to take place in supraoptic nucleus and median eminence in photosensitive birds exposed to prolonged daily photoperiods[9,10], and correlated to an increased gonadotropin release.

As dehydration implicates antidiuretic hormone release associated with depletion of neurosecretory material, a similar parallel can be drawn between the augmented phosphatase activity and the liberation of the octapeptide from the neurosecretory cells. This relation seems moreover strengthened by the fact that the breakdown of neurosecretory material from the pars nervosa of dehydrated mice has been seen to correspond with deformed and ruptured membranes of neurosecretory granules[8]. Acid phosphatase is apparently localized in lysosomes, a sub-cellular particle engaged, among other activities, in programmed cellular breakdown taking place in cases of apocrine and holocrine secretion[11]. Since optical[12] and ultrastructural[13–15] observations on neurosecretory systems of several species, including the rat[16,17], suggest that the release of neurosecretory material is made through a holocrine or apocrine mechanism, the increased hypothalamic acid phosphatase activity, reported in the present paper, provides a reliable biochemical basis for these morphological findings.

Resumen. Se constató un aumento significativo en el contenido de fosfatasa ácida del hipotálamo de ratas deshidratadas; estos resultados se discuten en relación a posibles mecanismos de secreción apócrina de las células neurosecretoras.

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The Role of the Pentose-Phosphate Pathway in Adjustment of the Heart to a High Load and the Development of Myocardial Hypertrophy

The compensatory hypertrophy represents an essential factor in adjustment of the heart to a prolonged increase of physiological load in deficiency, hypertension and intense physical work. The development of the compensatory hypertrophy proceeds on the base of a significant increase of the synthesis of nucleic acids and proteins in the myocardium. This ensures not only a timely replacement of worn myocardial structures but also a rapid augmentation of the mass of the myocardium[1].

Apparently the activation of the biosynthesis of nucleic acids and proteins in the myocardium in its hyperfunction is reached by way of coordinated increase of activity of a number of fermentative systems. It may be suggested that an important role in realization of these processes must belong to pentose-phosphate pathway as far as this metabolic process is the fundamental source of reduced NADP-H_2 and riboso-5-phosphate for the nucleic acids and protein synthesis.

In this connection, in the present work the change of activity of one of the most important ferments of the pentose pathway, transketolase, in the hyperfunction of the heart has been studied. Simultaneously the study of action of the antagonist of vitamin B_1 – oxythiamine, on the transketolase activity, protein synthesis and hypertrophy of the heart in its hyperfunction has been carried out.

The compensatory hyperfunction of the heart was experimentally produced in rabbits by creation of stenosis of the aorta with the earlier described method[1] ensuring a persistent narrowing of the transverse section of the aortic lumen 3 times. The activity of the transketolase was determined by the method of BRUNS[2] in control animals and in rabbits with hyperfunction of the heart 2 and 45 days following creation of stenosis.

As seen from Table I, 2 days following the onset of hyperfunction when the processes of biosynthesis of nuclear acids and proteins[3,4] in the myocardium are sharply intensified, the activity of transketolase in this organ is increased by more than 60%. Following 45 days when the process of hypertrophy is essentially completed, the transketolase activity decreases, approaching the normal level.

Apparently, these changes are specifically connected with the compensatory hypertrophy of the heart. They take place only in the myocardium and are lacking in other tissues, for instance in blood.

The close correlation between the activity of transketolase and the intensity of development of the myocardial hypertrophy is revealed in the analysis of data relating to different animals at the initial stage of hyperfunction and hypertrophy of the heart. From the Figure it is seen that the higher the activity of transketolase in the myocardium of the animal, the more increased the relative weight of the left ventricle, i.e. the more intense the development of the process of hypertrophy.

This suggests that activation of the transketolase is apparently one of the links of the biochemical mechanism of hypertrophy of the myocardium in its compensatory hyperfunction.

