REVIEW

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PATHOPHYSIOLOGY AND MANAGEMENT POSSIBILITIES OF THYROID-ASSOCIATED DEPRESSION

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Abstract. *Thyroid hormones and the hypothalamic-pituitary-thyroid (HPA) axis are responsible for multiple metabolic processes and psychological well-being. Hypothyroidism can induce mood changes, depressive symptoms and even major depressive disorder. This review is focused on the pathophysiology and mechanisms through which the low level of thyroid hormones may affect the brain function, causing the characteristic symptoms of depression. Key pathways of hypothyroid-associated depressive states include: morphological changes in some brain areas (mainly in the hippocampus – a reduction in its volume); a significant reduction of the cerebral blood flow (incl. hippocampus), and lowered levels of neurotrophic factors (e. g. BDNF – brain-derived neurotrophic factor), which are regulated by the thyroid hormones. An adequate and timely thyroid hormone replacement and treatment with conventional antidepressants often can reverse the psychological symptoms.*

Key words: *hypothyroidism, depression, brain-derived neurotrophic factor (BDNF), hippocampus*

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INTRODUCTION

Hypothyroidism is a medical condition, in which the level of thyroid hormones (THs) is reduced and insufficient to meet the needs of the body. THs, triiodothyronine (T3) and thyroxine (T4), play a major role in the regulation of metabolism, brain development, differentiation of neural cells, and synaptogenesis. [1-3]. Therefore, THs have an important place in the modelling of neural networks in the central nervous system (CNS), especially in the hippocampus, which is a well-known target for them [4]. Psychiatric manifestations of hypothyroidism are often presented by depression, anxiety, lack of assertiveness, and psychosis [5, 6]. Subclinical hypothyroidism may also be associated with depression in younger adults (under the age of 60 years), but data are controversial and this observation requires further research and investigation [7, 8].

Depression on the other hand is a big burden on modern society with 15-18% risk during the lifetime. Almost one in every five people will be or were experiencing a depressive episode at least once in their life [9].

The focus of the review is on the connection between THs and their linkage with brain development, hippocampus, neurotrophic factors, and depressive disorder.

THYROID HORMONES, BRAIN DEVELOPMENT AND FUNCTION

THs play a crucial role for brain development during the fetal period and in the developmental stages of CNS. During pregnancy, the maternal THs cross the placenta through specific transporters (THT – thyroid hormone transporter), which seem to be more selective for free T4 (fT4). T4 is converted to T3 by placental and CNS-specific deiodinases, which may be essential for neurogenesis, neuron differentiation, myelination and synaptogenesis [1, 10]. In the brain, the conversion of T4 to the active T3 is mostly by locally situated deiodinases and takes place in the neuroglial cells distributed in different brain regions [11]. The existence of those tissue-specific deiodinases and transport mechanisms for the THs in the brain tissue shows their significance for neural development. Furthermore, crucial genes responsible for the brain development are also regulated by the THs.

The hippocampus is highly rich of thyroid hormone receptors, which makes it an important target for THs in the brain [12]. In animal models it was found that different parts of the brain require THs at different points in their development – the basal ganglia require THs before the hippocampus, the posterior region of the cortex before the anterior part. Moreover, the time of thyroid hormone deficiency during brain development is of greater importance for some brain regions compared to others [13, 14]. In humans, the central thyroid system regulation does not occur before the third trimester and full function is achieved after birth [15].

The importance of the THs for neurodevelopment is well presented in congenital hypothyroidism, demonstrated by a developmental delay, poor growth, poor feeding, and cognitive deficits in infants [16]. Congenital hypothyroidism is still one of the leading causes of preventable intellectual disability [17]. Studies also show that children and adolescents with congenital hypothyroidism tend to have reduced hippocampal volume, especially on the left side, in comparison to healthy children. Moreover, the compromised development of the hippocampus in children with congenital hypothyroidism may contribute to a cognitive impairment [18].

