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Thyroid hormone signaling and adult neurogenesis in mammals

Sylvie Remaud, Jean-David Gothié, Ghislaine Morvan-Dubois and Barbara A. Demeneix*

UMR CNRS 7221, Evolution des Régulations Endocriniennes, Département Régulations, Développement et Diversité Moléculaire, Muséum National d'Histoire Naturelle, Paris, France

Edited by:
Frédéric Flamant, Ecole Normale Supérieure de Lyon, France

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***Correspondence:**
Barbara A. Demeneix, UMR CNRS 7221, Evolution des Régulations Endocriniennes, Département Régulations, Développement et Diversité Moléculaire, Muséum National d'Histoire Naturelle, Paris 75231, France
e-mail: bdem@mnhn.fr

The vital roles of thyroid hormone in multiple aspects of perinatal brain development have been known for over a century. In the last decades, the molecular mechanisms underlying effects of thyroid hormone on proliferation, differentiation, migration, synaptogenesis, and myelination in the developing nervous system have been gradually dissected. However, recent data reveal that thyroid signaling influences neuronal development throughout life, from early embryogenesis to the neurogenesis in the adult brain. This review deals with the latter phase and analyses current knowledge on the role of T_3, the active form of thyroid hormone, and its receptors in regulating neural stem cell function in the hippocampus and the subventricular zone, the two principal sites harboring neurogenesis in the adult mammalian brain. In particular, we discuss the critical roles of T_3 and TRα1 in commitment to a neuronal phenotype, a process that entails the repression of a number of genes notably that encoding the pluripotency factor, *Sox2*. Furthermore, the question of the relevance of thyroid hormone control of adult neurogenesis is considered in the context of brain aging, cognitive decline, and neurodegenerative disease.

Keywords: thyroid hormones, adult neurogenesis, brain functions, adult neural stem cells, plasticity, physiology

THYROID HORMONES AND ADULT BRAIN FUNCTION

Thyroid hormones (THs) are vital for brain organization and function throughout life. In the developing mammalian embryo prior to instigation of fetal thyroid function maternal THs are required for optimal neurogenesis (1, 2). At all life stages, but particularly during perinatal growth, T_3 is implicated in multiple processes including neurogenesis (cell cycle control and exit), synaptogenesis, migration, plasticity, and myelination (3). In adults, thyroid dysfunction correlates with neurological and behavioral disorders. Even if developmental hypothyroidism produces more deleterious, irreversible effects, adult hypothyroidism alters hippocampus function: memory impairment, anxiety, and depression-like symptoms in rodent models and humans (4, 5). In adults, the mechanisms underlying these cognitive problems are less well understood than during perinatal development. However, it is established that reduced neurogenesis, especially in the rodent hippocampus, due to either aging or stress, is associated with neurocognitive deficits such as anxiety, depression (6), and with neurodegenerative disease such as Alzheimer's (7, 8). In mammals, including humans, the subgranular zone (SGZ) of the hippocampal dentate gyrus and the subventricular zone (SVZ) represent the two main neurogenic niches. These niches produce newborn neurons from neural stem cells (NSC) throughout life and so, contribute to brain plasticity during learning, memory, and recovery from brain damage (9). Many extrinsic and intrinsic signaling factors regulate different stages of adult neurogenesis (10), with TH signaling being well known to control NSC homeostasis [see below and (11–16)]. Understanding the mechanisms underlying T_3 regulation of adult neurogenesis is crucial to develop treatments for neurocognitive disorders.

A rich literature links thyroid physiology and neurocognitive dysfunction in humans. Hypothyroidism is associated with mood instability and depression, dementia, memory impairment, and psychomotor problems (17). Most often, mood abnormalities reverse under T_4-supplementation, but can persist after long-term hypothyroidism (18). The mechanisms implicated are unknown, although T_3 levels affect serotoninergic and catecholaminergic signaling at multiple levels (19, 20), systems often targeted by antidepressants. Further, in children and adolescents (21), as well as adults (22), hypothyroidism, and reduced memory function are associated with decreased hippocampal size, suggesting that TH deficiency causes structural alterations. Thus, it is plausible that neurogenesis in rodents, and depression or other psychiatric diseases associated with hypothyroidism in humans, may be related to reduced hippocampal neurogenesis.

