17

Depressive Disorders and Thyroid Function

A. Verónica Araya[1], Teresa Massardo[2], Jenny Fiedler[3], Luis Risco[4], Juan C. Quintana[5] and Claudio Liberman[1]
[1]*Endocrinology Section, Clinical Hospital of the University of Chile*
[2]*Nuclear Medicine Section, Clinical Hospital of the University of Chile*
[3]*Faculty of Chemical and Pharmaceutical Sciences, University of Chile*
[4]*Psychiatric Clinic of the Clinical Hospital of the University of Chile*
[5]*Department of Radiology, School of Medicine, Pontificia Universidad Católica de Chile*
Chile

1. Introduction

The complex relationship of thyroid hormones (TH) with brain function is known since a century. The TH mediate important effects on central nervous system (CNS) during development and throughout life (Bauer et al., 2002a; Smith et al., 2002). Is well known that hyper and hypothyroidism are frequently associated with subtle behavioral and psychiatric symptoms. By the other side, patients with mood disorders show alterations in thyroid-stimulating hormone (TSH) release under thyrotropin-releasing hormone (TRH) stimulation although, circulating TH: triiodothyronine (T3) and thyroxine (T4) are usually in the normal range (Linkowski et al., 1981; Loosen, 1985; Larsen et al., 2004; Risco et al., 2003). Animal studies have provided considerable data on the reciprocal interactions between TH and neurotransmitter systems related with the pathogenesis of mood disorders (Bauer et al., 2002a). These studies provide the basis for several hypotheses, which propose that the modulatory effects of TH on mood are mediated by their actions on different neurotransmitter as norepinephrine and serotonin (Belmaker&Agam, 1998). There is also experimental evidence that some antidepressant drugs have some effects on brain TH concentration and T3 generation through a modulatory effect on deiodinases. Many trials have demonstrated that under certain conditions the use of TH can enhance or accelerate the therapeutic effects of antidepressants (Kirkegaard & Faber, 1998).

Considering that major depression is currently viewed as a serious public health problem with significant social and economic consequences, we found interesting to review how thyroid function and brain could interact in depressive disorders and how some new aspects as evaluation of some polymorphism of deiodinases and neuroimaging, can help in identifying depressive subjects susceptible to be treat with TH.

2. Thyroid hormones and brain

Thyroid hormones participate in the normal neurological development increasing the rate of neuronal proliferation in the cerebellum, acting as the "time clock" to end neuronal

proliferation, differentiation and also stimulating the development of neuronal processes, axons and dendrites. As well TH mediate effects on CNS occur throughout life (Bauer et al., 2002a; Smith et al., 2002). Different studies have demonstrated the presence of thyroid receptors in rat CNS with a particular distribution during development and adulthood (Bradley et al., 1992; Bradley et al., 1989). Thus, TH regulate the expression of genes implicated in myelination, neuronal and glial cell differentiation (Bernal, 2005; Bernal & Nunez, 1995) and neuronal viability and function (Smith et al., 2002). These hormones are able to modify cell morphology by acting on cytoskeleton machinery required for neuronal migration and outgrowth (Aniello et al., 1991; Morte et al., 2010). Additionally, TH are present in noradrenergic nuclei of CNS (Rozanov & Dratman, 1996) probably acting as neuromodulator or co-neurotransmitter (Dratman & Gordon, 1996). In line with this, TH increase β-adrenergic receptors levels (Ghosh & Das, 2007; Whybrow & Prange, 1981) and improve both cholinergic (Smith et al., 2002) and serotonin neurotransmission in animals (Bauer et al., 2002a). The effect of TH on serotonin (5 HT) has been explained by a desensitization of 5HT1A autoreceptor in the raphe nuclei which probably results in enhancement of firing and release of serotonin from raphe neurons (Heal & Smith, 1988). Furthermore, these hormones can stimulate the expression of neuronal growth factor (NGF) suggesting certain trophic actions on CNS (Walker et al., 1979; Walker et al., 1981).

In mice models, maternal hypo and hyperthyroidism cause some malformation and developmental defects in the cerebellar and cerebral cortex of their newborns. Concomitantly, there is some degeneration, deformation and severe growth retardation in neurons of these regions in both groups (El-Bakry et al., 2010). Therefore, TH play an important role in brain development, neuronal migration and axonal projection to target cells. *In vitro* and *in vivo* studies have shown that TH exert a non genomic action over the actin citoskeleton development in astrocytes and neurons. The lack of TH impaire cell growth, granule cells migration and explain those defects in the hypothyroid brain (Farwell et al., 2006; Leonard&Farwell, 1997; Farwell&Dubord, 1996).

Moreover, both acute and chronic Thyroxine treatment in rats increases the cognitive function, probably through an enhancement in cholinergic neurotransmission (Smith et al., 2002).

In humans, TH deficiency during the fetal and postnatal periods may cause irreversible mental retardation, neurological and behavioral deficits, and long lasting, irreversible motor dysfunctions. In adulthood, hypothyroidism may also determine profound behavioral consequences such as depressive symptoms, impaired memory, impairment in learning, verbal fluency, and spatial tasks (Miller et al., 2007; Samuels et al., 2007). Probably these alterations are due to neurotransmission impairment in brain areas related to learning and memory, such as hippocampus. Thus, the reduction of TH levels in CNS, can promote an altered neurotransmission activity contributing to some mood disorders like major depression.

The biologically active thyroid hormone T3 exerts its effects by interacting with their specific nuclear thyroid receptors (TRs) that are positively regulated by its own ligand, acting as transcription factors. TRs are encoded for two different genes: TRβ located on chromosome 3, encodes three isoforms: β1, β2 and β3, and TRα located on chromosome 17, encodes the isoforms α1, α2 and α3. TRα1 is expressed early in the embryonic development and TRβ is expressed at later stages of development. By the other hand, the expression of these isoforms

is tissue dependent; in the brain, the main isoforms of TRs are: TRα1, TRα2, TRβ1 and TRβ2. TRα1 and α2 accounting for most of TRs in the organ, whereas TRβ1 and β2 are detected in only a few areas as retina, cochlea, anterior pituitary and hypothalamus. In mice in which TRα or TRβ were inactivated, different phenotypes are observed indicating that TRs isoforms mediate specific functions but also, they can substitute each other to mediate some actions of T3 (Jones et al., 2007; Forrest et al., 1996a; Forrest et al., 1996b; Wikström et al., 1998; Fraichard et al., 1997; Göthe et al., 1999).

Some studies have reported, in propylthiouracyl-induced hypothyroidal adult rats, a decreased expression of TRα1 and TRβ in the hippocampus, associated with an increase in β-amyloid peptides in the same area. Hypoactivity of the thyroid signaling in the hippocampus could induce modifications in the amiloydogenic pathway and this could be related with a greater vulnerability of developing Alzheimer disease in hypothyroidal subjects (Ghenimi et al., 2010).

2.1 T3 generation in the central nervous system: The importance of deiodinases

Although both forms of TH (T4, T3) are present in the circulating blood, some studies have demonstrated that T4 is transported into the brain much more efficiently than T3 (Hagen & Solberg, 1974). In contrast to peripheral tissue, in the brain T4 and T3 are in equimolar range indicating mechanisms for an efficient transformation into biological active hormone.

TH production is regulated by the HPT axis, while its biological activity is mainly regulated by three selenodeiodinasas coded by different genes (D1, D2, D3). Deiodinases act at prereceptor level influencing both, extracellular and intracellular TH levels and its action. Whether it activates or inactivates it, will depend on the level where deiodination occurs (5 or 5` position on the iodothyronine molecule). In the periphery, in the kidney and liver, D1 isoform is responsible for the production of most of the circulating T3 (Bianco et al., 2002).

In the CNS, the most important isoforms are D2 and D3. In the brain, T3 is produced locally by the action of D2 which is also expressed in pituitary, thyroid, brown adipose tissue, skeletal muscle, and aortic smooth muscle cell, in humans. D2 activity varies extensively in different brain regions, with the highest levels found in cortical areas and lesser activity in the midbrain, pons, hypothalamus and brainstem (Bianco et al., 2002; Gouveia et al., 2005; Zavacki et al., 2005). It has been described in adult rats, that approximately 80% of T3 bound to nuclear receptors is produced locally by D2 activity (Crantz et al., 1982). Moreover, inactivation of TH is mainly carried out by D3 as well as glucoronosyltransferase and sulfotransferases. D3 is highly expressed within the CNS, with low peripheral expression. D3 degrades T_4 to rT_3 and T_3 to 3,3′-diiodothyronine (T2) therefore preventing or finishing actions of T3. Thus, combined actions of D2 and D3 can locally increase or decrease thyroid hormone signaling in a tissue -and a temporal- fashion, and more importantly in a way independent of thyroid hormone plasma levels. In addition, increasing evidences pointed out that deiodinase expression can be modulated by a wide variety of endogenous signaling molecules, suggesting a local modulation of T3 production in the brain (Gereben et al., 2008a, Gereben et al., 2008b). D2 enzymatic activity is increased also in hypothyroidism and decreased in hyperthyroidism (Kirkegaard & Faber, 1998).

