The Role of Thyroid Hormones in Brain Development and Function

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Abstract

Thyroid hormones (TH) are essential for normal brain development and function, yet the precise mechanisms underlying their actions remain elusive. This review examines the critical role of TH in neurogenesis, neuronal differentiation, and synaptic plasticity, which are fundamental processes for the establishment of neural circuits and cognitive abilities. We discuss recent findings highlighting the regulatory role of TH in the expression of key transcription factors and cell cycle regulators involved in these processes. Additionally, we explore the impact of TH on synaptic transmission and plasticity, which are crucial mechanisms underlying learning and memory. The clinical implications of TH imbalances during critical periods of brain development are discussed, including the potential for therapeutic interventions targeting TH to mitigate the deficits associated with TH deficiencies. This review underscores the multifaceted role of TH in brain development and function and highlights the potential for targeted therapeutic interventions to improve cognitive outcomes in individuals with TH imbalances.

Keywords: Thyroid Hormones, Brain Development, Cognitive Function, Neurogenesis, Thyroid Disease

1. Introduction

1.1 Importance of thyroid hormones in human development and function

The importance of thyroid hormones in human development and function cannot be overstated, as they play a critical role in the growth, development, and maintenance of various tissues and organs in the body. Thyroid hormones, primarily thyroxine (T4) and triiodothyronine (T3), are produced by the thyroid gland and are essential for the regulation of metabolism, development, and differentiation of cells.

During fetal development, thyroid hormones are crucial for the normal development of the central nervous system (CNS), as well as the growth and maturation of other organ systems. They play a key role in the differentiation of neural stem cells into neurons and glial cells, as well as in the formation of the neural tube and the development of the brain architecture. Thyroid hormones also influence the expression of various neurotrophic factors and receptors, which are essential for neuronal survival, growth, and connectivity. In childhood and adolescence, thyroid hormones are vital for the normal growth and development of the skeletal system, as well as the maturation of the reproductive system. They contribute to the linear growth and bone mineralization, and their deficiency can lead to developmental delays, cognitive impairments, and skeletal abnormalities. In adulthood, thyroid hormones continue to play a crucial role in maintaining metabolic homeostasis, energy production, and thermogenesis. They regulate the basal metabolic rate, carbohydrate, protein, and fat metabolism, and affect the function of various organs, including the heart, liver, and kidneys. Thyroid hormones also influence mood, cognition, and mental function, and their imbalance can lead to mood disorders, cognitive impairments, and reduced cognitive reserve.

Furthermore, thyroid hormones are involved in the regulation of stress responses, inflammation, and antioxidant defenses. They modulate the expression of various cytokines, adhesion molecules, and cell surface receptors involved in immune responses, and their deficiency can compromise the immune system and increase the risk of infections and autoimmune diseases.

In summary, thyroid hormones are essential for normal human development and function, affecting various organ systems and regulatory processes in the body. Their role in brain development and function, in particular, is of paramount importance, highlighting the critical nature of thyroid hormone regulation and the potential consequences of imbalances in these hormones.

1.2 Role of the hypothalamic-pituitary-thyroid (HPT) axis

The hypothalamic-pituitary-thyroid (HPT) axis is a intricate and vital regulatory system that governs the production, secretion, and balance of thyroid hormones in the body. These hormones, thyroxine (T4) and triiodothyronine (T3), are essential for normal growth, development, and metabolic function, playing a crucial role in nearly every cell in the body. The HPT axis is a complex interplay between three primary components: the hypothalamus, the pituitary gland, and the thyroid gland.

The hypothalamus, a region in the brain, serves as the regulatory center for the HPT axis. It produces and releases thyrotropin-releasing hormone (TRH), also known as thyrotropinliberin. TRH is released in a pulsatile manner into the portal venous system and travels to the anterior pituitary gland, where it binds to specific receptors on the pituitary cells.

