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Review Article

The Relationships between Thyroid Hormones and the Brain Serotonin (5-Ht) System and Mood: Of Synergy and Significance in the Adult Brain- A Review

MH Rahman[1], MY Ali[2]

Abstract:

The use of thyroid hormones as an effective adjunct treatment for affective disorders has been studied over the past three decades and has been conformed repeatedly. Interaction of the thyroid and monoamine neurotransmitter systems has been suggested as a potential underline mechanism of action. While catecholamine and thyroid interrelationships have been reviewed in detail, the serotonin system has been relatively neglected. Thus, the goal of this article is to review the literature on the relationship between thyroid hormones and the brain serotonin (5-HT) system. In humans, neuroendocrine challenge studies in hypothyroid patients have shown a reduced 5-HT responsiveness that is reversible with replacement therapy.

In the majority of the studies, the effects of thyroid hormone administration in animals will experimentally-induced hypothyroid sates include an increase in cortical 5-HT concentrations and a desensitization of auto inhibitory 5-HT_{1A} receptors in the rap he area, resulting in disinhibition of cortical hippocampal 5-HT release. Furthermore, there is some indication that thyroid hormones may increase cortical 5-HT_2 receptor sensitivity. In conclusion, there is robust evidence, particularly from animal studies, that the thyroid economy has a modulating impact in the brain serotonin system. Thus it is postulated that one mechanism, among others, through which exogenous thyroid hormones may exert their modulatory effects in affective illness is via an increase in serotonergic neurotransmission, specifically by reducing the sensitivity of 5-HT_{1A} auto receptors in the raphe area, and by increasing 5-HT_2 receptor sensitivity.

Key words: Serotonin system, T_3,T_4, thyroid system, adult brain, 5-HT receptor, mood modulation, affection disorders, depression.

Introduction:

Disorders of the thyroid gland are frequently associated with severe mental disturbances[1,2]. This intimate association between the thyroid system and behavior has been the impetus for exploring the effects of the thyroid hormones in modulating affective illness, and the role of the hypothalamic-pituitary thyroid (HPT) axis in the pathophysiology of mood disordes[3]. Thyroid hormones (TH) have a profound influence on behavior and mood, and appear to be capable of modulating the phenotypic expression of major affective illness[3,4,5,6]. Thyroid supplementation is now widely accepted as an effective treatment option for patients with affective disworders[7,8,9].

Action of thyroid hormones in the adult brain

It is well established that thyroid hormones are essential for both the development and maturation of the human brain, affecting such diverse events as neuronal processing and integration, glial cell proliferation, myelination, and the synthesis of key enzymes required for neurotransmitter synthesis[10,11]. Thyroid deficiency during the prenatal period results in irreversible brain damage and mental retardation. However, despite this accepted body of knowledge and in disregard of the clinical and therapeutic observations in association with affective illness, the action of thyroid hormones in CNS function in adults has not been widely acknowledged by general endocrinologists. This lack of interest seems to have originated in the 1950s and 1960s, when early physiological studies suggested that oxygen consumption the nature human brain did not change with changing thyroid status[12,13,14].

Thus, in contrast to our understanding of thyroid hormones critically important role in the development of the CNS, until recently, little has been known about the function and effects of thyroid hormones in the mature, mammalian brain[15]. However, with improved methods in basic research the action of thyroid hormones in the mature brain has become a subject of greater interest[16]. There are several lines of evidence suggesting that thyroid hormones affect mature brain function.

