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REVIEW ARTICLE

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# Thyroid hormone regulation of neural stem cell fate: From development to ageing

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**Abstract**

In the vertebrate brain, neural stem cells (NSCs) generate both neuronal and glial cells throughout life. However, their neuro- and gliogenic capacity changes as a function of the developmental context. Despite the growing body of evidence on the variety of intrinsic and extrinsic factors regulating NSC physiology, their precise cellular and molecular actions are not fully determined. Our review focuses on thyroid hormone (TH), a vital component for both development and adult brain function that regulates NSC biology at all stages. First, we review comparative data to analyse how TH modulates neuro- and gliogenesis during vertebrate brain development. Second, as the mammalian brain is the most studied, we highlight the molecular mechanisms underlying TH action in this context. Lastly, we explore how the interplay between TH signalling and cell metabolism governs both neurodevelopmental and adult neurogenesis. We conclude that, together, TH and cellular metabolism regulate optimal brain formation, maturation and function from early foetal life to adult in vertebrate species.

**KEYWORDS**

cell fate, development, evo-devo, metabolism, mitochondria, neural stem cell, thyroid hormone

## 1 | INTRODUCTION

The development of the vertebrate central nervous system (CNS) is a complex process that starts early in embryogenesis, and continues throughout adult life. It involves many coordinated cellular events including cell proliferation, cell fate decision, cell survival and cell death, migration, differentiation and maturation of both neuronal and glial cells. Both cell types are derived from neural stem cells (NSCs) populating the pseudostratified neuro-epithelium along the rostro-caudal axis of the CNS primordium.[1] They first divide symmetrically to enlarge the NSC pool while transforming into radial glia (RG), giving rise to the ventricular zone (VZ). They gradually start to divide asymmetrically, generating post-mitotic neuroblasts. Only after generating the bulk of neurons that make up the brain, RG become gliogenic, establishing the astrocyte and oligodendrocyte populations.[2-4] The entire process produces a fixed number of cells ultimately determining brain size.

The adult brain retains some of its neuro- and gliogenic potential, although considerable differences exist among vertebrates.[5] While neurogenic regions containing RG-like NSCs are widespread in the anamniote brain, sustaining neuro- and gliogenesis throughout life, amniotic species and mammals in particular only retain a few distinct telencephalic regions that support *de novo* generation of neural cells. This physiological trait is directly related to the rather limited capacity for self-repair in the mammalian brain, as compared to the high

regenerative potential seen for instance in fish and amphibians.[5,6] NSCs in the adult mammalian brain are predominantly found in the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampus, and are generally in a quiescent state.[7] The default state of the adult SVZ niche is gliogenic,[8] but several external and internal stimuli can induce specific cellular programs favouring a neurogenic environment. Elucidating which factors are involved, and how they interact with the SVZ niche in the developing, adult and ageing brain, will enhance our understanding of its underlying physiology, and how NSC homeostasis changes during the course of ageing. Moreover, unravelling the mechanisms underlying the regenerative potential, as well as NSC fate choice in pathophysiological conditions, is the key to understanding how NSCs can induce repair and regeneration in the adult brain.[9]

One of the most intriguing factors regulating NSC behaviour throughout vertebrate life is thyroid hormone (TH). An adequate TH supply is crucial for brain development and function throughout life in all vertebrates, including humans.[10] This vital role is well demonstrated in human cases of severe hypothyroidism during critical phases of neurodevelopment, resulting in an aberrant structure and function of brain regions such as the cerebellum, hippocampus, and neocortex.[11,12] However, while most studies have focussed on examining these adverse neurological outcomes following TH insufficiency in late pregnancy (reviewed in[13]), it remains debated whether THs are equally involved in embryonic development.[14] We do however know that maternal hypothyroidism in rodents and in humans during stages prior to thyroid gland activation and hypothalamus-pituitary-thyroid (HPT) axis maturation, can irreversibly damage the brain, leading to distinctive psychomotor and cognitive deficits in the progeny.[15,16] For instance, epidemiological data have shown that maternal hypothyroidism during the first trimester of pregnancy alters white/grey matter ratios, and is associated with a lower offspring general IQ and a decrease in verbal and motor performances during childhood.[17] Moreover, recent experimental findings also showed that TH is a crucial regulator of NSC fate determination in the two main neurogenic niches in mammals.[18-21] The question arises whether TH action converges on common pathways in embryonic neural progenitors.

Cell-specific TH action is tightly controlled by a complex set of evolutionary conserved proteins (eg, TH-transporters (THTs), deiodinases (DIOs), receptors), enabling coordination of tissue development, growth, maintenance and repair in vertebrates, from teleosts to mammals.[22,23] Triiodothyronine ($T_3$), the main biologically active form of THs, binds to TH receptors (TRs), positively or negatively regulating specific gene expression. Cellular uptake and efflux of THs occurs via transmembrane THTs. Monocarboxylate transporter 8 (MCT8) is a highly specific THT in the CNS, while MCT10 and organic anion transporting polypeptide 1C1 (OATP1C1) transport THs along with other substrates.[24] They have orthologues in all vertebrates showing similar transport characteristics.[25-27] Inside the cell, DIOs (in)activate THs.[28] DIO2 activates tetraiodothyronine ($T_4$) into $T_3$, while DIO3 inactivates $T_4$ into reverse $T_3$, and $T_3$ into diiodothyronine ($T_2$), and both are highly expressed in the brain. DIO1 catalyses all reactions but has a much lower affinity for THs,[29] and, while tissue-specific mRNA expression has been detected, no DIO1 activity has been reported in the vertebrate brain so far.[28,30,31]

In addition, THs are major modulators of cell metabolism, by affecting genomic and non-genomic pathways regulating mitochondrial activity.[32,33] NSC determination and differentiation also implicate metabolic shifts. Proliferating cells mainly use glycolysis associated with a low mitochondrial activity to generate energy, whereas differentiated cells primarily rely on oxidative phosphorylation (OXPHOS).[34,35] Moreover, NSC fate choice is associated with specific changes in metabolic status and mitochondrial morphology.[36,37] Increasing evidence shows that a complex interplay between TH signalling and cell metabolism is involved in cell commitment and differentiation.[20]

In this review, we focus on TH-dependent molecular and metabolic mechanisms governing NSC physiology in the developing and adult brain. First, we provide a vertebrate wide view on how TH locally influences NSC fate in the embryonic/foetal brain. Second, we elaborate on the role of THs in NSC fate in the adult mammalian brain, and specifically focus on an emerging concept that TH, as a key regulator of cellular metabolism, can mediate NSC fate decisions via mitochondrial pathways.

## 2 | EVIDENCE FOR THYROID HORMONE REGULATING EMBRYONIC NSC PHYSIOLOGY

### 2.1 | In non-mammalian vertebrates

Work on several non-mammalian vertebrates has contributed to understanding TH action in the developing brain. Besides the essential requirement of THs for development and metamorphic events, common mechanisms regulate TH uptake and metabolism across vertebrates. Moreover, experimental TH insufficiency or excess affects brain structure and function similarly in mammals and humans, indicating that TH action during neurodevelopment is conserved throughout evolution.[38] Furthermore, non-mammalian embryos (eg, those of birds, reptiles, amphibians and teleost fish) develop in a readily accessible extra-uterine environment, during which THs are derived from a maternal stock in the egg yolk. This fact allows manipulation of TH homeostasis from early stages onwards, independent of maternal physiology.[39,40] Here, we focus on the role of THs on embryonic neural progenitors in the most commonly used animal models in thyroid stem cell research.