2.2 Association between deionidase polymorphisms and thyroid hormone metabolism

Genetic variations in deionidade genes may impact significantly thyroid function and TH levels in euthyroid subjects (Hansen et al., 2007; Peeters et al., 2007; Peeters et al., 2006; Peeters et al., 2003). The effect of two polymorphisms in D1 gene, D1-rs11206244 (D1-C785T) and D1-rs12095080 (D1-A1814G) on thyroid hormone metabolism has been evaluated in randomly selected subjects (Peeters et al., 2003). The allele T of D1-rs11206244 was associated with high levels of rT3 and high rT3/T4 ratio and a low T3/rT3 in plasma; whereas the G allele of D1-A1814G was associated with a high T3/rT3 (de Jong et al., 2007; Peeters et al., 2003). These results suggest a lower activity in T carriers of rs11206244 than G carriers (Peeters et al., 2003).

Of special interest is the common polymorphism in humans: D2 rs225014 (D2-Thr92Ala), characterized by a threonine (Thr) change to alanine (Ala) at codon 92 (D2 Thr92Ala). It is associated with insulin resistance in different populations, suggesting that D2-generated T3 in skeletal muscle plays a role in insulin sensitivity (Mentuccia et al., 2002, Canani et al., 2005). The minor allele (G) is associated with a low D2 activity in thyroid samples obtained from patients (Canani et al., 2005). In accordance, G allele seems to predict the need for higher T4 intake in thyroidectomized patients (Torlontano et al., 2008). Nonetheless, it has been observed that GG subjects show a delayed serum T3 rise in response to TRH-mediated TSH secretion consistent with decreased D2 activity (Butler et al., 2010). Some studies have described a naturally occurring polymorphism located in 5'-untranslated region of the D2 gene (Coppotelli et al., 2006). In healthy blood donors, the minor allele of this polymorphism (D2-ORFa-Asp variant, rs12885300) is associated with an increase in circulating T3/T4 ratio but not with plasma T3 and TSH levels, suggesting an increased D2 gene expression (Peeters et al., 2005). In agreement, i*n vitro* studies suggested that D2-rs1288530 polymorphism leads to higher activity of D2 at the pituitary level (Coppotelli et al., 2006). In a long case-control Chinese study, the haplotypes ORFa-3Asp-92Ala and ORFa-3Gly-92Ala indicated higher susceptibility for bipolar disorders, while ORFa-3Asp-92Thr probably played a protective role (He et al., 2009). According to this evidence, it is feasible that variants of D2 gene can produce "brain hypothyroidism" limiting T3 action on CNS affecting brain neurotransmission.

3. Thyroid and depression

The similarity and overlapping between symptoms of depression and thyroid disorders has been the theoretical base for the hypothesis regarding a possible relationship between both entities. As we mention above, hypothyroidism could induce cognitive dysfunction and depressive symptoms besides psychological distress in a very similar way to primary depression (Constant et al., 2005; Bould et al., 2011; Mowla et al., 2011). Likewise, TH effect as augmentation therapy in refractory depression, and thyroid disorders as risk factors for rapid-cycling in bipolar disorder sustain a possible association between both types of diseases.

The involvement of HPT axis in the pathogenesis of depression is supported by multiple data. There are few studies that show normal range TH levels during a depressive episode; however most of them demonstrate diverse changes in different hormones associated with this axis. Concerning TSH levels, data are contradictory, some authors have reported a decrease in basal TSH values as well as in those observed in response to exogenous TRH

(Forman-Hoffman & Philibert, 2006; Stipcević et al., 2008) and other studies showed TSH elevation in bipolar depression (Brouwer et al., 2005; Saxena et al., 2000).

In reference to T3 levels, results are more conclusive, showing a trend to decrease in the presence of depression, as well as an association with high risk of long term relapse. In addition there seems to be a more pronounced T3 decrease in direct relation with the severity of depression (Stipcević et al, 2008; Saxena et al., 2000). Reported T4 levels in depression are also contradictory, since there is evidence showing a rise as well as a decrease of T4 during depressive episodes. (Saxena et al., 2000; Kirkegaard&Faber, 1998). In a study, with more than 6,000 subjects, it was shown that a low TSH and a high T4 levels were associated with depression specially in young men but, in women only a higher T4 levels correlated with current depression syndrome (Forman-Hoffman&Philibert, 2006). It is possible that these findings could be explained by a diversity of factors, such as differences in phenotypes of depressive patients, severity and duration of the disease, difficulties in isolating drugs effects in TH levels (antidepressants and mood stabilizers) and probably, gender and other differences.

Overt thyroid disease is infrequent among depressive patients. Nevertheless, many authors have seen that a subgroup of depressive patients manifest a subclinical hypothyroidism and this might be a negative prognostic factor (Fountoulakis et al., 2006). On the other side, some antidepressants as lithium inhibits TH secretion and could increase antithyroid antibodies, promoting hypothyroidism in susceptible subjects (Emerson et al., 1972; Myers et al., 1985).

There is still no hypothesis that can satisfactory integrate these data. Interactions between TH and neurotransmitters, gene expression and neurohormonal receptors are not clear yet. For instance, 5 HT seems to inhibit TRH secretion and somatostatin TSH secretion (Kirkegaard&Faber, 1998); both of them are reduced in cerebro spinal fluid (CSF) in patients with psychiatric illness and affective disorders (Gerner&Yamada, 1982, Roy-Birne et al., 1983; Rubinow et al., 1983). Otherwise, T3 influx to intracellular level in the brain is determined by many factors, including T3 and T4 circulating levels, protein transporters, and deiodinase activity.

About a 25% of major depressed patients show a reduction in TSH release under TRH stimulation (Loosen 1985, Risco et al, 2003). It has been proposed that in them exist a blunted response due to the raise of circulating cortisol, associated to hypothalamic-pituitary-adrenal axis hyperactivity. This response has also been observed in bipolar disorders (Linkowsky et al., 1981). On the other hand, in rapid cycling depressives, TSH hypersecretion is observed in response to TRH (20% of basal TSH levels above the normal range) (Szabadi, 1991, Larsen et al., 2004).

Nevertheless, as we mentioned before, the mechanism by which TH affect the adult brain is not completely clear, because the complex interactions between neurotransmitters and thyroid. One hypothesis is that TH modulate the number of post-synaptic β-adrenergic receptors in the cerebral cortex and cerebellum This could be relevant considering the influence of catecholamines deficit, mainly norepinephrine as a cause of depression (Atterwill et al., 1984). Another possible mechanism is the modulation of 5 HT and its receptors. It has been suggested that TH inhibit the impulse rate of neurons present at the raphe and reducing the release of 5HT. T3 administration to mice attenuates the function of 5HT1A and 5HT1B receptors, increasing the cortical and hippocampus synthesis and

turnover of 5-HT. Administration of T3 plus electroconvulsive shock markedly potentiated its actions on 5-HT2-mediated responses. (Heal&Smith, 1988). These findings provide evidences for possible antidepressant effects of T3 and/or potentiating therapy by TH. This issue is relevant in patients suffering depressive disorders, related with reduction in mono amine neurotransmission such as serotonin (reviewed in Belmaker&Agam 2008).

A positive correlation between serotonin levels and circulating T3 has been described in humans. Indirect evidences showed that brain serotonin is increased in hyperthyroidism and decreased in hypothyroidism (Singhal et al., 1975). In the last situation, this is reversed with TH replacement (Bauer et al., 2002b, Strawn et al., 2004). In depressed subjects, the decrease in serotoninergic tone could be related to lower brain T3 levels, perhaps due to a reduction of deiodinases activity. Furthermore, an imbalance in T3 conversion could account for depressive disorder and/or clinical outcome to antidepressants therapy. It has been suggested that in depression, T3 may favor the release of cortical 5-HT and thus synergize the response to antidepressants. Administration of desipramine a selective serotonergic reuptake inhibitor (SSRI) in rats, induces an increase of D2 activity and T3 concentration in cortical tissue. Interestingly, T4 concentrations were significantly lowered after administration of the antidepressant but, serum T3 levels were significantly reduced only after toxic dosis of desipramine. Other commonly used SSRI, fluoxetine also decreases D3 activity (Eravci et al., 2000). Based on these data, one might suggest that depression occurs by the inhibition of D2, determining decreased T3 levels and secondarily, reduced levels of brain 5HT.

The efficacy of T3 as a supplement of sertraline therapy, another SSRI, was studied recently in relation D1 polymorphism (Cooper-Kazaz et al., 2009). Patients carrying the T allele of D1-rs11206244 showed a significant response to 8 week of antidepressant treatment in comparison with non-carriers of the allele. Additionally, there was no effect of T allele on sertraline response, suggesting that the polymorphism is not associated to antidepressant effect (Cooper-Kazaz et al., 2009). As we mentioned, the T allele of D1-rs11206244 showed lower T3 and higher rT3 than non-T carriers (de Jong et al., 2007; Peeters et al., 2003). Thus, it seems that patients genetically characterized by poor conversion of T4 to T3, are better responders to T3-antidepressant co-treatment (Cooper-Kazaz et al., 2007; 2008). Another study evaluated whether baseline thyroid function and D2 rs225014 (D2-Thr92Ala) predict response to paroxetine. It showed that high TSH levels predict the response, and heterozygous patients showed lower TSH levels than the wild-type allele (A) (Brouwer et al., 2006). However, up to date there is no study evaluating the influence of T3 and D2 polymorphisms on antidepressant response.