However, the links between cognitive deficits and neurogenesis – "the neurogenic hypothesis of depression" – are still poorly understood. Even if there is evidence for adult neurogenesis in both SVZ (23) and SGZ (24) in humans, the contribution of adult neurogenesis to human brain function, and in particular to behavioral outputs, is still questioned, a point discussed in the next section.

However, there is increasing cellular and molecular understanding of the links between TH signaling and adult neurogenesis in rodents. Adult-onset hypothyroidism reduced the number of newborn neuroblasts in the dentate gyrus (14). Furthermore, in adult hypothyroid animals displaying depressive-like behavior, neurogenesis in the dentate gyrus is reduced and dendritic arborization is impaired. TH supplementation rescues these modifications (14).

THYROID HORMONE REGULATES ADULT NEUROGENESIS

Neural stem cells in adult SGZ and SVZ slowly divide asymmetrically, giving rise to progenitors. In rodents, these highly proliferative progenitors generate neuroblasts that migrate and integrate into the pre-existing neuronal networks of the hippocampus and the olfactory bulb (OB). More recent findings highlight a third neurogenic niche within the adult rodent hypothalamus, a region regulating energy balance, food intake, and body weight (25, 26).

In humans, the functional role of adult neurogenesis is controversial (27–30). Both generation of new neuroblasts and their functional incorporation, especially in the OB, is still questioned. However, recent data showed that new neurons, probably produced from the adult SVZ, are observed in the human striatum, showing that adult human SVZ can contribute to neurogenesis at least in this region (31). A decrease of neuroblasts, expressing the neuronal precursor marker doublecortin (DCX), is observed continuously from the first year after birth, in the SVZ and SGZ (29, 30, 32, 33). However, a recent study shows that a subpopulation of hippocampal neurons is able to renew, supporting the concept that adult neurogenesis occurs in humans and could contribute to cognitive functions (24).

SVZ AND SGZ NICHES

Thyroid hormone signaling is one of the main pathways vital for adult neurogenesis. Recently, T_3 was demonstrated to exert critical roles in cell proliferation and NSC commitment toward neuroblasts in both the rodent SVZ and SGZ *in vivo* (15, 16). T_3 acts on transcription through nuclear receptors, Thyroid Hormone Receptors (TRs). In vertebrates, different isoforms derive from the *Thra* (TRα2 and TRα2) and *Thrb* (TRβ1 and TRβ2) genes. The adult hippocampus expresses TRα1, TRβ1, and β2 isoforms (16, 34), whereas only TRα1 is expressed in the adult mouse SVZ (13, 15).

T_3 regulates adult neurogenesis at different steps (proliferation, survival, differentiation, and maturation). Hypothyroidism significantly reduces progenitor proliferation in the SVZ of adult mice, whereas a short T_3 pulse restores mitotic activity to euthyroid levels (13). Similarly, using Ki67 as a proliferation marker and a BrdU incorporation protocol to measure cell proliferation limiting labeling of postmitotic cells, Montero-Pedrazuela et al. (14) demonstrated that hypothyroidism in adult rats, induces a decrease of proliferation (about 30%) in the adult SGZ that is reversed by T_4 treatment. Furthermore, hypothyroidism does not affect cell survival. In contrast, two others studies shown that hypothyroidism had no observable effect on numbers of proliferative progenitors in the adult SGZ progenitor proliferation but their survival was reduced, suggesting a role of T_3 on the postmitotic progenitors (11, 12). The reasons for these differences may reside in (i) methods for the induction of hypothyroidism (ii) and potential differences in BrdU protocols used in these studies that may or may not include postmitotic cells.