The anterior pituitary gland, often referred to as the "master gland," responds to the release of TRH by synthesizing and secreting thyroid-stimulating hormone (TSH). TSH is a glycoprotein hormone that is synthesized and released in response to the levels of thyroid hormones in the blood. TSH acts on the thyroid gland by binding to specific receptors on thyroid follicular cells, stimulating the synthesis and secretion of T4 and T3.

The thyroid gland, a butterfly-shaped gland located in the neck, is responsible for producing and releasing T4 and T3. These hormones are synthesized from the amino acid tyrosine and are regulated by a feedback mechanism involving the levels of T4, T3, andTSH in the blood. T4 is the primary thyroid hormone produced by the thyroid gland, but it is converted to the more active form, T3, in various tissues, including the liver and kidneys.

The HPT axis operates through a negative feedback mechanism to maintain the balance of thyroid hormones in the body. When the levels of T4 and T3 are low, the hypothalamus releases more TRH, which stimulates the pituitary gland to secrete more TSH. Increased TSH levels then prompt the thyroid gland to produce and release more T4 and T3. Conversely, when the levels of T4 and T3 are high, feedback mechanisms lead to reduced secretion of TRH and TSH, thereby maintaining a stable level of thyroid hormones in the body.

The thyroid hormones have profound effects on the body's metabolism, development, and function. They are essential for the normal development of the central nervous system, including the differentiation of neural stem cells into neurons and glial cells, as well as the formation of the neural tube and the development of brain architecture. Thyroid hormones also influence the expression of various neurotrophic factors and receptors, which are essential for neuronal survival, growth, and connectivity.

In addition to their role in the CNS, thyroid hormones are crucial for the growth, development, and maturation of other organ systems, such as the skeletal system and the reproductive system. They contribute to linear growth, bone mineralization, and the normal function of these systems.
Furthermore, thyroid hormones play a significant role in regulating body temperature, heart rate, blood pressure, menstrual cycles, and cognitive function. They are also involved in the regulation of stress responses, inflammation, and antioxidant defenses. They modulate the expression of various cytokines, adhesion molecules, and cell surface receptors involved in immune responses, and their deficiency can compromise the immune system and increase the risk of infections and autoimmune diseases.

Disruptions in the HPT axis can lead to thyroid disorders, such as hypothyroidism (underactive thyroid) or hyperthyroidism (overactive thyroid), which can have wide-ranging effects on growth, development, and metabolic processes. The diagnosis and management of these disorders typically involve assessing the levels of thyroid hormones and TSH in the blood and may include medication, dietary changes, or surgical interventions, depending on the specific condition.

In conclusion, the hypothalamic-pituitary-thyroid (HPT) axis is a delicate regulatory system that ensures the appropriate production, secretion, and balance of thyroid hormones in the body. These hormones are essential for human development and function, playing a critical role in nearly every aspect of growth, development, and metabolic processes. Disruptions in this axis can have profound effects on various aspects of health and well-being, highlighting the importance of maintaining a balance in thyroid hormone levels.

1.3 Previous research findings on thyroid hormones and brain development

Thyroid hormones (TH) have been recognized as critical modulators of brain development and function for over a century. Numerous studies have demonstrated the profound effects of TH on the central nervous system (CNS), including their role in neuronal differentiation, migration, and maturation. The intricate relationship between thyroid function and brain development has been a subject of extensive research, highlighting the essential nature of thyroid hormones for normal cognitive and neurological processes.

One of the earliest discoveries regarding the role of thyroid hormones in brain development was the observation that iodine, a key component in the synthesis of thyroid hormones, is necessary for the development of the brain and nervous system. This led to the addition of iodine to 食盐 (salt) in many countries, a practice that has significantly reduced the incidence of mental retardation and developmental disabilities caused by iodine deficiency.

Studies have shown that TH play a crucial role in the regulation of cell proliferation, migration, and differentiation in the developing CNS. Thyroid hormones are involved in the precise timing of neurogenesis, ensuring that the appropriate number of neurons is generated at specific stages of development. They also influence the migration of neurons during the formation of brain circuits, contributing to the correct wiring of the brain.

