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Thyroid hormone's role in regulating brain glucose metabolism and potentially modulating hippocampal cognitive processes

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Abstract

Cognitive performance is dependent on adequate glucose supply to the brain. Insulin, which regulates systemic glucose metabolism, has been recently shown both to regulate hippocampal metabolism and to be a mandatory component of hippocampally-mediated cognitive performance. Thyroid hormones (TH) regulate systemic glucose metabolism and may also be involved in regulation of brain glucose metabolism. Here we review potential mechanisms for such regulation. Importantly, TH imbalance is often encountered in combination with metabolic disorders, such as diabetes, and may cause additional metabolic dysregulation and hence worsening of disease states. TH's potential as a regulator of brain glucose metabolism is heightened by interactions with insulin signaling, but there have been relatively few studies on this topic or on the actions of TH in a mature brain. This review discusses evidence for mechanistic links between TH, insulin, cognitive function, and brain glucose metabolism, and suggests that TH is a good candidate to be a modulator of memory processes, likely at least in part by modulation of central insulin signaling and glucose metabolism.

Keywords

Insulin; thyroid hormone; diabetes; GluT; glucose

1. Introduction

Multiple lines of evidence have established a direct link between glucose supply to the brain and cognitive performance, with acute interruptions to this supply impairing performance while acute provision of additional exogenous glucose results in enhanced cognition (Holmes et al. 1983; Holmes et al. 1986; Lee et al. 1988; Pelligrino et al. 1990; Long et al. 1992; Parsons and Gold 1992; Gold 1995; Korol and Gold 1998; Winocur and Gagnon 1998; McNay et al. 2000; McNay and Gold 2002; Gold 2005). Not surprisingly, regulators of brain glucose metabolism have been well-established to play a role in memory modulation; in particular, insulin has recently been shown not only to modulate neural metabolism, especially within the hippocampus, but also to be a critical component of hippocampal memory processes (McNay et al. 2004; Moosavi et al. 2006; Babri et al. 2007; McNay et al. 2010). The present review builds on these findings to suggest that an additional regulator of neural metabolic and mnemonic processes may be thyroid hormones (TH), which may both independently modulate brain glucose metabolism and also interact with insulin signaling. We summarize, very briefly, data on modulation of memory by glucose

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and insulin before reviewing in detail the multiple levels at which TH and glucose homeostasis may be connected, leading to the hypothesis that TH may act as a memory modulator.

2. Metabolic influences on memory processes

2.1 Effects of glucose on memory

Both systemic and direct intracerebral glucose administration are known to modulate memory in a variety of species with an inverted-U dose-response curve, the effects being brain-region dependent (Hall et al. 1989; Parsons and Gold 1992; Gold 1995; Manning et al. 1998; Erickson et al. 2006; Hoyland et al. 2008; Krebs-Kraft and Parent 2008). There are at least two major hypotheses for the mechanism by which systemic glucose administration might enhance cognitive processes: 1) by increasing the glucose supply to the brain through the blood-brain barrier glucose transporter 1 (GluT1), and 2) by affecting vagal activity which alters neurotransmission within the brain (Simpson et al. 1994; Vannucci et al. 1998; Talley et al. 2002; Hassert et al. 2004; Rao et al. 2006). Microinjections of glucose to specific brain areas have facilitative effects on memory formation and mimic the effects of systemic glucose administration under many circumstances (Ragozzino et al. 1998; Canal et al. 2005). Cognitively demanding hippocampally-based tasks produce an acute drainage of hippocampal extracellular glucose, reversed by a dose of glucose which improves memory, suggesting that provision of additional local metabolic support to specific brain regions may be critical for enhancing memory (McNay et al. 2000; McNay et al. 2001). The effects of glucose administration on cognitive performance depend on variables including age and metabolic regulation; the inverted-U dose-response curve relating glucose concentration and cognition shows an optimal range of brain and systemic glucose concentrations that depends on task difficulty, age, and insulin sensitivity (Parsons and Gold 1992; Gold 1995; McNay and Gold 2002; Gold 2005). Given the importance of glucose supply to memory processes, mechanisms that regulate the availability of glucose to the brain may also modulate memory.