In the SGZ, TRα1 has different effects on proliferation and differentiation (16, 35). First, progenitor proliferation is unaffected by TRα1 loss (TRα1$^{-/-}$ mutant) or overexpression (TRα2$^{-/-}$ mutant) (35). This finding correlates with the fact that TRα1 is not expressed in progenitors within the SGZ, but is highly expressed in post-mitotic progenitors corresponding to immature neurons (35). Second, neurogenesis is increased in TRα1$^{-/-}$ mice, whereas in TRα2$^{-/-}$ mice (overexpression of TRα1), decreased survival reduces numbers of post-mitotic neuroblasts (35). These studies suggest that in the SGZ, T_3 acts at later steps than in the SVZ, in the post-mitotic progenitors (16, 35) (**Figure 1A**). Interestingly, the damaging effects of adult hypothyroidism on hippocampal neurogenesis are recapitulated in TRα2$^{-/-}$ mice (35). The TRα2$^{-/-}$ mutant, in which TRα1 is overexpressed due to the ablation of TRα2, exhibit a mixed hypo- and hyperthyroid phenotype: reduced levels of T_4/T_3 in serum, decreased growth rate and body weight, elevated heart rate suggesting that the increased TRα1 levels is associated with increased receptor effects (35, 36). In a hypothyroid context, TRα1 – in this mutant – acts as an aporeceptor due to limited T_3 availability. How the role of TRα1 aporeceptor affects adult SVZ neurogenesis is unknown. Examining this possibility should identify new TRα1 targets (of both liganded and unliganded receptors) involved in regulating adult neurogenesis.

In the SVZ, although TRα1 is absent from NSCs, it appears in proliferative Dlx2+ progenitors and is high in DCX+ neuroblasts, suggesting that TRα1 favors NSC commitment toward a neuronal phenotype [(15), **Figure 1B**]. This hypothesis is bolstered by the observation that TRα1 gain of function *in vivo* generates migrating neuroblasts entering the rostral migratory stream. Inversely, shRNA-mediated TRα1 loss of function increases numbers of SVZ NSC/progenitors. Moreover, hypothyroidism also increases NSC/progenitor populations, a situation recapitulated in mutant *TRα°/°* mice (lacking all isoforms encoded by the *TRα* locus). In hypothyroidism, NSC/progenitors are blocked during interphase (13). Thus, absence of either TRα1 or T_3 induces similar effects: increasing NSC and progenitors pools, while decreasing neuroblast numbers.

In the adult SVZ, T_3, through TRα1, acts as a neurogenic switch by repressing a key gene involved in NSC pluripotency, *Sox2* (15) (**Figure 1B**). *In vivo* loss and gain of TRα1 function approaches demonstrated that *Sox2* is directly repressed by T_3/TRα1 in progenitors. Moreover, the progenitor to neuroblast transition – governed by T_3/TRα1 – may be reinforced by T_3 repression of *CyclinD1* and *c-Myc*, involved in cell cycle progression (13, 15, 37). Thus, T_3 could regulate adult SVZ homeostasis at two levels: (i) repression of a master gene involved in NSC pluripotency and (ii) repression of cell cycle regulators.

TH SIGNALING AND HYPOTHALAMIC NEUROGENESIS?

Some authors consider that certain tanycytes (glial-like cells) in the ependymal layer are NSCs. An emerging idea is that these tanycytes are diet-responsive adult NSCs, linking food intake, body weight, and energy balance to neuronal plasticity [for reviews, see (25, 26)]. Interestingly, T_3 is a strong regulator of energy metabolism at both peripheral and central, hypothalamic, levels (15). An exciting hypothesis is that T_3 may regulate adult hypothalamic neurogenesis and thereby modulate plasticity of hypothalamic neuronal networks regulating energy balance. Many components of TH signaling are expressed in tanycytes in the rodent brain (D2, OATP1C1, MCT8, see **Figure 1C**) and in turn, tanycyte activity is critical to control of the hypothalamic/pituitary/thyroid (HPT)

