Role of Sex Steroid Hormones and Nerobolil in the Regulation of Free Fatty and Amino Acid Metabolism

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Sex steroid hormones, androgens, and their synthetic analog nerobolil regulate the relationship between metabolism of free monoenic fatty acids with odd numbers of carbon atoms and essential branched amino acids in male rats both in physiological health and under conditions of disturbed protein metabolism caused either by 22-day starvation or by second- or third-degree thermal injury.

Key Words: *sex steroid hormones; nerobolil; free monoenic fatty acids with odd numbers of carbon atoms; essential branched amino acids; rats*

Synthetic analogs of sex steroid hormones with anabolic properties are widely used in the treatment of protein metabolism disorders. Unmonitored long-term treatment with high doses of anabolic steroids causes metabolic disturbances, toxic damage to the liver, intestine, etc. These effects are related to the disturbances of protein and lipid metabolism, including albumins and free fatty acids, which form transport complexes in the blood [2].

In the present study we investigated the role of sex steroid hormones and their synthetic analog nerobolil in the regulation of the interrelationship between the metabolism of some free fatty acids and amino acids.

MATERIALS AND METHODS

The study was carried out on 160 male rats weighing 190-230 g. Disturbances of protein and lipid metabolism were reproduced using two models: 22-day starvation or thermal injury. The animals were divided into 10 groups: 1 - intact rats, control (n=13); 2 - control + nerobolil (single daily administration during 13 days, n=18); 3 - control + nerobolil (single administration every 3rd-4th day during 22 days, n=18); 4 - gonadectomized rats (22 days postoperation, n=12); 5 -

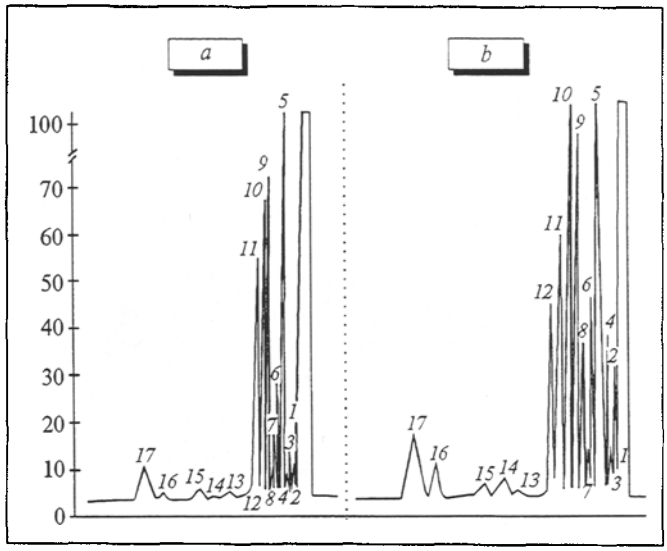

Fig. 1. Characteristic gas–chromatography profile of fatty acids from the blood of male rats. *a*) control; *b*) thermal injury + nerobolil (daily single injection during 13 days).

1 – 14:0	*7* – 17:0	*13* – 18:3
2 – 14:1	*8* – 17:1	*14* – 20:1
3 – 15:0	*9* – 18:0	*15* – 20:2
4 – 15.1	*10* – 18:1	*16* – 20:3
5 – 16:0	*11* – 18:2	*17* – 20:4
6 – 16:1	*12* – 19:1	

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gonadectomy+testosterone propionate (100 μg/kg daily during 22 days, n=15); 6 - starvation (n=14); 7 - starvation+nerobolil (single administration every 3rd-4th day during 22 days, n=16); 8 - thermal injury (22 days after injury, n=18); 9 - thermal injury+nerobolil (single administration every 3rd-4th day during 22 days, n=18); 10 - thermal injury + nerobolil (once daily during 13 days, n=18). Thermal injury of 20% of the body surface was inflicted with a special heating apparatus at 250°C for 10 sec. Nerobolil dissolved in oil was injected intramuscularly in a single dose of 5 mg/kg. The rats were decapitated under ether narcosis. Free fatty acids were separated in silica gel and analyzed by gas chromatography [1]; free amino acids were analyzed using a T-339 chromatograph (Czechoslovakia) by a standard method. Protein fractions were separated by paper electrophoresis. The data were processed statistically using the Student t test.