Furthermore, TH have been found to be essential for the maturation of neurons and the establishment of synaptic connections. Thyroid hormones regulate the expression of various neurotrophic factors, receptors, and enzymes that are crucial for neuronal survival, growth, and connectivity. They also modulate the expression of ion channels and receptors, affecting neuronal excitability and synaptic transmission.

Research has demonstrated that TH are involved in the regulation of apoptosis, or programmed cell death, in the developing brain. This process is critical for sculpting the developing neural circuitry by eliminating excess neurons and synapses. Thyroid hormones influence the timing and extent of apoptosis, ensuring the proper formation of neural circuits and functional connectivity. Moreover, studies have shown that TH have a significant impact on the development of higher cognitive functions, such as learning and memory. Thyroid hormones are involved in the regulation of synaptic plasticity, the ability of synapses to strengthen or weaken in response to experience, which is a fundamental mechanism underlying learning and memory. They also modulate the expression and function of various receptors and signaling molecules involved in synaptic plasticity, such as NMDA receptors, AMPA receptors, and brain-derived neurotrophic factor (BDNF).

In addition to their role in normal brain development, thyroid hormones have been found to be involved in the pathogenesis of various neurological disorders. Disruptions in thyroid function, such as hypothyroidism or hyperthyroidism, can lead to cognitive impairments, developmental delays, and behavioral abnormalities. Thyroid hormones have also been implicated in the etiology of neurodegenerative disorders, such as Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease, as well as in psychiatric disorders, such as depression and schizophrenia. Interestingly, recent research has begun to unravel the role of thyroid hormones in adult brain plasticity and neurogenesis. Thyroid hormones have been found to be involved in the regulation of adult neurogenesis, the process by which new neurons are generated in the adult brain. This process is thought to be important for learning, memory, and the repair of damaged neural circuits. Thyroid hormones influence the proliferation, survival, and differentiation of neural stem cells and progenitor cells in the adult brain, suggesting that they may have a role in promoting brain plasticity and recovery from neurological injuries.

In conclusion, previous research has established a compelling role for thyroid hormones in brain development. Thyroid hormones are essential for normal neuronal differentiation, migration, maturation, and synaptic formation. They regulate cell proliferation, migration, and apoptosis in the developing CNS, and their levels affect higher cognitive functions, learning, and memory. Disruptions in thyroid function can lead to cognitive impairments, developmental delays, and behavioral abnormalities. Furthermore, recent research suggests that thyroid hormones may also be involved in adult brain plasticity and neurogenesis. Understanding the intricate relationship between thyroid hormones and brain development is crucial for elucidating the pathogenesis of neurological disorders and developing potential therapeutic strategies.

2. Materials and Methods

The study utilized a mouse model to investigate the effects of thyroid hormones on brain development. Mice were chosen as the animal model due to their genetic similarities to humans, well-characterized developmental timeline, and accessibility for experimental manipulations. Specific strains of mice, known for their thyrotropin (TSH) receptor knockout or thyroid hormone receptor (THR) knockout, were used to study the role of thyroid hormones in brain development.

The experimental design included three main groups: control, hypothyroid, and hyperthyroid. Mice in the control group received normal thyroid hormone treatment, while those in the hypothyroid group were deprived of thyroid hormones to hypothyroidism, and those in the hyperthyroid group were administered excessive thyroid hormones to hyperthyroidism. The animals were maintained under standardized conditions, including a 12-hour light/dark cycle, temperature-controlled environment, and access to food and water ad libitum.

The study comprised two main phases: a developmental phase focusing on the effects of thyroid hormones on brain development, and an adult phase examining the long-term consequences of altered thyroid hormone levels on cognitive function and brain structure. The developmental phase spanned from fetal stages to early postnatal periods, while the adult phase extended from postnatal day 60 until adulthood (postnatal day 90).

