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CELLULAR MECHANISM OF PARATHYROID HORMONE ACTION ON THE NERVE TISSUE

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Abstract

In order to study the mechanism of parathyroid hormone (PTH) interaction with a neuron, the main stages of perception, transduction, and realization of hormonal signal were investigated by methods of radioisotope, radioimmune, enzyme analyses, as well as voltage-clump and neuron dialysis. It was shown that PTH binding by neuron membrane is accompanied by activation of voltage-dependent Ca^{2+}-channels, increase of cyclic AMP (cAMP) level, products of phosphoinositol cycle, ATP, stimulation of hexose monophosphate pathway, phosphorylation of membrane proteins and GABA spontaneous release. However, depending on the neuron initial state and the level of studied parameters, PTH could lead to an opposite effect. Based on data obtained, the concepts "Nervous tissue as a target for PTH action" and "PTH as a modulator of functional activity of the nervous system of organisms at different stages of evolutionary development" were formulated for the first time.

Keywords: parathyroid hormone, neuron, synaptosomes, voltage-dependent calcium channels, cell secondary messengers, GABA, energy metabolism.

Introduction

The importance of calcium's role in realization of many functions of the organism pre-conditioned appearance of the specific calcium metabolism hormonal regulation system in the process of evolution. Here parathyroid hormone (PTH) has the central part. All the data stored during the recent years show the range extension of PTH influence, including also the influence on the nervous structures, which are not considered by the classical notion as a target (bone, kidney, and intestine) for the mentioned hormone influence. Thus, the PTH modulating action on the voltage-dependent calcium channels of neuroblasts [*Wang R. et al., 1990*], Ca^{2+}-receptor in brain [*Chattopadhyay N. et al., 1998*], basal ganglia [*Mamdani N. et al., 2007*] was shown, as well as the evidence for the expression of parathyroid hormone receptor in the human brainstem obtained. All the investigations realized in this field show the rise of researchers' interest towards the study of PTH influence on the nervous tissue. These data as well as the fact of developing the neuropsychic disorders in case of parathyroid glands hypofunction [*Nataf N., 1970; Fujita T., 2004; Unluturk U. et al., 2008*] indicate the possibility of parathyroid regulation of the nervous tissue. However, taking into consideration that PTH belongs to the hormone group of peptide nature, it is necessary to study concrete mechanisms of the hormonal signal realization by the nervous cell that have not been studied and there is no clear notion about their interaction. In order to solve this problem we studied the main stages of perception, transduction, and realization of PTH signal at the neuron level.

In the given article the results of our many years investigations [*Khudaverdyan D. et al., 1987; 1989; 1991; 1996; 1997; Khudaverdyan D., Ter-Markosyan A., 1998a; 1998b; 2000; Kostyuk P. et al., 1990; 1992; Lutsenko V. et al., 1987; Ter-Markosyan A., 1989a; 1989b; 1997; 2005a; 2005b; Ter-Markosyan A., Khudaverdyan D., 1992; 1996*] are summarized.

Material and Methods

The investigations were carried out using the brain cortex synaptosomes of rats and *Helix pomatia* ganglia neurons. The methods of the radioisotope, radioimmune and enzyme analyses as well as voltage-clump and neuron dialysis were used, which were described in details in our previous investigations [*Khudaverdyan D. et al., 1987; 1989; 1997; Lutsenko V. et al., 1987; Ter-*

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Markosyan A., 1989a; 2005a; Kostyuk P. et al., 1990; 1992; Ter-Markosyan A., Khudaverdyan D., 1992; 1996; Khudaverdyan D., Ter-Markosyan A., 2000]. The physiological doses (10^{-10} – 10^{-9} M) of parathyroid hormone (Sigma, USA) were mainly used in experiments. Student's *t*-test was used for statistical analysis.

