Non Genomic Modulation of Ligand Gated Ionotropic Receptors by Thyroid Hormones

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Abstract: Ligand gated ionotropic receptors are responsible for the fast neurotransmission in the brain and are the target of widely used drugs, such as anxiolytics, anticonvulsant and antidepressant, and of endogenously produced substances, e.g. hormones. In this review, the fast regulatory effects of thyroid hormones (THs; T3 and T4) on ligand gated ion channels will be analyzed and discussed. More precisely, the focus will be on receptors that mediate the majority of inhibitory and excitatory neurotransmission in the brain, respectively γ -aminobutyric acid (GABA) and glutamate ionotropic receptors. Brain is an important target for THs, as proved by the profound alterations in its structure and functionality related to their imbalance. Indeed, dysthyroidism is often associated with several neuropsychiatric disorders that derive also from a dysfunction of GABAergic and glutamatergic neurotransmission. The molecular mechanisms responsible for these changes are not completely clarified yet. THs, through the binding of nuclear receptors, can modulate the expression of proteins directly or indirectly involved in neurotransmission; in addition, their non genomic fast modulation of ionotropic receptors mediating excitatory and inhibitory neurotransmission could also play an important role. THs modulate recombinant and native receptors activated by exogenous GABA or glutamate as well as synaptic and extrasynaptic excitatory and inhibitory neurotransmission. These non genomic effects do not depend on protein phosphorylation or on the membrane integrin receptor $\alpha\beta 3$ activation. Keeping in mind that a local regulation of THs levels can occur in different brain regions the fast modulation of THs on synaptic activity could provide a rapid and efficacious control of the function of several brain circuitries.

Keywords: Electrophysiology, endogenous modulators, GABA_A receptors, Glutamate receptors, ligand-gated receptors, neurosteroids, synaptic transmission, thyroid hormones non genomic effects.

INTRODUCTION

Ligand gated ionotropic receptors (LGIRs) are heteromeric proteins coupled to a channel whose gating depends on the binding of a neurotransmitter. Usually LGIRs are localized at synapses and convert the chemical signal of the neurotransmitter directly in electrical signal on the postsynaptic membrane ensuring a fast synaptic transmission. To this class of receptors belong nicotinic acetylcholine (nACh), serotonin 5HT₃, GABA_A, glycine, ionotropic glutamate (iGLUT) and P2X receptors. The basic biophysical and pharmacological properties of LGIRs were determined with the help of molecular biology techniques that allowed cloning and expression of recombinant receptors in heterologous systems. Most of LGIRs are associated with accessory proteins and with different types of structures involved in receptor trafficking. The activity of LGIRs is finely regulated by exogenous and endogenous substances that could directly bind the receptors or indirectly modulate their function through post-transcriptional modifications such as phosphorylation [1]. Among the endogenous molecules that can play an important role as modulators of LGIRs are thyroid

hormones (THs). The importance of THs on neurotransmission mediated by LGIRs, is supported by the evidence that deficit in THs level during development causes profound alterations in structure and function of the brain [2-4]. In addition, dysthyroidism in adult life is associated with several psychiatric disorders such as anxiety, depression, memory deficits, hallucinations and in severe cases seizures [5, 6]. For these reasons, animal models of hypo- or hyperthyroidism were always considered a valuable tool to shed light on the effect of THs in the central nervous system (CNS).

Adult onset hypothyroidism has been clearly linked to cognition and memory dysfunction both in animal models [7] and in humans [5]. Hypothyroidism has been shown to affect basic synaptic neurotransmission, short-term and long-term plasticity in hippocampus, a brain area known to be involved in memory processes.

A large amount of studies has been carried on in the last years on this topic but they did not provide a clear view of the changes in brain synaptic transmission when THs levels are altered. Basal neurotransmission was found to be decreased [8, 9, 10, 11], enhanced [12] or unaffected [13, 14] by THs imbalance. Long-term potentiation (LTP) [15], a widely accepted cellular model for long-term synaptic plasticity related to learning and memory, was also found to be increased [8, 10, 12], suppressed [11, 13, 14, 16] or unchanged [16] after THs deficit.