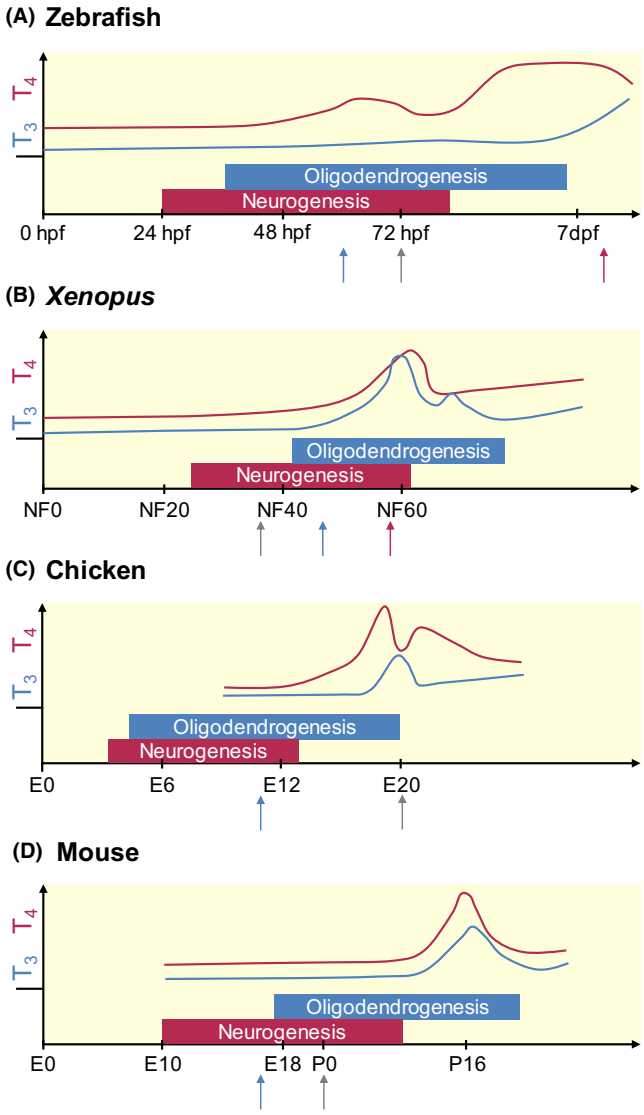


**FIGURE 1** Schematic representation of TH levels, and the timing of neurogenesis and oligodendrogenesis during the development of 4 classical vertebrate models. The x-axis represents the relative time scale of development for each species, the y-axis the relative concentrations of serum $T_4$ (red line) and $T_3$ (blue line) based on available data. The moment of hatching/birth is depicted by the grey arrow. Metamorphosis in fish (A) and amphibians (B) (red arrow) is characterized by a high TH peak. In contrast, the TH peak in chicken (C), a precocial bird, occurs at hatching, while a sharp TH peak is observed more than 2 weeks after birth in mice (D), a typical altricial species. For these, and possibly all vertebrates, the period of neurogenesis starts prior to that of oligodendrogenesis, although both phases overlap to some extent. The timing and regulation of these processes relies for a major part on maternal TH supply, prior to endogenous TH production by the foetal thyroid gland (tetrapods) or the thyroid follicles (fish) (blue arrow). While circulating TH levels are low in embryonic stages and generally reflect a high $T_4/T_3$ ratio, local regulators of $T_3$ availability are expressed during these stages in all vertebrates, enabling temporal and cell-specific control of TH action. dpf, days post fertilization; E, embryonic day; hpf, hours post fertilization; NF, Nieuwkoop-Faber stage; P, postnatal day. T3: triiodothyronine, T4: tetraiodothyronine

### 2.1.1 | Zebrafish

The zebrafish (*Danio rerio*), a teleost, became a popular model thanks to its rapid and transparent early development, and the recent emergence of a wide variety of genetic techniques allowing the generation of mutants.[41] As in other vertebrates, the zebrafish CNS consists of neurons, oligodendrocytes and other glial cells, but so far mature astrocytes have not been identified. Moreover, neuro- and oligodendrogenesis continue to occur at a relatively high rate throughout many regions of the adult zebrafish brain.[42,43] The majority of neuronal and oligodendroglial precursor cells (NPCs and OPCs respectively) are generated between 24 and 72 hours post-fertilization (hpf) (Figure 1A), and arise from stem cells in the VZ throughout the CNS.[42] A typical model used to investigate this process is the motor neuron progenitor (pMN) domain of the ventral spinal cord, where *olig2*-expressing progenitors generate motor neurons and OPCs in two successive waves under the influence of Hedgehog signalling.[44-46] The neuronal vs glial output is thereby under strict control of the evolutionary conserved Notch signalling pathway. High Notch signalling maintains the self-renewal state of neural progenitors and is necessary for OPC production, while decreased Notch signalling causes premature neurogenesis and the formation of primary motor neurons at the expense of OPCs and secondary motor neurons.[46-49]

During the 3-day period of embryogenesis, maternal THs are derived from the egg yolk prior to the activation of the HPT axis around 60-72 hpf.[50] In the last decade, several mutant fish for regulators of TH availability enabled studying the consequences of altered TH signalling.[41] Blocking TH uptake by either *mct8* knockdown (KD) or knockout (KO) strongly impairs zebrafish organ development, with a profound impact on the CNS.[51-53] In humans, inactivating mutations in the *MCT8* gene are responsible for the Allan-Herndon-Dudley Syndrome (AHDS), an X-linked psychomotor retardation syndrome.[54,55] In zebrafish, a transcriptome analysis at 25 hpf following KO of *mct8* showed dysregulation of the Wnt/Notch signalling pathways.[56] This downregulated the expression of *her2*, an important target of Notch and a homologue of the well-known TH-responsive *Hairless* gene in mammals. Her2 is normally required to maintain neural progenitor proliferation and to postpone neuronal differentiation during the neurogenic wave, while stimulating glial differentiation later in development, supporting a time-dependent balance between neuro- and gliogenesis.[57] Downregulation of Notch signalling also increased the expression of the cell cycle inhibitor genes *pax6a* and *neurod6a*, resulting in a premature depletion of the NSC population.[56] Correspondingly, the neural progenitor pool was smaller in the 48 hpf *mct8* mutant zebrafish brain.[58] This precocious cell cycle exiting of neuroblasts could explain the decrease or lack of certain neuronal cell types in the mid- and hindbrain of *mct8* morphants. In addition, medial spinal cord neurons were absent, while more ventral motor

neurons were observed, and only one type of dorsal neurons developed.[52] This imbalance indicates incorrect neuronal cell specification because of impaired TH uptake. Furthermore, impaired neuronal differentiation and/or altered cell survival could have contributed to, and possibly aggravated the phenotype, resulting in different local outcomes.[52,53]

Detailed cell counts in juvenile or adult *mct8* mutant zebrafish could indicate the extent of neuron and OPC production limitation in early stages. While no data were gathered on OPC numbers, decreased expression of *mbp* (a well-established TH-target gene involved in OPC differentiation) and *p0* (a marker of myelinating oligodendrocytes)[51] did suggest a failure of OPCs to differentiate into mature myelinating oligodendrocytes,[59] a process normally favoured by THs.[60] Consequently, the CNS of *mct8* KO zebrafish is in a hypomyelinated state.[51,59] Another surprising observation was the increased number of neural crest-derived Schwann cells in the peripheral nervous system (PNS),[51] suggesting that THs could affect cell fate and differentiation differentially throughout the nervous system. The authors suggested that *Mct8* deficiency induces a hyperthyroid state in PNS cells, thereby enhancing Schwann cell maturation,[59] but direct evidence is missing.