Based on these observations, we evaluated the presence of D2 polymorphism related with a lower activity of the enzyme: D2-Thr92Ala (T/C). The polymorphism was analyzed in 61 euthyroid patients with depression and 48 subjects of a population sample using the PCR-RFLP method. Clinical response to fluoxetine was evaluated before and after 8 weeks of treatment, using Hamilton Scale for Depression (HAM-D). We found that the CC genotype of Thr92Ala polymorphism was more frequent in depressed subjects and in non-responders patients (unpublished data). We concluded that Thr92Ala polymorphism of D2 gene could be considered a predictive marker of clinical response to fluoxetine, and hence of pharmacological therapy, but more studies are needed to confirm this preliminary results.

The presence of these polymorphisms could influence basal activity of type 2 deiodinase, and therefore of T3 bioavailability in the brain.

4. Use of thyroid hormone in depression

Several studies using thyroid hormones in the management of patients with mood disorders have been reported since the early seventies. TH have been used in euthyroid depressed patients to enhance the effects of antidepressants. In patients receiving electroconvulsive therapy, those treated with T3 required less sessions and presented less memory loss compared with placebo treated group (Stern et al., 1991). T3 has been employed in initial combination therapy, and T3 or T4 in refractary depression or non responder patients.

T3 in doses of 20 to 50 μg is able to enhance the effect of tricyclic antidepressants and shorten the depression period but, many studies have not demonstrated differences in the number of patients recovered (Prange et al., 1969; Wilson et al., 1970; Coppen et al., 1972; Wheatley, 1972). A meta-analysis showed that when T3 was used in refractary depression in addition to tricyclic antidepressant therapy, patients treated with it were twice as likely to respond as controls, decreasing depression severity scores (Aronson et al., 1996). However, samples size were small and deserve more evidence. Other studies, using T3 augmentation to SSRI-resistant depression, observed an improvement in mood scores (Agid&Lerer, 2003, Iosifescu et al., 2005, Abraham et al., 2006). Some authors found that patients who responded to T3 had higher serum TSH levels than non-responders and T3 appears to be less effective in men than in women (Agid&Lerer, 2003). Other authors reported that patients with atypical depression experienced significantly greater clinical improvement in final HAM-D with higher rates of treatment response and remission compared to subjects with non-atypical major depressive disorder (Iosifescu et al., 2005). All those cases were treated mainly with fluoxetine in a daily dose of 20 to 40 mg/ and 25-50 μg of T3, with few side effects.

L-thyroxine (T4) added to antidepressants has been used less frequently than T3. Some authors have suggested that T4 augmentation is less effective than T3 (Joffe&Singer, 1990) and that supra physiological doses (250-600 ug/day) are needed, as has been demonstrated in patients with resistant major depression or refractary uni and bipolar disorders (Baumgartner et al., 1994, Bauer et al., 1998, 2002). These results support the theory of a reduced deiodination of T4 compatible with an inhibition of the D2 or a stimulation of the D3 in brain tissues resulting in reduced local T3 concentration.

Nevertheless, the addition of T4 (100 ug /day during 4 weeks) to serotoninergic antidepressants obtained remission in 11 of 12 female patients with a resistant depressive episode but, these results did not show association with T3, T4 or TSH levels (Łojko & Rybakowski, 2007).

To date, the use of TH in mood disorders is controversial and the rationale for this therapy is still not completely clear. Main limitations of the studies are: small number of cases, lack of a placebo group, heterogeneity in diagnosis criteria, differences in observational period and in antidepressant therapy. For example, lithium has a known inhibitory effect on TH secretion; fluoxetine has a stimulatory effect over D2 as well as desipramine and both of them could induce deficit of T4.

In this line, we evaluated a group of euthyroidal adult female patients with major depression according to DSM IV-R criteria. All of them were free of antidepressants for at least for 6 month. We studied the effect of adding T3 in a dose of 50 ug per day (n=11) or placebo (n=10), to the standard antidepressant therapy with fluoxetine during 8 weeks. At the end of the observational period final HAM-D scores were similar in both groups. (See **Table 1**). Patients in T3 group showed significant T4, T3 and TSH changes; but they remain

clinically euthyroid during the whole treatment period. Their body mass index , heart rate and other clinical parameters did not change. The placebo group showed a non significant increase of THS at the end of the observation time (See **Figure 1**, unpublished results).

	T3 Group		**Placebo**		**p**	
Age (y.o.)	40±12		36±10		ns	
	Initial	2m	Initial	2m	Initial vs 2m	Groups
HAM-D	24±4	8±4	26±6	7±4	<0.0001	ns

Table 1. Age and Hamilton score (HAM-D) with 21 items, in the groups with T3 addition or placebo. Both initial and 2 months means±SD were similar (using non paired t student test). The difference between initial and 2 month was highly significant in both groups (using paired t tests).

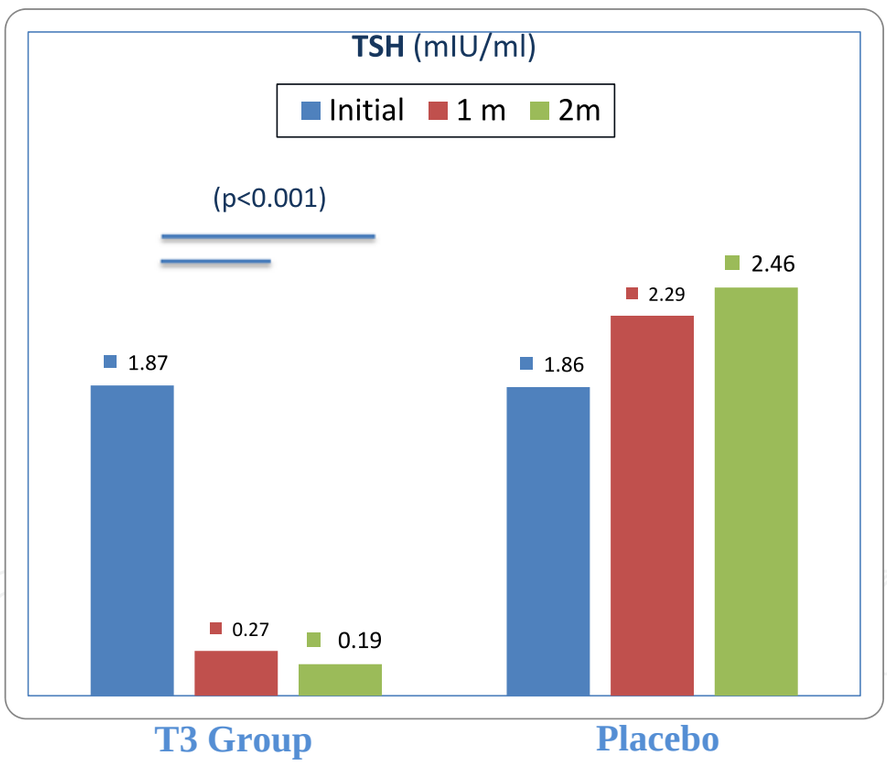


Fig. 1. TSH changes after addition of T3 or placebo in both groups. Measurements of TSH are shown at baseline, 1 month and 2 months using similar SSRI therapy. T3 hormone induced significant decreased TSH levels. No significant change was observed in placebo group.

Summarizing, our results suggest that TH addition to SSRI therapy in euthyroid depressed patients is safe and has not deleterious clinical effects in spite of TSH changes during treatment. Although, we could not demonstrated in this particular group, a significant antidepressant effect.

5. Hypothyroidism, depression and brain imaging

Single-photon tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are able to capture physiological events linked to underlying neuronal activity. They have been employed to image and quantify brain perfusion, flow and metabolism in several conditions as well as the radionuclide techniques have been used to map neurotransmissors, receptors, drug actions and many metabolic pathways. Functional imaging in mood disorders may show abnormalities at different brain levels that could normalize with therapy. Several serotonin and adrenergic markers have also been employed to study negative emotional stimuli response in mood disorders. For instance: thalamic activity was increased by reboxetine, whereas citalopram primarily affected ventrolateral prefrontal regions. It would be interesting to have a method able to predict therapy responses to either noradrenergic or serotoninergic antidepressants (Carey et al., 2004; Navarro et al., 2004; Zobel et al., 2005; Kohn et al., 2007; MacQueen, 2009; Brühl et al., 2011).

It is also known that even mild hypothyroidism may produce changes in brain regions modulating attention, motor speed, memory and visual-spatial processing. In severe hypothyroidism induced by thyroidectomy in cancer patients, it have been reported a clear parietal and partial occipital lobe hypoperfusion, measured with SPECT; the abnormalities improved after reaching normal thyroid function, in some subjects. However, fluorodeoxyglucose (FDG) and oxygen-15-labeled water studies, in similar patients, showed lower global brain glucose metabolism and flow. Hypothyroidal patients were also significantly more depressed, anxious and psychomotor slowered than euthyroidal subjects (Nagamachi et al., 2004; Constant et al., 2001).