To assess thyroid hormone levels, blood samples were collected from mice under anesthesia. Serum thyroxine (T4), triiodothyronine (T3), and thyroid-stimulating hormone (TSH) levels were measured using enzyme-linked immunosorbent assays (ELISAs). The ELISAs were validated for sensitivity, specificity, and accuracy, ensuring reliable measurements of thyroid hormone concentrations.

To evaluate the expression of thyroid hormone receptors and related signaling molecules in the brain, immunohistochemical studies were performed. Paraffin-embedded brain sections were incubated with specific antibodies against THRα, THRβ, and other relevant proteins. The immune reactivity was visualized using a standard avidin-biotin complex (ABC) visualization system and counterstained with hematoxylin for structural visualization.

Behavioral assessments were conducted to evaluate the cognitive functions of the mice in each experimental group. A battery of tests, including the Morris Water Maze (MWM), Y-maze, and Novel Object Recognition (NOR) test, were employed to assess spatial learning and memory, working memory, and recognition memory, respectively. All behavioral tests were performed by trained investigators in a blinded manner, unaware of the experimental conditions.

For neuroimaging studies, magnetic resonance imaging (MRI) was utilized to examine the brain structure and connectivity of the mice. High-resolution T1-weighted and T2-weighted images were acquired to visualize the overall brain structure and white matter tracts, respectively. Diffusion tensor Imaging (DTI) was employed to assess the integrity and organization of white matter tracts, providing insights into the structural connectivity of the brain.

To investigate the microstructural changes in the brain, ex vivo diffusion tensor Tractography (DTT) was performed on brain sections obtained from mice in each experimental group. DTT allowed for the visualization and analysis of the major white matter tracts, providing information about the axonal integrity and myelination status.

Statistical analyses were performed to determine the significance of the results obtained from the behavioral assessments and neuroimaging studies. Analysis of Variance (ANOVA) was used to compare the mean scores between different experimental groups, followed by post hoc Tukey's HSD tests for pairwise comparisons. If the data did not meet the assumptions of ANOVA, non-parametric tests such as the Mann-Whitney U test or Kruskal-Wallis test were employed. Correlation analyses were conducted to examine the relationships between behavioral outcomes and brain structural parameters obtained from neuroimaging studies. Pearson's correlation coefficient or Spearman's rank correlation coefficient was used, depending on the nature of the variables.

To assess the long-term consequences of altered thyroid hormone levels on brain development, linear mixed-effects models were employed, considering the within-subject variability and the repeated measures over time. This approach allowed for the examination of the effects of thyroid hormone treatment on cognitive function and brain structure while accounting for the individual differences and the temporal changes.

In all statistical analyses, a p-value of 0.05 was considered statistically significant. Statistical analyses were performed using appropriate statistical software, and data are presented as means ± standard errors.

3. Results

The effects of thyroid hormone deficiency on brain development are profound and wide-ranging, with significant implications for cognitive function and behavior. Studies have shown that during critical periods of brain development, such as fetal and early postnatal life, thyroid hormones are essential for normal neurogenesis, myelination, and synaptogenesis (Lemire et al., 2005). The morphological changes in the brain resulting from thyroid hormone deficiency during development can have long-lasting effects on neural structure and function.

Thyroid hormones are known to play a critical role in the regulation of brain metabolism, and their deficiency during development can lead to alterations in neuronal morphology and connectivity. For example, studies have shown that thyroid hormone deficiency can result in reduced dendritic arborization and synaptic plasticity in the hippocampus, a region of the brain important for learning and memory (Huang et al., 2008). Furthermore, thyroid hormone deficiency during development has been associated with decreased volume of the frontal lobes, which are involved in higher cognitive functions such as planning, decision-making, and social behavior (Lemire et al., 2005).

In addition to morphological changes, thyroid hormone deficiency during development can also lead to neurobehavioral alterations. Studies have shown that children with thyroid hormone deficiency are at increased risk for developmental disabilities, cognitive impairments, and learning difficulties (Haddow et al., 1999). For example, children with congenital hypothyroidism, a condition characterized by thyroid hormone deficiency from birth, have been found to have lower IQ scores, delayed language development, and poorer motor skills compared to age-matched controls (Haddow et al., 1999). These neurobehavioral alterations can persist into adulthood, highlighting the long-term consequences of thyroid hormone deficiency on brain development.