While less attention was paid to effects on neuro- and oligodendrogenesis in other zebrafish TH regulator mutants, KD of *dio3b* (the most important inactivating deiodinase in zebrafish[61]) also increased neural crest cell proliferation, migration and apoptosis, and *thraa* KD increased apoptosis, suggesting they are also involved in different cellular processes.[62] This is not surprising given that TR isoforms are expressed in the zebrafish CNS from 24 hpf onwards.[63,64] Activation of distinct thraa-regulated gene sets, sometimes in combination with other transcription factors such as retinoic acid,[62] as well as the unliganded aporeceptor all play an important role in early zebrafish development.[38,61] Another, less thoroughly explored action might occur via $T_4$ binding to the membrane-situated integrin $\alpha V\beta_3$ receptor.[65] Similarly, the spatio-temporal expression patterns of other regulators of TH availability throughout the developing zebrafish CNS[41] indicate they might also contribute to determine local neurogenesis and gliogenesis.

These findings suggest that the availability of maternal THs is one of the major factors involved in (a) maintaining normal physiology of the neural progenitor pool, and (b) the neuronal vs oligodendrocyte balance in the early developing zebrafish brain. It is worth mentioning that these actions largely precede endogenous TH production by the thyroid follicles (Figure 1A). How exactly these actions take place at the molecular level awaits a more in-depth transcriptomic and proteomic profiling.

### 2.1.2 | Xenopus laevis

*Xenopus laevis* is another frequently used model to investigate the role of THs in early neurogenesis, though most studies focused on metamorphosis.[66,67] However, earlier stages have been included to examine whether THs also impact NSC biology underlying neural circuit development. As in zebrafish, TH signalling is already present prior to thyroid gland activation[68] (Figure 1B). Both mRNAs encoding TRα and TRβ isoforms are detected in oocytes and embryos,[69-71] as are *dio1*, *dio2* and *dio3* mRNAs from the neurula stage onwards, enabling control of TH action in a tissue-dependent manner.[72]

Neuro- and oligodendrogenesis in the developing tadpole brain relies on widely conserved regulatory mechanisms and multiple genes controlling cell proliferation and differentiation, from pre-metamorphic stages onwards[73,74] (Figure 1B). The potential neurogenic action of TH was analysed in the midbrain-derived tectum opticum (TeO) and the forebrain-derived neuroretina. Administration of THs during a 72-hour period, either to the water or by local injection in the ventricles, or knocking down the TH-inactivating *dio3* during pre-metamorphosis (Nieuwkoop-Faber stage (NF) 46-49), increased expression of the proliferative genes *pcna* and *mcm5*. Consequently, increased NSC proliferation because of shortening of the cell cycle led to larger sizes of the TeO and retina, consistent with an increased number of neurons.[75] This action is likely TRα-dependent, as it is the only TR isoform detected in neurogenic areas of the embryonic tadpole brain.[67] Following expansion of the progenitor pool, THs induce a switch from a proliferative to a differentiation state, thereby orchestrating the timing of consecutive cellular processes necessary to establish a properly functioning neural circuit.[75]

Adding THs to the aquarium water prior to NF44 did not affect cell proliferation,[68,69] indicating that TH action is spatio-temporally controlled by local cellular regulators of TH availability, thus preventing precocious neurogenesis.[76] Accordingly, Dio3 was found to be strongly expressed in the dorsal ciliary margin zone of the eye, inhibiting the stimulatory effect of $T_3$ on retinal precursor cell proliferation, and notably also in rods and the shortwavelength-sensitive cones, thus limiting precocious TH-dependent responses in specific retinal cell types.[77,78] Overexpression of a mutant TRβ ineffective for gene repression strongly impaired eye development and disrupted expression of several important genes.[70] This suggests that unliganded TR action could be the mode of action for correct eye development at first. Other regulators of TH availability such as *mct8* and *oatp1c1* are also expressed from early stages onwards,[27] and are probably involved in these processes as well.

It was not investigated whether the generation of OPCs in the TeO was also affected by altered TH signalling,[75] although oligodendrocytes have been detected from NF41-42.[79] However, disrupting TH signalling during these early stages by exposing *Xenopus* tadpoles to a mixture of environmental chemicals found in human amniotic fluid impaired the neuron

vs oligodendrocyte ratio at the expense of neuroblasts.[69] Accordingly, the expression of the pluripotency genes (eg, *sox2*, *bdnf*, *tub2b* and *mcep2*) was reduced, as was that of the neuronal marker *dcx* and the myelination marker *mbp*,[69] suggesting that oligodendrocyte differentiation and maturation could be affected too. Altogether, these results suggest that elevated TH signalling favours progenitor cell commitment towards a neuronal fate in the pre-metamorphic tadpole brain. So far, the molecular programs that underlie these cell fate changes remain largely enigmatic. Early perturbations in TH signalling might produce irreversible long-term defects in brain structure and function, ultimately hampering locomotor and other behaviours, as for instance corroborated by the lower distance travelled by *Xenopus* larvae exposed to the mixture of TH disruptors.[69]

### 2.1.3 | Chicken

In birds, maternal THs stored in the egg yolk are taken up in the amniotic circulation via several THTs,[80] stimulating correct brain development prior to mid-embryogenesis when the thyroid gland starts producing THs[81] (Figure 1C). For instance, already at day 1 (E1) of the 21-day embryonic development, neural tube closure is responsive to $T_3$ signalling in the chicken (*Gallus gallus*) embryo,[82] and regulators of TH availability are present throughout the E4 and E8 brain.[28,83] The TeO of the chicken brain is particularly interesting to study the role of THs in the process of neuro- and gliogenesis, since it displays several features of cortical development and shares a similar cyto-architecture, such as the occurrence of layers, expression of the TH-responsive gene *RELN* (encoding reelin) and an inside-out developmental gradient.[84] Furthermore, both neurons and glial cells arise from a common progenitor during embryonic TeO development, giving rise to a structure that is essentially mature prior to hatching at E20.[85-87] KD of *MCT8* in TeO neural progenitors as early as E3 reduced intracellular TH signalling, decreased NSC proliferation, and caused a premature depletion of the progenitor cell pool, resulting in cellular hypoplasia at later stages. Consequently, glutamatergic and GABAergic neuronal populations were smaller, possibly disrupting the TeO visual processing function.[88] Since cell production has ceased by then, it is almost certain that the loss of cells is irreversible. Thus, these data indicate that MCT8-dependent, cellular uptake of THs in the chicken embryo is not only required to maintain neural progenitor proliferation, but also to induce a precisely timed switch from proliferation to differentiation.[88] A similar loss of cells was observed in the MCT8-deficient retina, which was linked to reduced proliferation of retinal precursor cells. More strikingly, cell fate was also altered in MCT8-deficient cones, with increased commitment towards more UV/blue cones at the expense of green/red cones.[89] Whether or not MCT8 KD in the TeO or retina affected OPC generation remains to be investigated, as are the underlying signalling pathways. Furthermore, as elaborated on earlier, the role of other regulators of TH availability besides MCT8 are worthwhile to explore in this context too. Most of them are dynamically expressed throughout various embryonic CNS regions, such as the pallium,[90,91] cerebellum,[92,93] and spinal cord.[26] Because TH signalling is vital for the development of each of these brain regions,[93] one may reasonably expect other THTs, DIOs and TRs to be involved in local neurogenesis and gliogenesis as well.