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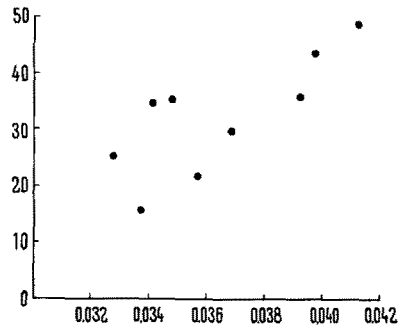
The increase of the synthesis of nucleic acids and proteins in the myocardium at the initial stage of hyperfunction underlying its hypertrophy certainly requires an increased inflow of precursors, in particular that of riboso-5-phosphate produced in the course of pentose-phosphate way of splitting of the carbohydrates. The majority of the riboso-5-phosphate necessary to the cell is formed from glucose-6-phosphate in the non-oxidative reactions of pentose-phosphate way catalyzed by transketolase and transaldolase[5-9]. The evidence obtained of the increase of activity of transketolase in the hypertrophied myocardium together with the data presented by other authors on the low activity of transketolase as compared to other ferments of the pentose-phosphate way[10,11], suggest that transketolase limits the rate of formation of riboso-5-phosphate. In the normal myocardium, the capacity of this enzyme seems to ensure the current requirements of metabolic processes in riboso-5-phosphate, but it does not create any reserve sufficient for a considerable increase of production of this metabolite.

In this connection, the increase of activity of the transketolase at the initial stage of hyperfunction of the heart apparently represents an indispensable condition for the increase of production of riboso-5-phosphate and the intensity of nucleic acids and protein synthesis for the replacement of worn structures and a simultaneous increase of the absolute mass of the myocardium.

Such a concept of the role of the transketolase is in agreement with the results obtained in the experiment with the antagonist of vitamino B_1-oxythiamine. As shown by the data presented in Table II, injection of oxythiamine in doses of 100–400 mg/kg daily to rabbits with experimental aortic stenosis inhibits the activity of transketolase and at the same time abolishes the activation of protein synthesis, thus essentially slowing down the myocardial hypertrophy.

The action of oxythiamine on the octivity of the transketolase incorporation of S^{35}-methionine into the proteins of the myocardium and the relative weight of the left ventricle in rabbits with experimental aortic stenosis.



Correlation between the activity of transketolase and the intensity of myocardial hypertrophy in rabbits at the initial stage of hyperfunction of the heart. Abscissa: Relative dry weight of the left ventricle in % of the body weight. Ordinate: Activity of the transketolase in sedoheptuloso-7-phosphate/h/g of dry tissue.

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Table I. Change of transketolase activity in compensatory hypertrophy of the heart

Examined index	Control	Compensatory hypertrophy	
		2 days	45 days
	I	II	III
Relative weight of the left ventricule in %	0.149 ± 0.005	0.178 ± 0.009	0.210 ± 0.008
Activity of transketolase in the myocardium, of sedoheptulose-7-phospate/h/g of fresh tissue	4.08 ± 0.06 (s-7-p)	6.65 ± 0.06 pI-II 0.02	5.00 ± 0.07
Activity of transketolase in blood of S-7-P/h/ml of blood	8.20 ± 0.36	7.55 ± 0.30	8.10 ± 0.42
No. of animals	7	8	7

Table II. The action of oxythiamine on the activity of the transketolase, incorporation of S^{35}-methionine into the proteins of the myocardium and the relative weight of the left ventricle in rabbits with experimental aortic stenosis

Examined index	Without oxythiamine		With oxythiamine	
	Control	Stenosis	Control	Stenosis
Activity of transketolase, of S-7-P/g/h	4.40 ± 0.05	6.22 ± 0.35	0.83 ± 0.17	0.60 ± 0.07
Relative specific activity of protein	3.20 ± 0.13	7.40 ± 0.79	2.65 ± 0.25	3.00 ± 0.60
Relative weight of the left ventricle, %	0.154 ± 0.005	0.192 ± 0.007	0.159 ± 0.008	0.165 ± 0.007
No. of animals	5	6	5	5

The inhibition of protein synthesis and myocardial hypertrophy by oxythiamine may be caused by disturbance of the synthesis of nucleic acids as a result of the inhibition of the transketolase and pentose-phosphate pathway, as well as by inhibition of the energy production due to the depression of ferments associated with vitamin B_1, e.g. pyruvate- and ketoglutarate dehydrogenase which catalyse the oxidating decarboxylation of keto acids. However, this latter explanation seems to be less plausible since, in disturbance of utilization of the carbohydrates, the myocardium may largely use, as a source of energy, fatty acids, the oxidation of which avoids the reaction of the oxidative decarboxylation of the keto acids[12,13].

On the whole the present results support the suggestion of the important role of the pentose-phosphate pathway in activation of nucleic acids and protein synthesis which underlies the hypertrophy and the adjustment of the heart to a sustained load.