2.2 Effects of insulin on memory formation

Insulin, a peptide hormone secreted by the pancreas (and perhaps, it is increasingly recognized, also synthesized within the brain) is the primary regulator of systemic glucose levels (Gerozissis et al. 2001; Gerozissis 2003; Gerozissis 2008; McNay and Recknagel 2011). Insulin promotes glucose uptake in liver, skeletal and adipose tissues via activation of phosphatidylinositol 3-kinase (PI3K) and subsequent translocation of the insulin-responsive glucose transporter GluT4 to the cell surface. In addition to this systemic role, insulin is well-established to be centrally active in regulation of food intake and satiety, and it was recently demonstrated that hippocampal insulin signaling and PI3K activation are critically important for hippocampally-mediated memory processes (McNay et al. 2004; Moosavi et al. 2006; Babri et al. 2007; McNay et al. 2010). In addition, it was confirmed that insulin can acutely increase local hippocampal metabolism (McNay et al. 2010). This work built on studies showing that insulin can both modulate hippocampal synaptic plasticity and increase cell-surface GluT4 levels in hippocampal neurons, that spatial memory training increases hippocampal insulin receptor expression, and that insulin administration acutely attenuates memory deficits in several human populations (Chiu and Cline; Lin et al. 2000; Man et al. 2000; Izumi et al. 2003; Benedict et al. 2004; McEwen and Reagan 2004; Watson and Craft 2004; Zhao et al. 2004; Reagan 2005; Reger et al. 2006; Benedict et al. 2007; Reger et al. 2008; Yasui et al. 2008; De Felice et al. 2009; Grillo et al. 2009; Craft et al. 2011). Together, these studies clearly establish insulin as a modulator of hippocampal memory processes, likely at least in part via modulation of local glucose metabolism. Consistent with these findings, systemic insulin resistance [such as that characterizing Type II Diabetes

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Mellitus (T2DM)] is associated with cognitive impairment and may cause insulin resistance, with associated cognitive impairment, in brain regions such as the hippocampus (Mielke et al. 2005; Brands et al. 2007; Starr and Convit 2007; Biessels et al. 2008; Ross et al. 2009; van den Berg et al. 2009; McNay et al. 2010). The effects of insulin resistance on cognition seem to be independent of vascular pathology, as they are also observed in younger patients with well-controlled diabetes (Gold et al. 2007). Moreover, although outside the scope of this review, impaired central insulin signaling has been suggested as a mechanism explaining at least part of the cognitive impairment and hypo-metabolism seen in Alzheimer's Disease (AD) (Rasgon and Jarvik 2004; Steen et al. 2005; Revill et al. 2006; Sun and Alkon 2006; Jolivalt et al. 2010). In general, there is now clear support for insulin acting to enhance and support memory processes, particularly within the hippocampus and likely involving increased local glucose metabolism.

3. Actions of TH

3.1 TH and glucose metabolism

Brain glucose metabolism may be regulated by TH at multiple levels. TH are synthesized in, and secreted by, the thyroid gland when stimulated by thyroid stimulating hormone (TSH) from the pituitary. The prohormone thyroxine (T4) is transported to the tissues and converted to triiodothyronine (T3) within cells by enzymes called deiodinases (Bianco et al. 2002). Three deiodinase enzymes, types 1, 2, and 3 (D1, D2, D3) catalyze the deiodination reactions and can result in production of the active form of TH (T3) or inactive forms of TH (Gereben et al. 2008; Gereben et al. 2008; St Germain et al. 2009). D2 and D3 are highly expressed in developing and mature brain (Bianco et al. 2002). The regulation of local T3 production and its action by brain-region specific expression of deiodinase enzymes, TH transporters and thyroid hormone receptors (THR; discussed in a separate section of this review) are believed to maintain TH homeostasis within the brain independent of peripheral levels (Hernandez et al. 2010; Shukla et al. 2010; Sittig et al. 2011). T3 and T4 have both genomic and non-genomic effects, with the latter including regulation of Ca++ entry and activation of several kinases (Davis and Davis 2002; Davis et al. 2002; D'Arezzo et al. 2004; Bergh et al. 2005; Sui et al. 2005; Diez et al. 2008; Sui et al. 2008; Caria et al. 2009). One kinase activated by TH is PI3K, suggesting the potential for this to be one site of crosstalk between TH and insulin (Moeller et al. 2006; Sui et al. 2008; Cao et al. 2009).

