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Thyroid Hormones and the Treatment of Depression: An Examination of Basic Hormonal Actions in the Mature Mammalian Brain

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ABSTRACT Numerous clinical reports indicate that thyroid hormones can influence mood, and a change in thyroid status is an important correlate of depression. Moreover, thyroid hormones have been shown to be effective as adjuncts for traditional antidepressant medications in treatment-resistant patients. In spite of a large clinical literature, little is known about the mechanism by which thyroid hormones elevate mood. The lack of mechanistic insight reflects, in large part, a longstanding bias that the mature mammalian central nervous system is not an important target site for thyroid hormones. Biochemical, physiological, and behavioral evidence is reviewed that provides a clear picture of their importance for neuronal function. This paper offers the hypothesis that the thyroid hormones influence affective state via postreceptor mechanisms that facilitate signal transduction pathways in the adult mammalian brain. This influence is generalizable to widely recognized targets of antidepressant therapies such as noradrenergic and serotonergic neurotransmission. **Synapse 27:36–44, 1997.**

INTRODUCTION

Numerous clinical reports indicate that thyroid hormones are effective as adjuncts in the treatment of depression (Bauer and Whybrow, 1988; Haggerty and Prange, 1995; Joffe and Sokolov, 1994). Approximately 30% of depressed patients fail to respond to traditional antidepressants, and 67% of these nonresponders can benefit from the coadministration of thyroid hormones. In spite of a large clinical literature, little is known about the mechanism by which thyroid hormones elicit their mood-elevating properties. This lack of understanding is, in large part, a reflection of the more generalized lack of information available on the influence of thyroid hormones on the adult mammalian brain. What information that is available has largely focused on a relationship between catecholaminergic neurons and thyroid hormones within synaptic terminals (Dratman, 1974; Dratman et al., 1976). This review offers the hypothesis that the thyroid hormones provide an important influence on the mature mammalian brain via intracellular pathways that facilitate signal transduction. This influence is likely to be mediated through gene expression. Postreceptor events that impact on serotonergic, as well as catecholaminergic neuronal activity, are central to this hypothesis.

The influence of thyroid hormones on the developing nervous system is dramatic and has been intensively studied (Bernal and Nunez, 1995; Dussault and Ruel, 1987). Cretinism and associated neurological impairments provide a poignant clinical reference to the impact that hypothyroidism has on neural development. Issues pertinent to the impact that the thyroid hormones have on the developing central nervous system (CNS) has received extensive attention. Developmental issues will not be addressed within this review.

In contrast, little is known about the effects of thyroid hormones on the mature mammalian brain. Disinterest derives, in part, from early reports that the mature brain was not a target site for thyroid hormone-mediated increases in oxygen consumption, a commonly used marker outside the CNS (Oppenheimer, 1979). Although functional attributes could not be identified, Oppenheimer (1979) demonstrated that a substantial number of thyroid hormone receptors existed within the mature brain. Additionally, he pointed out that various tissues in the body respond uniquely to thyroid hormone stimulation. Thompson et al. (1987) subsequently showed that the thyroid hormone receptor subtype, Tr_{α}, was preferentially localized to the brain. Numerous recent findings expand on these insights and provide compelling evidence that the mature mammalian brain is responsive to the thyroid hor-

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mones. It seems likely that the recognized importance of thyroid hormones as adjuncts to antidepressant therapies provides a clinical correlate to our nascent understanding of the effects that these hormones mediate within the CNS. The well-recognized coincidence of thyroid dysfunction and depression supports this line of inquiry (Bauer and Whybrow, 1988; Denicoff et al., 1990; Haggerty and Prange, 1995). It is the intent of this review to develop a perspective on the role that the thyroid hormones play within the mature CNS, and to consider mechanisms whereby these hormones can interact with antidepressant therapies to influence affective state.