Выводы. У кроликов с гиперфункцией сердца, вызванной экспериментальным стенозом аорты, активация синтеза нуклеиновых кислот и ьелков в миокарде сопровождается резким повышением активности транскетолазы - фермента пентозо-фосфатного пути превращения глюкозы - в миокарде. Подавление транскетолазы специфическим ингиьитором окситиамином полностью снимает активацию синтеза нуклеиновых кислот и тормозит развитие гипертрофии миокарда.

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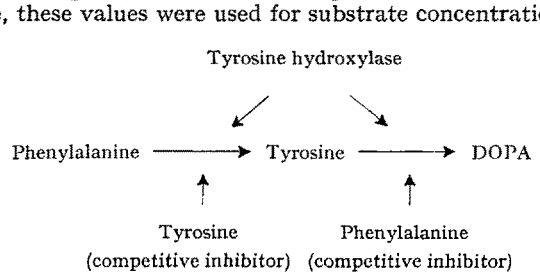
The Effect of High Phenylalanine Concentration on the Formation of DOPA from Phenylalanine and Tyrosine by Tyrosine Hydroxylase

IKEDA, LEVITT and UDENFRIEND[1] reported that the hydroxylation of phenylalanine to tyrosine is also catalysed by tyrosine hydroxylase[2], which catalyses the conversion of tyrosine to DOPA, the initial step of biosynthesis of norepinephrine, in brain and sympathetically innervated tissues. They found that phenylalanine and tyrosine are competitive inhibitors of the enzyme[1]. It has been suggested that in phenylketonuria huge amounts of phenylalanine may inhibit norepinephrine formation by competing with tyrosine on tyrosine hydroxylase[2]. However, it is not clear since phenylalanine also produces DOPA[1]. A theoretical and experimental study as to the effect of large amounts of phenylalanine on the formation of DOPA from both phenylalanine and tyrosine by tyrosine hydroxylase is reported in this communication.

In the theoretical kinetic treatment, the following values were used from the report of IKEDA, LEVITT and UDENFRIEND[1]: Km for phenylalanine, $3 \cdot 10^{-4} M$; Km for tyrosine, $5 \cdot 10^{-5} M$; V_{max} for tyrosine/V_{max} for phenylalanine, 20/1. Blood concentration of tyrosine and phenylalanine in health and that of tyrosine in phenylketonuria is about $1 \cdot 10^{-4} M$, whereas that of phenylalanine in phenylketonuria is as high as $3 \cdot 10^{-3} M$. Therefore, these values were used for substrate concentrations.



To calculate the amount of DOPA formed through the above-mentioned process[3], following symbols are used: P, concentration of phenylalanine; T, concentration of tyrosine; D, concentration of DOPA; K_P, Michaelis constant for phenylalanine; K_T, Michaelis constant for tyrosine; V_P, V_{max} for phenylalanine; V_T, V_{max} for tyrosine; t, time.

$$x = \frac{P}{K_P}, \qquad y = \frac{T}{K_T}, \qquad z = \frac{D}{K_T},$$

$$x' = \frac{dx}{dt}, \qquad y' = \frac{dy}{dt}, \qquad z' = \frac{dz}{dt},$$

$$a = -\frac{V_P}{K_P}, \qquad b = \frac{V_P}{K_T}, \qquad c = \frac{V_T}{K_T}.$$

The decrease of phenylalanine is expressed by LINEWEAVER-BURK equation[4] in the presence of a competitive inhibitor, tyrosine

$$\frac{dP}{dt} = -\frac{V_P}{1 + \frac{K_P}{P} + \frac{K_P}{P} \cdot \frac{T}{K_T}}$$

and is rewritten as

$$x' = \frac{a}{1 + \frac{1}{x} + \frac{y}{x}} = \frac{a\,x}{1 + x + y}.$$

The variation of tyrosine concentration dT/dt is expressed as the difference of 2 LINEWEAVER-BURK equations in the presence of competitive inhibitors

$$\frac{dT}{dt} = \frac{V_P}{1 + \frac{K_P}{P} + \frac{K_P}{P} \cdot \frac{T}{K_T}} - \frac{V_T}{1 + \frac{K_T}{T} + \frac{K_T}{T} \cdot \frac{P}{K_P}}$$

The first term in the right side is the one for tyrosine formation from phenylalanine and the second term is the