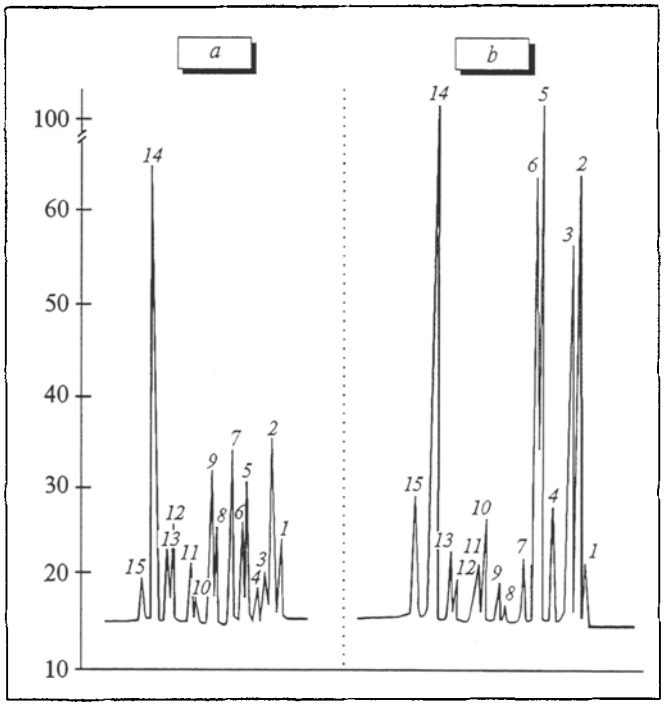

Fig. 2. Characteristic chromatography profile of free amino acids in the blood of male rats. *a*) control; *b*) thermal injury +nerobolil (daily single injection during 13 days). *1*) aspartic acid; *2*) serine; *3*) glutamic acid; *4*) proline; *5*) glycine; *6*) alanine; *7*) valine; *8*) isoleucine; *9*) leucine; *10*) tyrosine; *11*) phenylalanine; *12*) histidine; *13*) lysine; *14*) ammonia; *15*) arginine.

RESULTS

The results are presented in Table 1. Twenty-two days after starvation or thermal injury, which are known to be attended by hypo- and dysproteinemia, we observed a reduced level of albumins and an elevated content of free monoenic fatty acids with odd numbers of carbon atoms (FMFA) and essential branched amino acids (BAA) in the blood (groups 1, 6, and 8). Daily 13-day administration