In the adult brain THs are especially important for gyrus dentatus and CA1 and CA3 hippocampal regions. By using functional magnetic resonance imaging of the brain (FMRIB) integrated registration and segmentation tool (FIRST), Cooke et al. found a significant volume decrease in the right hippocampus in patients with adult-onset overt hypothyroidism in comparison with the euthyroid control group [19]. In addition, a cerebral blood flow, including hippocampus area was showed markedly reduced [20]. These findings highlight that hypothyroidism results in structural deficits and morphological changes in the adult brain. In the mature brain, THs are also responsible for modulating the local glucose metabolism, subtle behavioral and psychiatric symptoms.

HIPPOCAMPUS AND ITS LINK TO DEPRESSION

Depression (major depressive disorder) is a common mental disorder, considered as a chronic disease, which contributes to worldwide disability. It is often presented by physical symptoms, such as fatigue, insomnia, headache, unexplained pain, and gastrointestinal symptoms. Psychological and cognitive symptoms may include irritability, atypical anger, apprehension, slow thinking, impaired memory, poor attention and concentration [21]. The complete pathogenesis of major depression is still not well understood. Various interlinked pathophysiological mechanisms (including the biogenic amine hypothesis, the receptor hypothesis, neurotrophic factors, cytokine theory, and endocrine factors) are probably involved in the pathogenesis of the disease [22, 23].

One of the most studied brain regions in a depression research is the hippocampus. As a part of the limbic system it develops nerve fiber connections with other emotion-related brain regions, such as the prefrontal cortex and the amygdala. The hippocampus also regulates the hypothalamus-pituitary-adrenal (HPA) axis, which makes it more sensible to depression and stress [24]. A significantly smaller hippocampal volume has been observed consistently in individuals with major depressive disorder [25]. Furthermore, a study showed that hippocampal atrophy has been found in people at their first depressive episode [26]. This is consistent with the neurodevelopmental theory of depression that advocates hippocampal structure as a potential neuro-biomarker with a diagnostic value for depression. Therefore, a pre-existing volume reduction of the hippocampus makes these individuals more vulnerable and prone to depression. In support of this vulnerability hypothesis never-depressed individuals, but with a family history of depression, have been shown to have significantly smaller hippocampal volumes compared to the matched control participants [27].

BRAIN-DERIVED NEUROTROPHIC FACTOR – ROLE IN DEPRESSION

Brain-derived neurotrophic factor (BDNF) is a protein which belongs to the neurotrophin family of growth

factors, and is expressed at high levels in the limbic system. It is one of the most common and widely spread neurotrophins in the central and peripheral nervous system (Fig. 1) [23]. BDNF has many important functions related to the brain development, such as neuro- and gliogenesis, growth and differentiation of new neurons, synaptic plasticity, dendritogenesis and synaptogenesis [28]. It is active in the hippocampus, the cortex, the basal forebrain, which are areas associated with long-term memory, higher thinking, and learning abilities.

BDNF is of great importance and play a key role in the pathophysiology of major depressive disorder. There is evidence that low levels of BDNF are associated with depression and suicidal behavior [29]. The decreased circulating levels of BDNF in depressed patients are reversible with a treatment with antidepressants [30].

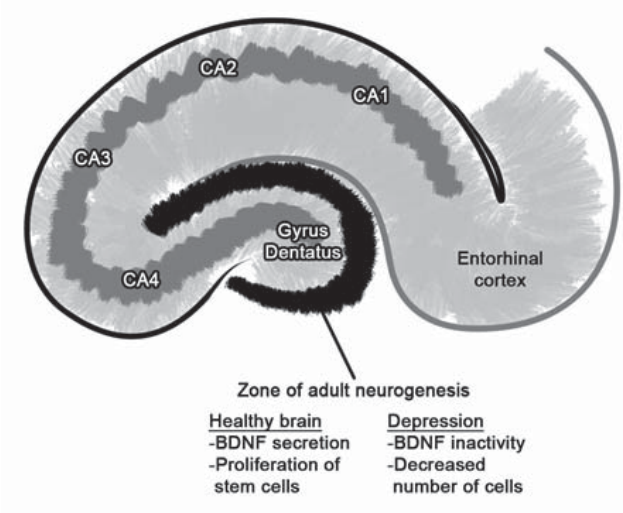

Fig. 1. Role of BDNF in adult neurogenesis (Bakalov et al., 2020 [23])

