6. S. N. Golikov, É. P. Zatsepin, M. A. Levshunova, et al., in: Pharmacology of Central Cholinolytics and Other Neurotropic Agents [in Russian], Leningrad (1969), p. 10.
7. V. A. Gusel', "Experimental study of the efficacy of pharmacological agents which interact with cholinergic systems in psychomotor epilepsy," Doctoral Dissertation, Leningrad (1975).
8. V. A. Gusel' and S. A. Sverdlov, Trudy Leningrad Nauch.-Issled. Psikhonevrol. Inst. im. V. M. Bekhtereva, 68, 45 (1974).
9. I. S. Zavodskaya, in: The Pharmacology of New Therapeutic Agents [in Russian], Leningrad (1953), p. 56.
10. A. N. Zaidel', Elementary Evaluation of Errors of Measurements [in Russian], Leningrad (1968).
11. N. A. Losev, "Pharmacological analysis of α- and β-derivatives of benactyzine and adiphenine," Candidate's Dissertation, Leningrad (1967).
12. N. A. Losev, Farmakol. Toksikol., 35, 544 (1972).
13. N. A. Losev, Fiziol. Zh. SSSR, 44, 1182 (1978).
14. M. Ya. Mikhel'son and Ya. R. Savinskii, Farmakol. Toksikol., 16, 57 (1953).
15. G. F. Rzhevskaya, "Pharmacological properties of phosphorylated acetals, aldehydes, and hydrazides," Doctoral Dissertation, Kazan' (1973).

SEROTONIN TURNOVER IN THYROTOXICOSIS

S. N. Fedchenko

UDC 616.441-008.61-07:616.313-008.94:577.175.823

KEY WORDS: stomach; serotonin-producing cells; thyrotoxicosis.

An important role in mechanisms of regulation of the function of the endocrine glands, including the thyroid, is played by biogenic amines, among which serotonin is particularly important. Information published on this subject is contradictory: Some data indicate an inhibitory effect of serotonin on thyroid function [1], whereas others support the view that serotonin activates thyroid function and is directly related to the synthesis and secretion of thyroid hormones [2, 3]. Accordingly an unambiguous answer to the question of serotonin turnover in thyrotoxicosis cannot be obtained.

For the above reasons, and also in view of the role of serotonin in the regulation of gastric secretion [4, 5, 8], in the investigation described below the state of the serotonin turnover was studied in experimental thyrotoxicosis.

EXPERIMENTAL METHOD

Mature male Wistar rats weighing 180-200 g were used. Experimental hyperthyroidism was produced by intraperitoneal injection of 2.5 mg/kg of thyroxine daily for 10, 20, or 30 days. Sixteen animals were used in each group. The corresponding volume of physiological saline was injected into control animals, kept under similar conditions. Serotonin-producing (enterochromaffin) cells (EC cells) were identified and their functional activity estimated by the method described previously [6]. EC cells were counted in an area of 1 mm^2 of longitudinal section through the gastric mucosa. The serotonin concentration in the mucosa, in whole blood, and in the gastric juice was determined by the method in [7]. To assess the morphometric and biochemical data, correlation analysis was used. From the total number of correlations, average (coefficient of correlation r = 0.5-0.69), strong (0.70-0.89), and strongest, or functional (0.9-1.0) were selected.

Central Research Laboratory, Grodno Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Kupriyanov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 95, No. 5, pp. 25-28, May, 1983. Original article submitted August 16, 1982.

TABLE 1. Parameters of Functional State of EC Cells in Mucosa of Pyloric Portion of Stomach of Normal Rats and Rats Receiving Thyroxine

Experimental conditions	Number of cells detected in 1 mm² area of measurement	P	Granulation index	P	Saturation index	P
Control	72±5		122±8		1,69±0,04	
Injection of thyroxine, 2.5 mg/kg daily for:						
10 days	97±4	<0,01	290±11	<0,01	2,98±0,03	<0,01
20 days	155±11	<0,01	425±17	<0,01	2,74±0,07	<0,01
30 days	148±12	<0,01	163±10	<0,01	1,10±0,04	<0,01