Brain metabolism and flow are usually decreased in major depression and bipolar disease being metabolism inversely associated with the severity of depression. Changes are variable and as we mentioned earlier, could reverse with adequate therapy. Subgenual prefrontal cortex presents abnormal blood flow and metabolism in the depressed state. Prefrontal cortex and limbic structures are involved in emotion regulation and amygdale is involved in emotional memory formation (Buchsbaum et al., 1997; Kennedy et al., 2007; Chen et al., 2011). In major depression patients, glucose metabolism in orbitofrontal and inferior frontal cortex correlates with therapy response; responders have a significant decrease in the orbitofrontal and ventrolateral regions compared with non-responders, implicating ventral prefrontal subcortical circuits in response to specific therapy with SSRI. In major depression and bipolar patients, FDG has shown an inverse correlation between brain metabolism and circulating TSH (Brody et al., 1999; Marangell et al., 1997; Milak et al., 2005).

Cerebral fMRI has been reported to be helpful in major depression intending to predict therapy response using brain activation. Morphometric studies have evaluated hippocampus volume association with response to treatment. Patients who remit have larger pretreatment hippocampus volumes bilaterally compared with those who do not remit. There are similar preliminary findings for the anterior cingulate cortex. A recent work demonstrated a significantly thinner posterior cingulate cortex in non-remitters than in remitters, and also significant decrease in perfusion in frontal lobes and anterior cingulate cortex in non-remitters compared with healthy controls, at baseline (MacQueen, 2009; Järnum et al., 2011).

There are reports with increased perfusion in anterior cingulate and prefrontal medial cortex when using SSRI or amesergide. Responders and non-responders to cognitive behavior therapy versus antidepressive pharmacotherapy and deep brain stimulation could also be

differentiated using brain perfusion SPECT or glucose metabolism with PET (Vlassenko et al., 2004; Kennedy et al., 2007; Richieri et al., 2011).

Another work with fMRI demonstrated also that successful paroxetine treatment decreases amygdala activation, presumably by improved frontolimbic control, in line with SSRI, induced increased functional connectivity between pregenual anterior cingulated cortex, prefrontal cortex, and amygdala. Changes in amygdala activation when processing negative faces expressions might serve as an indicator for improved frontolimbic control required for clinical response (Ruhé, 2011).

We recently studied a group of major depression middle age patients using brain perfusion SPECT, all in their first episode of major depression and /or without any specific therapy for at least six months. Their initial HAM-D scores corresponded to 24±4.8; all of them received standard SSRI therapy. Ninety-three percent were responders at 2 months (HAM-D decrease >50%) and 59% were remitters (HAM-D score ≤5). There was association of decreased perfusion in diverse brain areas with HAM-D changes in the whole group using Statistical Parametric Analysis (SPM) as covariate (See Figure 2). We did not observe significant neocortical perfusion change after 2 months of standard dose of fluoxetine therapy. However, there was a bilateral decrease in parahippocampal gyrus, thalamus and striatum as well as in anterior cingulate gyrus (Brodmann 32 area) after SSRI therapy. No significant difference was observed between remitters and non-remitters.

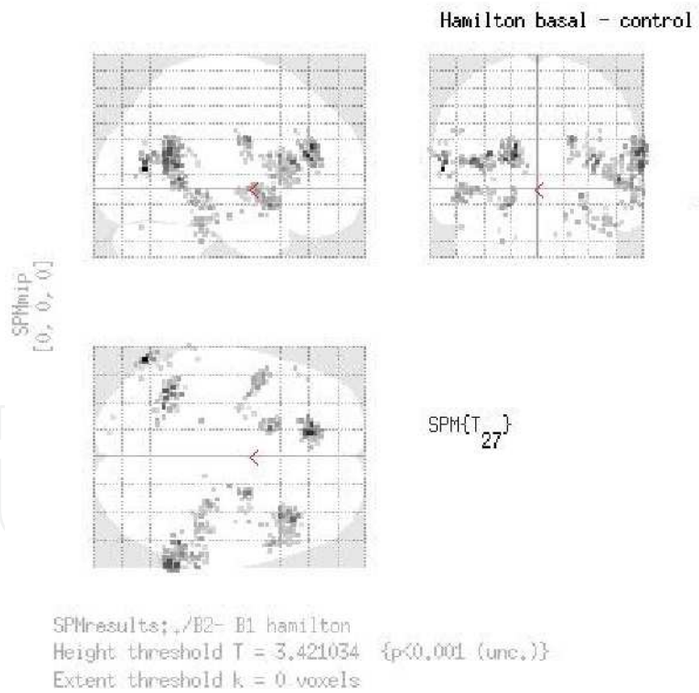


Fig. 2. In the whole group, SPM8 analysis demonstrated association between decreased perfusion and HAM-D scores considered as a covariate, at baseline and after 2 months of therapy (non corrected p <0.001): -at left: in amygdala, anterior cingulate, globus pallidum, putamen and Brodmann area 9 (mid frontal gyrus) -bilaterally: both hyppocampal gyrus, mid and superior temporal and insulas and cerebellar hemispheres -at right: in central and supramarginal gyrus

As we mentioned before, a half of the women in our group received T3 in addition of SSRI and the other half a placebo instead of T3. Our results showed no evidence that adding T3 to SSRI therapy in unipolar major depression females produces significant change in regional cerebral blood flow at neocortical level (See Figure 3). Only a small difference was found at deep structure level that could imply diverse brain mechanism involved [data not published].

These findings are in agreement with other reports showing relative normalization of perfusion and metabolism that were abnormally increased at baseline in patients with mood disorders. Some of these regional metabolism changes are correlated with emotional behavior. The amygdala and limbic structures have been associated with face recognition and emotional processing. It is well known that there is increased perfusion and metabolism in specific brain areas, reflecting molecular abnormalities in neurotransmitter systems. The development of new molecular imaging methods could help in the individualization of antidepressant therapies (Chen et al., 2011).

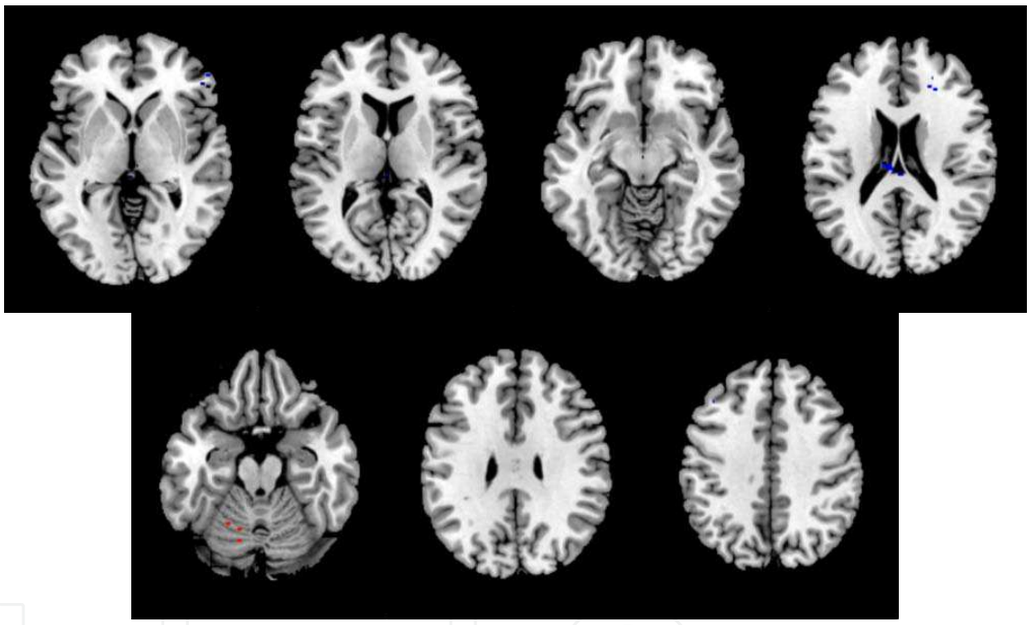


Fig. 3. Absence of regional cerebral blood flow change after SSRI therapy in T3 group, using Statistical Parametric Analysis (SPM8) with significant level <0.001; uncorrected p value.

6. Conclusions

Depressive and thyroid disorders are important public health problems. There is strong experimental evidence showing thyroid involvement on early stages of CNS development and on metabolic function of the mature brain. It is also accepted that overt hyper or hypothyroidism are not found frequently among mood disorders patients except in those with bipolar disorders, indicating that in most cases the underlying abnormality is at cellular or molecular levels. Although there is a prolific literature on the relationship between thyroid function and depressive disorders, clear results in humans on the role of TH in antidepressant therapy are still lacking. There are no randomized controlled trials, and the number of patients included in existing studies is too small. On the other hand,

more research is needed in order to define the importance of genetic variants in deiodinases and the role of neuroimaging into the complex interactions between HPT function and mood disorders and in clinical response to treatments.

Therefore, considering the available evidence and our own experience, we can recommend this strategy only as an alternative treatment in major depression patients who have failed to respond to other measures.

7. Acknowledgments

The work described in this chapter was partially financed by the grant "Líneas de Investigación Prioritarias" #240/07 HCUCH from the Clinical Hospital of the University of Chile, Santiago, Chile.