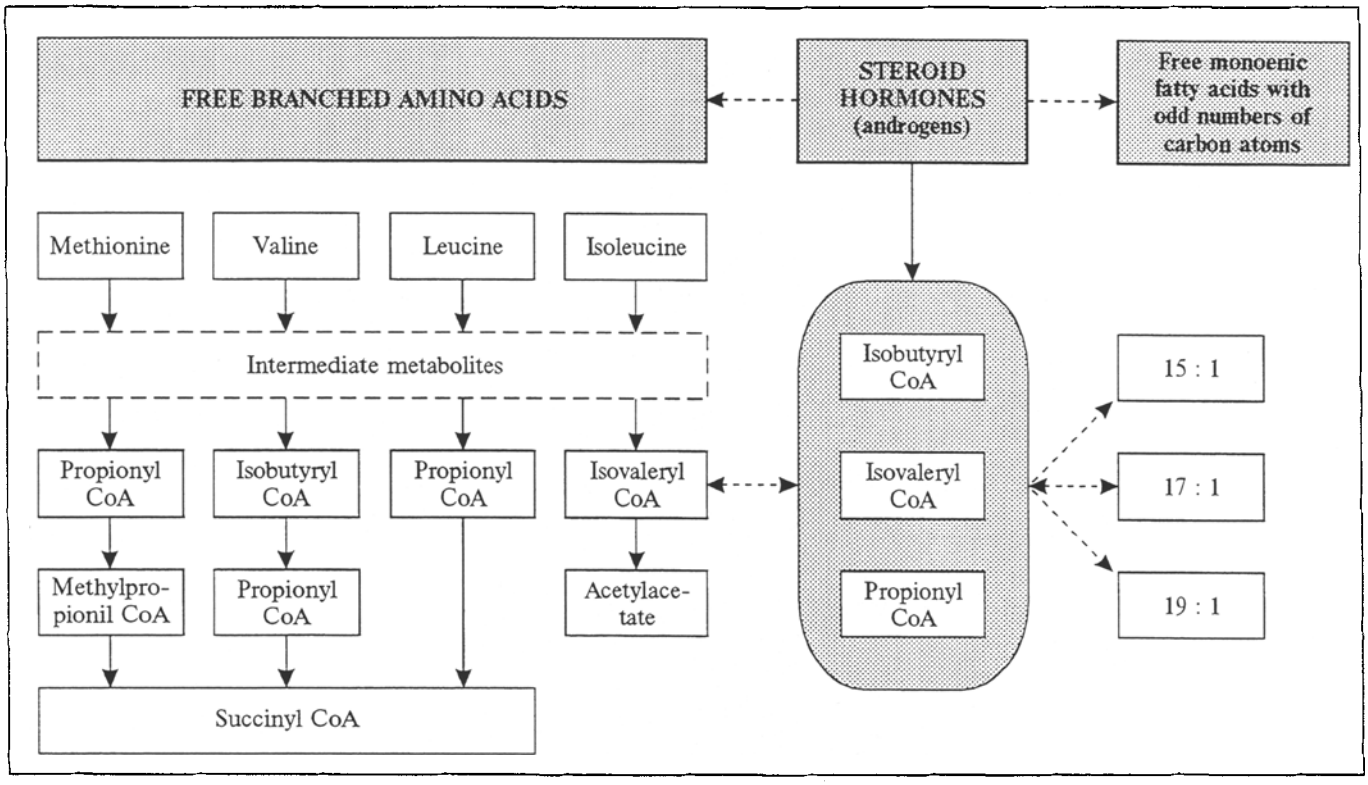

Fig. 3. Involvement of steroid hormones (androgens) in the regulation of amino acid and fatty acid metabolism.

of nerobolil (Fig. 1) led to a decreased content of albumins in control animals and to an increased content of FMFA due to heptadecanoic (17:1) and nonadecanoic (19:1) fatty acids, as well as to an elevated content of BAA (Fig. 2) due to valine and isoleucine (group 2).

Administration of nerobolil every 3rd-4th day resulted in the opposite effect: an increased level of albumins, leucine, and total content of FMFA (group 3). Twenty-two days after gonadectomy the content of isoleucine and 17:1 fatty acid rose (group 4), while administration of testosterone propionate against this background reduced these parameters to the control values (group 5). Administration of nerobolil during starvation prevented the changes in all studied fatty and amino acids (group 7). Analogous results were observed in group 9. In the rats with thermal injury daily 13-day administration of nerobolil (group 10) did not change the studied parameters in comparison with the untreated animals (group 8): both groups were characterized by a reduced content of albumins and considerably elevated levels of FMFA and BAA in the blood.

The presented results suggest that sex steroids regulating protein metabolism also affect the metabolism of their constituents, essential branched amino acids. For instance, a tendency toward a changed level of valine, leucine, and isoleucine was observed in gonadectomized animals, these reverting to physiological levels in the course of compensatory administration of testosterone propionate. A course of nerobolil exerting a catabolic effect on protein metabolism both in intact rats and in ani-

TABLE 1. Effect of Steroid Hormones (Androgens) and Nerobolil on the Levels of Albumins, Free Fatty Acids, and Amino Acids in the Blood of Male Rats ($M \pm m$)

