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Some Neuromodulators Implication in the Pathogeny of the Hypothyroidism and the Depressive Disorders

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ABSTRACT. Current studies try to demonstrate a tight correlation between the endocrine and the neuropsychiatric physiopathology by a total different approach of the common pathology supporting an essential link between the neuro-hormonal mechanisms triggering the disorders from the depressive sphere and those from the scope of the crude hypothyroidism and of the serious forms. The medicines interaction between the pharmacological agents used in the thyroid pathology and of the various psychic disorders highlight a new type of therapeutic approach both psychiatric, and endocrine.
KEYWORDS: hypothyroidism, depression, TSH, TRH, T3, T4.

INTRODUCTION

The thyroid stimulating hormone (TSH) is the main regulator of the thyroid hormones secretion (T3 and T4).

As regulator of the thyroid hormones release plays an indirect important role in the control of the decayed metabolic processes comprising the protein synthesis, the carbohydrates metabolism, the thermogenesis and the cell increase.

The notions on the mechanisms responsible with the TSH regulation developed significantly during the last years.

Particularly, major elements were acquired in understanding the intra-hypothalamus regulation of the TRH secretion, of the mechanisms by which the TRH and the thyroid hormones control the hypophysis hormones secretion. The TSH is a glycoprotein with molecular weight of 28000, it is synthesised and secreted by the hypophysis thyroid stimulating cells.

THE ETIOPATHOGENIC INVOLVEMENTS

The mechanism by which the thyroid hormones inhibit the basal secretion, the TSH release and the TRH induced release was insufficiently elucidated. Some studies suggested that the thyroid hormones induce the forming of an inhibiting protein which blocks the release of TSH. The TSH suppression by the T3 is mediated by forming an inhibiting protein in the thyroid stimulating cells.

Regulating the TSH secretion was widely studied. Of the total of the adenohypophisis cells, 5% are about to be thyroid stimulating. The circulating TSH is not homogenous, as there are at least 3 forms of the euthyroid individual. Two of them are represented by the TSH intact form, but one is larger than the native TSH. The third form is a substance tied to the α subunit. The circulating values of the β subunit have been identified in the patients with the peripheral hypothyroidism which are secreted by the hypophysis and they do not result in the TSH deterioration at the periphery. In addition, the idea that the thyroid hormones enter in the thyroid stimulating cell is accepted and it is connected to the nuclear receptors which have a saturating interface for T3 at nuclear level. The T3 connection to this receiver is 10 times higher than in T4, proving that T3 is a more effective suppressor than T4. It is known that many patients have increased TSH compared with the lower T4, and normal T3.

The patients with clinical goitre apparently euthyroid may have an increased TSH, a low T4, and a normal T3.

In vitro, it was proved that, after the entrance in cellular level, T4 is de-iodised in T3, increasing the cellular level of T3 and quickly decreasing the TSH. The T4 implants in the hypothalamus decrease the circulating level of thyroid hormones. The bilateral inoculations in the lateral hypothalamus area at the hypothyroid primates led to a significant and quick decrease of the circulating level of the TRH. Though, several TRH analogues were synthesised, only one has a stronger power than the natural one, a series of analogues have psychotropic effects with minimal effect of TSH stimulation.

Besides the increased concentrations of TRH in the hypothalamus, its presence was proved in other areas of the central nervous system. A substance with immune-reactivity and bio-activity identical with the TRH met in the APUD system.

The TRH distribution, its extra-hypophisar multiple actions on the isolated neurones, and its quick deterioration in the blood and tissues led to the idea that the TRH is an ubiquity neuro-transmitter, co-opted by the hypophisis as release factor.

The TRH secretion level may be supressed by administrating DOPA, bromocriptine sulphonate, glucocorticoids. The TRH release was regulated after administrating norepinephrine and it was inhibited by the somatostatin. The dopamine plays an inhibition role in the control of the TSH secretin, at humans, the dopamine infusions and the L-DOPA administration decrease the TSH serum levels in normal and

hypothyroid subjects and reduce the TSH answer to TRH.

EFFECTS OF THE PSYCHOTROPIC SUBSTANCES ON THE NEUROMODULATORS

Experimentally, there is a TSH increase in hypothyroid and eurothyroid subjects after administering dopamine antagonists such as metoclopramide.

The dopamine penetrates directly the portal capillaries of the terminal axons of the dopaminergic system of the tuberoinfundibular area and it is found in elevated quantities in the portal blood.

It was proven that the dopamine produces a TSD reduction depending on the administered dosage. The data allowed for the conclusion that TSH is under the dopaminergic inhibitor control probably by direct action on the hypophisis.

The damage of the periventricular nucleus leads to the somatostatin reduction with 90% in the median eminence associated with a long-lasting increase of the plasmatic TSH.

The somatostatin role as thyroid stimulating inhibitor explains why children with GH (growth hormone) deficit have a wider and longer response to TRH and why TSH is constantly low in acromegaly.

We talked about the TSH resistance by modifying the receptor.

The glucocorticoids exercise several effects on the hypothalamus- hypophisis – thyroid axis. It was stated that the circadian rhythm of TSH secretion is the result of the cortisol inhibitory effect, as there is an revers report between the circadian rhythms of the two hormones [85]. The cortisol pharmacologic dosage inhibits the TSH-based secretion, the nocturnal discharge and the TRH effect on the thyroid stimulating hormone. They are compatible with the idea that, due to the cortisol there is a TRH inhibition in the hypothalamus.

The TSH hypothalamus regulation is performed by the proper secretion of TRH. It is consentient accepted that it is essential to keep intact the hypothalamus-hypophisis axis in order to preserve a normal secretion of TSH as response to the physiological stimuli.

The hypothalamus region is considered as essential for preserving a normal thyroid function and it was named thyreo-stimulating area. It is located in the anterior hypothalamus and it was proved by experiment of stimulation or lesion of the area.

The interaction with the hypothalamus-hypophisis-thyroid axis is achieved at various levels. Besides the catecholaminergic and serotoninergic system at hypothalamus-hypophisis level, they act directly on the thyroid gland as well. In addition the catecholamines may also interfere in the T4 and T3 conversions.

The norepinephrine system activates the release of TSH. It was proven experimentally that it stimulate the TRS release in the hypothalamic cultures.

The serotoninergic control was interpreted through the prism of the action on the TRH-TSH. Intra-venous inoculation on the rats leads to sudden increase of the circulating TSH. The studies on the hypothyroidism from depressions led to the conclusion that the anti-depressives drugs reduce serotonin-caption inhibitors. In depression, as TSH secretion is under constant inhibition of somatostatin, it produces more accentuated stimulation of the TSH.

A new feedback installs in case of depression, with increase of the TRH and TSH. Administering T3 stimulates the serotonin increase with improvement of the depression. The serotonin levels in humans are low in hypothyroidism and increased in hyperthyroidism.

Of all the other GABA hypothalamic neuropeptides, the vasoactive peptides and the bombesins can influence the TSH secretion.

It was also proven the calcitonin neuropeptide role, as it is able to penetrate in the median eminence, after intra-venous inoculation, and to reduce the TRH response to the TSH secretion.

The endogenous opiates and opioids administration leads to the reduction of the TSH secretion. The TSH secretion reduces after the inoculation of morphine in the anterior hypothalamus, in addition, the leu-enkephalin reducing the TSH response to TRH. Other studies claim the idea that the morphine action on the hypothalamus reduces the TRH secretion in the port-hypophisis system and so it appease a decrease in the TSH secretion, however the effects are minimal in humans.

The involvement in depression of the 5HT (serotonin) system perturbation was largely discussed, observing reduced 5HT neuro-transmittal in the brains. The 5HT circulating values are increased at the patients with hyperthyroidism, with a tight positive correlation between the 5HT and the circulating T3, highlighted in the hyperthyroidism therapy.

At nervous system level, 5HT is similarly affected in hypothyroidism, the synthesis and the turnover are low, the 5HT receptors density is increased in hypothyroid animals, probably due to some up-regulation secondary to some low 5HT synaptic levels. The α phenyl-fluoramine is an active agent of 5HT central release and with receptors inhibition. In hypothyroidism, the response to alpha phenyl-fluoramine was low, indicating a low level of 5HT in the hypothalamus as neuro-transmittal factor.

It is said related to the affective conditions that the depression is associated with a reduction of the central 5HT. The hypothyroidism with low central 5HT may occur as risk factor in triggering depression.

Consequently, 5HT shows up together with some other mono-amines as noradrenalin and dopamine as a factor that may have an influence in explaining the depression in hypothyroidism. Some more recent data converge to the idea that the psychic stress alters the immunologic monitoring, possibly through the hypothalamus-pituitary gland axis.
It was not fully clarified the measure how the psychic and immunologic factors combine themselves.

CONCLUSIONS

The multi-directional clinical and experimental surveys allow for formulating some conclusions certifying usually the role played by the

neuro-transmitters in the thyroid deficits, in triggering and evolving the depression; they also show the possibility of the occurrence of hypothyroidism as important pathogenic factor in the evolution of the untreated depression.

TSH calculations in patients with depression and without apparent hypothyroidism may be regarded as useful in proving the existence of a crude hypothyroidism. The signs of psychic suffering depression-like present both in women patients with moderate and severe hypothyroidism confirm a gradual increase depending on the seriousness of the disorder.

The thyroid deficit found out in hypothyroidism is an aggravating factor of the depression expressions, the thyroid hormones representing a major factor in maintaining a good functionality of the central nervous system.

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