## 2.2 | In mammals

Most evidence for a role of THs in embryonic neural progenitors has been obtained from mammalian models, especially eutherian species, because of the easy genetic engineering as well as their genetic, anatomical and physiological similarity to humans. In these species, maternal THs are transferred to the embryo via the placenta, and are implicated in neurodevelopment from early stages onwards[13,94,95] (Figure 1D). For instance, expression of *Thra*, *Dio2* and *Mct8* mRNAs in the VZ of the embryonic rat neocortex suggests that THs act on neural progenitors prior to the activation of the thyroid gland. Furthermore, maternal hypothyroidism during neocorticogenesis delayed mitotic divisions, and shortened cell cycle length, reducing the progenitor pool.[96] These effects echo observations in non-mammalian vertebrates following MCT8 deficiency, causing altered TH activity in neural progenitors.[51,88] The adverse effects of maternal TH deficiency on progenitor cell pool size ultimately resulted in cellular hypoplasia in the telencephalon, which at least partially contributed to the learning and memory impairment observed when these rats reached adulthood.[96,97]

Excess $T_3$, mimicking a state of hyperthyroidism, also reduces the progenitor cell pool size. Although it may seem contradictory, this reflects the current idea that tilting the TH balance towards either end outside of the normal TH range negatively affects early brain development.[13,17] $T_4$ administration increased *Hes* expression, hampered neuronal differentiation and likely altered cell specification in the foetal rat cortex,[98] while *Hes* inhibition stimulated pro-neural gene expression in NSCs, thereby accelerating neurogenesis.[99] Similarly, exposing neural cultures derived from the E16 rat cortex to 3 nM $T_3$ also promoted generation of oligodendrocytes at the expense of neurons.[100] In contrast, somewhat unexpectedly, adding $T_3$ to mouse cell cultures derived from the embryonic telencephalon resulted in neurogenic effects through TRα1 while inhibiting gliogenesis.[97] Similarly, hyperthyroidism stimulated in vivo dopaminergic neuronal differentiation through increased TRα-induced *Otx2* expression in the ventral mouse midbrain.[57] Either these observations could be a consequence of in vitro vs in vivo conditions, or

they could imply that regulators of TH availability are able to confine TH action to certain CNS regions, resulting in different spatio-temporal responses. It is plausible that TH acts as a neurogenic signal in one brain area, while acting as a gliogenic signal elsewhere and/or at another time point. A difference in regional or cellular TH responsiveness could for instance explain why hypothyroid perinatal mice displayed increased 5′-bromo-2′-deoxyuridine (BrdU)-labelling in the olfactory bulb (OB) and cerebral cortex, but decreased labelling in the SVZ and neocortex, while no change was observed in the hypothalamus.[16,101] The importance of local TH regulators is well demonstrated in *Mct8/Oatp1c1* double KO mice with their complex phenotype characterized by profound hypomyelination, delayed cerebellar development and reduced γ-aminobutyric acid (GABA)ergic cell differentiation, because of a strongly impaired TH uptake.[102] Whether neuro- and oligodendrogenesis were affected per se remains unanswered and could be relevant for future studies in mouse models harbouring mutations in one or several genes encoding other TH regulators.[103]

In addition to its stimulatory effect on cell proliferation, $T_3$ also induces a switch to neuronal differentiation in the developing brain,[97,104] and later stimulates OPC differentiation into mature oligodendrocytes,[60] indicating that specific generic programs are initiated in a precisely timed manner during development. For example, COUP-TF1 is an important transcription factor regulating the timing of $T_3$-stimulated gene expression required for normal corticogenesis.[105] In fact, THs influence transcription of numerous genes to guide these complex processes in a coordinated manner.[106-108]

Another interesting question is whether TH deficiency during embryogenesis has long-term effects on the biology of adult NSC pools, notably by mechanisms such as epigenetic modulation that alter the gene response repertoire over the course of time.[109,110] This hypothesis fits with the "developmental origins of health and disease" (DOHaD) paradigm, stating that many non-communicable diseases originate in early development.[111] While defects might be less evident at early stages of development, they could render the brain more susceptible to pathological processes later in life, and could for instance affect the potency of adult NSCs to respond to brain damage caused by acute insults or neurodegenerative diseases. In rats, propylthiouracil (PTU)-induced hypothyroidism during gestation and perinatal development reduced cell proliferation and survival in the adult hippocampus, a well-established neurogenic niche (see part 3, *Thyroid hormones regulate NSC cell fate in the adult mammalian brain*), leading to smaller brains.[104] Furthermore, prenatal PTU exposure led to the occurrence of heterotopias, resulting in abnormal brain function in later life.[112,113] These data indicate that embryonic NSCs are sensitive to altered TH signalling from early stages onwards with potentially adverse long-term effects in the adult brain, even if the period of TH perturbation was only transient.[113]

As far as we are aware, little is known regarding the role of THs in embryonic NSCs in non-human primates and humans. However, especially with regard to the gyrencephalic neocortex, the situation is deemed far more complex in the sense that a higher NSC output is required to allow for its disproportionate expansion relative to the rest of the brain.[114,115] Additional progenitor cell types have been identified in the developing neocortex, among which intermediate progenitors serve to amplify cell production.[116] THs could have played a crucial role guiding these local changes in the growth of the human neocortex throughout the course of evolution.[117] One group proposed that $T_4$ could act on the integrin $\alpha V\beta_3$ receptor, thereby stimulating basal progenitor proliferation, with consequent exponential expansion of the progenitor cell pool.[118]

Lastly, magnetic resonance imaging-based studies in humans have revealed structural alterations and hypomyelination as key features following maternal hypothyroidism,[119,120] indicating problems with the generation of NPCs and OPCs, and/or the differentiation of these progenitors into mature neurons and oligodendrocytes. Moreover, a large cohort study recently showed that both mild hypo- and hyperthyroidism in the first trimester of prenatal brain development altered grey/white matter ratios in the progeny, suggesting that lineage specification was altered in embryonic development.[17] Other neurological disorders including attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and schizophrenia, characterized by abnormal neuronal numbers and networks, are also suspected to have a developmental aetiology of which suboptimal TH levels might be one of the underlying causes.[14,121-127] Lastly, a histological analysis of the brain of an MCT8-deficient foetus showed loss of some neuronal subtypes, and a hypomyelinated state, suggesting similar problems in NSC biology and specification caused by insufficient TH uptake during early development.[128] To elucidate the associated pathophysiological mechanisms, Vatine and co-workers recently generated a "disease in a dish" model using induced pluripotent stem cells (iPSCs) obtained from healthy individuals and MCT8-deficient human patients.[129] They showed that the lack of a functional MCT8 in neural cells significantly reduced TH transport, but without affecting proliferation, neuronal differentiation and TH-dependent neuronal maturation. However, by allowing MCT8-deficient iPSCs to differentiate into brain endothelial cells, the same authors showed that the loss of MCT8-dependent TH transport across the in vitro BBB impaired proper neural differentiation. Hence, they concluded that the cause of the human AHDS phenotype is primarily the result of impaired TH uptake at the BBB, rather than an incapacity of MCT8-deficient neural cells to generate mature neurons.[129] This implies the BBB itself can be considered as

an additional regulator in controlling TH-induced NSC differentiation. Applying cell type-specific approaches, both in vitro and in vivo, could provide an all-encompassing understanding of the local role of THs, in addition to the current approaches that predominantly rely on systemic hypo- and hyperthyroidism.

Taken together, data derived from non-mammalian as well as mammalian species have provided substantial evidence that (a) tightly regulated TH levels are essential for embryonic brain development prior to foetal thyroid gland activation, (b) THs regulate the proliferative potential of neural progenitors and commitment to neuronal and glial precursors and (c) THs are most likely able to alter NSC fate within a temporally and spatially refined manner, ultimately affecting the final cyto-architecture and function of presumably every brain region.