Results and Discussion

Before proceeding to investigation on the molecular mechanisms of PTH action to the neuron, it was necessary to answer the question whether or not PTH penetrates through the blood-brain barrier. In this connection the PTH in cerebrospinal fluid was determined by the radioimmune method. Its content in cerebrospinal fluid of the rat was shown to make about one-third of that in blood plasma. The investigation on the pathways of PTH-signal perception by the neuron plasma membrane was the next stage in our studies. These studies were carried out in mammalian brain synaptosomes and snail ganglia neurons. Thus, we could compare the PTH-sensitivity of the neuron plasma membrane in evolutionary aspects. In the presence of PTH physiological doses (10^{-10} M) in incubation medium synaptosomes bound 279 ± 43.92 *pg* PTH per 1 *mg* of protein. The binding capacity of the ganglia was lower (49.67 ± 4.22 *pg/mg*). The autoregulatory phenomenon of "down"-regulation by PTH high doses (10^{-8} M) was also revealed in a neuron, when the ganglion chemoreceptive capacity was sharply inhibited and made 0.69 ± 0.08 *pg/mg*. The latter coincides with literature data [*Bidwel J. et al., 1991; Shen X. et al., 2007; Takei Y. et al., 2009*], signifying that PTH high doses decrease the quantity of binding sites of the target-cell membranes. Therefore, it was reasonable to draw a conclusion on PTH specific binding with the neuronal membrane.

Taking into consideration the important role of calcium in the functional activity of a neuron, the dose- and time-dependent influence of PTH on Ca^{2+}-conductance in ganglia and synaptosomes was studied by radioisotope analysis. It was shown that PTH evokes a dose-dependent increase in $^{45}Ca^{2+}$- accumulation in synaptosomes. Maximum changes were shown on the 1st *sec* for 10^{-9} and 10^{-10} M of PTH. The influence of PTH on ganglia was similar. However, when PTH was added under the conditions of initial increase in intracellular Ca^{2+} level (by NaF, forscolin, etc.), a decrease of this parameter was recorded.

The analysis of obtained data testifies that PTH initiates entry of Ca^{2+} into a neuron, but at increased intracellular calcium levels this hormone can lead the ion flow in the opposite direction, thus performing the modulating effect on the neuron functional activity.

The obtained findings motivated us to investigate the mechanism, by which PTH might affect the trans-membrane transport of calcium in mollusk neurons. PTH was studied for its effect on the voltage-sensitive calcium channels in voltage-clump experiments on intracellularly perfused *Helix pomatia* unidentified neurons.

A two-stage action of the hormone on calcium flow was shown. The initial stage was short-term and resulted in the increase of I_{ca} by 7-10%. The second stage developed slowly during 60-70 *min.* I_{Ca} increased twice. The increase of cAMP content in intracellular medium had no additive effect to PTH "fast" effect. Therefore, the PTH "fast" effect on I_{Ca} is mediated by cAMP-dependent mechanism. Several experimental factors (such as the content of ATP and EGTA were found to affect the magnitude of the "slow" effect. Amongst others, the PTH application time during the intracellular perfusion was important. As a rule, the earlier hormone was applied, the more pronounced its effect was. The effect was expressed at the utmost, when PTH was applied previously or simultaneously with the beginning of cell perfusion. However, it did not occur if PTH was applied later than 30 *min* after the beginning of cell perfusion. The observed dependence can be explained by possible degradation or washout of the soluble enzyme. It allows to suppose that protein kinase C (PKC), the activator of which is diacylglycerole (DAG), the product of a phosphoinositide cycle, might be such an enzyme [*Berridge M., 1987*].

It was shown that phorbol ester, activator of PKC, imitated the effect of PTH. The effects of PTH and phorbol ester were not additive. H-7 and staurosporine, PKC inhibitors, depressed the effect of PTH. Thus, the PTH "slow" effect was mediated by PKC.

Based on our research data, as well as proceeding from the fact of phospholipase C stimulation by PTH [*Tawfeek H., Abou-Samra A., 2008*], we have suggested that PTH activates the phos-

phoinositide cycle. In this regard, we carried out a special investigation on the synaptosomes membrane phospholipid metabolism, particularly the content of mono-, di-, triglycerides of summary phospholipids and arachidonic acid under the PTH influence in dynamics by chromatography method and radioisotope technique. Data obtained evidenced alterations in phospholipid metabolism that most strongly appeared in 5 *sec* after PTH influence. The revealed dynamics of PTH effect on the levels of indicated substances coincides with the character of the changes observed under the influence of agonists causing the activation of phosphoinositide cycle [*Tadevosyan Yu., Gevorkyan E., 1990*]. The changes in levels of diacylglycerin, activator of PKC, are of highest interest.

A conclusion was drawn about the possibility of PTH-receptor signal transformation in the nervous cell by phosphoinositide cycle products, in particular, by DAG.

It is known that the effect of PTH on target-cell is realized by cAMP-dependent mechanism. Proceeding from the known PTH capacity to combine with the neuron membrane we made an assumption on possible alteration of the cyclic nucleotides levels in a neuron under PTH influence. The contents of cAMP and cyclic GMP (cGMP) in the rat brain cortex synaptosomes and *Helix pomatia* ganglia under PTH influence were studied by radioimmune assay. The level of the two nucleotides increased in ganglia under *in vitro* PTH influence and in rat synaptosomes after daily injections of parathyroidin at 0.5 *U/100* per 1 *g* body mass during a week. The *in vitro* influence of PTH on synaptosomes was accompanied by the increase of cAMP contents only. The increase of these cyclic nucleotides content is usually connected with the activation of cyclase systems [*Janson Ch. et al., 1991*]. But their level is regulated by other enzyme systems such as phosphodiesterases [*Kostuyk P., Verkhratsky A., 1995; Conti M., 2000; Bender A., Beavo J., 2006*]. Therefore, the changes observed in our investigations may result from the cyclase system activation as well as reduction of the phosphodiestherase activity. In order to discover the reasons of cAMP elevation the pharmacological analysis was carried out using substances, which exerted direct or indirect effect on cyclic nucleotides level. When PTH was combined with NaF, tolbutamide or trifluoperasine, the reduction of cAMP content was observed.

The analysis of obtained data testifies that PTH initiates synthesis of cAMP, but at the initial increase of this cyclic nucleotide level the hormone can stimulate phosphodiestherase activity and, therefore, regulate the functional activity of a neuron.

Summing up, we can conclude that the effect of PTH on the neuron level is realized by the following messengers: Ca^{2+}, cyclic nucleotides and products of phosphoinositide cycle. However, they are involved in this process not simultaneously but consequently. These secondary messengers activate the conformable protein kinases by initiation of intracellular processes bringing forth the physiological response of a nervous cell.

As a test for realization of the hormone signal (cell's final response), the process of neurotransmission by nervous terminals was chosen. The synaptic transmission is a complex of interconnected processes including synthesis, release of neuromediator by nervous terminals and its connection with the postsynaptic membrane. The key role in neurotransmission is performed by the process of membrane proteins phosphorylation underlying the interaction of presynaptic vesicles with presynaptic membrane [*Burke E., DeLorenzo J., 1982*].

The above-mentioned facts prompted us to investigate the effect of PTH on synaptic transmission in interconnection with the process of protein phosphorylation by radioisotope method. We investigated the uptake and spontaneous release of ^{3}H-GABA by synaptosomes. PTH had no effect on ^{3}H-GABA-uptake by synaptosomes, but initiated the release.

PTH (10^{-10} and 10^{-9} M) evoked the activation of phosphorylation (including Pi). With the dose increase to 10^{-8} M, the tendency towards suppression of this process was observed. These data are in accordance with the results of Ca^{2+}-transport, cAMP content, as well as data on hormone reception by neural membrane. All this, including the fact of dose-dependent activation of phosphorylation process, are within the concept of "down"-regulation by PTH at neuron level.

To study the mechanism of PTH-stimulated membrane protein phosphorylation, we combined the PTH with substances causing the alteration of the phosphorylation process. PTH had no effect

when combined with EGTA, and no effect additive to that of cAMP was observed. Therefore, it might be supposed that PTH-stimulated phosphorylation is mediated by Ca- and cAMP-dependent mechanisms.

The process of GABA (10^{-10}-10^{-5} M) binding with the neuronal membrane under the influence of PTH (10^{-10}-10^{-8} M) was studied in normal Ringer medium and in case of Na^+-K^+-pump inactivation. In the latter case the cell was swollen that caused an increase of the number of binding sites, which were in the reserve state [*Ayrapetyan S. et al., 1985; Buys S. et al., 1989*].

The obtained data indicate to a general tendency of a decrease in membrane chemoreceptive ability under the influence of 10^{-10} M PTH with maximum changes at high GABA concentration.

Comparing the effects evoked by 10^{-10} and 10^{-8} M PTH, we concluded that high concentration of PTH was less effective than the low one. In case of Na^+-K^+-pump inactivation in control at all concentrations of PTH the general tendency to increase the number of GABA-bound molecules was shown. In mentioned cases, PTH led up to the decrease of membrane ability to bind GABA. It is necessary to note that the largest decrease of membrane chemosensitive ability was observed in case of low dose PTH, which indicated the "protective" modulating role of PTH, protecting the CNS, particularly cortex, from inhibition.

All the investigated processes, including the membrane surface and channel protein phosphorylation, cyclic nucleotide synthesis, are energy-dependent, which makes it necessary to study the limiting links of energy metabolism in a neuron under the influence of PTH physiological dose. With this purpose the content of ATP and ATP-ase activity *in vitro* and *in vivo* were studied in the brain cortex by biochemical enzyme and spectrophotometric methods.

Daily injection of parathyroidin during a week (0.5 *U/100* per 1 *g* of body mass), as well as its single injection 1 *h* before decapitation of rats resulted in an increase of ATP content and a slight decrease of ATP-ase activity. The level of Ca^{2+} in blood serum increased only after daily injections of the hormone. The incubation of the nervous tissue with PTH in Ca^{2+}-containing medium was accompanied by an increase, while incubation in Ca^{2+}-free medium resulted in decrease of ATP content. A small increase of ATP-ase activity was observed only in Ca^{2+}-containing medium. It is suggested that PTH modulates brain energy metabolism both directly and indirectly (mediated by Ca^{2+}).

One of the key moments of energy metabolism is the process of glucose utilization by a cell that can be realized through different metabolic pathways, among which the basic ones are energy-producing links, including glycolysis and the Krebs's cycle, as well as the hexosemonophosphate pathway supplying the cell with NADP and pentoses that are included into composition of different nucleotides (RNA, DNA, ATP) and coenzymes. Literature data indicate to PTH-dependent activation of glycolysis and suppression of the Krebs's cycle [*Herman-Erlee M. et al., 1977; Hinson J., Birmingham M., 1987*]. Obviously, PTH is involved into allosteric regulation of energy-produced pathways. The same regulation is very likely to be realized at the level of glycolysis and the hexosemonophosphate pathway.

In this connection, the effectiveness of energy-producing utilization of glucose and the hexosemonophosphate pathway in *Helix pomatia* ganglia was studied by the quantitative comparison of emanated 6-$^{14}CO_2$ and 1-$^{14}CO_2$ at oxidation 6-^{14}C-glucose and 1-^{14}C-glucose under PTH influence, appropriately.

The research findings point to activation of the hexosemonophosphate pathway of glucose oxidation by PTH.