The authors thank Dr. Rodrigo Jaimovich (Department of Radiology, School of Medicine, Pontificia Universidad Católica de Chile) who processed and analyzed all SPECT data; Dr. Tamara Galleguillos (Psychiatric Clinic of the Clinical Hospital of the University of Chile) by her collaboration in patient´s recruitment, selection and follow up; Mr. Egardo Caamaño for his technical laboratory support and Ms. Clara Menares who performed the molecular biology studies.

8. References

Abraham, G.; Milev, R. & Stuart Lawson, J. (2006). T3 augmentation of SSRI resistant depression. *Journal of Affective Disorders*, Vol.91, No.2-3 (April 2006), pp. 211–215.

Agid, O. & Lerer, B. (2003). Algorithm-based treatment of major depression in an outpatient clinic: clinical correlates of response to a specific serotonin reuptake inhibitor and to triiodothyronine augmentation. *International Journal of Neuropsychopharmacology*, Vol.6, No.1 (March 2003), pp.41-49.

Altshuler, L.L.; Bauer, M.; Frye, M.A.; Gitlin, M.J.; Mintz, J., Szuba, M.P., Leight, K.L. & Whybrow, P.C. (2001). Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *American Journal of Psychiatry*, Vol.158, No.10 (October 2001), pp. 1617-1622.

Aniello, F.; Couchie, D.; Bridoux, A.M.; Gripois, D. & Nunez, J. (1991). Splicing of juvenile and adult tau mRNA variants is regulated by thyroid hormone. *Proceedings of National Academic of Sciences*, Vol. 88, No.9 (May 1991), pp. 4035-4039.

Aronson, R.; Offman, HJ.; Joffe, RT. & Naylor, CD. (1996). Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. *Archives General of Psychiatry*, Vol. 53, No.9 (September 1996), pp. 842-848.

Atterwill, C.K, Bunn S.J., Atkinson, D.J., Smith, S.L., Heal. D.J. Effects of thyroid status on presynaptic alpha 2-adrenoceptor function and beta-adrenoceptor binding in the rat brain. *Journal of Neural Transmission*, Vol. 59, N°1, (1984), pp.43-55.

Bauer, M., Heinz, A., Whybrow, P.C. (2002a). Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. *Molecular Psychiatry*, Vol.7, N° 2,(2002a) pp.140-156.

Bauer, M.; Berghöfer, A.; Bschor, T.; Baumgartner, A.; Kiesslinger, U.; Hellweg, R.; Adli, M.; Baethge, C. & Müller-Oerlinghausen, B. (2002b). Supraphysiological doses of L-

Thyroxine in the maintenance treatment of prophylaxis-resistant affective disorders. *Neuropsychopharmacology*, Vol.27, No.4 (October 2002), pp. 620–628.

Bauer, M.; Hellweg, R.; Gräf, KJ. & Baumgartner, A. (1998). Treatment of refractory depression with high-dose thyroxine. *Neuropsychopharmacology*, Vol.18, No.6 (June 1998), pp. 444-455.

Baumgartner, A.; Bauer, M. & Hellweg, R. (1994). Treatment of intractable non-rapid cycling bipolar affective disorder with high-dose thyroxine: An open trial. *Neuropsychopharmacology*, Vol.10, No.3 (May 1994), pp. 183–189.

Belmaker, RH. & Agam, G. (2008). Mechanisms of Disease: Major Depressive Disorder. *New England Journal of Medicine*, Vol.358, No.1 (January 2008), pp. 55-68.

Bernal, J. & Nunez, J. (1995). Thyroid hormones and brain development. *European Journal of Endocrinology*, Vol.133, No.4 (October 1995), pp. 390-398.

Bernal, J. (2005). Thyroid hormones and brain development. *Vitamines and Hormones*, Vol. 71, pp. 95-122.

Bianco, A.C.; Salvatore, D.; Gereben, B.; Berry, M.J. & Larsen, P.R. (2002). Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocrine Reviews*, Vol.23, No. 1 (February 2002), pp. 38-89.

Bould, H., Panicker, V., Kessler, D., Durant, C., Lewis, G., Dayan, C., Evans, J. (2011). Investigation of thyroid dysfunction in general practice is more likely in patients with high psychological morbidity. *Family Practice* (September 2011) [Epub ahead of print]

Bradley, D.J.; Towle, H.C. & Young, W.S., 3rd. (1992). Spatial and temporal expression of alpha- and beta-thyroid hormone receptor mRNAs, including the beta 2-subtype, in the developing mammalian nervous system. *Journal of Neurosciences*, Vol.12, No.6 (June 1992), pp. 2288-2302.

Bradley, D.J.; Young, W.S. 3rd & Weinberger, C. (1989). Differential expression of alpha and beta thyroid hormone receptor genes in rat brain and pituitary. *Proceedings of National Academy of Sciences U S A*, Vol.86, No.18 (September 1989), pp. 7250-7254.

Breteler, M.M., (2007). The association of polymorphisms in the type 1 and 2 deiodinase genes with circulating thyroid hormone parameters and atrophy of the medial temporal lobe. *Journal of Clinical Endocrinology and Metabolism*, Vol.92, N°2, (February 2007), pp.636-640.

Brody, A.L., Saxena,S., Silverman, D.H., Alborzian, S., Fairbanks, L.A., Phelps, M.E., Huang, S.C., Wu, H.M., Maidment, K., Baxter, L.R. Jr. (1999). Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. *Psychiatry Research*, (October 1999), Vol 91, N°.3 91, pp.127-139.

Brouwer, J.P., Appelhof, B.C., Hoogendijk, W.J., Huyser, J., Endert, E., Zuketto, C., Schene, A.H., Tijssen. J.G., Van Dyck, R., Wiersinga, W.M., Fliers, E. Thyroid and adrenal axis in major depression: a controlled study in outpatients. *European Journal of Endocrinology,* Vol.152, N°2, (February 2005) pp.185-191.

Brouwer, J.P.; Appelhof, B.C.; Peeters, R.P.; Hoogendijk, W.J.; Huyser, J.; Schene, A.H.; Tijssen, J.G.; Van Dyck, R.; Visser, T.J.; Wiersinga, W.M. & Fliers, E. (2006). Thyrotropin, but not a polymorphism in type II deiodinase, predicts response to paroxetine in major depression. *European Journal of Endocrinology*, Vol.154, No.6 (June 2006), pp. 819-825.

Brühl, A.B., Jäncke, L., Herwig, U. (2011). Differential modulation of emotion processing brain regions by noradrenergic and serotonergic antidepressants. *Psychopharmacology (Berlin)*, (August 2011), Vol. 216. N°3, pp.389-399.

Buchsbaum, M.S., Wu, J., Siegel, B.V., Hackett, E., Trenary, M., Abel, L., Reynolds, C. (1997). Effect of sertraline on regional metabolic rate in patients with affective disorder. *Biological Psychiatry*, Vol. 41, N°1. (January 1997), pp.15-22.

Butler, P.W.; Smith, S.M.; Linderman, J.D.; Brychta, R.J.; Alberobello, A.T.; Dubaz, O.M.; Luzon, J.A.; Skarulis, M.C.; Cochran, C.S.; Wesley, R.A.; Pucino, F. & Celi, F.S. (2010). The Thr92Ala 5' type 2 deiodinase gene polymorphism is associated with a delayed triiodothyronine secretion in response to the thyrotropin-releasing hormone-stimulation test: a pharmacogenomic study. *Thyroid*, Vol.20, No.12 (December 2010), pp. 1407-1412.

Campos-Barros, A., Meinhold, H., Kohler, R., Muller, F., Eravci, M., Baumgartner, A., (1995). The effects of desipramine on thyroid hormone concentrations in rat brain. *Naunyn Schmiedebergs Archives of Pharmacology,* Vol.351, N°5, (May 1995), pp.469-474.

Canani, L.H., Capp, C., Dora, J.M., Meyer, E.L., Wagner, M.S., Harney, J.W., Larsen, P.R., Gross, J.L., Bianco, A.C., Maia, A.L., (2005). The type 2 deiodinase A/G (Thr92Ala) polymorphism is associated with decreased enzyme velocity and increased insulin resistance in patients with type 2 diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism,* Vol.90, N°6, (June 2005). pp.3472-3478.

Carey, P.D., Warwick, J., Niehaus, D.J., van der Linden, G., van Heerden, B.B., Harvey, B.H., Seedat, S., Stein, D.J. (2004). Single photon emission computed tomography (SPECT) of anxiety disorders before and after treatment with citalopram. *BMC Psychiatry,* (October 2004) 14;4:30.

Chen, Q., Liu, W., Li, H., Zhang, H., Tian, M. (2011). Molecular imaging in patients with mood disorders: a review of PET findings. *European Journal of Nuclear Medicine and Molecular Imaging*, Vol. 38, N°7, (July 2011), pp. 1367-1380

Constant, E.L., Adam, S., Seron, X., Bruyer, R., Seghers, A., Daumerie, C. (2005). Anxiety and depression, attention, and executive functions in hypothyroidism, *Journal of the International Neuropsychological Society,* (2005), Vol.11, N°5, (September 2005), pp.535–544.