1. Dr. Md. Hafizur Rahman, MBBS, Principal Medical Officer, Institute of Nuclear Medicine & Allied Sciences, Faridpur.

2. Dr. Md. Yusuf Ali, FCPS (Medicine) Professor and Head, Dept. of Medicine, Faridpur Medical College.

Address of correspondence :
Dr. Md. Hafizur Rahman, MBBS, Principal Medical Officer, Institute of Nuclear Medicine & Allied Sciences, Faridpur.
Mobile: +88-01711235280, Email: mhrn08@yahoo.com

Monoamines and mood

Over the past two decades it has become apparent that the monoamines, specifically norepinephrine and serotonin play a major role in mood modulation[17-21]. These long track systems which begin in the brainstem and extend through the midbrain into the limbic system and cortex modulate the activity of many of the brain regions related to emotion and memory. The interdependence of these long tracks-including the dopamine system-with thyroid hormone metabolism has become better understood as our technology has improved.

The catecholaminergic system was initially investigated largely because of the known physiological association between sympathetic activity and thyroid hormones. 20 Thyroid hormones appear to play an important role in regulating central noradrenergic (NA) function and it has been suggested that thyroid dysfunction may be linked with abnormalities in central NA neurotransmission[21]. Evidence for a thyroid-NA interaction derives largely from immunohistochemical mapping studies demonstrating T_3 is concentrated in both nuclei and projection sites of central NA systems[22]. Recent evidence that T_3 is also delivered from the locus ceruleans to its NA targets via anterograde axonal transport indicates that T_3 may function as a co-transmitter with nor-epinephrine in the adrenergic nervous system[23].

However, the neuropharmacological effects and functional pathways underlying the therapeutic effects of thyroid hormones in patients with affective disorders are still unclear. One of the most intuitive hypotheses postulates the existence of a brain thyroid hormone deficiency in affective illness. Thyroid hormone therapy can then be considered a replacement therapy with a possible mechanism of action being its pharmacological adrenergic receptor activity and thus promoting the action of catecholamines at central receptor sites[21].

The CNS serotonin system

As with the noradrenergic and dopaminergic systems, the bulk of the CNS serotonergic nerve terminals originate in the neuronal cell bodies of the brainstem raphe nuclei and project, both rostrally and caudally, to neuroanatomically discrete areas throughout the brain but with extensive innervation of the cerebral cortex and the limbic system[24]. Although the serotonin system has been given prominence in recent deliberation regarding mood modulation, particularly since the advent of drugs that specifically interfere with serotonin neuronal reuptake systems, there has been little investigation of the relationship of this system to the thyroid system. This paper analyzes the existing literature pertaining to this relationship and explores areas which may be fruitful for further study.

The brain serotonin system and its role in depression

Basic and clinical research of the past three decades has yielded compelling evidence that the serotonergic system is intimately involved in the pathogenesis of depression[17,19,25,26]. Changes in serotonergic neurotransmission have been repeatedly associated with the therapeutic response to antidepressant and mood stabilizing medacation[17,27]. Almost all currently employed treatments for depression, including the tricycle antidepressants, the SSRIs, the MAO inhibitors, lithium and ECT, directly or indirectly augment serotonergic neurotransmission[28]. Another line of evidence derives from the tryptophan-depletion paradigm, a procedure that lowers central serotonin levels, and which produces a rapid relapse of SSRI-responsive depression[27,29]. Other support comes from studies demonstrating lowered levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of 5-HT whose levels reflect central serotonin activity, in the CSF in unmediated depressed patients[19]. In brain imaging studies, clinical depression was associated with reduced serotonin transporter availability[30,31].

Results of the review

Effects of experimentally-induced hypothyroid states on brain serotonin system in animals, studies in neonatal animals: Stimulated by the essential role of thyroid hormones in brain development, the effects of hypothyroidism on serotonergic neurotransmission were originally studied in neonatal rats. In these studies, 5-hydroxytryptamine (5-HT, serotonin) and 5-HIAA, the main 5-HT metabolite, were found to be significantly elevated and the serotonin precursor 5-hydroxytrytophan (5-HTP) to be decreased compared to euthyroid controls indicating an increased serotonin turnover rate in the neonatal period[32]. Other data have demonstrated that neonatal hyperthyroidism induced by daily application of T_3 also resulted in an increased turnover of 5-HT[33].