PET studies suggest a direct link between thyroid activity and brain glucose metabolism. The spectrum of thyroid disorders reflects varying levels of thyroid activity and includes both subclinical thyroid states, such as subclinical hypo- and hyperthyroidism, and overt thyroid imbalances. Brain hypometabolism is commonly observed in thyroid disorders. Clinical data suggest that there is a significant and global decrease in brain glucose metabolism in severe hypothyroidism of short duration, and that both neural activity and regional glucose metabolism are reduced in the brains of mild-moderate hypothyroid patients (specifically, in hippocampus, bilateral amygdala, anterior, left subgenual, and right posterior cingulate cortex) and restored to control levels following TH replacement therapy (Constant et al. 2001; Bauer et al. 2009). Likewise, in patients with hyperthyroidism, lowered glucose metabolism is observed in limbic, frontal, and temporal lobes and the cerebral hypometabolism is corrected after antithyroid treatment (Miao et al. 2011). Older studies suggested that changes in vascular resistance subsequent to thyroid imbalance might be responsible for decreased cerebral blood flow and reduced neural activity (Scheinberg et al. 1950; O'Brien and Harris 1968). However, in recent studies it was observed that there are decreases in direct measures of cerebral glucose metabolism, such as the ratio of phosphocreatine to inorganic phosophate, in hypothyroid brains, suggesting that a direct effect of TH on brain glucose utilization cannot be ruled out and that changes in vascular

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resistance may be secondary to decreased cerebral metabolism (Scheinberg et al. 1950; Smith and Ain 1995; Miao et al. 2011).

Preclinical studies have provided insight into several specific potential mechanisms for TH's regulation of glucose metabolism, including activation of the sympathetic nervous system, modulation of glucose transport (including insulin-regulated glucose transport), and interaction with glucocorticoid signaling. Administration of T3 to the hypothalamic paraventricular nucleus increases glucose production, as long as sympathetic input to the liver is intact, suggesting that TH regulates hepatic glucose output via actions within hypothalamic nuclei that regulate autonomic input to the liver (Klieverik et al. 2008; Klieverik et al. 2009; Fliers et al. 2010). *In vitro* studies suggest that TH may regulate basal glucose transport through GluT1 and/or modulation of responsiveness to insulin. Cultured liver cells treated with 10^{-7} M of T3 showed a 57% increase in glucose transport over 6h and 240% increase over 24h, accompanied by increased GluT1 expression as measured by all of mRNA, total-protein, and membrane-protein levels (Kuruvilla et al. 1991). Similarly, basal glucose transport and GluT4 protein expression increased in skeletal muscle tissue from rats treated with TH systemically (Casla et al. 1990; Weinstein et al. 1994). In isolated adipocytes from rats made systemically hyperthyroid for a week, insulin-stimulated glucose transport increased by 43.6% with a similar increase observed in the levels of GluT4; conversely, adipocytes from hypothyroid animals had reduced GluT4 expression (Matthaei et al. 1995). Interestingly, a functional thyroid hormone response element (TRE) in the promoter region of the GluT4 gene has been identified, suggesting that thyroid hormone may directly increase GluT4 synthesis and hence lead to increased insulin-sensitive glucose transport (Torrance et al. 1997; Santalucia et al. 2001).