## 3 | THYROID HORMONES REGULATE NSC FATE IN THE ADULT MAMMALIAN BRAIN

As described above (see part 2), the role of THs has been largely studied during neurodevelopment in most vertebrate species. However, many studies highlight that THs continue to regulate NSC behaviour in the young and ageing brain, especially in mammals.[130,131] In non-mammalian vertebrates (eg, zebrafish and amphibians), a role in CNS regeneration has been investigated, suggesting that TH acts on adult brain function.[67,132,133] However, a direct action of THs on NSCs has not been demonstrated in these models yet. Here, we focus on the critical influence of TH in the regulation of NSC fate and its functional implication on neurocognitive outcome in mammals.

### 3.1 | Heterogeneous populations of NSCs

In the adult rodent brain, NSCs are almost exclusively located in two main germinal brain regions: the SVZ, lining the lateral ventricles and the SGZ of the dentate gyrus of the hippocampus. Both sources of NSCs differentially sustain lifelong neurogenesis and oligodendrogenesis. However, unless specifically exposed to pro-oligodendrogenic molecules, NSCs derived from the SGZ seem to exclusively produce new neurons[134,135] that subsequently migrate to the granule cell layer of the dentate gyrus where they give rise to glutamatergic granule cells.[136] Under homeostatic conditions, adult NSCs derived from the SVZ generate mainly neuroblasts via highly proliferative progenitors. Then, mature neuroblasts migrate towards the OB where they differentiate into different types of interneurons.[137] A few NSCs are also able to generate glial cells, both astrocytes and oligodendrocytes.[137] However, the oligodendrogenic potential of SVZ-NSCs strongly increases in response to a pharmacologically demyelinating insult.[19,138,139] SVZ-derived OPCs migrate towards the corpus callosum, the striatum and the cerebral cortex within close range of the lateral ventricle, where they differentiate into mature myelinating oligodendrocytes.[137]

It is still unknown whether all NSCs in different SVZ microdomains are able to either generate both neurons and glia, or if distinct neurogenic and gliogenic NSCs exist. Recent evidence shows that adult NSC functions are heterogeneous and depend primarily on their regional identity acquired during development. Within the adult SVZ, it is well-established that NSCs reside in regionally distinct microdomains, thus determining the type of neurons generated in the OB.[140] Adult NSCs that retain RG hallmarks[2,141] are generated during early embryonic development, then entering in a quiescent state until being activated in the adult.[142] Hence, the adult neurogenic niche is constituted of a mosaic of NSCs regionally located in distinct microdomains that reflect their developmental identities.[143,144] Given the crucial role of THs during (a) neurodevelopment and (b) adult NSC behaviour (see below), it will be interesting to investigate whether THs regulate embryonic SVZ-NSC specification, thereby determining NSC long-term behaviour, especially the neurogenic and gliogenic potential. Notably, which SVZ microdomain(s) is (are) specifically targeted by TH signalling to generate either neuroblasts or SVZ-OPCs remains unexplored. Moreover, impaired NSC behaviour caused by disrupted TH signalling during early development could render SVZ-NSCs unable to respond to a brain insult in the adult, thus limiting NSC plasticity in response to injury.

### 3.2 | TH action on NSC behaviour

In the murine SVZ, adult onset hypothyroidism decreases NSC and progenitor proliferation by blocking cell cycle progression.[145] An exogenous TH-pulse is sufficient to restore cell proliferation within the adult SVZ.[145] In the rodent SGZ, the consequences of hypothyroidism on cell proliferation and survival are more obscure. In some studies, hypothyroidism in adult rats decreased progenitor survival without affecting cell proliferation.[146,147] Again, TH treatment was sufficient to restore progenitor survival and neuronal differentiation.[146] In contrast, other studies showed that progenitor proliferation decreased without any effect on cell survival.[148] These inconsistent data may originate either from distinct experimental approaches used to induce adult hypothyroidism (eg, goitrogens or thyroidectomy), or because of labelling tissues with BrdU.[149] Recently generated transgenic mice, expressing specific markers of progenitor cells at different

stages of lineage development, provided more compelling evidence that adult hypothyroidism decreases the number of immature and post-mitotic neuroblasts without affecting the proliferation of early non-committed progenitors within the SGZ.[150,151]

In the adult SVZ, a hypothyroid state is also associated with lower numbers of both early committed neuronal progenitors and mature neuroblasts,[20] thus decreasing migrating neuroblasts along the rostral migratory stream (RMS).[18,145] Similarly, low TH levels reduce the generation of immature hippocampal neurons in the adult SGZ.[146-148] Taken together, these results show that TH acts as a neurogenic factor both in the SVZ and in the SGZ by promoting NSC commitment towards a neuronal fate.[18-20,130]

In contrast, a TH-free environment promotes the generation of new OPCs derived from SVZ-NSCs under physiological and pathological conditions.[19,20] Following a demyelinating insult, these newly generated SVZ-OPCs generate mature myelinating oligodendrocytes in the corpus callosum.[19] Compared to remyelination accomplished by resident parenchymal OPCs, myelin formed by oligodendrocytes derived from the SVZ has a normal thickness, and these newly generated OPCs provide functional remyelination, restoring normal conduction speed.[19,139,152] Correspondingly, a one-month TH-free window enhanced the regenerative capacity by triggering oligodendrogenesis from SVZ-NSCs.[19]

Thus, TH availability determines opposing effects of TH-dependent NPC and OPC commitment in the adult SVZ. Interestingly, the fate of newly generated neural cells changes with ageing: neurogenesis declines[153,154] whereas oligodendrogenesis is preserved.[155,156] Moreover, low circulating THs are a typical feature of normal ageing.[157] Thus, declining circulating TH levels as a function of ageing could preserve generation of oligodendroglial cells while decreasing neuron production. Taken together, these results identify TH signalling as a master pathway, tightly regulating the balance