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Mechanisms underlying THs modification of synaptic neurotransmission could be mediated by protein synthesis and be considered “genomic” [17, 18, 2], or depend on fast changes not dependent on transcriptional mechanisms and be, for this reason, called “non genomic”. Many of the non genomic actions of THs are initiated in the plasma membrane, at the level of the $\alpha v \beta_3$ integrin receptor [19, 20], or in the cytoplasm. These effects, opposite to the genomic ones, are prompt in onset, independent of new protein synthesis, associated with changes in ion transport systems or lead to complex cellular modifications [21]. The non genomic events could also ultimately result in transcriptional modification of specific genes [20, 21].

The genomic mechanisms have been extensively investigated but studies on non genomic effects of THs at the level of synaptic neurotransmission were limited.

Dratman in 1976 [22] proposed a role for T3 as neurotransmitter based on the findings that T3 localize in the nerve ending fractions. Mason [23], supporting this view showed that T3 could be released from synaptosomes with Ca^{2+} dependent mechanisms. Further studies provided evidences for a selective distribution of labeled THs and of antibody against T3 in specific brain areas of the adrenergic system [24, 25]. A naturally occurring metabolite of THs, the thyronamine T₁AM can rapidly activate a G-protein coupled receptor and stimulate adenylate cyclase [26], and in a recent report evidences were provided of its physiological role in the brain as adrenergic blocking agent [27].

In an electrophysiological study, Caria *et al.* [28] showed that T4 inhibits field excitatory postsynaptic potentials in hippocampus *in vivo*. In *in vitro* studies performed on CA1 neurons in slices, the same group showed that T3 and T4 have opposite effects on noradrenaline-evoked firing rate: T4 reduces while T3 enhances cell firing rate.

Various other neurotransmitter systems, such as cholinergic, serotonergic, adenosinergic, and dopaminergic are affected by THs [18, 29] but while the contribution of genomic mechanisms in THs modulation is acknowledged, their fast non-genomic effects at the level of these systems have not been investigated yet.

In this paper information concerning the non genomic effects of THs on two of the major players in the fast synaptic transmission in the CNS, i.e. iGLUT and GABA_A receptors will be reviewed.

NON GENOMIC REGULATION OF IONOTROPIC GLUTAMATE RECEPTORS BY THYROID HORMONES

Ionotropic Glutamate Receptors: General Features

Glutamate receptors mediate the majority of excitatory neurotransmission in CNS and are localized on neuronal and non-neuronal cells. They are classified, according to the signal transduction mechanism, in ionotropic (iGLUT) or metabotropic (mGLUT). Three classes of iGLUT receptors have been identified: α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), kainate, and N-methyl-D-aspartic acid (NMDA) receptor [30].

All iGLUT receptors are assembled from different subunits (AMPA receptor: GLUA1-4, kainate receptor: GLUK1-5, NMDA receptor: GLUN1-4) whose expression is developmentally regulated and brain region specific. The different subunit combination confers to the receptors diverse physiological and pharmacological properties [30]. Several drugs are known to act at the level of these receptors by potentiating or by blocking their activities. Among them are substances that antagonize glutamatergic neurotransmission that are potential therapeutic agents in neurodegenerative diseases, when an excess of glutamate could be responsible for neuronal death [30].

On the other side, compounds able to potentiate glutamate receptor function are considered nootropic drugs that improve cognitive performance and are potential medications for a number of psychiatric and neurological conditions [30].

A large amount of exogenous substances modulate glutamatergic neurotransmission but endogenous compounds able to regulate its functionality are relatively limited (mono- and divalent ions, polyamines, kinurenine and steroid molecules) [30]. There are steroid molecules that are synthesized in the brain and called neurosteroids (NSs) [31]. The central effects of these compounds are mediated by interactions with several neurotransmitter-gated channels [32], including AMPA and NMDA receptors.

Ionotropic Glutamate Receptors and Thyroid Hormones

Preliminary evidence of an interaction between THs and glutamate receptors was provided by Oguro *et al.* [33], who found that THs displace NMDA-sensitive L- (³H) glutamate binding competitively.

Recently, it has been shown that THs are able to modulate glutamatergic neurotransmission in hippocampal neurons in primary cultures and in slices [34]. T3 and T4 reduced NMDA-evoked currents with potency in the micromolar range and the effect is not competitive for the glutamate or the glycine binding site. T3 and T4 were active in mouse fibroblasts expressing NR1a-NR2A, NR1a-NR2B subunits of the NMDA receptors, and no subunit selectivity was detected. In Figure 1 are shown the effects of T3 on NMDA-evoked current either on cultured neurons (Fig.1A) or in mouse fibroblast expressing NR1-NR2a (Fig.1B).