Despite these findings, there has been little study of the impact of TH on CNS glucose transport and/or metabolism in the adult brain. To our knowledge, only a single study of TH and brain GluTs has been reported, in which, apparently paradoxically, both hypo- and hyperthyroid conditions produced a decrease in whole-brain GluT1, highlighting the importance of maintaining brain euthyroidism (Mooradian et al. 1997). Initial studies in our lab, using primary hippocampal cultures treated with thyroid hormone and/or insulin, have demonstrated increased expression of GluT4 in as little as 30 minutes post-treatment (unpublished data). Further study and extension of these experiments *in vivo* is indicated.

3.2 Interactive effects of TH and glucocorticoids on glucose metabolism

TH interact with another potent regulator of blood glucose levels, glucocorticoids. In humans, an excess of glucocorticoids, whether endogenous or exogenous, impairs glucose metabolism and leads to the development of an insulin-resistant state and hyperinsulinemia (Wajchenberg et al. 1984; van Raalte et al. 2011). Conversely, basal levels of glucocorticoids are commonly elevated in diabetic patients with poor glycemic control suggesting that elevations in circulating insulin and glucocorticoids may deleteriously reinforce each other; consistent with this, treatments aimed at normalizing (i.e. lowering) glucocorticoid levels are under development as a therapy for patients with T2DM (Couch 1992; Ge et al. 2010; Wang 2011). These data suggest that significant interactions exist between the hypothalamic-pituitary-adrenal axis and insulin. In both peripheral tissues and hippocampus, elevated levels of glucocorticoids impair GluT4 functioning, thus possibly causing or contributing to insulin resistance, and directly modulating hippocampal glucose metabolism (Dimitriadis et al. 1985; Garvey et al. 1989; Piroli et al. 2007).

A detailed exploration of the metabolic effects of glucocorticoids, both acute and chronic, is beyond the scope of this review, but has been the topic of an excellent recent review (Reagan 2011); Reagan also notes the clinical correlation between diabetes and stressors in general, of which elevation in glucocorticoids is a common symptom and effector

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mechanism. However, given the metabolic effects of glucocorticoids, it is interesting to note that glucocorticoids decrease plasma TSH levels in both hypothyroid and normal human subjects (Wilber and Utiger 1969; Brabant et al. 1989; Samuels 2000). Dexamethasone, a synthetic glucocorticoid, significantly decreases TSH and T3 but not T4 levels, suggesting that glucocorticoids may interfere with conversion of T4 to T3 (via D1 and/or D2) or potentiate T3 inactivation (due to induction of D3 activity) (Duick et al. 1974; Re et al. 1976; LoPresti et al. 1989; Bianco et al. 2002). Both these mechanisms may be especially relevant to a mature brain which expresses these enzymes (St Germain et al. 2009). One case-report has suggested treating hyperthyroidism (Graves' Disease) with a combination of anti-thyroid therapy and glucocorticoids to achieve longer remission (Peter 1991). Glucocorticoid treatment lowers TH levels by suppressing TSH secretion, as well as via immuno-suppressive properties that may aid in controlling autoimmune processes in conditions like Graves' Disease (Chrousos 1995; Tsigos and Chrousos 2002). Taken together these data suggest that clinically it may not be uncommon to encounter combined glucocorticoid-TH disturbances which may together exacerbate imbalances in brain and peripheral glucose metabolism.

3.3 Crosstalk between TH and insulin

Clinically, disorders of insulin and TH may be linked. For instance, diabetic patients have a 33-40% increase in prevalence rates of thyroid disorders over that of the non-diabetic population, with higher prevalence encountered in women (Vondra et al. 2005). T1DM (autoimmune in origin and insulin-dependent) has the strongest association with TH imbalances, possibly due to shared autoimmune mechanisms (Levin et al. 2004). The association between T2DM and TH imbalance is not so clear. Some recent studies have found no significant association between T2DM and thyroid dysfunction in selected populations, while others have identified thyroid dysfunction in routine TH screening tests of diabetic subjects (Radaideh et al. 2004; Gopinath et al. 2008; Ishay et al. 2009; Diez et al. 2011). In a clinical study, 48% of the patient-population sampled with poorly controlled T2DM had subclinical hypothyroidism (high TSH but normal free T4) and 24% of the patients had subclinical hyperthyroidism (low TSH but normal free T4) (Celani et al. 1994). Some of the TH alterations observed in these patients may be due to metabolic disturbances other than T2DM. However, in a subset of the patients sampled by Celani et al. (with abnormal TSH values, no evidence of autoimmunity, not receiving drugs that affect hypothalamic-pituitary-thyroid axis, and free of diseases other than T2DM), TSH levels reverted to normal when their diabetes was controlled with insulin or oral hypoglycemic agents, suggesting that TH imbalance was secondary to impaired insulin sensitivity (Celani et al. 1994). Overall, the presence of TH dysfunction in T2DM patients may lead to impaired metabolic homeostasis and may thus be a significant contributor to cognitive and neural dysfunction. A model of disease in which insulin resistance and TH disturbances may coexist is polycystic ovarian syndrome (PCOS). A genetic basis has been suggested for the comorbidity of TH and insulin imbalances and impaired glucose metabolism in PCOS. Thus, Li et al. (2011) have implicated a polymorphic variant of gonandotrophin-releasing hormone receptor, which is believed to impair both TSH secretion and insulin sensitivity. Another case where coexistence of TH and insulin imbalances is observed is that of T2DM patients presenting with diabetic complications such as diabetic ketoacidosis. In these patients significantly lower serum T3 and significantly higher serum reverseT3 (rT3; an endogenous antagonist of T3) levels are reported, with improvement in TH levels when their diabetes iscontrolled (Custro et al. 1991). Deficits in circulating T3 levels in such patients have been attributed to both a defect in extrathyroidal conversion of T4 to T3 and a pituitary defect (Naeije et al. 1978; Gavin et al. 1981; Saini et al. 1993; Peeters et al. 2003). Chubb et al. reported subclinical hypothyroidism as a common but incidental finding in women with T2DM and advocated adjunct T4 replacement therapy in T2DM patients to counter

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dyslipidemia which may modify insulin sensitivity (Chubb et al. 2005; Chubb et al. 2005). Indeed, alterations in thyroid function tests have been associated with obesity even in non-diabetic individuals suggesting that thyroid hormone, in addition to influencing glucose metabolism, may also affect lipid metabolism (Biondi 2010). Lastly, but not least, treatment of diabetes with drugs aimed to improve blood glucose levels (such as metformin) has been recently reported to affect thyroid function, further suggesting a relationship between TH homeostasis and glucose metabolism (Morteza Taghavi et al. 2011).

Findings from preclinical studies are supportive of a relationship between impaired insulin function and thyroid hormone disturbances. Preliminary work in our lab suggests that combined hippocampal administration of TH and insulin, at doses that are individually ineffective, may combine dose-dependently to produce acute impairment of spatial working memory, with impairment appearing after as little as 10 min and becoming marked by 30 min. Although preliminary, these data support direct interaction of TH and insulin in modulation of mnemonic processes, and the rapid onset of effect is consistent with acute modulation of metabolism and/or signaling pathways such as PI3K. There may be other mechanisms by which chronic elevation of both TH and insulin together might worsen brain function, in similar vein to the impairments seen subsequent to the chronic elevation of many variables that cause acute memory enhancement, such as glucose, glucocorticoids, and insulin. TH is known to regulate transcription of gluconeogenic and metabolic genes whose protein products are decreased in T2DM (Iglesias et al. 1995; Patti et al. 2003; Cano-Europa et al. 2008; Wulf et al. 2008). Further, TH directly regulates mitochondrial oxidative metabolism genes in rat brain (Iglesias et al. 1995; Wulf et al. 2008). Additionally, optimal levels of TH appear to be critical to prevent cellular oxidative stress, with both hypo- and hyperthyroidism inducing oxidative stress (Das and Chainy 2004; Venditti and Di Meo 2006; Cano-Europa et al. 2008; Morrison et al. 2010). Interestingly, in lean but insulin-resistant offspring of patients with T2DM, defective mitochondrial gene expression may be a strong predictor of the development of diabetes (Petersen et al. 2004). As TH imbalances seem to directly modulate mitochondrial activity, disturbances of TH levels may thus be also predictive of incipient diabetes.

There is evidence to suggest that insulin may act to regulate TH directly. A common polymorphism of type 2 deiodinase (that reduces bioavailability of TH) has been strongly associated with insulin resistance (Mentuccia et al. 2002; Canani et al. 2005; Dora et al. 2010; Estivalet et al. 2011). *In vitro*, insulin has been shown to stimulate deiodination of T4 to T3 in hepatocytes, so that impaired insulin responsiveness might well be a causative factor in elevation of T4 levels (Sato and Robbins 1981). Intriguingly, regulation of TH may play a role in insulin's upregulation of PI3K activity and hence metabolism: muscle cells from mice lacking deiodinase showed impaired PI3K activation in response to insulin and insulin-sensitizing drugs upregulate type 2 deiodinase activity by 1.5-1.9 fold (Grozovsky et al. 2009). These interactions have not yet been directly studied either *in vivo* or in neural tissue (see Fig 1 for suggested possible interactions of TH and insulin within the hippocampus). As the major conversion of T4 to T3 within the brain takes place within astrocytes, studies using astrocytic culture may perhaps offer insight into the central interactions between insulin and TH and their potential cognitive modulatory roles (Guadano-Ferraz et al. 1999; Freitas et al. 2010).

In addition to altered thyroid function in diabetic patients, patients with thyroid disorders may show altered insulin responsiveness. In hyperthyroid patients, glucose tolerance is impaired, a finding duplicated in rat models of hyperthyroidism where insulin resistance occurs along with deteriorating glucose tolerance (Dimitriadis et al. 1985; Roubsanthisuk et al. 2006; Holness et al. 2008). Conversely, hypothyroid patients have decreased basal plasma insulin, insulin sensitivity, and basal adipocyte metabolism (Pedersen et al. 1988;

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Handisurya et al. 2008). Thus, it appears that the effects of insulin may be altered in altered TH states. However, because a large percentage of hypothyroid and hyperthyroid cases are autoimmune in origin, the possibility that changes in insulin levels in these conditions may be, to some extent, a direct effect of autoimmunity on pancreatic beta cells cannot be discounted; a potential link between autoimmune effects on insulin and TH may repay further investigation.

3.4 Role of thyroid hormone in memory modulation

Clinically, the association between TH deficiency and cognition has been acknowledged since the realization that cretinism, a form of mental retardation, stems from congenital iodine and TH deficiency (Reed 1995). Additionally, findings from population-based studies suggest that subtle deficits in specific cognitive domains, such as working memory and executive function, may exist in subclinical or overt hypo- and hyperthyroidism and may be missed unless interventional and functional imaging studies are employed (Samuels 2008). However, data are inconclusive about the extent of TH as a modulator of memory function; the picture is complicated by potential interactions with aging, itself a potent cause of cognitive decline. Thus, in a euthyroid elderly population, total and free T4 levels (but not total T3 levels) positively correlate with cognition (Prinz et al. 1999). However, slightly elevated free T4 levels are associated with cognitive decline and hippocampal atrophy (de Jong et al. 2006; Hogervorst et al. 2008). It is important to note that in the study by de Jong et al., thyroid function (specifically TSH level) was however not associated with the risk of developing AD or the extent of brain atrophy and as such the functional significance of brain atrophy associated with high free T4 levels remains unknown (de Jong et al. 2006). Taken together, conflicting findings from multiple studies could be a reflection of differences in the study-design, sampling population, the age-ranges under consideration, the thyroid function indicator, the cognitive domains examined and/or the follow-up duration. Given the limitations of the extant clinical studies, an unresolved role for normal levels of TH in mediating cognitive processes may perhaps be better investigated in animal models. . Evidence from preclinical studies seems to support the hypothesis that TH may be an important modulator of mnemonic processes, especially within the hippocampus, due to its potential ability to regulate glucose metabolism and contribute to insulin signaling (Gould et al. 1991; Smith et al. 2002; Samuels 2008; Fernandez-Lamo et al. 2009).