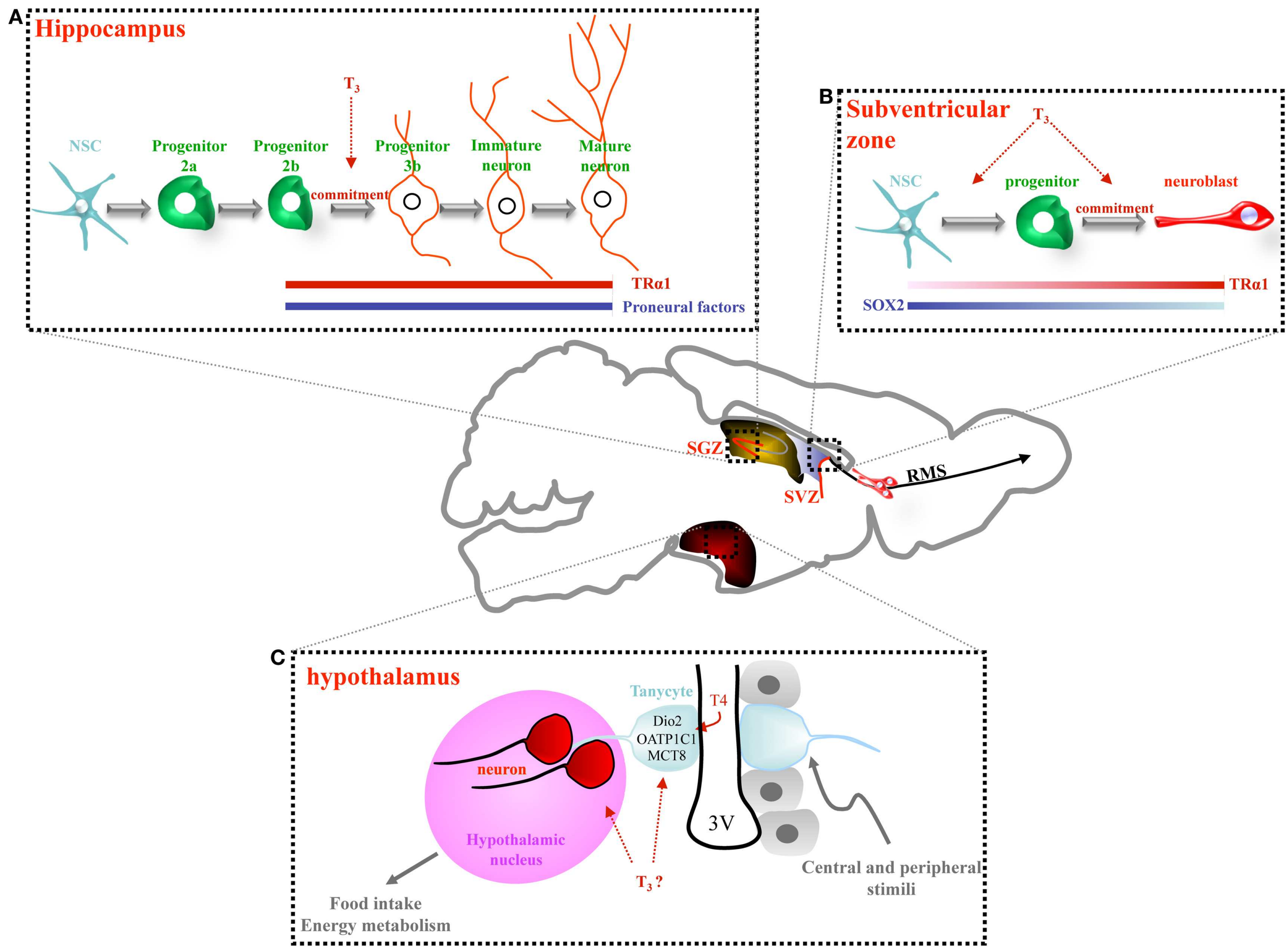

FIGURE 1 | Thyroid hormone signaling regulates adult neurogenesis in the hippocampus, the subventricular zone and, potentially, the hypothalamus. **(A)** In the hippocampal niche (SGZ), NSC gives rise proliferating progenitors (2a) and then, more committed progenitors (2b) and post-mitotic neuroblasts (type 3). Type 3 progenitors give rise to immature and mature granule neurons. A role of T_3, in concert with TRα1, has been observed in non-proliferating progenitors, from type 2b cells to mature granule cell neurons. Adult-onset hypothyroidism or TRα1 overexpression ($TR\alpha 2^{-/-}$ mice) alters survival of post-mitotic neuroblasts, decreasing hippocampal neurogenesis. **(B)** In the adult SVZ, lining the lateral ventricle, three main cell types are located: NSCs that divide asymmetrically to give rise to proliferating progenitors. Progenitors divide rapidly producing neuroblasts that migrate along the rostral migratory stream (RMS) to the olfactory bulb (OB) where they differentiate into interneurons. SOX2 and TRα1 are inversely expressed within the SVZ: cells expressing high levels of TRα1 express low levels of SOX2 (neuroblasts). T_3 is involved in both progenitor proliferation and determination. TRα1 overexpression in NSC and progenitors drives progenitor commitment toward a neuronal phenotype since cells overexpressing TRα1 are found in clusters entering the RMS. **(C)** In the adult hypothalamus, the third ventricle is lined by ependymal cells (in gray) interspersed with tanycytes (in blue). Some of these tanycytes are stem cells. They possess a long process that projects into hypothalamic nuclei (in pink). Some recent data support the idea that tanycytes are able to generate new neurons that migrate into adjacent hypothalamic nuclei. Tanycytes express many key actors of the TH pathway (Dio2, OATP1C1, and MCT8) thus, facilitating TH entry into the hypothalamus. These tanycytes could be considered as an "integrative platform" relaying central and peripheral signals to adapt adult neurogenesis to food intake and energy metabolism. A key role of TH in the regulation of adult hypothalamic neurogenesis is an exciting hypothesis.

axis (38). How TH status and signaling affect adult hypothalamic neurogenesis in relation to feeding and energy balance is an important future research question.

CONTROL OF T3 AVAILABILITY DURING ADULT NEUROGENESIS

Some T_3 effects on stem cell biology can seem paradoxical, T_3 enhancing both proliferation and differentiation and exerting different actions at successive steps of neural commitment. The biological outcome of TH signaling clearly relates to cellular context, notably, chromatin state and presence of ligand, TRs, and co-factors.