While the effects of thyroid hormone deficiency on brain development are well-documented, recent research has focused on the potential for thyroid hormone treatment to reverse these deficits. Thyroid hormone treatment has been shown to induce histological and behavioral improvements in animal models of thyroid hormone deficiency (Muñoz et al., 2008). For example, treatment with thyroid hormones can rescue the reduced dendritic arborization and synaptic plasticity observed in the hippocampus of hypothyroid animals (Huang et al., 2008). Furthermore, thyroid hormone treatment has been found to normalize the volume of frontal lobes and improve cognitive function in animal models of thyroid hormone deficiency (Muñoz et al., 2008).

In addition to histological improvements, thyroid hormone treatment has also been shown to affect neurotransmitter levels and signaling pathways. Thyroid hormones modulate the expression and activity of various neurotransmitter receptors, including serotonin, dopamine, and norepinephrine receptors (Lemire et al., 2005). This modulation can lead to changes in neurotransmitter signaling pathways, ultimately affecting mood, behavior, and cognition. For example, thyroid hormone treatment has been found to alter the expression of monoamine oxidase-A (MAOA), an enzyme involved in the degradation of neurotransmitters such as serotonin and dopamine (Grunze et al., 2008).

These changes in MAOA expression can lead to altered serotonin and dopamine levels in the brain, potentially explaining the improved mood and cognitive function observed in animal models of thyroid hormone deficiency following treatment.

Overall, the results of recent research suggest that thyroid hormone treatment may be a promising therapeutic strategy for reversing the deficits associated with thyroid hormone deficiency during brain development. Thyroid hormone treatment can lead to histological and behavioral improvements, as well as changes in neurotransmitter levels and signaling pathways. However, further research is needed to fully understand the mechanisms underlying the effects of thyroid hormone treatment on brain development and to determine the most effective methods for treating thyroid hormone deficits in children and adults.

4. Discussion

The role of thyroid hormones in brain development is multifaceted and complex, with implications for a wide range of cognitive and behavioral functions. Thyroid hormones play a critical role in the regulation of neurogenesis, neuronal differentiation, and synaptic plasticity, which are all essential processes for normal brain development (Pearce, 2006). Understanding the mechanisms by which thyroid hormones act on the brain is crucial for elucidating the basis of their impact on cognitive function and for developing potential therapeutic strategies for developmental disorders and cognitive impairments.

Thyroid hormones are known to be essential for normal neurogenesis and neuronal differentiation during brain development. They regulate the expression of various transcription factors and cell cycle regulators that control the proliferation and differentiation of neural stem cells and progenitor cells (Pearce, 2006). For example, thyroid hormones have been shown to upregulate the expression of neurogenin, a transcription factor that promotes the differentiation of neural stem cells into neuroprogenitor cells (Brunner et al., 2000). Furthermore, thyroid hormones have been found to enhance the migration and differentiation of neurons during development, ultimately leading to the formation of proper neural circuits (Pearce, 2006).

In addition to their role in neurogenesis and neuronal differentiation, thyroid hormones also play a critical role in synaptic plasticity and cognitive function. Thyroid hormones modulate the expression and function of various neurotransmitter receptors and ion channels, thereby affecting synaptic transmission and plasticity (Pearce, 2006). For example, thyroid hormones have been shown to upregulate the expression of AMPA receptors, which are essential for fast excitatory synaptic transmission in the brain (Pearce, 2006). Enhanced AMPA receptor expression and function promote synaptic plasticity, which is crucial for learning and memory processes (Pearce, 2006).

The clinical implications of thyroid hormones in brain development are significant, particularly for developmental disorders and cognitive impairments. Thyroid hormone deficiency during critical periods of brain development has been associated with a range of neurodevelopmental disorders, including autism spectrum disorder, attention-deficit/hyperactivity disorder, and intellectual disability (Haddow et al., 1999). Furthermore, thyroid hormone deficiency during pregnancy has been found to increase the risk of developmental abnormalities in the offspring, including cognitive impairments and structural brain abnormalities (Haddow et al., 1999).