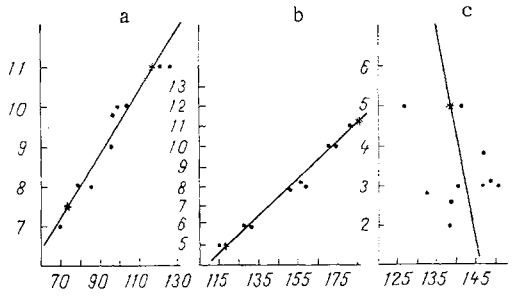

Fig. 1. Correlation between number of EC cells detected (abscissa) and serotonin content in mucosa of antral portion of stomach (ordinate) following administration of thyroxine (2.5 mg/kg) daily for 10 days (a), 20 days (b), and 30 days (c). a: $r = 0.97$, $y = -15.90 + 12.20x$, $P < 0.01$ ($n = 10$); b: $r = 0.99$, $y = 65.60 + 10.60x$, $P < 0.01$ ($n = 10$); c: $r = -0.31$, $y = 149.00 - 2.30x$.

EXPERIMENTAL RESULTS

Injection of thyroxine for 10 and 20 days led to an increase in the number of EC cells detected in the mucosa of the pyloric portion of the stomach (Table 1) and to an almost threefold increase in the granulation index and the saturation index.

Ultrastructural analysis of EC cells in the stomach of rats receiving thyroxine for 10 and 20 days confirmed that most EC cells were in a state of increased functional activity, as has been shown after injection of hydrocortisone and thyroxine [6].

Injection of thyroxine for 10 and 20 days increased the serotonin concentration in the mucosa of the pyloric portion of the stomach by 77 and 47% respectively; the serotonin concentration in the blood under these circumstances was increased to 397 and 229%. Comparison of the results of histochemical and electron-microscopic investigations with the results of biochemical analysis revealed the following correlation: The increase in the number of detectable EC cells corresponded to the rise in the serotonin level in the mucosa of the pyloric portion of the rats' stomach ($r = 0.97$ and $r = 0.99$, respectively, Fig. 1).

The increased number of EC cells detected, the increased granulation index, and the increased index of saturation of the cytoplasm of the EC cells with granules, and also the corresponding ultrastructural characteristics of these cells, coupled with the biochemical data (increased concentration of serotonin in the blood and gastric mucosa), are probable evidence of intensified functional activity of the EC cells of the rat stomach after administration of thyroxine for 10 and 20 days.

During prolonged hyperthyroidization, despite the fact that the number of EC cells detected was increased, as before, the granulation index and saturation index were reduced by more than 1.6 times (Table 1).

Ultrastructural analysis of the EC cells showed that most of them were degranulated. In some EC cells all stages of destructive changes could be observed: spatial disintegration of the tubules of the endoplasmic reticulum, focal dilatation of the tubules, the appearance of

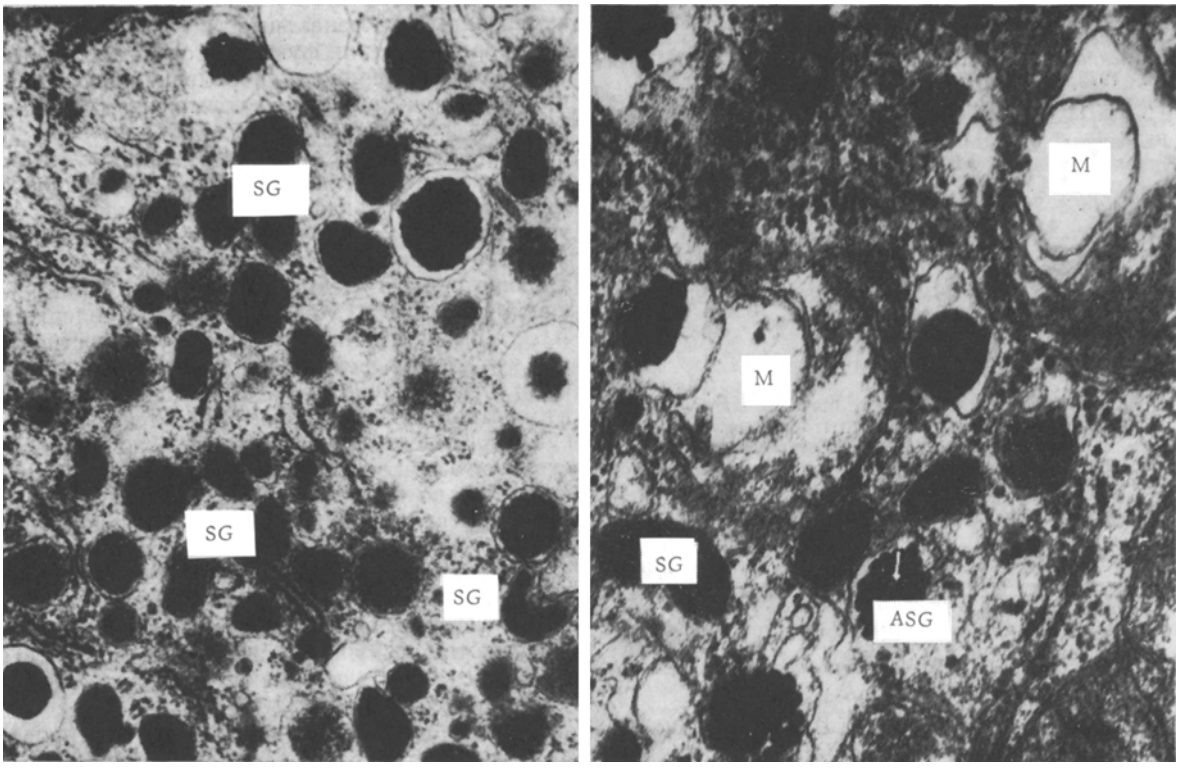

Fig. 2. Ultrastructure of enterochromaffin EC cells in the stomach of an intact rat (a) and a rat receiving thyroxine (2.5 mg/kg) daily for 30 days (b). Matrix of mitochondrion (M) translucent and homogeneous; besides typical secretory granules (SG), cytoplasm of cell also contains atypical secretory granules (ASG) resembling a mulberry (arrow). 50,000 ×.

numerous phagosomes, swelling of the mitochondria, and conversion of their matrix into floccular substance. Atypical secretory granules with a mulberry-like appearance were seen in the cytoplasm of these cells (Fig. 2b).

The results of the biochemical tests showed that hyperthyroidization for 30 days was accompanied by a fall in the serotonin level in the mucosa of the pyloric portion to 57% compared with the control. The study of correlation between the number of detectable EC cells and the serotonin level in the mucosa of the pyloric portion of the stomach showed the presence of negative correlation ($r = -0.31$) (Fig. 1).

The raised serotonin level in the gastric mucosa of rats in the early stages of hyperthyroidism may be due, first, to activation of synthesis of this biogenic amine in EC cells (this conclusion is based on both histochemical and ultrastructural data). Second, one possible cause of elevation of the gastric serotonin level could be storage of this biogenic amine. Finally, blockade of serotonin release from the EC cell, due to an excess of thyroid hormones in the body and to activation of a negative feedback mechanism, may also be possible, for we know that serotonin stimulates the synthesis and secretion of iodinated thyronines. During prolonged hyperthyroidization, lowering of the serotonin level in the gastric mucosa may be the result both of sudden release of serotonin from the depots (EC cells) and of a disturbance of granule formation, reflecting the breakdown of the negative feedback mechanism.

These results may be interesting for clinicians as a basis for a diagnostic test for determination of the severity of thyrotoxicosis.

LITERATURE CITED

1. M. D. Kurskii and A. N. Fedorov, Usp. Sovrem. Biol., 67, No. 2, 190 (1969).
2. E. V. Naumenko and N. K. Popova, Serotonin and Melatonin in the Regulation of the Endocrine System [in Russian], Novosibirsk (1975).
3. V. V. Natarov, E. S. Rom-Boguslavskaya, and M. R. Ozerova, Probl. Éndokrinol., No. 1, 16 (1981).

