of the experimental rats were significantly higher than those of the control. By the 30th day the body weight of the experimental rats was 39% greater and their body length 10% greater than the control. The acceleration of growth varied in degree at different age periods. From the 7th to the 14th day the rate of increase of weight and body length of the rats receiving potassium orotate was significantly greater than in the control. Between the 14th and 21st days the rate of increase of the body weight in the experimental rats was the same as in the control, but the rate of increase in body length was actually significantly lower ($P < 0.001$). Between the 21st and 30th days the rate of increase of body weight and length of the experimental rats was again significantly higher than in the control. At 14 days, a higher heart and respiration rate and body temperature and a greater oxygen consumption were recorded in the rats receiving potassium orotate than in the control (Table 1). At the age of 21 days the respiration rate of the experimental rats was higher than the control, the heart rate and body temperature were indistinguishable from the control, and the oxygen consumption was lower than the control. At the age of 30 days the rats receiving potassium orotate had a lower respiration and heart rate and a lower oxygen consumption. Their catecholamine concentration was lower than the control (noradrenalin concentration in the brain stem 0.20 ± 0.003 compared with 0.28 ± 0.008 μg/g in the control, $P < 0.001$; total content of adrenalin and noradrenalin in the adrenals 430.0 ± 8.0 compared with 490.0 ± 6.0 μg/g in the control, $P < 0.001$). No significant differences in ACE and BCE activity in the blood and heart were found [experiment: ACE (in μmoles/sec) in the blood 1.89 ± 0.13, in the atria of the heart 3.90 ± 0.30, in the ventricles 2.86 ± 0.04; BCE (in μmoles/sec) in the blood 1.20 ± 0.08, in the atria 4.40 ± 0.6, in the ventricles 2.65 ± 0.04; control: ACE (in μmoles/sec) in the blood 1.76 ± 0.12, in the atria 3.10 ± 0.5, in the ventricles 3.0 ± 0.12; BCE (in μmoles/sec) in the blood 1.13 ± 0.07, in the atria 3.11 ± 0.8, and in the ventricles 2.8 ± 0.06].

Acceleration of growth of the experimental animals took place on account of what Shmal'gauzen [17] calls the "active" parts of the body and, in particular, on account of an increase in the muscle mass. The absolute muscle mass in the experimental rats was 28,500 ± 95 mg (36.5% of the body weight) and 16,500 ± 80 mg (27.6%) in the control rats. In the rats receiving potassium orotate the weight of the heart, lungs, and liver (500 ± 0.5, 750 ± 6.8, and 5400 ± 10 mg respectively) was higher than in the control (340 ± 2.7, 680 ± 8.5, and 3960 ± 12 mg respectively). The differences were statistically significant ($P < 0.001$) for all the

TABLE 1. Changes in Oxygen Consumption, Heart Rate, Respiration Rate, and Rectal Temperature of Rats (M ± m)

Day of life	O_2 consumption (in ml/kg/min)			Heart rate (in beats/min)		
	Experiment	Control	P	Experiment	Control	P
14th	86,2 ± 1,2	76,5 ± 0,9	<0,001	438,0 ± 2,1	427,0 ± 1,8	<0,002
21st	64,2 ± 1,4	66,9 ± 1,2	>0,5	470,0 ± 1,2	472,0 ± 1,3	>0,5
30th	46,8 ± 1,2	60,9 ± 0,6	<0,001	428,0 ± 1,0	460,0 ± 1,2	<0,001
Day of life	Respiration rate per minute			Rectal temperature (°C)		
	Experiment	Control	P	Experiment	Control	P
14th	142,0 ± 0,8	135,0 ± 0,2	<0,001	35,4 ± 0,06	35,9 ± 0,08	<0,001
21st	120,0 ± 0,6	118,0 ± 0,5	>0,5	36,2 ± 0,04	36,2 ± 0,05	>0,5
30th	100,0 ± 0,6	116,0 ± 0,8	<0,001	36,5 ± 0,05	36,6 ± 0,04	>0,5

organs. Considerable hypertrophy of the adrenals (32.0 ± 0.3 mg) and thymus (480.8 ± 8.0 mg) and a decrease in the absolute (6.0 ± 0.1 mg) and relative (0.008%) weight of the thyroid gland were found in the rats receiving potassium orotate. In the control the corresponding figures were 17.0 ± 0.5, 255.0 ± 10.0, 11.3 ± 0.2 mg, and 0.020% respectively.

Chronic administration of potassium orotate, starting from the 5th day of life, thus causes true acceleration of growth and development of young rats. The differences in the rates of acceleration at different age periods can be explained by the dynamics of functional and biochemical parameters. Soon after birth, before the animal is able to stand, the intensity of growth is maintained by high activity of the sympathico-adrenal control mechanisms and by the high level of activity of the internal organs [2-4, 13, 14]. In the present experiments from the 5th to the 14th day of life the acceleration of growth of the experimental rats took place against the background of an increase in oxygen consumption, respiration rate, and heart rate. Accordingly, the experimental animals matured sooner. They were able to see earlier (after 12.8 ± ± 0.3 days compared with 15.8 ± 0.2 days for the control) and they were able to stand and to walk sooner. The earlier reorganization of activity of the autonomic systems of the body evidently resulted in temporary slowing of the rates of growth of the experimental rats. After the assumption of the standing posture the decrease in activity of the adrenergic control mechanisms and the autonomic systems entirely determined the subsequent growth of the animal [3, 4, 13, 14, 16]. Acceleration of growth was accordingly resumed in the rats receiving potassium orotate.

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