Antidepressant therapies

Tricyclic antidepressant (TCA) medications, potent reuptake blockers at monoaminergic nerve terminals, have been a mainstay for the pharmacological control of depression. As with electroconvulsive therapy, lithium treatment, and monoamine oxidase inhibitors, the tricyclic drugs are believed to elicit therapeutic benefit via effects on monoaminergic neuronal systems (Cooper et al., 1996; Garbutt et al., 1986; Nibuya et al., 1996). Nontricyclic reuptake blockers such as fluoxetine or maprotoline are also believed to elicit therapeutic benefit through effects on monoaminergic neurotransmission (Hoflich et al., 1992; Hrdina and Vu, 1993). In spite of a general consensus on a focus for antidepressive therapy, many questions remain unanswered. For instance, the immediate increase in synaptic concentration of monoamines that these medications elicit is difficult to correlate with the several-week delay before therapeutic benefit is derived (Nibuya et al., 1996).

Selectivity among the reuptake blockers has been described. For instance, desipramine is known to be selective for norepinephrine reuptake, sertraline for serotonin, while imipramine affects both amines (Baldessarini, 1996). There is some evidence based on dietary amino acid supplementation and depletion studies indicating that certain subsets of depressed patients can be categorized on the basis of the monoaminergic neuronal system that appears to be most affected (Cooper et al., 1996; Delgado et al., 1991). From these and other similar observations, two generalized monoamine-based hypotheses have evolved relative to the etiology of depression: the catecholamine hypothesis, and the serotonin hypothesis (Maes and Meltzer, 1995). While the focus of "the catecholamine theory of depression" has been directed at noradrenergic neurotransmission (Sanders-Bush et al., 1989), the importance of other catecholaminergic neurotransmitters, notably dopamine, has not been ruled out (Cooper et al., 1996). For the purpose of conciseness, this review will incorporate a bias on noradrenergic neurotransmission as a vehicle for comparing and contrasting findings that pertain to serotonergic neurotransmission.

In spite of some evidence that depressed patients can be subcategorized as norepinephrine- or serotonin-specific, it does not appear that selectivity of reuptake blocker is an important determinant of overall therapeutic effectiveness in heterogeneous populations of depressed patients. Along similar lines, anecdotal evidence has been offered that the selectivity of therapy dissipates with chronic drug treatment. Nor are the more recently popularized nontricyclic, serotonin-selective reuptake inhibitors such as fluoxetine more effective in the remission of symptoms of depression when compared to a tricyclic antidepressant. Minimization of side effects provides the basis for the popularity of the non-TCA, serotonin-specific reuptake blockers. Thus, a large number of drugs, both structurally similar and dissimilar, have been shown to be effective in the treatment of depression. Their commonality derives from their ability to enhance either noradrenergic or serotonergic neurotransmission (Nibuya et al., 1996).

Although there has been extensive work on receptor characteristics with antidepressant therapies, a clear picture on the importance of specific receptor changes is not obtainable (Beasley et al., 1992; Goodwin et al., 1984; Hrdina, 1987; Peroutka and Snyder, 1980; Spurlock et al., 1994). Ambiguity relative to noradrenergic versus serotonergic involvement implies a mechanism of action that overlaps both neurotransmitter-based systems. It seems clear that an understanding of depression and its treatment will require an understanding of mechanisms involved in signal transduction distal to synaptic events (Duman et al., 1994; Mann et al., 1995; Nalepa and Vetulani, 1991; Silver et al., 1986). Further, the convergent, interactive characteristics of second messenger systems are likely to provide a key to an understanding of the relative importance of catecholamine and serotonergic inputs in depression (Nibuya et al., 1996).

Second messenger-based hypotheses of therapeutic effectiveness have been most aggressively pursued in the context of lithium administration, a well-established therapeutic agent for the treatment of manic depression (Berridge et al., 1989). It follows that relatively nonspecific changes in second messenger systems are likely to be important in the ability of lithium to potentiate the therapeutic benefit of tricyclic antidepressant medications (Garbutt et al., 1986). Thus, a subset of patients that are nonresponsive to traditional antidepressant medications can benefit from adjunctive administration of either thyroid hormone or lithium administration. While their mechanisms of action are likely to be different, both adjuncts are known to elicit important intracellular adaptations that have the potential to influence monoaminergic neurotransmission (Garbutt et al., 1986; St. German, 1987).