Group	Albumins, mg/ml	BAA				FMFA			
		valine	leucine	isoleucine	total	15:1	17:1	19:1	total
1. Control ($n=13$)	27.3±0.6	7.2±0.2	5.9±0.3	2.4±0.1	15.5±0.6	3.5±0.2	2.7±0.4	2.1±0.3	8.3±0.5
2. Control+nerobolil (13 injections, $n=18$)	21.4±1.1*	25.8±2.2*	8.2±0.6	7.6±0.5*	41.6±3.2*	5.1±0.5	4.2±0.7*	4.5±0.7*	13.9±1.2*
3. Control+nerobolil (every 3rd−4th day, $n=18$)	33.9±1.1*	7.0±0.5	2.2±0.4*	1.8±0.2	13.0±1.0	1.4±0.3	1.6±0.4	1.2±0.3	4.2±0.4*
4. Gonadectomy ($n=12$)	23.4±2.6	9.3±0.7	6.5±1.2	9.5±1.6*	25.3±4.2*	3.8±0.4	4.6±0.5*	2.2±0.3	10.6±0.7
5. Gonadectomy+testosterone dipropionate ($n=18$)	26.7±3.7	8.6±0.6	6.3±0.5	4.2±0.4	19.1±0.5	2.2±0.5	2.4±0.3	3.1±0.5	7.9±0.7
6. Starvation for 22 days ($n=14$)	22.4±2.3*	20.4±2.3*	14.7±1.9*	10.4±1.8*	45.4±2.1*	6.1±0.5*	5.2±0.4*	4.1±0.6	15.4±1.7*
7. Starvation+nerobolil (every 3rd−4th day, $n=16$)	26.7±2.9	5.1±0.7**	4.8±0.6**	3.1±0.7**	13.0±1.1**	4.6±0.8	3.5±0.4**	3.2±0.5	11.3±0.9**
8. Thermal injury ($n=18$)	20.6±0.9*	29.1±3.3*	26.3±2.4*	13.1±1.5*	67.5±3.4*	5.2±0.9	6.3±0.7*	6.1±0.7*	17.6±2.1*
9. Thermal injury+nerobolil (every 3rd−4th day, $n=18$))	23.3±1.1	5.8±0.8***	4.6±0.7***	3.4±1.0***	14.8±1.6**	3.7±0.8	3.8±0.7***	2.7±0.6***	10.3±1.6***
10. Thermal injury+nerobolil (13 injections, $n=18$)	17.7±1.9*	28.3±2.4*	30.6±3.5*	16.3±2.3*	75.2±3.7*	6.8±1.0*	7.6±1.3*	6.2±0.9*	20.6±1.8*

Note. Asterisks denote reliability of differences ($p<0.05$): one − in comparison with the control, two − with starvation group, three − with group 9 (thermal injury+nerobolil).

mals with thermal injury led not only to a significant accumulation of BAA, which implies an inhibition of their incorporation into proteins, but also to a considerable increase of the content of FMFA (2-3-fold). Probably, excessive administration of nerobolil, inducing the accumulation of BAA, accelerates degradation of valine, leucine, and isoleucine with the simultaneous activation of the synthesis of fatty acids with odd numbers of carbon atoms from products of their incomplete degradation. Course administration of nerobolil exerting an anabolic effect in intact animals and in rats with thermal injury helped normalize the levels of the amino acids and albumins in question.

Thus, sex steroid hormones and their synthetic analog nerobolil regulate the relationship between the metabolism of essential BAA and FMFA with odd numbers of carbon atoms both under physiological conditions and in disturbed protein metabolism. It is well known (Fig. 3) that the biosynthetic and catabolic pathways of FMFA and BAA are characterized by some common intermediates: propionyl CoA, valeryl CoA, and isobutyryl CoA, which are probably the key intermediates in the realization of steroid activity. Moreover, anabolic steroids affect energy metabolism via regulation of the levels of free fatty acids and BAA, which in turn affect the energetics of muscle tissue [4] and some components of the citric acid cycle [3].

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Response of Hypothalamic Accessory Nonapeptidergic Centers to Hypophysectomy in Rats

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Accessory centers were calculated to contain more than 600 nonapeptidergic cells, most of which proved to be oxytocinergic. One week after hypophysectomy, morphometric measurements and morphofunctional changes in the nonapeptidergic cells of accessory centers indicated decreased synthesis of oxytocin and vasopressin by these cells as well as diminished transport of these neurohormones along their fibers. In contrast to the supraoptic, postoptic, and paraventricular nuclei, no degenerative cells were present in the accessory centers following hypophysectomy.

Key Words: *hypothalamus; accessory centers; oxytocinergic cells; vasopressinergic cells; hypophysectomy*

In addition to the supraoptic, postoptic, and paraventricular nuclei, the rat hypothalamus contains small accumulations of nonapeptidergic (NPE) neuroendocrine cells referred to as accessory centers (AC) [3,6,8,11]. The microanatomy of these centers has not been studied in sufficient detail, and the existing evaluations of their functional role are contradictory [1,2,7,12]. The question of how oxytocinergic (OTE) and vasopressinergic (VPE)

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