Since NMDA receptors are known targets for protein kinases [30], the hypothesis that THs effect could occur via PKC-mediated phosphorylation of the channel was tested. The effect was not achieved through this mechanism because neither blocking nor stimulating the kinase had an effect on the inhibition. AMPA and Kainate-evoked currents were also inhibited by T3 but not by T4 [34].

Analysis of the effect of THs on synaptic transmission in hippocampal slices show that only T3 is active on excitatory postsynaptic currents (EPSCs). This hormone reduces the frequency of the events (see Fig.1C) but leaves unaffected peak and decay of the currents [34]. The authors suggest that T3 reduces the release of neurotransmitter through modulation of presynaptic glutamatergic receptors or other types of receptors, e.g. nicotinic $\alpha 7$ or sigma receptors [35].

Fig. (1). Modulatory effects of THs on native and recombinant NMDA receptors.

A). Representative traces showing the effect of T3 (10 μM) on NMDA (100 μM + glycine 10 μM)-evoked currents in primary culture of hippocampal neurons. The effect of T3 is reversible. **B).** NMDA-evoked current recorded in fibroblasts stably expressing NR1-NR2a subunits of the NMDA receptor. The current is reduced by the application of T3 (10 μM). **C.)** Spontaneous excitatory postsynaptic currents (sEPSCs) recorded from a pyramidal neuron of the hippocampus from a 15 days old rat slice, in control (upper traces) and after bath perfusion of T3 (20 μM; lower traces). All experiments were performed using the patch-clamp technique in whole cell configuration.

Changes in the release of neurotransmitter could also depend on the dynamic of cytoskeleton remodeling at the pre-synaptic terminal, indeed there are several evidence of THs effect at the level of cytoskeleton protein [36, 37, 38].

Glutamate is fundamental for the neurotransmission in the brain and for the processes of learning, but an increase in the aminoacid concentration produces an excessive activation of the receptors that can lead to neuronal death [39]. Considered the antagonistic effect of THs on iGLUTR, it is likely that they could have a neuroprotective role against glutamate-induced toxicity. Indeed Losi *et al.* [34] observed that THs, at concentrations similar to those active on NMDA and AMPA receptors, prevent glutamate-induced neuronal death in cortical cultures. Similarly Mendes-de-Aguiar *et al.* [40] showed that also in cerebellar primary cultures THs protect from glutamate-induced neuronal death. The effect was achieved mainly through an increased synthesis of the glutamate transporters GLAST and GLT-1 in cerebellar astrocytes even though the authors did not rule out a direct action on glutamate receptors.

NON GENOMIC REGULATION OF GABA_A RECEPTORS BY THYROID HORMONES

GABA_A Receptors: General Features

GABA is the principal inhibitory neurotransmitter in adult mammalian brain and plays important roles also during development. Its action is mainly mediated by metabotropic GABA_B and ionotropic GABA_A receptors. Ionotropic GABA_A receptors are heteropentameric structures derived from the assembly of different type of subunits (α, β, γ, δ, ε) that confer to the receptor distinct biophysical and pharmacological features [41, 42]. In the last years it has been recognized that GABA_A-mediated inhibition in the brain depends on two types of current: a phasic one mediated by synaptically released GABA and a tonic current produced by the activation of extrasynaptic receptors by ambient low concentrations of GABA [43].

Synaptic and extrasynaptic GABA_A receptors differ not only in their localization but also in the subunit composition, and in the biophysical and pharmacological properties [44]. Extra synaptic GABA_A receptors possess higher affinity for GABA and slower rate of desensitization than synaptic ones [45]. Tonic inhibition plays a crucial role in regulating neuronal excitability because it sets the threshold for the generation of action potential and allows the integration of excitatory signals.

GABA_A receptor is the target of several clinically important drugs (e.g. barbiturates, benzodiazepines, anesthetics and ethanol) and of endogenous substances (e.g. endozepines and NSs) [42, 46, 47].

NSs can act as bimodal modulators of GABAergic neurotransmission; indeed some of them potentiate GABA_A receptor function (ALLO, THDOC) [47, 48, 49] while others (PS, DHEAS) decrease receptor activity [50].

