PHYSIOLOGY

Effect of the Parathyroid Hormone—Calcium System on Functional Activity of the Hypothalamus-Neurohypophysis Complex

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The effect of single and repeated parenteral administration of parathyroid hormone on the protein synthesis in neurosecretory cells of the supraoptic nucleus and on the blood vasopressin content is studied. The hormone enhances the synthesis of RNA in the supraoptic nucleus and the blood vasopressin content, particularly after a single administration.

Key Words: *parathyroid hormone; calcium; vasopressin; RNA; hypothalamus; neurohypophysis*

Although the effect of parathyroid hormone (PTH) on various organs and systems has been extensively studied, the central mechanisms of its action so far remain obscure. In parathyroidectomized animals, functional activity of the hypothalamic supraoptic nucleus (SON) and vasopressin (VP) content are changed, which may result from the PTH deficiency and related processes [1,6]. In the present study we examined the direct effects of PTH on protein synthesis in the SON cells, and, consequently, on the synthesis and release of VP.

MATERIALS AND METHODS

Experiments were performed on male albino rats weighing 120-200 g. The rats were divided into three groups: group 1 were intact controls, group 2 consisted of rats receiving daily intravenous injections of PTH in a dose of 0.5 U/100 g body weight for 7 days, and group 3 included rats given the same dose of PTH in a single injection. The animals of group 3 were decapitated 30 min postinjection. The frontal hypothalamic area was fixed in formalin. Serial frontal paraffin sections were processed by routine morphological and histochemical methods (staining with hematoxylin and eosin and the method of Einarson with the RNA-specific dye halocyanide-chromium alum). The RNA content in the neurosecretory cells of SON was measured by the single-wave method in a LYuMAM-I2 apparatus (λ=550 nm, probe diameter 0.1 mm) and expressed in arbitrary optical units. Serum Ca^{2+} content was determined spectrophotometrically. The content of ionized calcium was measured with a Kone-Microlit ion-selective analyzer, inorganic phosphorus was measured using Bio-Lab-Test kits, and the VP content was determined in a radioimmunoassay with Buhlmann-Laboratories kits. The results were analyzed using Student's t test.

RESULTS

Chronic administration of PTH elevated serum content of ionized Ca^{2+} and lowered that of phosphorus (Table 1). The RNA content in neurosecretory cells of the SON increased from 0.95±0.03 to 1.38±0.01

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TABLE 1. Effect of Intramuscular Injection of PTH (0.5 U/100 g) on Serum Concentration of Total and Ionized Ca^{2+}, Phosphorus, and VP and RNA Content in Neurosecretory Cells of the SON

Parameter	Control (n=10)	PTH injection	
		single (n=8)	repeated (n=9)
Total Ca^{2+}, mM	2.07±0.03	2.02±0.03	1.98±0.04
Ionized Ca^{2+}, mM	0.77±0.01	0.79±0.03	0.93±0.02*
Phosphorus, mM	2.03±0.4	1.99±0.1	1.55±0.2
VP, ng/ml	5.7±0.2	31.1±2.1*	17.87±1.9*
RNA, arb. units	0.95±0.03	1.65±0.02*	1.38±0.01**

Note. *p<0.001, **p<0.01 in comparison with the control.

arb. units (p<0.01) and blood VP level rose from 5.7±0.2 to 17.78±1.9 pg/ml (p<0.001). A single administration of PTH increased the RNA content in the SON cells (to 1.65±0.02 arb. units), considerably elevated blood VP level (to 31.1±0.7 pg/ml), and had no effect on serum content of total and ionized Ca^{2+} and phosphorus.

Bearing in mind the ability of PTH to cross the blood-brain barrier [8,10] and interact with brain receptors [8], it can be suggested that the increase in the SON RNA content caused by chronic administration of PTH is linked to the stimulation of protein synthesis and, consequently, to enhanced synthesis and release of VP. This was confirmed by the finding that PTH increases the rate of the PTH RNA synthesis [4] and blood content of VP. The rapid rise of blood VP content in the absence of hypercalcemia after a single administration of PTH may testify to a direct effect of PTH on the plasma membranes of neurosecretory cells. This may account for the higher effect of a single PTH injection compared with that of chronic administration of PTH. For instance, experiments on isolated rat neurohypophysis revealed that depolarization of the supraoptic-neurohypophysis tract endings and enhanced calcium entry through the terminal plasmalemma cause a more rapid VP release from the VP—neurophysin complex into the incubation medium. This fact and the data on the depolarizing effect of PTH on neuronal membranes [13] and PTH-induced stimulation of $^{45}Ca^{2+}$ entry into frontal hypothalamic neurons [7] account for the effect of a single PTH injection on the blood level of VP. This phenomenon results from a rapid release of the readily-realized VP pool (about 20% of total hormone reserve in the hypophysis) into the circulation. On the other hand, activation of RNA synthesis is the earliest and strongest manifestation of the action of hormones, particularly of steroids, observed as soon as 10 min postinjection [11]. The excess of PTH caused by its chronic administration produces an opposite effect as a result of down-regulation and desensitization of PTH receptors. This is promoted by the excess of Ca^{2+} in physiological fluids [5]. Presumably, very high (pharmacological) concentrations of PTH aggravate these processes, which follows from the fact that intramuscular injections of PTH in a dose of 10 U/100 g for 1 week reduce the number of neurosecretory granules and block synaptic transmission in neurosecretory cells of the SON [2]. This should be taken into account in clinical application of the hormone.

Our findings suggest that the observed shifts result from the PTH-induced modulation of calcium-dependent processes at the level of membrane and intracellular structures, which are responsible for calcium transport and storing and activation of the enzyme systems involved in RNA, protein, and VP synthesis.

We previously described the PTH-induced activation of the mechanisms responsible for the transport of $^{45}Ca^{2+}$ across the plasma membrane [7], including potential-operated potassium channels of the neuronal membrane [3], and the effect of Ca^{2+} on RNA and protein synthesis in various tissues [9, 11,12].

The biological significance of PTH-induced activation of the synthesis and release of VP can be discussed in the light of consecutive involvement of PTH and VP in stress reaction [4]. The hypothalamo-neurohypophyseal system is triggered as a stress-realizing mechanism of adaptation following activation of the parathyroid glands and elevation of blood calcium. This promotes the onset of the resistance stage through an enhanced release of VP and direct activation of the secretion and release of adrenocorticotropic hormone and glucocorticoids. Thus, the PTH-induced activation of the synthesis and release of VP in the blood resulting from the stimulation of calcium-dependent and protein-synthetic processes suggests that the function of the hypothalamo-neurohypophyseal complex is strongly influenced by the PTH—Ca^{2+} system.

REFERENCES

1. A. A. Asratyan, S. V. Vladimirov, A. V. Aznauryan, and D. N. Khudaverdyan, *Arkh. Anat.*, **99**, No. 9, 31-34 (1990).
2. I. I. Babichenko, *Byull. Eksp. Biol. Med.*, **104**, No. 8, 231-235 (1987).
3. P. G. Kostyuk, B. A. Lukyanets, A. S. Ter-Markosyan, and D. N. Khudaverdyan, *Neurofiziologiya*, **22**, No. 3, 373-380 (1990).
4. V. D. Slepushkin, Yu. B. Lishmanov, G. K. Zeloev, and I. A. Prum, *Uspekhi Fiziol. Nauk*, **16**, No. 4, 106-118 (1985).
5. V. G. Shalyapina (Ed.), *Physiology of Hormonal Receptors* [in Russian], Leningrad (1986).
6. D. N. Khudaverdyan, A. A. Asratyan, S. V. Vladimirov, and A. V. Svishchev, *Probl. Endokrin.*, **38**, No. 1, 64-66 (1992).
7. D. N. Khudaverdyan, K. S. Kishoyan, A. A. Asratyan, *et al.*, *Neurofiziologiya*, **24**, No. 1, 113-115 (1992).
8. D. N. Khudaverdyan and A. S. Ter-Markosyan, *Uspekhi Fiziol. Nauk*, **23**, No. 1, 92-102 (1992).
9. M. P. Yavich, *Byull. Eksp. Biol. Med.*, **104**, No. 9, 290-292 (1987).
10. S. Balabanov, U. Toller, H. Ritcher, *et al.*, *Acta Endocrinol. Suppl. (Copenh.)*, **109**, No. 270, 118-125 (1985).
11. C. O. Brostom, S. B. Cjcckino, and M. A. Brostrom, *J. Biol. Chem.*, **258**, 14390-14399 (1983).
12. G. G. Gick and C. Bancroft, *Ibid.*, **260**, 7614-7618 (1985).
13. D. S. Mearws, *Endocrinology*, **88**, 7614-7618 (1971).

Extremely Low Doses of Oxytocin Reduce Pain Sensitivity in Men

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The effect of extremely low doses of oxytocin (vapor) on the perception of pain (pricking of the finger) is studied on 48 healthy volunteers. Inhalation of oxytocin vapor from the standard solution in doses producing a sensation of smell lowers pain threshold by 56.5%. Inhalation of oxytocin vapor creating no sense of smell has a lower hypalgesic effect. The oxytocin-induced hypalgesia is consistent with reduction in the heart reactivity to pain.

Key Words: *oxytocin; hypalgesia; pain*

Previously, we found that some compounds creating the sense of smell (odogens) [5] change the activity of the autonomic nervous system and the sensitivity of the olfactory analyzer [3]. On the basis of these findings it was hypothesized that odogens may modulate the perception of pain.

It was reported that parenteral administration of oxytocin (OT) produces an analgesic effect [6]. In the present study we examined the effect of extremely low (nanomolar) doses of OT applied as an odogen on the perception of pain by young healthy men.

MATERIALS AND METHODS

Forty-eight 18-24-year-old volunteers were enrolled in the study. Observations were carried out against the background of usual psychoemotional and physical activity of each individual during two preceding days, in the absence of changes in the nasal breathing, 1.5-2.5 h after the last meal, and a 2-h abstention from smoking.

A volunteer was lying on a couch with a high head-rest, wearing ear caps and a light-proof mask. Prior to the test, differential rheogram was recorded in a 4-RG-1-M apparatus and an EK 4T-02 electrocardiograph. The results were analyzed using Statgraphics software.

We studied how the subjective perception of pain caused by the pricking of the finger changes after inhalation of vapor from distilled water and an aqueous solution of OT in concentrations inducing and not inducing a sensation of smell. Pain was induced by pricking the 4th then the 3rd finger on the right hand with the use of a blood lancet.

The standard aqueous solution of OT (5 IU/ml, Gedeon Richter, 16 volunteers) and freshly prepared OT solution of a subthreshold concentration (0.02 IU/ml,

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