TH actions are mediated via thyroid hormone receptors (THR) which are members of a nuclear receptor superfamily and act as powerful transcription factors. THR can exert their actions liganded or unliganded, with unliganded THR largely suppressing the expression of target genes (Glass and Rosenfeld 2000; Venero et al. 2005). Distinct genes encode for two structurally related thyroid hormone receptors (THRα and β). Both genes produce alternatively spliced isoforms – THRα1, THRα2, THRα3, THRβ1, THRβ2, and THRβ3(Cheng et al. 2010). Another protein related to THRα (Rev-ErbAα) is derived from a non-encoding strand of THRα1/α2 gene (Lazar 1993). THRα1 and THRβ are T3-sensitive but the alternative spliced variants (THR α2 and α3) and Rev-ErbAα have no T3-binding activity (Mitsuhashi et al. 1988). Expression of THR isoforms is age- and brain-region specific with THRα1, THRα2, and THRβ2 all being expressed highly in adult rat brain; the adult hippocampus is rich in THR, and induction of hypothyroidism causes region- and isoform-specific changes in expression of THR (Bradley et al. 1989; Puymirat et al. 1991; Lechan et al. 1993; Constantinou et al. 2005).

Although the physiological role played by the distinct receptor subtypes within the brain remains to be determined, data suggest that THRα modulates genes mediating synaptic plasticity and that decreases in circulating TH or THRα-deficiency may reduce expression of proteins critical for synaptic plasticity, particularly within the hippocampus (Thompson and Potter 2000; Guadano-Ferraz et al. 2003; Desouza et al. 2005; Venero et al. 2005;

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Wilcoxon et al. 2007; Vallortigara et al. 2009; Zhu et al. 2011). Both short and long-term synaptic plasticity are impaired in adult-onset hypothyroidism, and experimental induction of hypothyroidism both impairs LTP and increases LTD (Gerges et al. 2001; Sui et al. 2006; Alzoubi et al. 2007; Fernandez-Lamo et al. 2009). Concomitantly, basal levels of signaling molecules required for LTP (e.g. adenyl cyclase 1, PKA, MAPK, CREB and CAMKIV) are depressed in hypothyroidism, and TH replacement reverses the reduction (Gerges and Alkadhi 2004; Gerges et al. 2005; Alzoubi and Alkadhi 2007; Alzoubi et al. 2009). On an anatomical level, hippocampal dendritic spine density is reported to be altered in both hypo- and hyperthyroid rats (Sala-Roca et al. 2008). In addition to effects on synaptic plasticity and neuroanatomy, induction of hypothyroidism produces impaired spatial memory in rats; treatment with TH reverses this impairment and is also able to attenuate memory impairment caused by scopolamine administration, suggesting a possible link between TH and hippocampal cholinergic processes in modulation of memory (Smith et al. 2002; Carageorgiou et al. 2007; Alzoubi et al. 2009); hippocampal cholinergic function has often been implicated as a key mediator of glucose's effects on cognition (Gorell et al. 1981; Ghajar et al. 1985; Walker et al. 1991; Gold 1995; Ragozzino et al. 1998; Stefani and Gold 2001; Degroot et al. 2003; Messier 2004; Pych et al. 2005). Administration of either glucose or insulin causes markedly increased hippocampal glucose metabolism along with enhancement of memory performance, but as yet there are no data reported regarding the effect of TH on hippocampal metabolism during memory processes. However, activity of a key consumer of glycolytic ATP, Na+K+ATPase, is decreased by ~45% in the hippocampi of both hypo- and hyperthyroid rats, suggesting a potential role for TH in regulation of hippocampal glucose usage (dos Reis et al. 2002; Wyse et al. 2004; Carageorgiou et al. 2007). Findings from enzymatic studies suggest that maintenance of ion gradients during periods of increased activity (such as would be seen during memory processing) may be impaired by thyroid dysregulation, which could provide a mechanistic link between hypometabolism and memory impairment in altered thyroid states (Carageorgiou et al. 2007).