GABA_A Receptors and Thyroid Hormones

The first evidence that THs could be active on GABA_A receptors is from the late '60s [51]. The interactions between GABAergic and thyroid system are very complex and bidirectional: THs have effects on the enzymes responsible for synthesis and degradation of GABA, levels of glutamate and GABA, release and reuptake of GABA by neurons; on the other side GABAergic system regulates the pituitary-thyroid axis at different levels [17].

The majority of these effects are mediated by transcriptional mechanisms but several reports in the last decade indicate that there is also a direct action of THs on GABA_A receptors.

Martin *et al.* [52] showed that THs are able to modulate recombinant GABA_A receptors expressed in HEK 293 cells. T3 and T4 decrease GABA-evoked current with EC₅₀ in the low micromolar range and selectively act on certain subunit combinations. In fact, THs effect was present both on α1β2γ2L and on β2γ2, but not on receptors assembled from

$\alpha 6\beta 2\gamma 2$ subunits. THs do not bind to the benzodiazepine (BZ) site since RO15-1788, a competitive BZ antagonist, does not block their effects. In injected *Xenopus* oocytes THs decrease, in a non-competitive fashion, GABA-evoked current in $\alpha 1\beta 2\gamma 2$ but not in $\beta 2\gamma 2$ and in $\alpha 6\beta 2\gamma 2$, suggesting that $\alpha 1$ subunit is important for THs modulation. In the experiments performed in oocytes T3 was also able to directly open the channel and this effect was present in all the GABA_A subunit combination tested [53]. The fact that T3 activates the channel at the same concentrations that block the channel open by GABA is a bit surprising and raises the question of which could be the predominant effect *in vivo*. In other studies performed in HEK293 cells [52] and in neurons in culture [54] the direct effect of T3 was not evident. It is possible that in these systems the amount of GABA_A receptor expressed is considerably lower than in injected oocytes making difficult the detection of T3-induced current that is much smaller (160 fold) than the GABA-evoked one. The agonistic effect of T3 was blocked by picrotoxin but not by bicuculline suggesting that it acts at a site different from the classical agonist site [53]. It is possible that T3, having a very low efficacy, behaves like a partial agonist, and in presence of the full agonist, i.e. GABA, antagonizes its effect. Only when the number of receptors is very high, as it happens in injected oocytes, the agonist effect is detectable.

In a very recent work, Puia *et al.* [54] investigated in detail THs modulation of native GABA_A receptor expressed in cultured hippocampal neurons. T3 and T4 decreased GABA-evoked currents with potencies in the micromolar range (Fig. 2A). The antagonism was non-competitive, as previously shown also by Chapel *et al.* [53] and Martin *et al.* [55].

THs modulation of GABA_A receptor could depend on receptor phosphorylation [56], intracellular Ca^{2+} [37, 57] or could be mediated by the integrin receptor $\alpha \nu \beta 3$ [19, 20]. To address these points the activity of THs was measured in presence of protein kinase blockers, of BAPTA, and of TET-RAC, a selective antagonist of the integrin receptor. None of these treatments changed the effect of the hormones [54].

Exogenous application of GABA (GABA-evoked current) recruits all GABA_A receptors present on cell surface, but it is possible that THs exert a diverse modulation on synaptic vs. extra-synaptic receptors. GABA released in the synaptic cleft evokes spontaneous inhibitory postsynaptic currents (sIPSCs) that are sensitive to both hormones. The frequency and the amplitude of sIPSCs, recorded from hippocampal neurons in culture, were reduced by T3 or T4 (both at 10 μM) but the current decay was unaffected [54] (see Fig. 2B). While the decrease in current amplitude is explained by THs effect at the level of postsynaptic GABA_A receptors, the reduction in frequency could depend on pre-synaptic mechanisms. It is possible that THs modify the release of neurotransmitter by binding to some pre-synaptic receptors regulating the GABA release or by acting at the level of cytoskeleton proteins [36, 38]. Extra-synaptic GABA_A receptors are activated by low concentrations of GABA, which diffuses from the neighboring synapses, and have higher affinity for the agonist and slower rate of desensitization than synaptic GABA_A receptors [45]. T3 and T4

have a diverse activity on GABA tonic current mediated by extra-synaptic receptors. T3, but not T4, reduces the current evoked by low concentration of GABA, indicating that the two hormones should have different modulatory roles on GABAergic neurotransmission.