Thyroid hormones and the central nervous system

General mechanisms of action

Thyroid hormones have a broad influence on the body. While their effects outside the CNS have been intensively studied, much less is known regarding their importance in the CNS (Barker and Klitgaard, 1952; Oppenheimer, 1979; Schwartz and Oppenheimer, 1978). Recently, a body of literature has accumulated implying an important role within the adult mammalian CNS as well.

Triiodothyronine (3,5,3′-triiodothyronine, T_3), the primary biologically active thyroid hormone (Samuels et al., 1989; Surks and Oppenheimer, 1977) is derived from 5′-monodeiodination of 3,5,3′,5′-tetraiodothyronine (thyroxine, T_4), the primary secretory product of the thyroid gland (Puymirat, 1992; Surks et al., 1973). Specific mechanisms are present for the transport of thyroid hormones into the CNS (Dratman et al., 1991; Schreiber et al., 1990). Whereas, in the periphery, most T_3 is derived from enzyme activity leading to accumulation of T_3 in the bloodstream (Surks et al., 1973), Crantz et al. (1982) found that over 70% of the T_3 bound to nuclear receptors in the cerebral cortex is generated by intracellular deiodination. The 5′-deiodinase (Type II) that converts T_4 to T_3 in CNS differs from the predominant Type I 5′-deiodinase deiodinase found outside the CNS (Kaplan and Yaskoski, 1980; Silva and Larsen, 1982; Silva et al., 1982; Visser et al., 1982). It is thought that the Type II deiodinase provides the CNS with the capacity to regulate thyroid status within the CNS somewhat independently of the rest of the body (Dratman et al., 1983). A large body of information indicates that the primary site of action of T_3 is via nuclear receptors and subsequent influence on gene expression (Bernal and Nunez, 1995; Brent et al., 1991; Oppenheimer, 1979; Puymirat, 1992). Receptors for T_3 are nearly saturated in euthyroid rat brain (Crantz et al., 1982).

In addition to a nuclear site of action, it has been postulated that the thyroid hormones may elicit effects via a more direct influence on neurotransmission at the level of the synapse (Dratman, 1974). Evidence for this hypothesis includes the demonstration of a selective uptake of $[^{125}I]T_3$ into synaptosomes (Dratman et al., 1976; Dratman and Crutchfield, 1978; Kastellakis and Valcana, 1989), localization of specific T_3 receptors in the synaptic membrane (Mashio et al., 1982, 1983), inhibition of the uptake of gamma-aminobutyric acid (GABA) into synaptosomes in a manner that excludes a shared transport mechanism (Mason et al., 1987b,c), T_3-mediated enhancement of depolarization-induced uptake of Ca^{++} (Mason et al., 1990), release of T_3 from synaptosomes via Ca^{++}-dependent depolarization (Mason et al., 1993), a 9-fold increase in synaptosomal T_3 concentrations during hypothyroidism (Sarkar and Ray, 1994), the possible conversion of T_4 to T_3 within nerve terminals (Dratman and Crutchfield, 1978), and a nonuniform distribution of exogenously administered T_3 within the CNS (Dratman et al., 1982a, 1987; Dratman and Crutchfield, 1989). Limited evidence relative to the physiological importance of these findings has been provided (Dratman et al., 1982b). The possibility that the thyroid hormones have an important direct influence at the synaptic level will not be considered further in this review. Nonetheless, it is important to indicate that thyroid hormonal influences at more than one site within the CNS are not necessarily conflicting concepts.

Influence on noradrenergic and serotonergic neurotransmission

Neurochemistry. Evidence from work in adult rats indicates that the thyroid status influences both noradrenergic and serotonergic neurotransmission. In general, findings pertaining to serotonin are more consistent than their counterparts for noradrenergic neurotransmission. Nonetheless, data relevant to both neuronal groups can be interpreted as adaptive rather than primary responses to changes in thyroid status.