4. V. M. Uspenskii, V. G. Ivashkin, and G. I. Dorofeev, Klin. Med., No. 11, 37 (1975).
5. I. D. Frenkel' and I. V. Komissarova, Ter. Arkh., No. 2, 142 (1975).
6. S. N. Fedchenko, Arkh. Anat., No. 12, 76 (1977).
7. V. N. Kulinskii and L. S. Kostyukovskaya, Lab. Delo, No. 7, 390 (1969).
8. S. Canfield and J. Spencer, Br. J. Pharmacol., 74, 253 (1981).

EXPERIMENTAL TREATMENT OF ACUTE RENAL FAILURE WITH PROSTENON, A SOVIET PROSTAGLANDIN E_2*

R. M. Glants, B. V. Kachorovskii, V. L. Turchin, I. O. Kushch, B. R. Kotsai, and L. V. Mudrovskaya

UDC 616.61-008.64-036.11-092.9-085. 357:577.175.859

KEY WORDS: acute renal failure; prostaglandin E_2.

As a result of the use of hemodialysis, hemoperfusion, and gravitational surgery [3] the treatment of acute renal failure (ARF) has improved considerably, but even now the mortality from this disease is 40% [12]. Hence the importance of developing methods of treatment of ARF which would restore kidney function.

One cause of ARF is transfusion of patients with incompatible blood. Under these circumstances blood transfusion shock develops and goes on to ARF. Moreover, blood transfusion shock is regarded as the first stage of ARF [1] and, consequently, experimental heterologous transfusion provides a model of ARF which corresponds to the clinical form. The writers showed previously that during complications of blood transfusion, changes take place in all renal and extrarenal factors controlling kidney function: The adrenalin concentration in the kidney rises and this correlates with an increase in functions of the blood clotting and fibrinolysis system (the sympathico-adrenal system) [7], changes take place in the function of the endocrine system (anterior and posterior lobes of the pituitary, adrenal medulla, and cortex, endocrine part of the pancreas) [4], and metabolism is disturbed [9]. Heterologous blood transfusion causes changes in all components of the kinin system [2] and raises the serum ADH level in dogs [8]. Prostaglandin (PG) E_2, which has a selective vasodilator action on vessels of the renal cortex and medulla, so that not only is the total blood flow increased but it is redistributed, with a relative decrease in cortical blood flow, also has maximal activity in the kidney. PG released under the influence of catecholamines are their physiological antagonists and, like ADH and ACTH, PG interact with the kinin system and the sympathicoadrenal system [13]. They restore normal metabolism, especially protein metabolism, in the organs and tissues and depress the functional state of the sympathicoadrenal system in the kidney [10].

The facts described above are the basis for the use of PGE_2 in the experimental treatment of ARF.

EXPERIMENTAL METHOD

PGE_2 of Soviet origin (prostenon), synthesized in the Sector of Pure Substances, Academy of Sciences of the Estonian SSR (Professor J.E. Lille) was used. ARF was induced in dogs by a method developed in the laboratory: After massive blood loss (20-25 ml/kg) heterologous blood (human blood, 25-30 ml) was transfused. The animals developed heterologous transfusion shock, which turned into ARF, as shown by the severe oliguria or anuria, the sharp rise in the blood urea (to 64.185 mM), an increase in the plasma potassium concentration (to 6.477 mM), and a decrease in the sodium concentration (to 127.000 mM) and the blood alkaline reserve (to 126.10 meq/liter) [6]. Experiments were carried out on 20 female mongrel dogs weighing

*Presented at the First All-Union Conference on "Synthesis and Investigation of Prostaglandins" held in Riga on September 30, 1982.

Experimental Department, L'vov Research Institute of Hematology and Blood Transfusion.
(Presented by Academician of the Academy of Medical Sciences of the USSR N. A. Fedorov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 95, No. 5, pp. 28-29, May, 1983. Original article submitted October 25, 1982.

 0007-4888/83/9505-0596$07.50