THYROID HORMONES AND NEUROSTEROIDS: SIMILARITIES AND DIFFERENCES IN THEIR ACTIONS AT THE LEVEL OF IONOTROPIC GLUTAMATE AND GABA_A RECEPTORS

THs share a lot of similarity with some of the endogenous molecules called NSs [31]. In particular, the chemical structure of T3 is very close to that of the sulphate steroid pregnenolone sulfate (PS) [55], and also the modulation of THs at the level of different neurotransmitter systems is comparable to that of this NS.

PS can regulate learning and memory at low concentrations [58] and infusion of low doses (ng) of this NS into hippocampus can reverse cognitive impairment in aged rats [59]. THs deficiency impairs learning and memory in adults [9] and intra-hippocampal infusion of T3 favours LTP [60].

At the molecular level PS, similarly to T3, inhibits, in a non-competitive way, AMPA and GABA_A receptors function [50, 53, 54, 55, 61, 62]. The modulation of the GABA_A receptor by both compounds does not require the presence of γ subunit in the receptor assembly [48, 53], and is not mediated by the binding to the benzodiazepine site [52]. Even though the two molecules share many similarities their site of action on GABA_A receptor is probably different because, when applied together at concentrations able to elicit a maximal response, they have an additive effect [54].

Hosie *et al.* [63, 64] identified three or four distinct sites for NSs in the GABA_A receptors: a "potentiating" site, responsible for the positive modulatory action of ALLO and THDOC, an "acting" site, connected with the agonist activity of both compounds, and one or possibly two other sites for inhibitory sulphate steroids [65]. Further studies are needed to identify other sites in the GABA_A receptor responsible for THs action.

Both THs and PS reduce GABAergic neurotransmission by decreasing sIPSCs frequency. PS effect on sIPSCs is mediated by presynaptic $\sigma 1$ receptors and is elicited by nanomolar concentrations of the NS [66], while the modulatory effect of THs is obtained at micromolar concentrations and the mechanism of action is still unknown [54].

THs, depending on the experimental system [53], could behave as agonist of the GABA_A receptor and its action is blocked by picrotoxin, a non-competitive antagonist of the receptor. PS does not show agonist properties but some other NSs such as ALLO and THDOC are capable of opening GABA_A channels at micromolar concentrations and their agonistic action is blocked by bicuculline [48]. Furthermore these NSs at nanomolar concentrations are positive allosteric modulators of GABA_A receptor [48, 49].

Both THs and PS modulate NMDA receptor function, but in different way: THs inhibit NMDA receptors and this effect is independent on the subunit assemblies [34], while PS,

Fig. (2). Modulatory effect of THs on native GABA_A receptors.

A). GABA-evoked current from a cortical neuron in primary culture at 8DIV (days *in vitro*) voltage clamped at -60 mV. Representative traces showing the response to 1 μ M GABA alone and in the presence of T3 (20 μ M) and after wash out. **B).** Spontaneous inhibitory post-synaptic currents (sIPSCs) recorded from a cortical neuron in culture at 12DIV. Representative traces in control conditions (CNQX 5 μ M, MK801 10 μ M)(left) and after bath perfusion of T3 (10 μ M)(right). In the middle: averaged sIPSCs in control and after T3 with indication of the decay time constant (τ_w). The current amplitude was reduced by 50% while the τ_w was not significantly changed after T3 perfusion.

depending on the subunit combination expressed, potentiates or reduces NMDA-evoked current [61, 67, 68].

PS, like other NSs, is synthesized *ex novo* in the brain [31]. Previous works claimed that NSs production occurs mainly in glial cells [69], but recently evidence was provided of the expression of the neurosteroidogenic enzymes in neurons. Agis-Balboa *et al.* [70] reported that the synthetic enzymes (5 α -RI and 3 α -HSD) were coexpressed in cortical and in hippocampal pyramidal neurons as well as in output neurons of the amygdala, thalamus, cerebellum and striatum, but not in GABAergic interneurons or in glial cells [70, 71].