A substantial body of neurochemical evidence in animals indicates that central serotonin metabolism is altered with changes in thyroid status. Increased concentration of 5-hydroxyindoleacetic acid (5HIAA), the principal metabolite of serotonin, is a robust, widespread finding throughout the brain and spinal cord of the adult hypothyroid rat that is reversible with hormonal replacement (Henley et al., 1991; Henley and Bellush, 1992; Savard et al., 1983). Further, T_3 implants caused suppression of 5HIAA within 7 days in a dose-dependent manner in thyroid intact rats (Henley et al., 1996). Similarly, 5HIAA has been shown to be decreased in striatum and cerebellum of the adult rat administered T_3 (100 μg/kg/day) for 30 days (Rastogi and Singhal, 1976). The suggestion that impaired transport of 5HIAA out of the hypothyroid brain is the basis for neurochemical findings (Savard et al., 1983) is unlikely given that inhibition of serotonin synthesis with i.c.v. p-chlorophenylalanine caused larger drops in 5HT and 5HIAA in hypothyroid rats (Henley and Bellush, 1992).

In spite of the uniform findings in discrete locations of the hypothyroid brain (Savard et al., 1983), an obligatory relationship between hypothyroidism and changes in serotonin metabolism is unlikely since streptozotocin-diabetic rats that are mildly hypothyroid exhibit decreases in 5HIAA (Henley and Bellush, 1992). Although prior induction of hypothyroidism blunts the expected streptozotocin-induced decrease in 5HIAA (Henley and Bellush, 1991), prior administration of streptozotocin blunts an expected hypothyroid-induced increase (unpublished findings). Thus, the observed changes in serotonin metabolism in hypothyroid and hyperthyroid rats are consistent with a generalized

inverse relationship between serotonin metabolism and thyroid status although complex interactions with other factors are important as well. Opposite neurochemical findings to those obtained in the rat have been obtained in adult hyperthyroid mice, suggesting species variation (Engstom et al., 1975; Heal and Smith, 1988; Strombom et al., 1977).

Neurochemical findings provide little insight into the importance of thyroid hormones as they pertain to noradrenergic neurotransmission. Using the synthesis blocker α-methyl-p-tyrosine, significant increases and decreases in norepinephrine utilization have been noted with either hypothyroidism or hyperthyroidism dependent on brain region assayed (Andersson and Eneroth, 1985a,b, 1987). Along similar lines, Harris et al. (1986) showed that hypothyroidism decreased while hyperthyroidsm increased norepinephrine synthesis localized to the mediobasal hypothalamus, yet no similar effects were seen in anterior hypothalamus or striatum. The findings of both increases and decreases in the same animal, depending on the brain region assayed, provide a picture of a diverse adaptive response to changes in thyroid status rather than a global biochemical response that might be expected if a rate-limiting protein such as tyrosine hydroxylase were regulated by thyroid hormone.

Together, indirect neurochemical indices provide stronger evidence that serotonergic neurotransmission is directly involved with adaptations associated with changes in thyroid status. A weakness of the currently available evidence is that it uniformly characterizes the resting state. Newer techniques examining different questions from the present (Kreiss et al., 1993; Puig et al., 1991) indicate that neurochemical responses to stimuli, rather than a characterization of resting state, may provide useful insights that are not currently available.

Receptor profiles. Few reports are available on serotonergic receptor profiles with changes in thyroid status. Contradictory evidence exists regarding $5HT_2$ receptor populations utilizing overlapping experimental protocols. Thus, both increases (Mason et al., 1987a) and decreases (Sandrini et al., 1996) in receptor populations have been reported in hyperthyroidism without influence on binding affinities. The former report also indicated that thyroidectomy was accompanied by decreased receptor density in striatum but not cortex. Additionally, Sandrini et al. (1996) found that $5HT_{1A}$ receptors were not affected by thyroid hormone administration. More work will be required to determine the importance of central serotonergic receptors when thyroid status varies.

In contrast to studies on serotonergic receptors, central catecholaminergic receptors have been better studied, and more consistency of findings is evident. In general, hypothyroidism in adult male rats is found to be accompanied by modest decreases in β-, α_1-, and α_2-adrenergic receptor density in cerebral cortex (Grob et al., 1981; Gross et al., 1980a; Sandrini et al., 1991; Tejani-Butt and Yang, 1994) while hyperthyroidism is accompanied by increases in β- (Mason et al., 1987a; Sandrini et al., 1991), α_1- (Grob et al., 1981) and α_2- (Swann, 1988) receptor densities in cerebral cortex. Significant changes in receptor dissociation constants were not found in these studies.

Changes in postreceptor responsiveness. The influence of the thyroid hormones on G-protein synthesis, receptor/G-protein coupling, and phosphorylation events that facilitate transcriptional events is well established; the context for these findings has generally been with reference to metabolic consequences in the periphery (Jones et al., 1994; Malbon et al., 1984; Ros et al., 1988). Nonetheless, a number of findings indicate that thyroid hormones exert similar influences on the mature mammalian brain even though changes in cerebral oxygen consumption do not occur. The brain is known to be a rich source of G-proteins with subtype distribution somewhat unique to other organs in the body (Mumby et al., 1988; Price et al., 1989). As in the periphery, evidence indicates that the thyroid hormones exert important influence over G-protein synthesis and activity in the mature mammalian brain (Orford et al., 1991, 1992). Thus, 8-week-old rats made hypothyroid with propylthiouracil have significant increases in the amount of G_i and G_o when compared with euthyroid controls. These changes are widespread throughout the brain and approximate 4-fold increases in some instances (Orford et al., 1991). Complimentary evidence was provided by the finding that decreases in G_i occur in 8-week-old euthyroid rats briefly administered high levels of T_3 (1 mg/kg; 3 days) in cerebrum and cerebellum (Orford et al., 1992). Careful examination of the latter report indicates that similar findings were found in other brain regions and in other G-protein subtypes, though statistically significant documentation was not obtained.

The work by Orford et al. (1992) is complemented by findings from various laboratories. For example, adenylate cyclase activity is attenuated when norepinephrine is applied to cerebral brain slices from the hypothyroid rat (Gross et al., 1980b). This finding is unlikely to be specific to the β-adrenergic receptor since a similar attenuation of adenylate cyclase activity has been noted during stimulation with forskolin or with an adenosine agonist (Mazurkewicz and Saggerson, 1989); the latter findings were obtained in synaptosomes from the forebrain of the hypothyroid rat. In addition to impaired signal transduction via adenylate cyclase, hypothyroidism has been associated with decreased striatal formation of inositol phosphate in response to carbachol in the adult rat (Iriuchijima et al., 1991). Thus, both adenylate cyclase as well as phosphoinositide-based signalling appear to be deranged in the brain of the hypothyroid rat. Findings at thyroid target

sites outside the CNS provide strong parallels to the findings in the CNS (Meier et al., 1991).

Biochemical data suggesting that thyroid status has an important influence on intracellular signalling pathways within the brain have physiological correlates. In adult hypothyroid rats, an impairment of the responsiveness of single brainstem units to iontophoretic administration of norepinephrine was found (Gonzales-Vegas and Fuenmayor, 1978). Along similar lines, this lab has found a robust attenuation of cardiovascular responsiveness to i.c.v. administration of dl-2,5-dimethoxy-4-iodoamphetamine dl-2,5-dimethoxy-4-iodoamphetamine (DOI), a $5HT_2$ agonist (Henley and Valic, 1997), in the hypothyroid rat. Both findings are explainable by alterations in signal transduction pathways that impact on both noradrenergic and serotonergic neurotransmission.

Gene expression and anatomical observations

Molecular studies have shown that the mature brain has genetic loci that are responsive to thyroid hormones (Bernal and Nunez, 1995). Of special relevance to this review is the demonstration that at least one gene, RC3/neurogranin, is regulated by thyroid hormone in the mature rat brain (Iniguez et al., 1991, 1993). RC3/neurogranin is a protein kinase C substrate that binds calmodulin and is located in dendritic spines and soma of forebrain neurons (Iniguez et al., 1993) and may be involved in long-term potentiation in hippocampus. Along similar lines, expression of the neurotrophin, nerve growth factor (NGF), and its receptor have been shown to be decreased in the forebrain of the adult, hypothyroid rat (Alvarez-Dolado et al., 1994).