Constant, E.L., de Volder, A.G., Ivanoiu, A., Bol, A., Labar, D., Seghers, A., Cosnard, G., Melin, J., Daumerie, C. (2001). Cerebral blood flow and glucose metabolism in hypothyroidism: a positron emission tomography study. *Journal of Clinical Endocrinology and Metabolism*, Vol 86, N° 8, (August 2001), pp.3864-3870.

Cooper-Kazaz, R., Apter, J.T., Cohen, R., Karagichev, L., Muhammed-Moussa, S., Grupper, D., Drori, T., Newman, M.E., Sackeim, H.A., Glaser, B., Lerer, B.(2007). Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial. *Archives of General Psychiatry*, Vol.64, N°6, (June 2007), pp. 679-688.

Cooper-Kazaz, R., van der Deure, W.M., Medici, M., Visser, T.J., Alkelai, A., Glaser, B., Peeters, R.P., Lerer, B. (2009). Preliminary evidence that a functional polymorphism in type 1 deiodinase is associated with enhanced potentiation of the antidepressant effect of sertraline by triiodothyronine. *Journal of Affective Disorders,* (July 2009), Vol.116, N°1-2, pp.113-116.

Cooper-Kazaz, R.Lerer, B. (2008). Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors. *International Journal of Neuropsychopharmacology*, Vol.11, N°5, (August 2008), pp. 685-699.

Coppen, A.; Whyborw, PC.; Noguera, R.; Maggs, R. & Prange, Jr AJ. (1972). The comparative antidepressant value of L-tryptophan and imipramine with and without attempted potentiation by liothyronine. *Archives of General Psychiatry*, Vol. 26, No.3 (March 1972), pp. 234–241.

Coppotelli, G., Summers, A., Chidakel, A., Ross, J.M., Celi, F.S. (2006). Functional characterization of the 258 A/G (D2-ORFa-Gly3Asp) human type-2 deiodinase polymorphism: a naturally occurring variant increases the enzymatic activity by removing a putative repressor site in the 5' UTR of the gene. *Thyroid*, (July 2006),Vol.16, N°7, pp. 625-632.

Crantz, F.R., Silva, J.E., Larsen, P.R. (1982). An analysis of the sources and quantity of 3,5,3'-triiodothyronine specifically bound to nuclear receptors in rat cerebral cortex and cerebellum. *Endocrinology*, Vol.110, N°2, (February 1982) pp.367-375.

de Jong, F.J., Peeters, R.P., den Heijer, T., van der Deure, W.M., Hofman, A., Uitterlinden, A.G., Visser, T.J., T.J. & Breteler M.M. (2007). The association of polimorphisms in the type 1 and 2 deidinase genes with circulating thyroid hormone parameters and atrophy of the medial temporal lobe. *Journal of Clinical Endocrinology and Metabolism*, Vol.92,No 2 (February 2007), pp. 636-640.

Dratman, M.B. & Gordon, J.T. (1996). Thyroid hormones as neurotransmitters. *Thyroid*, Vol.6; N°6 (December 1996) pp.639-647.

Dussault, JH. & Ruel, J. (1987). Thyroid hormones and brain development. *Annual Review of Physiology*, Vol.49, No. 3 (March 1987), pp. 321-334.

El-Bakry, A.M., El-Gareib, A.W., Ahmed, R.G. (2010). Comparative study of the effects of experimentally induced hypothyroidism and hyperthyroidism in some brain regions in albino rats. *Journal of Developmental Neuroscience*, Vol.28, No.5 (August 2010), pp. 371–389.

Emerson, CH.; Dyson, WL. & Utiger, RD. (1973). Serum thyrotropin and thyroxine concentrations in patients receiving lithium carbonate. *Journal of Clinical Endocrinology and Metabolism*, Vol. 36, No.2 (February 1972), pp. 338–346.

Eravci, M., Pinna, G., Meinhold, H., Baumgartner, A. (2000). Effects of pharmacological and nonpharmacological treatments on thyroid hormone metabolism and concentrations in rat brain. *Endocrinology,* Vol.141, N° 3, (March 2000) pp.1027-1040.

Farwell, A.P., Dubord, S.A. (1996) Thyroid hormone regulates neurite outgrowth and neuronal migration onto laminin. *Thyroid,* Vol.6, (Suppl 1) (1996) pp.S-6

Farwell, AP.; Dubord-Tomasetti, SA.; Pietrzykowski, AZ. & Leonard, JL. (2006). Dynamic nongenomic actions of thyroid hormone in the developing rat brain. *Endocrinology*, Vol.147, No.5 (May 2006), pp. 2567–2574.

Forman-Hoffman, V., Philibert, R.A. (2006). Lower TSH and higher T4 levels are associated with current depressive syndrome in young adults. *Acta Psychiatrica Scandinava*, Vol. 114, N°2, (August 2006) pp.132-139

Forrest, D.; Erway, LC.; Ng, L.; Altschuler, R. & Curran, T. (1996a). Thyroid hormone receptor beta is essential for development of auditory function. *Nature Genetics,* Vol.13, No.3 (July 1996), pp. 354–357.

Forrest, D.; Hanebuth, E.; Smeyne, RJ.; Everds, N.; Stewart, CL.; Wehner, JM. & Curran, T. (1996b). Recessive resistance to thyroid hormone in mice lacking thyroid hormone receptor beta: evidence for tissue-specific modulation of receptor function. *The EMBO Journal*, Vol.15, No.12 (June 1996), pp. 3006–3015.

Fountoulakis, K., Kantartzis, S., Siamouli, M., Panagiotidis, P., Kaprinis, S., Iacovides, A., Kaprinis, G. (2006). Peripheral thyroid dysfunction in depression. *The World Journal of Biological Psychiatry*, Vol.7, N°3, (2006), pp.131-137.

Fraichard, A.; Chassande, O.; Plateroti, M. Roux, JP.; Trouillas, J.; Dehay, C.; Legrand, C.; Gauthier, K.; Kedinger, M.; Malaval, L.; Rousset, B. & Samarut, J. (1997). The T3R alpha gene encoding a thyroid hormone receptor is essential for post-natal development and thyroid hormone production. *The EMBO Journal*, Vol.16, No.14 (July 1997), pp. 4412–4420.

Gereben, B., Zavacki, A.M., Ribich, S., Kim, B.W., Huang, S.A., Simonides, W.S., Zeold, A., Bianco, A.C., (2008a). Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. *Endocrinology Review* Vol.29, N° 7, (December 2008) pp. 898-938.

Gereben B, Zeöld A, Dentice M, Salvatore D, Bianco AC. (2008b). Activation and inactivation of thyroid hormone by deiodinases: local action with general consequences. *Cellular and Molecular Life Sciences,* Vol. 65, N°4, (February 2008), pp.570-590.

Gerner, RH. & Yamada, T. (1982). Altered neuropeptide concentrations in cerebrospinal fluid of psychiatric patients. *Brain Research*, Vol.238, No.1 (April 1982), pp. 298–302.

Ghenimi, N.; Alfos, S.; Redonnet, A.; Higueret, P.; Pallet, V. & Enderlin, V. (2010). Adult-onset hypothyroidism induces the amyloidogenic pathway of amyloid precursor protein processing in the rat hippocampus. *Journal of Neuroendocrinology*, Vol.22, No.8 (August 2010), pp. 951–959.

Ghosh, M. , Das, S. (2007). Increased beta(2)-adrenergic receptor activity by thyroid hormone possibly leads to differentiation and maturation of astrocytes in culture. *Cellular and Molecular Neurobiology*, Vol.27, N°8, (December 2007), pp.1007-1021.

Göthe, S.; Wang, Z.; Ng, L.; Kindblom, JM.; Barros, AC.; Ohlsson, C.; Vennström, B. & Forrest, D. (1999). Mice devoid of all known thyroid hormone receptors are viable but exhibit disorders of the pituitary-thyroid axis, growth, and bone maturation. *Genes & Development* , Vol.13, No.10 (May 1999), pp. 1329–1341.

Gouveia, C.H., Christoffolete, M.A., Zaitune, C.R., Dora, J.M., Harney, J.W., Maia, A.L., Bianco, A.C. (2005). Type 2 iodothyronine selenodeiodinase is expressed throughout the mouse skeleton and in the MC3T3-E1 mouse osteoblastic cell line during differentiation. *Endocrinology*, Vol.146, N°.1, (January 2005), pp. 195-200.

Hagen, G.A.Solberg, L.A., Jr. (1974). Brain and cerebrospinal fluid permeability to intravenous thyroid hormones. *Endocrinology*, Vol. 95, N°.5, (November 1974), pp.1398-1410.

Hansen, P.S., van der Deure, W.M., Peeters, R.P., Iachine, I., Fenger, M., Sorensen, T.I., Kyvik, K.O., Visser, T.J., Hegedus, L. (2007). The impact of a TSH receptor gene polymorphism on thyroid-related phenotypes in a healthy Danish twin population. *Clinical Endocrinology (Oxf),* Vol.66, N°6, (June 2007), pp. 827-832.