T3 and T4 are synthesized in the periphery and from the circulation enter the brain through the blood brain barrier using plasma membrane transporters. T3 present in the brain derived only partially (20% in fetal life) from the periphery but is produced locally from T4 by deiodinase type 2 (D2)-mediated activity. D2 is present predominantly in glial cells, tanycytes and astrocytes [72] and its expression and activity is regulated by pharmacological treatments [73] and in physiological or in pathophysiological situations [74]. The expression of D2 in astrocytes suggests the existence of interplay between astrocyte and neurons in regulating THs levels. T4 and T3 are metabolized in neurons by the deiodinase type 3 (D3) in rT3 and T2 respectively. RT3 is genomically inactive but is able to modulate both GABA- and NMDA-evoked currents [34, 54]. THs are charged amino-acid derivatives and necessitate protein carriers to cross the plasma membrane. Indeed several THs transporters have been identified [75] including monocarboxylate transporter 8 (MCT8), aminoacid transporters, and organic anion transporting polypeptides (OATP14). MCT8 is a specific transporter for T4 and T3, expressed in neurons from all brain areas very sensitive to THs such as neocortex, hippocampus, hypothalamus and Purkinje cells [76], while OATP14, a carrier and for T4, is predominantly expressed in astrocytes.

The concentrations of T3 and T4 in the brain are regulated by complex mechanisms involving THs plasma membrane transport and D2 and D3 activity [77, 78]. All these findings favour the idea that THs concentrations in the brain should be not homogeneous and peaks of high concentrations could be present in selected brain areas. In Figure 3 is schematized a synapse and the putative sites of action of THs at this level. Different factors may concur to activate the genomic or the non genomic pathway and this issue should be further investigated.

PUTATIVE ROLE OF THYROID HORMONES NON GENOMIC EFFECTS ON GLUTAMATERGIC AND GABAERGIC NEUROTRANSMISSION IN PHYSIOLOGICAL AND PATHOLOGICAL SITUATIONS

Role of Thyroid Hormones Non Genomic Effects on Ligand -Gated Ionotropic Receptors in Development

THs influence brain development very early in fetal life. The nuclear THs receptors are expressed in the brain as early as from the 10th week of gestation in humans and increase during the second trimester. THs have very important actions on neuronal migration, synaptogenesis and differentiation of neurons and astrocytes. All these maturational processes are regulated in a narrow time window [2] and changes in THs level during this period may result in profound and long lasting alterations in the cytoarchitecture and functionality of the whole brain [3, 4].

THs differently affect GABA system in developing versus adult brain: they stimulate GABA function in development while inhibit it in adults [2]. It is known that developmental effects of THs in mammalian brain are mainly mediated by nuclear receptors regulating gene expression, even though also the non-genomic mechanisms are recognized as determinant in many developmental processes [36].

Fig. (3). Non genomic effects of THs at the level of the synapse.

Schematic view of a synapse where are evidenced the hypothetical interaction of T3 and T4 with ligand gated ionotropic receptors. THs deriving from the periphery or T3 produced in astrocytes can modulate synaptic function in a fast way by acting at the level of presynaptic (a) postsynaptic (b) or extrasynaptic (c) receptors.

Which is the possible involvement of the non-transcriptional regulation of THs of glutamatergic and GABAergic neurotransmission in development?

Several mechanisms govern neuronal migration and among them, the activation of specific GABA and glutamate receptors is particularly important because, by acting as motility promoters, they can accelerate or stop the migration [79]. GABA and glutamate receptors are expressed in migrating neurons at early developmental stages and their activation produces changes in intracellular Ca^{2+} concentration. In fact, NMDA receptor is highly permeable to Ca^{2+} and, early in development (until P2-5 in hippocampus), GABA acts also as an excitatory neurotransmitter [79] and increases the intracellular Ca^{2+} concentration. Being Ca^{2+} very important for different cellular functions such as changes in cytoskeleton dynamics [80], the antagonism of GABA and glutamate receptors by THs could affect developmental processes. The inhibition of NMDA receptors retard cell migration because speed and direction of the process are modulated by extrinsic Ca^{2+} signals related to the receptor activation prior to synapses formation. Indeed, in hypo thyroidal pups the migration of glutamatergic neurons is disorganized and there is a decrease in dendritic arborization [2, 3, 4, 81].

During development, the fast modulation of synaptic transmission by THs could also operate a selection among different inputs: blockade of one synapse activity could promote the suppression of that input.