One hypothesis is that adult NSCs do not integrate T_3 signaling until neural determination is underway, as TRα1 appears in neural progenitors, with the signal increasing in neuroblasts (15). In the TRα1:GFP knock-in mouse (39), expression of TRα1:GFP was not investigated closely in the SVZ. Although more data is needed on the kinetics of TR expression, a critical factor will be T_3 availability, largely determined by deiodinases. Two deiodinases are expressed in the brain, the activating deiodinase 2 (or D2, encoded by *Dio2*) and the inactivating deiodinase 3 (or D3, encoded by *Dio3*). However, there is little published data on control of TH availability during neural determination and the little available is from *in vitro* systems. For instance, during *in vitro* neuronal differentiation of a human embryonal carcinoma stem cell line (NT2 cells derived from a teratocarcinoma), TRα1 and TRβ1 expression is down regulated, with TRα2 expression unchanged (40). T_3 treatment induced stronger upregulation of *Dio3* in NT2 precursors than in differentiated cells.

Though hypothyroid brains show reduced NSC/precursor proliferation, no clear relationship between T_3 availability and control of NSC cell cycle has yet been established. Interestingly, *Dio3* expression correlates with proliferative status in solid tumors (41). This finding fits with *in vitro* data [from Ref. (42)] where *Dio3* expression is high in early progenitors compared to human embryonic stem cells and neural progenitors. The biological significance of this finding in terms of NSC biology is hard to decipher. According to current data, local hypothyroidism favors maintenance of NSC/progenitor populations (13, 15) with T_3 being a proliferation and neurogenic factor (15, 43). Similarly, expression of *Dio3* within the imprinted *dio3-dlk1* locus is associated with stemness (44). From an evolutionary point of view, the conservation of synteny in this locus among vertebrates seems to indicate that control of TH signaling is associated with stemness.

TH CONTROL OF ADULT NEUROGENESIS IN THE AGING BRAIN

Circulating TH levels decrease as a function of age in humans (45, 46) and rodents (47). In the aging human population, both increases and decreases in circulating TSH have been observed (48–51), suggesting reduced or impaired pituitary responses in elderly people. However, higher TSH is associated with greater longevity in numerous human cohorts [see for example: (52)]. Further, neurogenesis decreases with age (53–55). THs being vital for adult neurogenesis (13), it will be interesting to address the links between these phenomena during aging.