HYPOTHYROIDISM AND DEPRESSION

In subclinical hypothyroidism, the levels of thyroid-stimulating hormone (TSH) are elevated, but the fT4 is in the reference range. In overt hypothyroidism, fT4 is lowered and the levels of TSH are elevated [31]. The symptoms of hypothyroidism range from very mild to life-threatening (myxedema coma). Common clinical presentations associated with low levels of THs include fatigue, weight gain, constipation, puffy face, increased sensitivity to cold. The symptoms vary, based on the severity of the hormone deficiency, and they tend to develop slowly, during a prolonged time.

Hypothyroidism is often associated with a depressive-like behavior. In patients with subclinical hypothyroidism, mental symptoms are more likely to be presented with nonspecific manifestations such as fatigue, cognitive impairment, and altered mood [32, 33]. Some recent data even did not observe associated increased risk for depression in such patients with subclinical hypothyroidism [8, 34]. Among older adults, subclinical hypothyroidism is more probably to be associated with higher risk of dementia and a larger cognitive decline [35].

In overt hypothyroidism, many symptoms of psychological dysfunction have been described. Most frequently, mental slowness, forgetfulness, and emotional lability are seen [32]. Hypothyroid patients show also depression, cognitive impaiment, apathy, and decreased psychomotor activity [36, 37]. In severe forms of hypothyroidism, the clinical symptoms may resemble those of melancholic depression and dementia [38, 39]. In addition, we have previously described in a rat model a significantly longer immobilization time for the hypothyroid animals by Forced swimming test [40]. All these findings may link the depression to changes in the hypothalamic-pituitary-thyroid axis.

Many studies evaluated cognitive function and quality of life in patients with Hashimoto thyroiditis on long-term T4 replacement. Data showed persistent impairment in both cognitive function, and anxiety and depression scores among some hypothyroid patients, despite proper hormonal therapy [41, 42]. So, thyroid replacement therapy alone is not effective enough to induce a total remission of depressive symptoms. Many observations have shown that the treatment with both antidepressants and T4 lead to an increase in BDNF concentrations and a decrease in proinflammatory cytokines, correlating with clinical improvement of depression [43].

Conventional antidepressants exert antidepressant effects by increasing BDNF in forebrain regions, in particular the hippocampus, making BDNF a key transducer of antidepressant efficacy [44]. In several studies BDNF has been linked with antidepressants and their mechanism of action [45]. An increase in the expression of the BDNF mRNA in the hippocampus and the cortex parallels the antidepressant-like response of traditional antidepressant agents, such as selective serotonin reuptake inhibitors (SSRIs) [44].

THs regulate serotonin neurotransmission by enhancing its metabolism and receptors expression. Additionally, serotonin modulates the basal level of BDNF in the hippocampus and also contributes to stress-induced BDNF mRNA down-regulation [46]. Furthermore, THs regulate BDNF and other neuro-

trophic factors during the critical fetal period of brain development [47]. It was found that prenatal exposure to propylthiouracil (PTU) led to a reduced hippocampal BDNF in neonatal rats [48]. THs are essential for the adult hippocampal neurogenesis [49]. Their insufficiency may lead to a drastically decreased BDNF expression in the amygdala and hippocampus in adult hypothyroid patients [50]. T4 can also play an important role in promoting the regeneration of injured neurons through inducing and up-regulating BDNF [51].

CONCLUSION

THs play a crucial role in numerous metabolic processes, physical and psychological well-being. Their reduction can have devastating effects. Hypothyroidism is associated with both functional and structural brain alterations, also seen in patients with major depression. Hypothyroid-associated depressive-like behavior can be caused by a number of factors, including reduced levels of BDNF in the CNS, morphological changes in the hippocampus, and reduction of the blood flow in some brain areas. Mental disturbances and depressive symptoms are mainly reversible with thyroid hormone replacement therapy and antidepressants like SSRIs.

We may hypothesize that THs could affect the response to antidepressants through their modulation on serotonin and BDNF expression in the brain.

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