He, B.; Li, J.; Wang, G.; Ju, W.; Lu, Y.; Shi, Y.; He, L. & Zhong, N. (2009). Association of genetic polymorphisms in the type II deiodinase gene with bipolar disorder in a subset of Chinese population. *Progress in Neuropsychopharmacology & Biological Psychiatry*, Vol. 33, No.6 (August 2009), pp. 986-990.

Heal, D.J., Smith, S.L. (1988). The effects of acute and repeated administration of T3 to mice on 5-HT1 and 5-HT2 function in the brain and its influence on the actions of repeated electroconvulsive shock. *Neuropharmacology*, Vol.27, N°.12, (December 1988), pp.1239-1248.

Iosifescu, DV.; Nierenberg, AA.; Mischoulon, D.; Perlis, RH.; Papakostas, GI.; Ryan, JL.; Alpert, JE. & Fava, M. (2005). An open study of triiodothyronine augmentation of selective serotonin reuptake inhibitors in treatment-resistant major depressive disorder. *Journal of Clinical Psychiatry*, Vol.66, No.8 (August 2005), pp. 1038-1042.

Järnum, H., Eskildsen, S.F., Steffensen, E.G., Lundbye-Christensen, S., Simonsen, C.W., Thomsen, I.S., Fründ, E.T., Théberge, J., Larsson, E.M. (2011). Longitudinal MRI study of cortical thickness, perfusion, and metabolite levels in major depressive disorder. *Acta Psychiatrica Scandinavica,* (September 2011)16. doi: 10.1111/j.1600-0447.2011.01766.x. [Epub ahead of print]

Joffe, RT. & Singer, W. (1990). A comparison of triiodotironine and thyroxine in the potentiation of tricyclic antidepressants. *Psychiatry Research*, Vol.32, No.3 (June 1990), pp. 241-251.

Jones, I.; Ng, L., Liu, H. & Forrest, D. (2007). An intron control region differentially regulates expression of thyroid hormone receptor beta2 in the cochlea, pituitary, and cone photoreceptors. *Molecular Endocrinology*, Vol.21, No.5 (May 2007), pp. 1108–1119.

Kennedy, S.H., Konarski, J.Z., Segal, Z.V., Lau, M.A., Bieling, P.J., McIntyre, R.S., Mayberg, H.S. (2007). Differences in brain glucose metabolism between responders to CBT and Venlafaxine in a 16-week randomized controlled trial. *American Journal of Psychiatry*, Vol.164, N°5. (May 2007), pp.778–788

Kirkegaard, C., Faber, J. (1998). The role of thyroid hormones in depression. *European Journal of Endocrinology,* (January1998), Vol.138, N°1, pp.1-9.

Kohn, Y., Freedman, N., Lester, H., Krausz, Y., Chisin, R., Lerer, B., Bonne, O. (2007). 99mTc-HMPAO SPECT study of cerebral perfusion after treatment with medication and electroconvulsive therapy in major depression. *Journal of Nuclear Medicine*, Vol. 48, N°8, (August 2007) pp. 1273-1278

Larsen, JK.; Faber, J.; Christensen, EM.; Bendsen, BB.; Solstad, K.; Gjerris, A. & Siersbaek-Nielsen, K. (2004). Relationship between mood and TSH response to TRH stimulation in bipolar affective disorder. *Psychoneuroendocrinology*, Vol.29, No.7 (August 2004), pp. 917–924.

Leonard, JL. & Farwell, AP. (1997). Thyroid hormone-regulated actin polymerization in brain. *Thyroid,* Vol.7, No.1 (February 1997), pp. 147–151.

Lifschytz, T., Segman, R., Shalom, G., Lerer, B., Gur, E., Golzer, T., Newman, M.E. (2006). Basic mechanisms of augmentation of antidepressant effects with thyroid hormone. *Current Drug Targets*, Vol.7, N°2, (February 2006), pp. 203-210.

Linkowski, P.; Brauman, H. & Mendlewicz, J. (1981). Thyrotrophin response to thyrotrophin-releasing hormone in unipolar and bipolar affective illness. *Journal of Affective Disorders*, Vol. 3, No.1 (March 1981), pp. 9–16.

Łojko, D. Rybakowski, JK. (2007). L-thyroxine augmentation of serotonergic antidepressants in female patients with refractory depression. *Journal of Affective Disorders*, Vol. 103, No. 1-3 (November 2007), pp. 253-256.

Loosen, PT. (1985). The TRH-induced TSH response in psychiatric patients: a possible neuroendocrine marker. *Psychoneuroendocrinology*, Vol.10, No.3, pp. 237–260.

MacQueen, G.M. (2009) Magnetic resonance imaging and prediction of outcome in patients with major depressive disorder. *Journal of Psychiatry & Neurosciences*, Vol. 34, N°5, (September 2009) pp.343-349.

Marangell, L.B., Ketter, T.A., George. M.S., Pazzaglia, P.J., Callahan, A.M., Parekh, P., Andreason, P.J., Horwitz, B., Herscovitch, P. & Post, R.M. (1997) Inverse

relationship of peripheral thyrotropin-stimulating hormone levels to brain activity in mood disorders. *American Journal of Psychiatry*, Vol.154, N°2, (February 1997), pp.224-230,

Mentuccia, D., Proietti-Pannunzi, L., Tanner, K., Bacci, V., Pollin, T.I., Poehlman, E.T., Shuldiner, A.R., Celi, F.S. (2002). Association between a novel variant of the human type 2 deiodinase gene Thr92Ala and insulin resistance: evidence of interaction with the Trp64Arg variant of the beta-3-adrenergic receptor. *Diabetes*, Vol.51, N°3, (March 2002), pp. 880-883.

Milak, M.S., Parsey, R.V., Keilp, J., Oquendo, M.A., Malone, K.M., Mann, J.J. (2005). Neuroanatomic correlates of psychopathologic components of major depressive disorder. *Archives of General Psychiatry*, Vol. 62, N°4, (April 2005), pp. 397-408,

Miller, K.J., Parsons, T.D., Whybrow, P.C., Van Herle, K., Rasgon, N., Van Herle, A., Martinez, D., Silverman, D.H., Bauer, M. (2007). Verbal memory retrieval deficits associated with untreated hypothyroidism. *Journal of Neuropsychiatry and Clinical Neurosciences*, Vol.19, N°2, (2007), pp. 132-136.

Morte, B., Diez, D., Auso, E., Belinchon, M.M., Gil-Ibanez, P., Grijota-Martinez, C., Navarro, D., de Escobar, G.M., Berbel, P., Bernal, J. (2010). Thyroid hormone regulation of gene expression in the developing rat fetal cerebral cortex: prominent role of the Ca2+/calmodulin-dependent protein kinase IV pathway. *Endocrinology*, Vol. 151,N°2, (February 2010), pp. 810-820.

Mowla, A., Kalantarhormozi, M.R., Khazraee, S. (2011) Clinical characteristics of patients with major depressive disorder with and without hypothyroidism: A comparative study. *Journal of Psychiatric Practice,* (January 2011), Vol 17, N°1, pp.67–71.

Myers, DH.; Carter, RA.; Burns, BH.; Armond, A.; Hussain, SB. & Chengapa, VK. (1985). A prospective study of the effects of lithium on thyroid function and on the prevalence of antithyroid antibodies. *Psychological Medicine*, Vol. 15, No.1 (February 1985), pp. 55–61.

Nagamachi, S., Jinnouchi, S., Nishii, R., Ishida, Y., Fujita, S., Futami, S., Kodama, T., Tamura, S., Kawai, K. (2004). Cerebral blood flow abnormalities induced by transient hypothyroidism after thyroidectomy-analysis by tc-99m-HMPAO and SPM96. *Annals of Nuclear Medicine,* Vol.18, N°6, (September 2004), pp. 469-77.

Navarro, V., Gasto, C., Lomena, F., Mateos, J.J., Portella, M.J., Massana, G., Bernardo, M., Marcos, T. (2004). Frontal cerebral perfusion after antidepressant drug treatment versus ECT in elderly patients with major depression: a 12-month follow-up control study *Journal of Clinical Psychiatry,* Vol. 65, N°5, (May 2004), pp. 656-661.

Peeters, R.P., van den Beld, A.W., Attalki, H., Toor, H., de Rijke, Y.B., Kuiper, G.G., Lamberts, S.W., Janssen, J.A., Uitterlinden, A.G., Visser, T.J. (2005). A new polymorphism in the type II deiodinase gene is associated with circulating thyroid hormone parameters. *American Journal of Physiology, Endocrinology and Metabolism*, Vol. 289, N°1, (July 2005), pp.E75-81.

Peeters, R.P., van der Deure, W.M., van den Beld, A.W., van Toor, H., Lamberts, S.W., Janssen, J.A., Uitterlinden, A.G., Visser, T.J. (2007). The Asp727Glu polymorphism in the TSH receptor is associated with insulin resistance in healthy elderly men. Clinical Endocrinology (Oxf), Vol. 66, N°6, (June 2007), pp. 808-815.

Peeters, R.P., van der Deure, W.M., Visser, T.J. (2006). Genetic variation in thyroid hormone pathway genes; polymorphisms in the TSH receptor and the iodothyronine

deiodinases. *European Journal of Endocrinology* Vol.155, N°5, (November 2006), pp. 655-662.