Among the numerous genes involved in adult neurogenesis, an increase in $p16^{INKA4}$ (CDKN2a) has been causally related to neurogenic decline during aging (56). $p16^{INKA4}$ can itself be inhibited by the synergistic action of Bmi1 and c-Myc (57, 58). Direct activation of *c-Myc* by T_3 through a TRE was shown in Xenopus intestinal stem cells (59), whereas in adult SVZ T_3 directly inhibits a *c-myc* reporter construct through an identified TRE (13). Thus, a potential indirect regulation of $p16^{INKA4}$ by T_3 could differ according to species, cell populations and function of developmental context.

DECREASING CIRCULATING THs ARE ASSOCIATED WITH COGNITIVE DECLINE AND NEURODEGENERATION

Cognitive deficiency is frequently observed in the elderly humans and in aging rodents (60, 61). Marked effects are seen on learning and memory, processes that implicate neurogenesis in the dentate gyrus of the hippocampus (62, 63), a structure that diminishes with age and in many neurodegenerative pathologies (62, 64). TH treatment can improve cognitive performances in hypothyroid mice (8) and in humans (65), leading to speculation that cognitive deficiency can be causally linked to reduced TH signaling in aging. Despite declining neurogenesis with age, Yeung et al. recently demonstrated that 13-month-old mice still have the capacity to generate new neurons after a selective neuronal loss in the hippocampus, but without cognitive recovery (66). These results suggest that although some neurogenesis can still occur in aged mice, it might not be sufficient to compensate for neurodegeneration. TH facilitate repair after neurodegenerative lesions (67, 68). It is plausible that their decline is linked to decreased repair in neurodegenerative diseases of aging.

Mitochondrial biogenesis also reduces with aging (69), along with an increase in mitochondrial dysfunction (70). Thyroid signaling influences cellular metabolism and mitochondrial functions (71). Impaired thyroid signaling impacts mitochondrial respiration and hence reactive oxygen species (ROS) production, with either beneficial or damaging cellular effects (72). Since activity changes in mitochondrial respiration are linked to changes in cell proliferation rates (73), such as those occurring in the early phases of NSC differentiation, it can be postulated that mitochondrial dysfunctions impact neurogenesis, again linking reduced neurodegenerative repair capacity to decreased circulating T_3/T_4 levels. However, little is known about control of T_4/T_3 availability (deiodinase and TH transporter expression) during aging in the NSC niches, nor on the consequences of these modification for NSC metabolism, questions that it will be interesting to address.

Circadian rhythm perturbations also increase with age (74, 75). TSH (and to a lesser extent T_3) levels display circadian rhythms (76–78), as does neurogenesis (79). Moreover, circadian clock-associated genes influence neuronal differentiation of adult NSC/progenitors (80). Two major circadian rhythm regulation genes, *Bmal1* and *Clock*, are cooperatively activated by *Sirt1* and *Pgc1a,* a function that changes with age (81). In turn, SIRT1 can act as a coactivator of TRβ (82) and is implicated in neurogenesis (83). Further, *Pgc1a* is directly regulated by T_3 (84), and can itself modulate *Thra* expression (85). Some circadian clock-related genes are regulated by T_3 (86). Thus, multiple arguments converge to suggest that impairments of circadian rhythm with age can be linked to changes in thyroid signaling, thereby impacting neurogenesis.

Induction of a chronic inflammatory state has been associated with aging (87, 88), and inflammation can significantly reduce neurogenesis (89–91). Brain inflammation is characterized by macrophages and microglia producing proinflammatory cytokines (TNFα, IL-1β, and IL-6) during prolonged inflammation. These same cytokines increase in the aging brain (92), and may enhance gliogenesis at the expense of neurogenesis (93–96). TNFα activates the p38 MAP kinase (MAPKp38) that triggers IL-1β production (97). As T_3 can represses MAPKp38 activation by TNFα (98), reduced T_3 dependent repression of proinflammatory cytokines with aging could negatively impact neurogenesis.

CONCLUSION

Thyroid hormone is one of the few endocrine signals that exerts marked effects on both hippocampal and SVZ neurogenesis in adult mammalian brains. Although distinct differences are noted in expression of TRs and the consequences of their activation in these respective niches, it is well established that hypothyroidism adversely affects both populations. Given the frequency of thyroid disorders in the general population, notably in women and during aging, it is important to consider the consequences of these disorders on the incidence and severity of psychiatric and neurodegenerative disease.

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