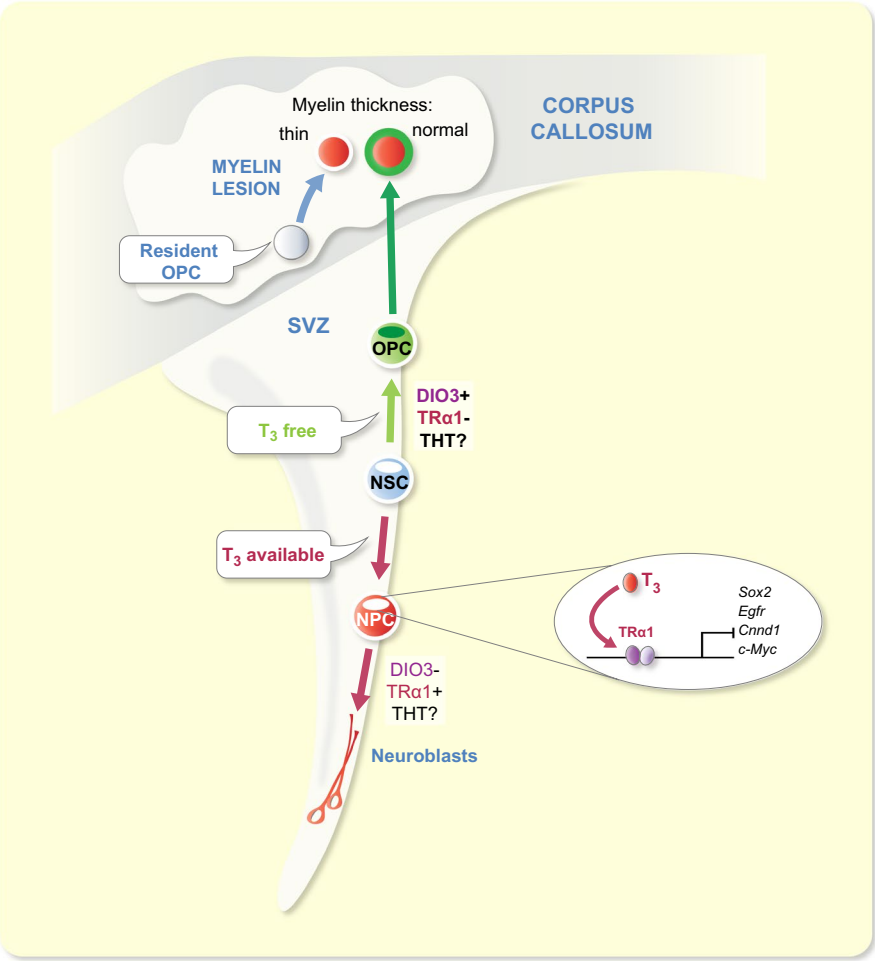


**FIGURE 2** TH signalling regulates cell fate decision within the SVZ niche of the adult mouse. $T_3$ drives NSC commitment preferentially towards a neuronal fate. $T_3$, through its nuclear receptor TRα1, downregulates many target genes, thus promoting *de novo* generation of neuroblasts. In contrast, determination of glial cell fate depends on a $T_3$-free window. SVZ-OPCs are protected from the effects of $T_3$ by (i) the expression of DIO3 and (ii) the absence of TRα1. Later, $T_3$ is necessary to induce differentiation and maturation of oligodendrocytes capable to functionally repair a myelin lesion in the corpus callosum. Compared to SVZ-OPCs (complete remyelination), resident parenchymal OPCs (thin, insufficient remyelination) are less efficient for functional brain repair

between neurogenesis and oligodendrogenesis in the young, adult and ageing brain.

### 3.3 | Regulation of TH availability in the adult NSC niche

TH entry into the brain is facilitated by THTs at the BBB and the blood-cerebrospinal fluid barrier (BCSFB). Since the SVZ is located adjacent to the ventricular walls, $T_4$ is most likely supplied via the cerebrospinal fluid (CSF), through binding of $T_4$ to transthyretin (TTR), a TH distributing protein synthesized by the choroid plexus epithelial cells.[158-162] TTR null mice have lower TH levels in the brain, associated with reduced apoptosis of NSCs and progenitors within the adult SVZ.[159,162] Interestingly, the level of apoptosis of NSCs/progenitors in TTR null mice was similar to wild type mice rendered hypothyroid.[162] So far, it is unknown whether TTR influences SVZ-NSC fate. Following entry into the brain, local TH availability is tightly regulated, allowing precise temporal and cell-specific control of TH action.[29,163,164] Fine-tuning of cell-specific TH availability is particularly important in complex target cell populations such as the NSC niche, as it could affect cell fate choices during different stages of neurogenesis and oligodendrogenesis.

In the adult mouse SVZ, only the TRα1 isoform is detected.[18,131,145] Interestingly, TRα1 is not detected by immunohistochemistry in SVZ-NSCs but starts being expressed in early committed neuronal progenitors and strongly persists in mature neuroblasts.[18] In contrast, TRα1 is not detected in SVZ-OPCs, showing that TRα1 expression is mainly associated with neuronal cells[19] (Figure 2). Accordingly, TRα1 overexpression induces the generation of new migrating neuroblasts[18] whereas shRNA directed against *TRα1* mRNA increases expression of NSC/progenitor (*Sox2*, *Musachi*) and oligodendroglial (*Ng2*) markers, suggesting that the pool of NSC/progenitors and OPCs is enlarged.[18] Moreover, DIO3, the $T_3$-inactivating enzyme, is strongly expressed in SVZ-OPCs, showing that glial fate determination requires a TH-free environment (Figure 2). Accordingly, shRNA directed against *Dio3* increases the number of SVZ-OPCs.[19] Thus, OPCs are protected from the neuralizing effects of $T_3$, by the combination of the absence of TRα1 and the expression of DIO3. So far, the potential role of DIO2 and THTs in these cell types has not been investigated. Few TH target genes have been identified underlying the control of adult SVZ-NSC fate. In presence of $T_3$, TRα1 downregulates two cell cycle genes (*c-Myc* and *Ccnd1*) within the adult mouse SVZ[145,165] and acts as a neurogenic switch by repressing (i) *Sox2* in progenitors, a gatekeeper of NSC identity[18] and (ii) *Egfr*, a well-established gliogenic factor[19] (Figure 2).

In the adult mouse SGZ, TRα1 is also mainly detected in the neuronal lineage, especially in post-mitotic hippocampal progenitors, but not in non-committed proliferating progenitors.[21,130,150] This suggests that, similar to the adult SVZ, TRα1 promotes neuronal fate in the adult SGZ, but at later steps of neuronal lineage progression. In a mutant mouse line that overexpresses TRα1 (the unliganded TRα1 aporeceptor is overexpressed in $TR\alpha 2^{-/-}$ mice), neurogenesis is decreased, showing that unliganded TRα aporeceptor overexpression recapitulates the effects induced by a lack of $T_3$ in hippocampal neurogenesis.[146-148] Accordingly, exogenous $T_3$ treatment rescued the decrease in neurogenesis.[166] In contrast, both progenitor survival and immature hippocampal neurons are increased in TRα null mice ($TR\alpha 1^{-/-}$), without effect on early progenitor proliferation.[166] Thus, like in the adult SVZ, $T_3$ through TRα1 enhances neuronal differentiation. To further elucidate how TH availability is locally controlled in the adult SGZ, studies on the expression and function of both DIOs and THTs are needed.

### 3.4 | Functional significance of TH-dependent adult neurogenesis

Adult neurogenesis is involved in several cognitive functions, notably memory and learning,[167,168] olfactory discrimination,[169] and social and reproductive behaviour.[170] In rodents, a decline in neurogenesis impairs olfactory function, thus influencing olfactory-dependent/driven behaviour.[171] One might therefore expect that decreased SVZ-neurogenesis caused by hypothyroidism affects olfactory function. Hypothyroidism reduces mature olfactory receptor neurons[172] and induces anosmia (loss of smell) in adult mice.[173] Interestingly, TH signalling involving TRβ is also required in the olfactory epithelium of Pacific salmons to discriminate their natal stream during the seaward migration.[174] However, the links between neurogenesis underlying TH and olfactory function are not established yet in this model.

In humans, neurocognitive deficits as well as neurodegenerative diseases are also associated with alterations in adult neurogenesis, especially within the hippocampus.[175-177] Moreover, neuropsychiatric manifestations ranging from anxiety, depression and dementia to schizophrenia are linked to adult hypothyroidism[178-181] or developmental hypothyroidism.[121] Again, further studies are needed to explore whether TH-dependent neurogenesis is altered in neurological diseases to provide a mechanistic basis for the epidemiological observations. Several research groups have demonstrated that the generation of new neuronal cells occurs throughout adult life.[182-184] However, more recent papers show contradicting results. One study shows that neurogenesis in the dentate gyrus is limited to the first year of life,[185] whereas two others demonstrate that hippocampal adult neurogenesis persists throughout ageing.[186,187] These discrepancies probably relate

to different methods used (*post-mortem* brain samples or fresh tissues from biopsy). The small sample sizes available for human analysis are another limiting factor to draw unequivocal conclusions.