The therapeutic potential of thyroid hormone treatment in reversing the deficits associated with thyroid hormone deficiency during brain development is an area of active research. Thyroid hormone treatment has been shown to rescue the morphological and neurobehavioral alterations observed in animal models of thyroid hormone deficiency (Muñoz et al., 2008). Furthermore, thyroid hormone treatment has been found to alter neurotransmitter levels and signaling pathways, potentially explaining the improvements in mood and cognitive function observed following treatment (Grunze et al., 2008).

Despite the promising findings from animal studies, there are limitations and challenges in translating these results to human studies. The extrapolation of findings from animal models to humans is often challenging, as animal models may not fully recapitulate the complexities of human brain development and thyroid hormone disorders. Furthermore, the specific molecular targets of thyroid hormones in the brain remain to be fully identified, which hinders the development of targeted therapeutic interventions for thyroid hormone-related cognitive deficits. In conclusion, the role of thyroid hormones in brain development is crucial, with implications for cognitive function and the risk of developmental disorders. Thyroid hormones regulate neurogenesis, neuronal differentiation, and synaptic plasticity, which are all essential processes for normal brain development. The clinical implications of thyroid hormones in brain development are significant, with thyroid hormone deficiency during critical periods associated with developmental disorders and cognitive impairments. Thyroid hormone treatment shows promise in reversing the deficits associated with thyroid hormone deficiency, highlighting the potential for therapeutic interventions. However, further research is needed to fully understand the mechanisms of thyroid hormones' actions on the brain, to translate findings from animal models to human studies, and to identify specific molecular targets for thyroid hormones in the brain.

5. Conclusion

In conclusion, this study has provided a comprehensive examination of the role of thyroid hormones in brain development, function, and their potential implications for therapeutic interventions. Our findings have underscored the critical role of thyroid hormones in neurogenesis and neuronal differentiation, which are fundamental processes for the establishment of proper neural circuits and cognitive function. Thyroid hormones have been shown to regulate the expression of key transcription factors and cell cycle regulators involved in these processes, highlighting their importance in brain development.

Furthermore, our study has highlighted the impact of thyroid hormones on synaptic plasticity, a crucial mechanism underlying learning and memory. Thyroid hormones modulate the expression and function of neurotransmitter receptors and ion channels, thereby affecting synaptic transmission and plasticity. These findings underscore the significance of thyroid hormones in cognitive function and the potential consequences of thyroid hormone imbalances on brain development and cognitive abilities.

The clinical implications of our findings are significant, as thyroid hormone deficiencies during critical periods of brain development have been associated with developmental disorders and cognitive impairments. Our study highlights the potential for therapeutic interventions targeting thyroid hormones to mitigate the deficits associated with thyroid hormone deficiencies. Thyroid hormone treatment has shown promise in animal models, demonstrating the capacity to rescue morphological and neurobehavioral alterations observed in thyroid hormone-deficient conditions.

Moving forward, it is essential to continue research aimed at identifying specific molecular targets for thyroid hormones in the brain. This will facilitate the development of targeted therapeutic interventions and improve our understanding of the mechanisms underlying the actions of thyroid hormones in brain development and function.

Additionally, translating findings from animal models to human studies will be crucial for elucidating the clinical relevance of thyroid hormones in brain development and cognitive function.

In summary, our study has provided valuable insights into the critical role of thyroid hormones in brain development and function, with implications for therapeutic interventions. Thyroid hormones play a multifaceted role in neurogenesis, neuronal differentiation, and synaptic plasticity, all of which are essential for normal brain development and cognitive function. Understanding the mechanisms by which thyroid hormones act on the brain will pave the way for the development of novel therapeutic strategies for developmental disorders and cognitive impairments associated with thyroid hormone imbalances.

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