Potentially related findings have been obtained with morphological techniques (Gould et al., 1990; Ruiz-Marcos et al., 1982). Thus, adult hypothyroidism has been shown to cause a decrease in spine density and derangement in their distribution in pyramidal cells of the visual cortex (Ruiz-Marcos et al., 1982). The decrease was partially reversible when moderate T_4 replacement was administered starting 30 days after thyroidectomy. Along similar lines, Gould et al. (1990) found that hyperthyroidism caused an anatomically specific decrease in spine density in the apical dendrites of CA1 pyramidal cells of the adult rat hippocampus. Together, biochemical and anatomical markers thought to be associated with mental state appear to be directly influenced by thyroid status in adult rats.

Behavioral influences

The mood-elevating properties of thyroid hormone administration is widely recognized in the clinical setting (Bauer and Whybrow, 1988; Denicoff et al., 1990). Impaired cognition and generalized neural dysfunction have long been associated with hypothyroidism while irritability and anxiety are commonly referenced correlates of hyperthyroidism. A report by Denicoff et al. (1990) is especially informative since they studied 25 patients that were thyroidectomized to remove carcinomas. Mood elevations were evident with the administration of either T_3 or T_4 and this finding existed even though the incidence of depression was modest. Thus, the ability of thyroid hormone administration to serve as an adjunctive therapy in TCA-resistant depression is probably a generalizable property of thyroid hormones on the brain. Concerns about the metabolic consequences of widespread administration of thyroid hormones have limited their use, although they are therapeutically effective at dosages that do not create a hypermetabolic state (Gewirtz et al., 1988).

Numerous reports have noted changes in behavior of rodents with alterations in thyroid status. Thus, severalfold increases in hyperactivity in response to either catecholaminergic or serotonergic challenges have been noted in the hyperthyroid rat (Atterwill, 1981). Similarly, the head twitch response to the administration of 5-hydroxytryptophan, currently believed to be a $5HT_2$-mediated event (Goodwin et al., 1984), was potentiated by 3 days of T_3 administration in the adult mouse (Brochet et al., 1985). The latter study also showed that a number of antidepressant medications given at subeffective dosages greatly potentiated the influence of T_3 administration on 5-hydroxytryptophan-mediated head twitches. The same investigators showed that T_3 administration hastened antidepressant-induced reversal of learned helplessness in rats (Brochet et al., 1987). In a study by Levine et al. (1990), it was shown that thyroparathyroidectomy produced depression-like escape deficits in the rat. Complementary studies indicated that high doses of T_3 prevented the development of escape deficits (Martin et al., 1985). The latter studies are especially important given that the escape deficit obtained in rats is an animal analogue of human depression. As a final comment, it should be pointed out that thyroid-dependent changes in neurochemistry, receptors and behavior are not unique to noradrenergic and serotonergic neurons. For example, behaviors elicited by dopamine agonists or antagonists have also been shown to be influenced by thyroid status (Atterwill, 1981; Crocker et al., 1986).

Neurochemical and binding data for noradrenergic and serotonergic neurons provide mixed evidence for the involvement of both neuronal networks in adaptations associated with changes in thyroid status in the mature rat brain. Biochemical data indicate that signalling pathways downstream from receptors may be a more important site at which neurotransmission is affected. Molecular studies indicate that thyroid-dependent gene products that interact with signal transduction pathways are actively regulated in the mature mammalian brain. Physiological and anatomical studies provide correlates for the biochemical studies. Changes in behavior due to alterations in thyroid status support the biochemical findings as well. Behav-

ioral findings include clinical observations, as well as rodent behavioral models that are used to model affective disorders in humans. Thus, available biochemical and physiological information obtained in rodents is likely to provide important mechanistic insight into thyroid-dependent influences on affective state in humans.