The importance of non genomic modulation of THs in adults is more acknowledged than during development. It is possible that in adult THs, as other endogenous neuromodulators, act to fine tuning inhibitory and excitatory neuro-

transmission, since their effect is fast but reversible. Selective expression and activity of the synthetic and metabolic enzymes [72] and the specificity of THs action [53] prompt to think that their roles in the different brain areas may be different.

Role of Thyroid Hormones Non Genomic Effects on Ligand Gated Ionotropic Receptors in Dystyroidism in Adults

Thyroid dysfunction in adult can affect the activity of several neurotransmission [2], such as serotonergic [82, 83, 84], adrenergic [82, 85, 86, 27] cholinergic [87, 88, 89], GABAergic and glutamatergic system, and the functional alterations consequent to this pathological situation derived by an impairment in all the systems. Pathological increase or decrease of THs modify GABAergic and glutamatergic systems; for example, hypothyroidism produces changes in the enzymes responsible for the synthesis and metabolism of GABA and glutamate, in neurotransmitter release and reuptake, in the expression and functionality of the receptors [17, 90].

All these modifications are mainly determined by the genomic effects, but it is important to know whether the non genomic actions of THs on GABAergic or glutamatergic transmission could be equally important in determining the functional changes found in dystyroidism in adults.

Let us consider the mechanism by which hypothyroidism affects learning and memory. Many studies have shown that there is impairment in LTP in several circuits of the hippocampus in hypothyroidism. Since T3, acutely administered, can contribute to the degree of LTP [60] in euthyroidal animals, a decrease in T3 concentrations due to a hypo thyroidal

state could impair LTP [11]. T3 effect could be mediated by a decrease in GABA inhibitory drive, even though other neurotransmitter systems could be involved.

Considering the different activity of T3 and T4 either on glutamatergic neurotransmission (T3 but not T4 reduces AMPA receptors activity) or on GABAergic neurotransmission (T3 but not T4 decrease GABA tonic current) it is very likely that, since normal activity of the brain requires certain level of T3 and T4, changes in the relative concentrations of the two hormones produce alterations in the functionality of the brain circuitry.

Interestingly the diverse brain areas are differently affected by hypo- or hyper- thyroidism [74]. T4 and T3 concentrations and the activity of the enzymes D2 and D3 selectively change in some areas. For example in an experimental model of hyperthyroidism, the concentrations of T4 increase two to three fold in all brain regions whereas T3 levels were reduced in some areas while remaining unchanged in others such as cortex, hippocampus and amygdala that are very sensitive to THs [74]. All these data suggest that the T3 and T4 effects in the brain are very complex and that their role could be different in different brain areas.

It is also possible that the fast modulatory action of THs on neurotransmission could serve, in case of hormonal imbalance, as a compensatory mechanism to re-tune the system, but if the imbalance persists can trigger more stable changes through the activation of genomic machinery.

CONCLUSIONS

THs act as modulators of GABAergic and glutamatergic neurotransmission *in vitro*. Considered that their levels in the brain are finely regulated by complex mechanisms, it is plausible that they have a role as endogenous modulators of brain functions. In particular, in development through their non genomic effects, they can regulate cell migration and differentiation, while in adult life they can rapidly and finely tune the network activity of defined brain areas.

A better understanding of the non genomic mechanisms of THs at the level of diverse neurotransmitter systems are fundamental to try to correct the imbalance in brain functionality derived from pathological THs levels and eventually for the development of new therapeutic agents that could be useful in the treatments of psychiatric disorders.

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ABBREVIATIONS

5alpha-RI	=	5alpha-reductase type I
3alpha-HSD	=	3alpha-hydroxysteroid dehydrogenase
ALLO	=	Allopregnanolone (3 α -hydroxy-5 α -pregnan-20-one)
AMPA	=	γ -amino-3-hydroxy-5-methylisoxazol-4-propionic acid
CNS	=	Central Nervous System

DHEAS	=	Dehydroepiandrosterone sulfate
GABA	=	γ -aminobutyric-acid
NMDA	=	N-methyl-D-aspartic acid
rT3	=	Reverse-triiodothyronine
PS	=	Pregnenolone sulfate
THs	=	Thyroid hormones
T4	=	L-thyroxine
T3	=	3,3',5-L-triiodothyronine
T2	=	3,5-diiodothyronine
THDOC	=	Tetrahydrodeoxycorticosterone (3 α ,21-dihydroxy-5 α -pregnan-20-one)

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