Peeters, R.P., van Toor, H., Klootwijk, W., de Rijke, Y.B., Kuiper, G.G., Uitterlinden, A.G., Visser, T.J. (2003). Polymorphisms in thyroid hormone pathway genes are associated with plasma TSH and iodothyronine levels in healthy subjects. *Journal of Clinical Endocrinology and Metabolism*, Vol. 88, N°6, (June 2003), pp. 2880-2888.

Prange Jr, AJ.; Wilson, IC.; Rabon, AM. & Lipton, MA. (1969). Enhancement of imipramine antidepressant activity by thyroid hormone. *American Journal of Psychiatry*, Vol.126, No.4 (October 1969), pp. 457–469.

Richieri, R., Boyer. L., Farisse, J., Colavolpe, C., Mundler, O., Lancon, C., Guedj, E. (2011). Predictive value of brain perfusion SPECT for rTMS response in pharmacoresistant depression. *European Journal of Nuclear Medicine and Molecular Imaging,* Vol. 38, N°9, (September 2011), pp.1715-1722.

Risco, L., González, M., Garay, J., Arancibia, P., Nuñez, A., Hasler, G., Galleguillos, T. (2003). Evaluación funcional del eje hipotálamo-hipófisis-tiroides en episodio depresivo mayor único: ¿desregulación a nivel central?. *Revista de Neuro-Psiquiatría*, Vol.66, N°.4, (2003), pp. 320-328.

Roy-Byrne, P.; Post, RM.; Rubinow, DR.; Linnoila, M.; Savard, R. & Davis, D. (1983). CSF 5HIAA and personal and family history of suicide in affectively ill patients: a negative study. *Psychiatry Research*, Vol.10, No.4 (December 1983), pp. 263-274.

Rozanov, C.B.Dratman, M.B., (1996). Immunohistochemical mapping of brain triiodothyronine reveals prominent localization in central noradrenergic systems. *Neuroscience,* Vol. 74, N°3 (October, 1996), pp. 897-915.

Rubinow, DR.; Gold, PW.; Post, RM.; Ballenger, JC.; Cowdry, R.; Bollinger, J. & Reichlin, S. (1983). CSF somatostatin in affective illness. *Archives of General Psychiatry*, Vol.40, No.4 (April 1983), pp. 377–386.

Ruhé, H.G., Booij, J., Veltman, D.J., Michel, M.C., Schene, A. (2011). Successful pharmacologic treatment of major depressive disorder attenuates amygdala activation to negative facial expressions: a functional magnetic resonance imaging study. *Journal of Clinical Psychiatry*, (August 2011), [Epub ahead of print]

Samuels, M.H., Schuff, K.G., Carlson, N.E., Carello, P., Janowsky, J.S. (2007). Health status, mood, and cognition in experimentally induced subclinical hypothyroidism. *Journal of Clinical Endocrinology and Metabolism,* Vol. 92, N°7, (2007), pp.2545-2551.

Saxena, J., Singh, P.N., Srivastava, U., Siddiqui, A.Q. (2000). A study of thyroid hormones (T3, T4 & TSH) in patients of depression. *Indian Journal of Psychiatry,* Vol. 42, N°3, (July 2000) pp.243-246.

Singhal, R.L., Rastogi, R.B., Hrdina P.D. (1975) Brain biogenic amines and altered thyroid function. *Life Sciences,*Vol. 17, N°11, (December 1975),pp. 1617-1626.

Smith, J.W., Evans, A.T., Costall, B., Smythe, J.W. (2002). Thyroid hormones, brain function and cognition: a brief review. *Neurosciences and Biobehavioral Reviews,* Vol. 26, N°1, (January 2002), pp.45-60.

Stern, RA.; Nevels, CT.; Shelhorse, ME.; Prohaska, ML.; Mason, GA. & Prange Jr, AJ. (1991). Antidepressant and memory effects of combined thyroid hormone treatment and electroconvulsive therapy: Preliminary findings. *Biological Psychiatry*, Vol. 30, No.6 (September 1991), pp. 623–627.

Stipcević T, Pivac N, Kozarić-Kovacić D, Mück-Seler D. (2008) Thyroid activity in patients with major depression. *Collegium Antropologicum*, Vol. 32,No3 (September 2008),pp. 973-976.

Strawn, JR.; Ekhator, NN.; D'Souza, BB. & Geracioti Jr, TD. (2004). Pituitary-thyroid state correlates with central dopaminergic and serotonergic activity in healthy humans. *Neuropsychobiology*, Vol.49, No.2, pp. 84–87.

Szabadi, E. (1991). Thyroid dysfunction and affective illness. *British Medical Journal*, Vol.302, No. 6782 (April 1991), pp. 923–924.

Torlontano, M., Durante, C., Torrente, I., Crocetti, U., Augello, G., Ronga, G., Montesano, T., Travascio, L., Verrienti, A., Bruno, R., Santini, S., D'Arcangelo, P., Dallapiccola, B., Filetti, S., Trischitta, V. (2008). Type 2 deiodinase polymorphism (threonine 92 alanine) predicts L-thyroxine dose to achieve target thyrotropin levels in thyroidectomized patients. *Journal of Clinical Endocrinology and Metabolism*, Vol. 93, N°3, (March 2008) pp. 910-913.

Vlassenko, A., Sheline, Y.I., Fischer, K., Mintun, M.A. (2004). Cerebral perfusion response to successful treatment of depression with different serotoninergic agents. *Journal of Neuropsychiatry and Clinical Neurosciences*, Vol.16, N° 3, (Summer 2004), pp. 360-363.

Walker, P., Weichsel, M.E., Jr., Fisher, D.A., Guo, S.M. (1979). Thyroxine increases nerve growth factor concentration in adult mouse brain. *Science*, Vol. 204, N°4391, (April 1979), pp.427-429.

Walker, P., Weil, M.L., Weichsel, M.E., Jr., Fisher, D.A. (1981). Effect of thyroxine on nerve growth factor concentration in neonatal mouse brain. *Life Sciences*,Vol 28, N°15-16 (April 1981), pp. 1777-1787.

Wheatley, D. (1972). Potentiation of amitriptyline by thyroid hormone. *Archives of General Psychiatry*, Vol. 26, No.3 (March 1972), pp. 229–233.

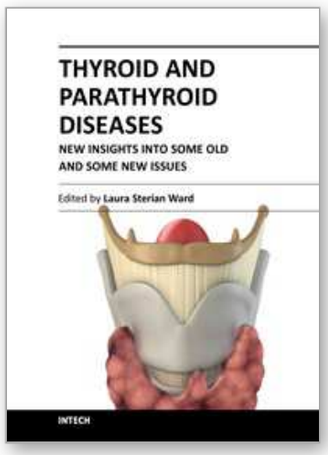
Whybrow, P.C.Prange, A.J., Jr. (1981). A hypothesis of thyroid-catecholamine-receptor interaction. Its relevance to affective illness. *Archives of General Psychiatry,* Vol. 38, N°1, (1981), pp. 106-113.

Wikström, L.; Johansson, C.; Saltó, C.; Barlow, C.; Campos Barros, A.; Baas, F.; Forrest, D.; Thorén, P. & Vennström, B. (1998). Abnormal heart rate and body temperature in mice lacking thyroid hormone receptor alpha 1. *The EMBO Journal*, Vol.17, No.2 (January 1998), pp. 455–461.

Wilson, IC.; Prange Jr, AJ.; McClane, TK.; Rabon, AM. & Lipton, MA. (1970). Thyroid hormone enhancement of imipramine in nonretarded depressions. *New England Journal of Medicine*, Vol. 282, No.19 (May 1970), pp. 1063–1067.

Zavacki, A.M., Ying, H., Christoffolete, M.A., Aerts, G., So, E., Harney, J.W., Cheng, S.Y., Larsen, P.R., Bianco, A.C., (2005). Type 1 iodothyronine deiodinase is a sensitive marker of peripheral thyroid status in the mouse. *Endocrinology,* Vol.146, N°3, (March 2005)pp. 1568-1575.

Zobel, A., Joe, A., Freymann, N., Clusmann, H., Schramm, J., Reinhardt, M., Biersack, H.J, Maier, W., Broich, K. (2005). Changes in regional cerebral blood flow by therapeutic vagus nerve stimulation in depression: An exploratory approach *Psychiatry Research,* Vol. 139, N 3, (August 2005), pp. 165-179.



Thyroid and Parathyroid Diseases - New Insights into Some Old and Some New Issues

Edited by Dr. Laura Ward

ISBN 978-953-51-0221-2
Hard cover, 318 pages
Publisher InTech
Published online 07, March, 2012
Published in print edition March, 2012

This book was designed to meet the requirements of all who wish to acquire profound knowledge of basic, clinical, psychiatric and laboratory concepts as well as surgical techniques regarding thyroid and parathyroid glands. It was divided into three main sections: 1. Evaluating the Thyroid Gland and its Diseases includes basic and clinical information on the most novel and quivering issues in the area. 2. Psychiatric Disturbances Associated to Thyroid Diseases addresses common psychiatric disturbances commonly encountered in the clinical practice. 3. Treatment of Thyroid and Parathyroid Diseases discusses the management of thyroid and parathyroid diseases including new technologies.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen