Data on survival of the mice in Table 2 are given for the first 3 days after injection of the serum, for the number of mice was unchanged on the following days. Dog serum remained pathogenic for the first 3 days, rabbit serum for 7 days.

The data in Table 3 are evidence of active involvement of the mast cell system in the general reaction of the organism and of the rapid decline in activity of this system during hyperthermia by the scheme adopted. This is shown by the presence of a large number of cells which had completely or partly exhausted their functional powers. The evident predominance of cells of group I until the 7th day, subsequently giving way to a tendency for restoration of the initial ratio between them, suggests that hyperthermia has a stimulating action on mast cell production.

This demonstration of the toxic properties of the serum and considerable exhaustion of one of the physiological mechanisms of immediate defense are evidence of the systemic character of the pathogenesis of hyperthermia.

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HYPOCLYCEMIC EFFECT OF EXCESS OF THYROID HORMONES IN INSULIN-DEFICIENT RATS

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KEY WORDS: thyrotoxicosis; diabetes mellitus; glucose; free fatty acids; insulin.

The view is widely held that hyperthyroidism aggravates the course of diabetes mellitus [1, 7, 9]. However, it has been shown that experimental thyrotoxicosis is accompanied not only by inhibition of insulin secretion, with "disinhibition" of hepatic glucose production, but also by an insulin-independent acceleration of glucose utilization by extrahepatic tissues and, in particular, by muscles [4, 11]. This effect is manifested particularly clearly when the liver is "excluded" from the circulation [3, 10].

Assuming that the aggravating effect of an excess of thyroid hormones on the course of diabetes mellitus may be connected with inhibition of the residual secretion of insulin, it

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TABLE 1. Parameters of Carbohydrate and Lipid Metabolism in Fasting (I) and Satiated (II) Rats (M ± m)

Experimental conditions	Blood sugar, mg/100 ml		Blood FFA, μeq/ml		Glucosuria, g/day	IRI concentration, microunits/ml	
	I	II	I	II		I	II
Control	78±2,3	114±9,8	0,38±0,03	0,18±0,02	—	24±2,6	50±6,1
Thyrotoxicosis	77±4,7	150±10,6*	0,56±0,04*	0,28±0,03*	—	16±2,1*	25±3,2*
Streptosotocin diabetes	254±10,8*	569±16,4*	0,52±0,05*	0,25±0,04*	3,51±0,3	0	0
Streptosotocin diabetes + thyrotoxicosis	99,4±11,3	374±12,1*	0,54±0,04*	0,27±0,05*	2,52±0,3*	0	0

*P < 0.05 compared with control; mean values obtained from results of experiments on 6-10 animals.

was decided to attempt to show that thyrotoxicosis in animals with total insulin deficiency is accompanied by a fall in the degree of hyperglycemia.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing initially 160-210 g. Streptosotocin (from Calbiochem, USA) was injected into the animals' jugular veins in a dose of 80 mg/kg. The substance was dissolved in 0.01 M citrate buffer, pH 4.0. The rats were kept on the ordinary animal house diet. On the 5th-8th days after injection of streptosotocin, the glucose concentration in the blood serum of the fasting animals (deprived of food for 12-14 h) and also 1 h after access to food was determined (by the glucose oxidase method, using an analyzer from Beckman, USA). In the next experiment rats with a fasting blood sugar level of not less than 180 mg/100 ml were selected. The serum immunoreactive insulin (IRI) level was determined by the double antibody method [13], using radioimmunoanalytical kits (Hungary); the serum free fatty acid (FFA) concentration was determined by Duncombe's method [6]. Animals with hyperglycemia were given daily subcutaneous injections of L-thyroxine (from Reanal, Hungary) in a dose of 400 μg/100 g body weight for 3 days. The preparation was dissolved in alkalified physiological saline, which was subsequently neutralized. The development of acute thyrotoxicosis as a result of this measure was monitored by the appearance of tachycardia (mean increase in heart rate 15%) and the loss of body weight (mean decrease 12%). In the 24 h before the end of the experiment the animals were placed in metabolism cages and the urine was collected; after sugar had been detected by a qualitative test in the urine its concentration was measured quantitatively. At the end of the experiment the fasting and satiated rats were decapitated and the concentrations of glucose, IRI, and FFA in the blood serum were again determined. Besides intact rats and animals with hyperglycemia receiving injection of physiological saline, rats receiving injections of L-thyroxine without preliminary administration of streptosotocin also served as controls.

EXPERIMENTAL RESULTS

The results showed (Table 1) that, in agreement with the results obtained previously on rabbits with experimental thyrotoxicosis [4], injection of large quantities of thyroxine into rats even for a short time leads to a fall in the initial serum IRI concentration. The reaction of insulinemia to the taking of food also was depressed. Inhibition of insulin secretion under these conditions also was confirmed by the rise in the fasting serum FFA level, which could indicate "disinhibition" of lipolysis in the adipose tissue, a sign of insulin deficiency. It is demonstrative, however, that no hyperglycemia was observed under these circumstances in the fasting animals. In rabbits with a longer duration of experimental thyrotoxicosis a tendency toward hypoglycemia actually was observed [4]. This evidently confirms the view that an excess of thyroid hormones has a twofold action on carbohydrate metabolism: a simultaneous increase in both production and utilization of glucose. In the early stages of hypermetabolism, increased hepatic sugar production may completely allow (or even more than allow) for its more rapid utilization, whereas with intensification of hypermetabolism the latter effect predominates. However, the fact must be noted that after rats receiving thyroxine took food, their blood sugar rose by a greater degree than that of intact animals. This also can be connected with the reduced ability of the "thyrotoxic" liver to eliminate glucose from the blood [3, 4].

