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Differential Metabolic Pattern of Muscle and Liver After the Administration of a β-Adrenergic Agonist

The sympathetic involvement in cardiovascular, respiratory and gastrointestinal functions is well known as are the effects on mobilization of energy reserves through glycogenolysis and lipolysis (10, 14). Furthermore, other metabolic actions are to increase heat production and a potential anabolic action accomplished by a repartitioning effect on the utilization of nutrients, from fat deposition towards protein accretion (15). Thus, the use of sympathomimetic agents has received a great deal of interest since it has been established that some β-adrenergic agonists affect growth and body composition by increasing lean tissue and decreasing fat content (2, 12, 17). However, the mechanism of action involved remains still under study.

Protein deposition in any tissue results from a fine balance between the processes of protein synthesis and breakdown, which is mainly determined by interactions of the dietary supply of aminoacids and energy-yielding nutrients and the hormonal and nervous systems (16).

Since changes in protein turnover which accompany growth are not the same in all tissues, the aim of this communication is to report evidence about the different behaviour of muscle and liver protein metabolism —assessed by its nucleic acid content— from rats administered with a non-selective β-agonist.

Male wistar rats, of about 90 g were fed *ad libitum* on a standard laboratory diet. They were injected s.c. twice daily (9 h a.m. and 5 h p.m.) with orciprenaline (1 mg/kg) or vehicle for 23 days, and killed by cervical dislocation. The liver and gastrocnemius muscle were carefully dissected.

Protein and nucleic acid determinations were carried out as per standard methodology (1, 7). A parallel trial was conducted to measure total carcass water, fat, protein and ash as previously described (8). The significance of differences between groups was determined by the Student's t test.

No changes in growth rate were observed in the treated animals (7.0 g/day vs 6.9 g/day). Muscle weight was significantly increased while liver proportions underwent no significant changes in rats with orciprenaline (table I), which reduced body fat (9) but also promoted the deposition of body protein (table II), with no changes in the food conversion efficiency ratio (FCE) (3.4 g/ΔP vs 3.2 g/ΔP), which is consistent with data obtained for other structurally related compounds in different species (6, 12).

The response to catecholamines from each tissue differs markedly according to the adrenergic receptors it possesses and to the post-receptor events activated within a particular tissue. Thus, the circulat-

Table I. *Gastrocnemius muscle and liver weight, protein and nucleic acid content from control and treated rats with the β-adrenergic agonist for 23 days.*
Mean values ± SEM are given with the number of animals in parentheses. Student «t» test was used. NS: not significant; ** $p < 0.01$; *** $p < 0.001$.

	MUSCLE		LIVER	
	CONTROL (8)	TREATED (8)	CONTROL (8)	TREATED (8)
Weight (%)	0.49 ± 0.01	0.54±0.02**	4.05±0.10	3.78±0.14^{NS}
Protein (mg/g)	203.60±2.69	204.90±3.03^{NS}	199.90±4.17	201.10±3.69^{NS}
DNA (mg/g)	0.52±0.03	0.79±0.05***	3.43±0.18	3.64±0.32^{NS}
Protein/DNA (mg/mg)	397.90±20.9	271.20±18.24***	59.30±3.20	57.90±4.54^{NS}
RNA/Protein (μg/mg)	5.90±0.26	5.80±0.26^{NS}	32.20±0.99	34.60±1.17^{NS}

ing adrenaline and noradrenaline act on both α and β receptors while orciprenaline is considered act a non selective β-agonist with specificity for β_1 and β_2 receptors. The metabolic effects mediated by β_1 receptors are generally recognised as lipolytic and also antilipogenic (2, 10, 14), while β_2 receptors appears to be associated to actions on glycogenolysis and, as recently published on protein turnover (4, 11). The β-agonist seem to act through the β-receptor-coupled adenylate system whose activation causes an increase in intracellular cAMP, the mobilization of fat and glycogen reserves and apparently changes in muscle protein anabolism and (or) catabolism (4, 11, 15, 17).

The growth of tissues and organs in terms of increase in total DNA (hyperplasia) and in protein/DNA ratio (hypertrophy) is well documented (16). Because of the special nature of muscle tissue, the muscle cells have been defined in operational terms as the volume of cytoplasm controlled by a single nucleus.

Total muscle DNA is invariably increased in those circumstances where sex or treatment enhances muscle growth, which is inversely related to protein/DNA ratios (3). Our results are in good agreement since they show a similar trend towards smaller amounts of muscle protein per unit DNA when DNA is increased (table I). This situation might be explained by an additional incorporation of nuclei from satellite cells or a more prolonged cell replication and hence growth, although other mechanisms cannot be discarded (3). Liver DNA content is similar in both groups which corroborates previous findings that muscle and liver responses are in many ways very different (1, 5, 13).

Cellular RNA or RNA/protein ratio, indirect measures of total ribosome content, are assumed to be good indicators of the protein synthesis capacity each nucleus controls (16). The treatment with the β-agonist apparently did not change the RNA/protein ratio and protein content either on muscle or liver which seems to indicate that no variations in protein synthesis occur (table I).

Previous reported evidence using different approaches confirms this suggestion that the anabolic action found in muscle

Table II. *Body composition from control and treated rats with the β-adrenergic agonist for 23 days.*
Mean values < SEM are given with the number of animals in parentheses. Student «t» test was used. NS: not significant; * $p < 0.05$; ** $p < 0.01$.

%	CONTROL (8)	TREATED (8)
Protein	19.9 ± 0.19	20.9 ± 0.39*
Fat	6.2 ± 0.27	3.2 ± 0.27**
Water	65.0 ± 0.69	66.9 ± 0.68*
Ash	3.2 ± 0.44	3.3 ± 0.04^{NS}

after the administration of β-agonists would be mediated by a reduction in protein degradation with little or no changes in protein synthesis (2, 11, 17), with a single exception (4). The effects of orciprenaline are similar in various aspects to those observed with B_2 agonists. However, any comparison have to be made with caution, bearing on mind the differences in species, body size, maturity, route of administration and receptors specificity (11).

It can be concluded that the non-selective β-agonist orciprenaline has a direct effect on muscle mass involving a phenomenon of hyperplasia accompanied by a reduction in cell size, while liver shows a clearly differenciated pattern since no changes in the nucleic acid content were found. Investigations about these newly described actions of β-agonists on muscle protein metabolism should be useful in developing antiobesity, antidistrophy and growth-promoting agents.

Key words: β-Agonist, Muscle, Liver, Protein turnover, Nucleic acids.

Palabras clave: β-agonista, Músculo, Hígado, Metabolismo proteico, Acidos nucleicos.

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