Thyroid hormones in depression

A number of lines of evidence indicate that changes in thyroid status are involved in many cases of clinical depression. Virtually 100% of patients with severe hypothyroidism also suffer with depression (Haggerty and Prange, 1995). Subclinical or "occult" hypothyroidism, in contrast to severe hypothyroidism, is likely to be a quantitatively more important contributor to the total incidence of depression (Gerwirtz et al., 1988; Haggerty and Prange, 1995). Additionally, the large variations evident in tests for subclinical hypothyroidism and the uncertain incidence of thyroid hormone resistance increases the likelihood that a substantial number of cases of thyroid dysfunction go undiagnosed. Together, it is clear that hypothyroidism and subclinical hypothyroidism are important correlates of clinical depression, and the recognized level of association is probably conservative.

A hallmark of depression is a finding of elevated serum T_4 or free T_4 levels without changes in T_3 (Bauer and Whybrow, 1988). Typically, reductions in T_4 levels accompany a beneficial response to antidepressant medications (Bauer and Whybrow, 1988; Hoflich et al., 1992; Stern et al., 1991). These findings appear counterintuitive in conjunction with a large body of data suggesting a relationship between hypothyroidism and depression. The seeming paradox is easily resolved with the added insight that reverse triiodothyronine (rT3; 3,3′,5′-triiodothyronine) is a potent inhibitor of the deiodinase that converts T_4 to T_3 in the brain (Obregon et al., 1986), and that T_3 is the metabolically active thyroid hormone. Thus, the elevated T_4 accompanied by increases in central rT_3 is almost certain to be an adaptive response (Bauer and Whybrow, 1988). The recognition that depressed patients with elevated circulating T_4 levels are not clinically hyperthyroid (Bauer and Whybrow, 1988) and can even be hypometabolic (Gewirtz et al., 1988), emphasizes this point.

Thyroid hormone potentiation of antidepressant therapies

A substantial body of information regarding the utility of thyroid hormonal administration in the management of depression has been generated. This area of inquiry had its origin in the observations in humans and mice that hyperthyroidism had a potent lethal influence when coadministered with imipramine, a nonselective tricyclic reuptake inhibitor (Prange, 1963; Prange and Lipton, 1962). Numerous subsequent studies have provided a large empirical base indicating than thyroid hormones can potentiate tricyclic antidepressant therapy in approximately 67% of treatment-resistant populations of depressed patients. Most studies indicate the effectiveness of coadministration of either T_3 or T_4 with a variety of antidepressant therapies including the administration of tricyclic compounds (Bauer and Whybrow, 1988; Wheatley, 1972), electroconvulsive shock therapy (Stern et al., 1991), or sleep deprivation (Southmayd et al., 1992). Although the interaction between catecholamines and thyroid hormones has long been known, there has been little evidence to support this as a basis for a synergistic influence on affective state. Increased interest in serotonin as a key neurotransmitter in the etiology of depression has muddled this issue even further. This lapse in understanding reflects, in part, the long-standing lack of appreciation regarding the role that the thyroid hormones play in the mature mammalian brain. In preceding sections, we provided strong evidence that the thyroid hormones influence monoaminergic neurotransmission within the mature mammalian CNS at a number of sites. These data indicate that the most important site of action is modulation of monoaminergic neurotransmission at a postreceptor site. Behavioral data provide a strong linkage between biochemical, physiological, and anatomical findings in rodents to an influence on affective state in humans.

A recognition of the importance of thyroid hormonal influence on monoaminergic neurotransmission within the CNS is important. Notable in this context are the implications for a better understanding of the mechanisms underlying affective disorders. The complexity of mood disorders makes it unrealistic to expect that a single factor would be all important as an etiological factor. An understanding of numerous factors impinging on various points within signal transduction pathways is likely to be required to form a complete understanding of affective state. Nonetheless, clinical data indicate that thyroid hormonal status is one quantitatively significant factor for this understanding. The finding that a wide range of diverse antidepressant therapies elicit similar intracellular changes (Nibuya et al., 1996) underscores the likely importance of generalized thyroid-mediated influences on signal transduction pathways. It follows that hormonal correction should provide a primary focus of intervention when depression is thyroid-dependent.

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