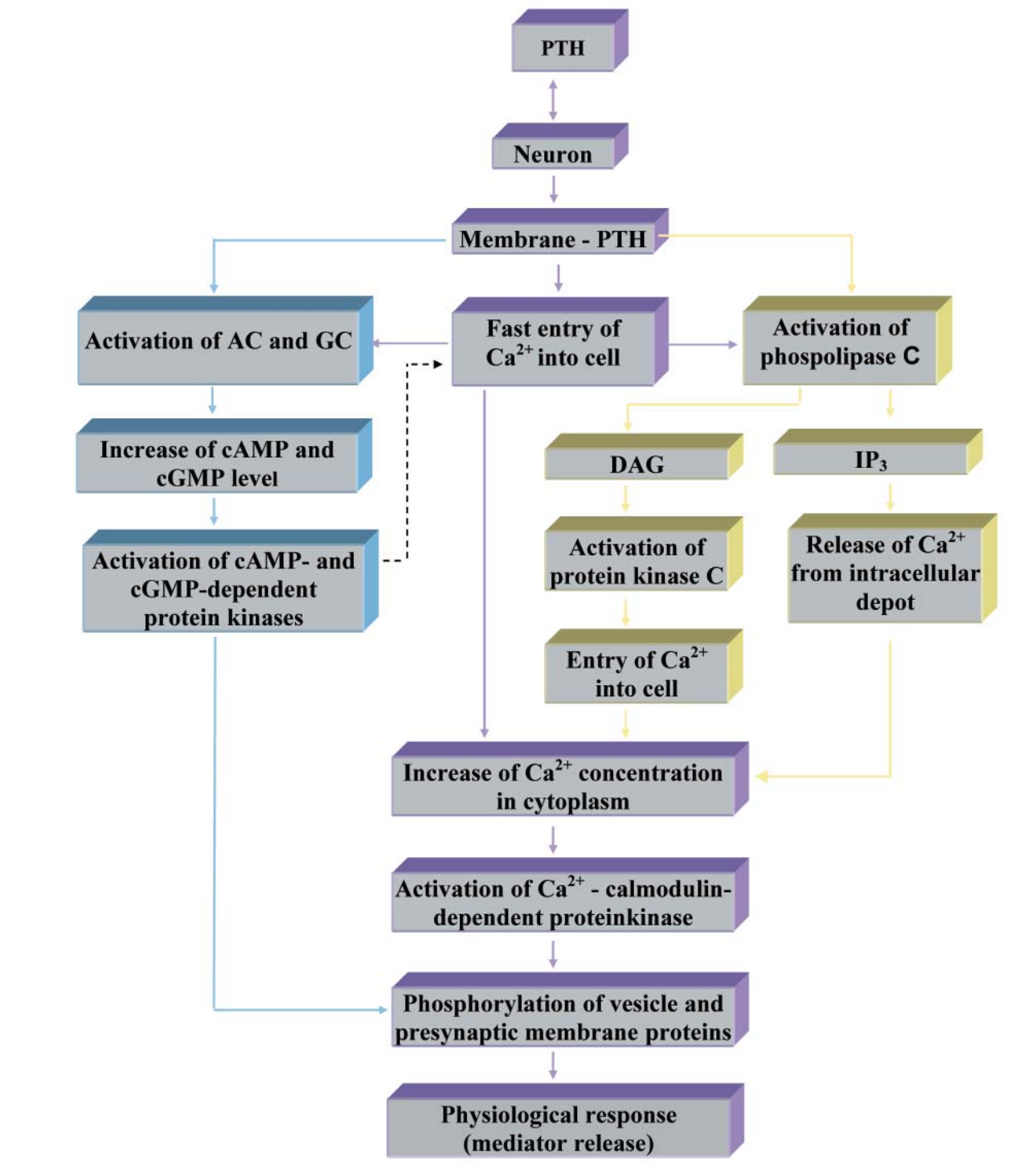
Obviously, the activation by PTH hexosemonophosphate pathway causes the observed abundant synthesis of RNA, DNA and protein under the influence of PTH [*Pereira R., Canalis E., 1999; Kwok S. et al., 2005*]. Thus, PTH activating the hexosemonophosphate pathway exerts the integratory and modulatory effect on the nervous tissue metabolism.

The following succession of processes occurring in the nervous cell under PTH action is proposed (Scheme) due to analysis of obtained data.

PTH is bound to the neuron membrane and signal transmission to phospholipase C and adenylate cyclase system follows. The "fast" stimulating effect of PTH for calcium entry is realized through cyclic nucleotides and the "slow" one is carried out through phosphoinositide cycle products, particularly DAG, activating PKC. The activation of corresponding protein kinase initiating intracellular processes brings to the physiological response of the nervous cell.

Scheme.

The possible mechanism of PTH and neuron interaction.



Conclusions

Summarizing the above-stated, the concepts "Nervous tissue as a target for PTH action" and "PTH as a modulator of functional activity of the nervous system of organisms at different stages of evolutionary development" are formulated for the first time.

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