### 3.5 | Emerging areas in research on adult NSC and THs

One key question is how does ageing alter the balance between neurogenesis and oligodendrogenesis? Ageing decreases NSC activity and the neuroblast population size in both the SVZ and the SGZ.[153,156,188] Furthermore, several studies have shown that fate of newly generated cells changes with ageing: neurogenesis declines whereas oligodendrogenesis seems to be preserved within the SVZ.[189,190] Apparently, myelin loss and disruption with ageing are not caused by OPC depletion since numbers of OPCs appear stable.[191,192] The higher level of oligodendrogenesis in the ageing brain could be crucial for maintenance of brain functions, also in humans. Although the generation of new SVZ-derived neuroblasts is still debated in humans,[185,186] oligodendroglial cells are detected throughout adult life, both in the young human SVZ under physiological[189] and pathological[138] conditions, and in the ageing SVZ.[156,193] Given the well-established role of TH on NSC fate, it will be interesting to analyse how the slightly lower TH levels and/or TSH levels associated with healthy longevity[157,194] might preserve the oligodendrogenic capacity of the neurogenic niche in the ageing brain. Interestingly, *Egfr* mRNA levels increased throughout adulthood in the human SVZ.[156] Moreover, *Egfr*, a key gliogenic factor,[195] is downregulated by $T_3$ through TRα1 in the young adult SVZ.[19] Thus, upregulation of *Egfr* during ageing, combined with a decreasing TH environment may be a key molecular mechanism modulating neuronal and glial fate determination in the ageing SVZ. Further research should address this point, notably in the context of myelin maintenance in ageing brains and degenerative diseases.

In this context, it is worth noting that the contribution of TH signalling to the thickness of the myelin sheath remains unclear in the adult brain. Two types of OPCs are potential candidates to participate in myelin repair in the adult mammalian brain: (i) the pre-existing resident parenchymal OPCs (pOPCs)[196] and (ii) newly-generated OPCs from NSCs within the SVZ.[138] However, pOPCs repair myelin poorly, producing thin myelin.[139,152] Recent research demonstrates that SVZ-OPCs are key targets for enhancing endogenous myelin repair.[19,139,152] After a demyelinating insult, SVZ-OPCs restore myelin of normal sheath thickness, whereas pOPCs do not. In particular, a TH-free environment enhances generation of SVZ-OPCs, but not pOPCs, thereby promoting functional remyelination.[19] Understanding how THs differentially regulate SVZ-OPCs vs resident OPCs could shed new light on how a key endocrine signal specifically targets SVZ-OPCs, a promising source of remyelinating cells for demyelinating diseases.

Despite a wealth of data describing how the perinatal and adult SVZ generate distinct neuronal populations from spatially segregated microdomains (see above *TH action on NSC behaviour*), it remains largely unknown whether there is a regionalized origin of fully remyelinating oligodendrocytes within the adult SVZ. It is well-established that morphogen signalling pathways determine the regionalized origin of neuronal cells. For example, *Sonic Hedgehog* (*Shh*) is expressed specifically in the ventral SVZ and contributes to driving NSC fate towards specific ventral neuronal cell types.[197] In contrast, canonical Wnt signalling determines dorsalization of the adult SVZ.[198] Azim et al. (2014)[199] showed that Wnt/β-catenin signalling promotes NSC determination towards a glial fate in the adult SVZ. However, the precise location of the remyelinating oligodendrocytes capable of producing a myelin sheath of normal thickness remains unknown. An interesting hypothesis is that TH availability is differentially regulated across the SVZ, creating a dorso-ventral gradient, thus affecting NSC fate differentially in the dorsal vs latero-ventral SVZ.

## 4 | IMPLICATIONS OF CELL METABOLISM ON NEUROGENESIS AND TH-INDUCED CELL FATE DETERMINATION

Besides changes in terms of gene and protein regulation, stem cell activation and commitment also involve profound metabolic modifications. These internal changes, intrinsically linked to each other, allow differentiating cells to acquire their functional and morphological specificities. Such metabolic changes are crucial for NSC fate commitment and differentiation.[200] THs are major modulators of cell metabolism, and TH-induced mitochondrial responses are directly implicated in stem cell differentiation.[32,33,201] Here, we will discuss how changes in cell metabolism influence NSC commitment and differentiation, and how TH signalling impacts cell metabolism during neurogenesis.

### 4.1 | Mitochondrial activity regulates NSC proliferation and fate decisions

Stem cell niches such as the SVZ generally experience lower oxygen tensions compared to surrounding tissues, rendering them hypoxic.[202] Hypoxic conditions favour both stem cell proliferation and multipotency.[202-204] NSCs and progenitors principally rely on a high glycolytic metabolism and a low mitochondrial respiration, as opposed

to mature differentiated cells, which primarily produce their energy using OXPHOS.[204-206] The hypoxia inducible factor 1 α (HIF1α), a key factor in glycolysis activation and OXPHOS inhibition, is only stable in low intracellular oxygen conditions, and its degradation allows differentiating cells to shift from a glycolytic to an OXPHOS-based metabolism.[34,207] Interestingly, HIF1α directly induces *Dio3* expression,[208,209] and thus could be involved in regulating the TH-free environment required for both undetermined cells and OPC commitment, as discussed earlier.

Mitochondrial activation, which allows the glycolytic to OXPHOS-based metabolism shift, is necessary for NSC and progenitor differentiation. Most enzymes involved in glycolysis decrease during neuronal differentiation of human iPSCs, and genes associated with mitochondrial respiration simultaneously increase.[34] Similar observations were made in cells isolated from the adult mouse SVZ[210] and SGZ.[211] Moreover, perturbations of mitochondrial activity strongly alter neuronal differentiation during both embryonic and adult neurogenesis, confirming that increased mitochondrial respiration is necessary for this process.[207,212,213] Inversely, stimulating mitochondrial respiration helped to restore normal adult-born hippocampal neuron maturation rates in a mouse model of Alzheimer's disease.[214]

Changes in cell respiration also influence NSC proliferation and fate choice. For instance, culturing foetal and postnatal human SVZ progenitor cells in hypoxia (5% of $O_2$, physiological oxygen tension in the nervous system) strongly increases proliferation, whereas 20% of $O_2$ (ambient oxygen level) is more favourable for cell differentiation.[36] This result confirms that proliferative and differentiating cells require distinct oxygenation levels. Moreover, hypoxic conditions favour progenitor cells to commit to OPCs, while exposing OPCs to 20% of $O_2$ stimulates differentiation, as seen in cultured human SVZ precursors[36] and in primary cultures of rat oligodendroglial progenitors.[215] The inhibition of HIF1α signalling in human iPSCs promotes neuronal rather than glial differentiation, confirming that low mitochondrial activity is required during glial commitment.[37] Inhibiting mitochondrial respiration in adult mice SVZ progenitors similarly impairs their commitment towards a neuronal phenotype.[20,216] Thus, NSCs differentiating into glia maintain a high glycolytic activity, whereas neuronal commitment requires an early increase in OXPHOS.

The modulating effects of THs on NSC mitochondrial metabolism are not well understood yet, especially during embryonic neurogenesis. In contrast, in adult rodents, it was demonstrated that NSC fate is modulated by TH-mediated metabolic changes in a cell lineage-specific manner. Using a mitochondrial membrane potential dye, Gothié et al (2017) showed that hypothyroidism decreased mitochondrial activity in neuroblasts in vivo, whereas mitochondrial respiration remained low in SVZ-derived OPCs both in euthyroid and hypothyroid adult mice.[20] Inhibiting mitochondrial activity in vitro using Oligomycin significantly reduced the proportion of SVZ-derived NSCs committed to neuroblasts, confirming the importance of TH-induced mitochondrial activation for neuronal differentiation[20] (Figure 3).