Measurements of 5-HA and its metabolites in adult hypothyroid animals: In the adult rat brain, hypothyroidism generally induced lesser changes in the serotonergic system compared to the studies in neonatal animals. Thirteen studies were identified that measured the effects of experimentally -induced hypothyroidism on the serotonergic system. One early study measured brainstem 5-HT concentrations and did not fine significant differences compared to euthyroid animals[34]. Later, using more sensitive assay techniques, five studies measured 5-HT and 5-HIAA concentration or the 5-HIAA/5-HT ratio as an indicator of the serotonin turnover and reported increased 5-HT metabolites in the brainstem[35-39] (notice: one study calculated the inverse ratio, 5-HT/5-HIAA[41]). Reduced 5-HT concentrations

in the cortex[40,41] and reduced concentrations of the serotonin precursor 5-HTP were reported in the whole brain[42] of hypothyroid adult rats. These findings of increased 5-HT turnover in the brainstem and decreased levels of 5-HT and its precursors in the cortex/whole brain are in accordance with the hypothesis that increased brainstem 5-HT turnover might active raphe 5-HT_{1A} auto receptors and subsequently decrease serotonin release in the cortical projection areas[17].

In Summary, 5-HT receptor studies in adult euthyroid rodents indicate that thyroid hormone application may desensitize presynaptic 5-HT_{1A} raphe auto receptors, and thus increase cortical serotonin release, an effect similar to that described after addition of the 5-HT_{1A} receptor antagonist pindolol to an ongoing SSRI treatment[43]. The receptor studies also indicate that thyroid hormone application may increase cortical 5-HT_2 receptor sensitivity. This increase in 5-HT_2 receptor function does not seem to be linear, as stress-induced activation of hypothalamic 5-HT_2 receptor was blunted in hyperthyroid rats[44]. Cortical 5-HT_2 receptor densities were only increased after prolonged treatment with relatively high doses of thyroid hormone in thyroidectomized rats. In contrast, standard does of T_3 in euthyroid rats resulted in a decrease in the number of cortical 5-HT_2 receptors.

Implication for thyroid hormone modulation of mood disorder

The molecular mechanisms underlying the efficacy of thyroid hormone treatment in patients with mood disorders, and in patients with primary hypothyroidism who have co morbid depression, are not known. From the few studies in humans with thyroid dysfunction, there in some evidence from the neuroendocrine challenge studies that hypothyroid status is associated with a reduced 5-HT responsiveness, Furthermore, this appears to be reversible with thyroid replacement therapy[45,46]. However given the small number of studies in studies in humans definitive conclusion cannot be drawn. Not only is the number of studies limited but the sample sizes in the studies were small and the methods employed to assess central 5-HT function varied considerably. It is also questionable whether the peripheral blood and CSF content of 5-HT and its metabolites provide an index of brain serotonergic neurotransmission[47] while neuroendocrine challenge studies provide only an indirect way of 'probing' central 5-HT function[48].

Conclusion:

In review found evidence, particularly from results in animal studies, to support the hypothesis that thyroid status impacts the serotonin system in the adult brain, and that increasing thyroid hormone levels increase serotonin neurotransmission. Give the important role of the serotonin system in the pathogenesis of depression is speculate that the serotonin system may be involved in the mood modulating effects of thyroid hormones among patients with affective disorders. This hypothesis would explain why thyroid hormones are most effective in patients with affective disorders when administered as an adjunctive treatment to antidepressant and/or mood stabilizes that perturb the serotonin system. This is also supported by evidence that thyroid hormones alone appear to have limited clinical use in affective illness[4,5].

It must be emphasized however that this interaction with the serotonin system is probably only one of the mechanisms through which thyroid hormones may have modulatory effects in mood disorders. Thyroid hormones interact with a broad range of neurotransmitter systems thought to be involved in the regulation of mood including post-receptor and signal transducing, as well as gene regulatory mechanisms.

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