It is interesting to observe that in several studies reviewed here both hypothyroidism and hyperthyroidism states elicit similar effects. It has been suggested that this apparent paradox may be due to hypo- and hyperthyroidism activating distinct mechanisms that have similar end results (Pantos et al. 2004). As discussed elsewhere in the review, the brain tries to maintain central TH homeostasis. This is likely achieved by regulating peripheral levels of TH via the thyroid-pitutary axis or by altering local TH bioavailability by either altering the expression of deiodinases enzymes, TH transporters, or expression profiles of THR. Given TH's influence on glucose metabolism, the obligate fuel for the brain, central homeostasis of TH seems to be a protective mechanism in regulation of neural energy use.

4. Conclusions

The limited data available suggest that TH may be an important modulator of mnemonic processes in an adult brain, with support being strongest for modulation of hippocampal activity. Despite the significant attention paid to the role of glucose, and more recently insulin, in memory modulation, as well as clinical data linking abnormal thyroid levels to impaired cognitive function, few studies have directly addressed the role of TH in modulating cognition in an adult brain. Because TH may be a key regulator of brain insulin signaling, such studies would perhaps be especially relevant in light of the recent focus on insulin signaling as a common factor linking diabetes with neurodegenerative conditions, particularly AD, and the hypothesis that cognitive impairments seen in both conditions may be directly caused by impairments in central insulin signaling (Rasgon and Jarvik 2004; Steen et al. 2005; Revill et al. 2006; Sun and Alkon 2006; Jolivalt et al. 2010). We suggest that improved understanding of the role of TH in modulation of cognitive processes may

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have the potential to drive future therapies targeting improved cognitive function in patients with impaired insulin signaling, as well as offering insight into the basic mechanisms of hippocampal and wider brain processing.

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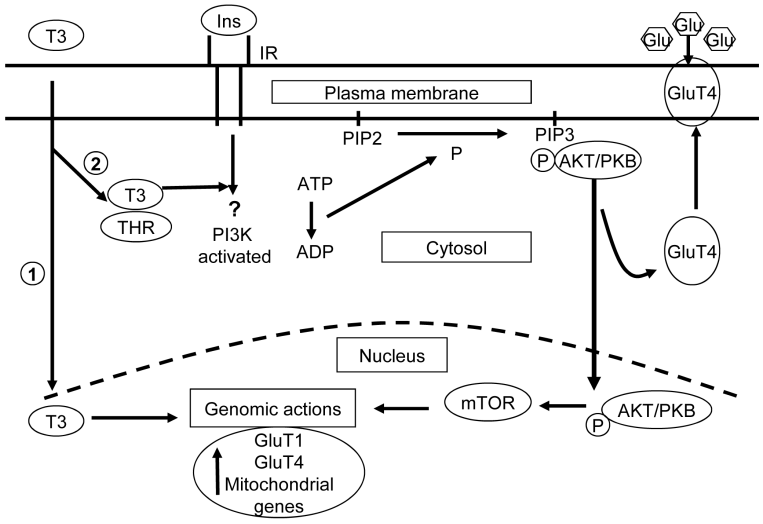

Fig 1.

Suggested possible interactions between thyroid hormone and insulin within the hippocampus. 1) Genomic actions of triiodothyronine (T3) may influence hippocampal glucose metabolism by regulating expression of GluT1 and GluT4. 2) TH and insulin activate PI3K, and *hence may possibly combine to cause* activation of Akt/PKB-mTOR and translocation of GluT4 to the plasma membrane, with a resultant increase in cellular glucose uptake. THR-thyroid hormone receptor; Glu-glucose; Ins-Insulin; IR-insulin receptor; THR-thyroid hormone receptor; PI3K-phosphoinositide 3-kinase; ATP-adenosine triphosphate; ADP-adenosine diphosphate; P-phosphate; PIP2-phosphatidylinositol-4,5-bisphosphate; PIP3-phosphatidylinositol-4,5-trisphosphate; GluT4-glucose transporter 4; AKT/PKB-protein kinase B; mTOR-mammalian target of rapamycin; GluT1-glucose transporter 1