Streptosotocin diabetes in rats was characterized by high hyperglycemia both in the fasting state and, in particular, after taking food. Large quantities of sugar also were found in the urine. The FFA concentration in the serum also rose, indicating distinct insulin deficiency. Direct determinations of IRI in fact revealed no significant quantities of it in the blood serum. The severity of damage to the β-cells of the insular apparatus also was manifested by the absence of any increase in the IRI concentration after feeding. It can evidently be concluded that under the experimental conditions used severe diabetes with absolute insulin deficiency were present.

Assuming that under these conditions an excess of thyroid hormones could no longer cause any further decrease in insulin secretion and, consequently, no further increase in the supply of glucose into the blood stream, it was argued that this could mean a distinct manifestation of a second, insulin-independent, effect of hypermetabolism, i.e., the appearance of a hypoglycemic effect, linked with accelerated sugar utilization.

As the results in Table 1 (the last column) show, this hypothesis was completely confirmed. In the presence of damage to the pancreatic β-cells by streptosotocin, injection of thyroxine naturally did not change the parameters of insulin secretion. The FFA concentration in the blood serum also remained raised. However, the blood sugar level fell considerably. This was demonstrated both in the fasting state and after feeding, although in the latter case the effect of hypermetabolism was weaker than against the background of starvation. Excess of thyroxine had no hypoglycemic action, evidently because of lowering of the renal threshold for sugar, since "pure" thyrotoxicosis was not accompanied by glucosuria, and in combined pathology not only the blood sugar but also the glucosuria was reduced.

When these results are analyzed, attention must be paid to the fact that under the conditions of thyrotoxicosis the inhibitory action of an excess of FFA on glucose utilization (Randle's cycle [12]) was not manifested. In fact, with the same FFA level in the blood serum, the blood sugar in streptosotocin diabetes was found to be much higher than in the presence of combined pathology. These data agree with results obtained previously, according to which hypermetabolism significantly weakens competition between glucose and FFA at the level of the peripheral tissues [2, 5].

Excess of thyroid hormones thus increases sugar utilization in the body independently of the action on insulin. Just as the shifts in carbohydrate metabolism in thyrotoxicosis and in other states characterized by enhancement of oxidative metabolism (during physical work, for example, [8]) exhibit considerable similarity, so also evidently hypermetabolism, by reducing the effectiveness of the Randle cycle, accelerates utilization of carbohydrate substrates. There are strong grounds for considering that inhibition of insulin secretion under these conditions is a compensatory reaction, maintaining the supply of oxidation substrates to the tissues. From this standpoint, the principal physiological role of insulin in the body may be not to provide for utilization of glucose by peripheral tissues (as is generally considered at present), but to inhibit the production of glucose and FFA for supply to the blood stream. This view is confirmed by the considerable difference in insulin concentrations required to carry out its two effects [14].

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TRANSFORMATION OF THE CHOLINOLYTIC EFFECT OF ATROPINE ON THE DENERVATED HUMAN SALIVARY GLAND INTO CHOLINOMIMETIC DURING REFLEX STIMULATION*

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In previous communications an atropine salivatory paradox was described, namely extremely intensive secretion of saliva, high in amplitude, steady and protracted, in response to small and ordinary doses of atropine by the denervated human parotid salivary gland, reproducible for many years [1, 2]. Denervation occurred after trauma to the base of the skull, a fracture of the petrous part of the temporal bone, and operations and pathological processes in the zone of the tympanic cavity. Disappearance of unconditioned secretion and increased sensitivity to cholinomimetics, i.e., reflex-humoral dissociation, are characteristic of the first, milder stage of denervation, arising 10-14 days after acute trauma. Later, however, after 1-2 months or sometimes after a few years, a more profound degree of denervation develops progressively and responses to cholinolytics (atropine, scopolamine, oxyphenonium) 20-30 min after subcutaneous injection are reversed, i.e., a clear form of atropine paradox is observed. In some patients (35 subjects) the denervation syndrome did not progress, i.e., stage I of denervation was stabilized. In 55 subjects the paradox was seen in a clear form.

In 20 subjects the paradox was masked or latent in type, and to bring it to light additional stimulation (induction) by a very weak food or acid stimulus was necessary in addition to atropinization.

Let us examine this latent form of atropine paradox, not previously described. The group of subjects consisted of 12 patients with injury to the base of the skull, five patients after radical operation on the ear for chronic suppurative otitis with caries of the walls of Fallopius' canal, two patients after removal of an acoustic neurinoma (previously suffering from chronic otitis), and one patient with a glomus tumor of the petrous temporal bone. In the last three patients the level of paradoxical secretion was depressed because the patients had not been treated by x-ray therapy (in the parotid region).

EXPERIMENTAL METHOD

The technique includes elements of restorative therapy because atropine is widely used for the treatment of craniocerebral trauma [8]. Durgs acting on the autonomic nervous system were used (in small doses) to characterize autonomic functions and to determine the level of the lesion, the time course and progressiveness of the disease, and its stability or restitution. Lashley-Krasnogorskii capsules were fixed on the efferent ducts of the parotid glands on the denervated and normal (control) sides. Secretion was recorded as follows: spontaneous, in response to swallowing 30 ml of 0.5% citric acid, after subcutaneous injection of cholinomimetics (0.5 ml of 1% pilocarpine, 0.5 ml of 1:5000 carbachol), after injection of

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