## 4.2 | Mitochondrial dynamics are involved in the regulation of NSC differentiation

Mitochondrial dynamics (involving mitogenesis, mitochondrial fusion and fission, intracellular trafficking and mitophagy) is adjusted appropriately in response to changing energetic needs.[217] Accordingly, the metabolic shift associated with NSC differentiation implies important changes in mitochondrial morphology: increased mitochondrial activity involves high mitochondrial dynamics. Mitogenesis and fusion increase mitochondrial volume. Fission is implicated in segregation of damaged mitochondria before their destruction (mitophagy), and is essential for mitochondrial trafficking and distribution in the cell and its extensions.[218,219] Interestingly, defects in mitochondrial dynamics are associated with various neurodegenerative disorders, including Alzheimer's disease,[220-222] Parkinson's disease,[223] Huntington's disease[224,225] and multiple sclerosis,[226,227] suggesting that impaired dynamics could be detrimental for brain cell physiology.

In the embryonic SVZ of mice, mitochondria appear elongated in NSCs and progenitors, fragmented in cells committing towards a neuronal fate, and elongated again in mature neurons.[212] These morphological changes are important to increase OXPHOS and ROS production during neuronal differentiation.[212] In the adult SVZ, the main inducer of mitochondrial fission, dynamin-related protein 1 (DRP1), is acutely activated during neuronal commitment.[20] Although morphological changes in mitochondria have not been formally studied in the adult SVZ, this result suggests that mitochondria are fragmented during early neuronal differentiation, similar to the situation in the embryonic SVZ. In the adult SGZ, however, mitochondria appear small and fragmented in NSCs, and progressively elongate during neuronal differentiation.[207] The fact that normal cell migration requires mitochondrial fragmentation[228,229] could explain the differences observed between the SVZ and the SGZ. SVZ neuroblasts migrate further than those of the SGZ do, and an increase in mitochondrial fission may be necessary for migration through the RMS towards the OBs. Accordingly, DRP1 inhibition prevents the migration of SVZ-derived neuroblasts, and hinders their differentiation,[216] bolstering this hypothesis.

THs amplify the activation of DRP1 during NSC neuronal commitment in the adult SVZ[20] (Figure 3). However, the molecular mechanisms underlying DRP1 activation during neuronal commitment are still unknown. Given that the

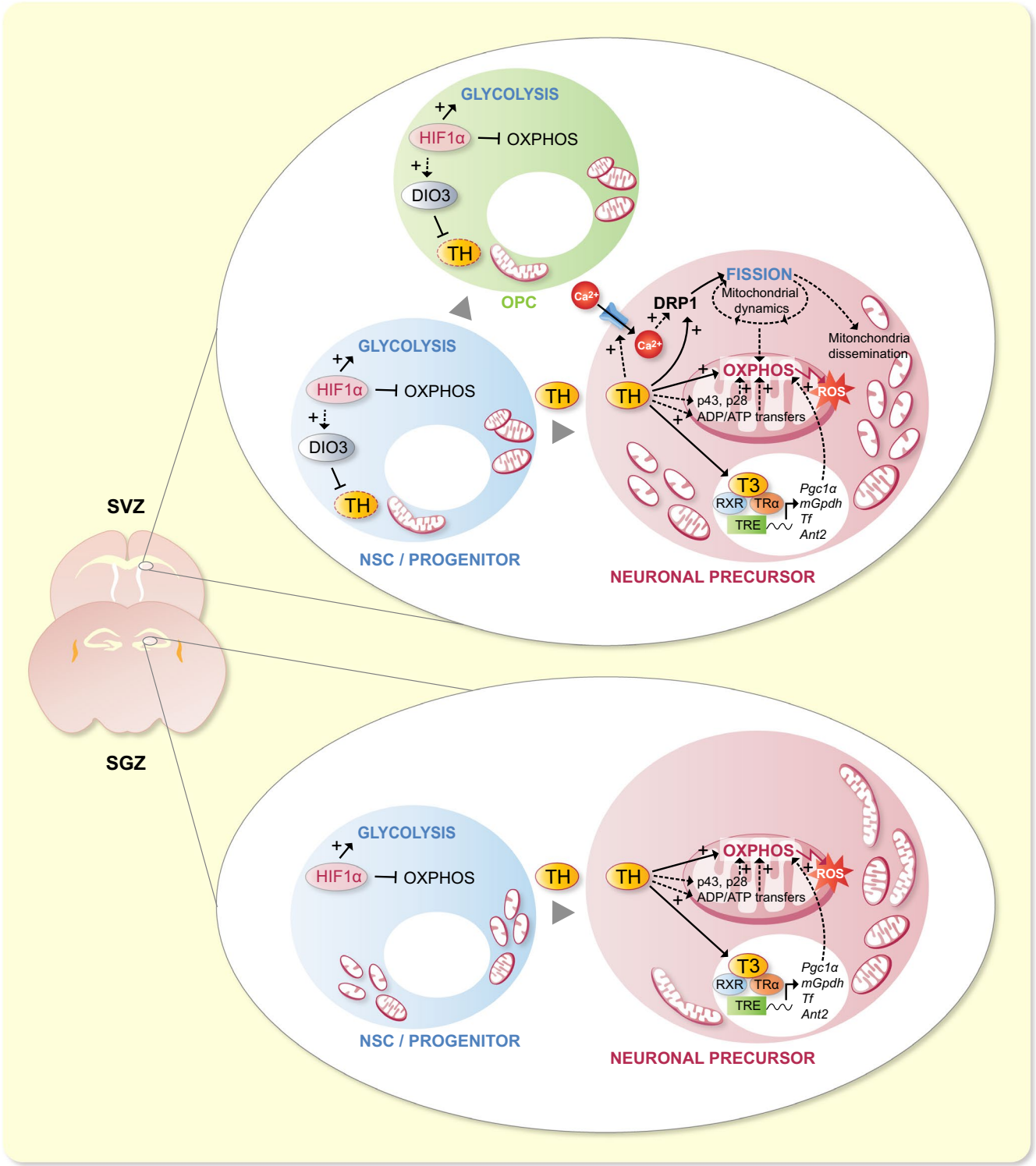


**FIGURE 3** TH signalling activates mitochondrial metabolism during NSC commitment to neuronal precursor cells in rodents. In the adult murine SVZ, HIF1α activates OXPHOS and inhibits glycolysis in NSCs. TH signalling activates OXPHOS and drives NSC commitment towards a neuronal precursor cell (NPC) fate. The metabolism of cells committing to an oligodendroglial fate (OPC) maintains predominantly based on glycolysis. HIF1α may participate in the activation of *Dio3*.[208,209] THs also activate DRP1, which induces mitochondrial fission in NPCs. The same process might occur in the embryonic SVZ, where mitochondria fragment during NPC commitment. Processes involved may include the activation of $Ca^{2+}$ entry in the cell, interaction with mitochondria-specific TH receptors (p43 and p28), activation of ADP/ATP transfer between mitochondria and the cytoplasm, and the activation of TH-target gene expression. In the adult SGZ, NSC commitment and differentiation is also associated with an increase in OXPHOS. In contrast to what is observed in SVZ cells, mitochondria appear as fragmented in NSCs, and elongated in NPCs in the SGZ. Here too, TH signalling is needed for NSC commitment to NPC and OXPHOS activation, through processes poorly explored to date in the SGZ

calcium-dependent phosphatase calcineurin favours DRP1 activation,[230,231] and that THs can non-genomically activate $Ca^{2+}$-ATPases,[232,233] an interesting hypothesis to test is whether a TH-mediated increase in intracellular calcium leads to DRP1 activation. Besides, it has been hypothesized that the Doublecortin (DCX) protein, which drives microtubules polymerization specifically in neuroblasts, could be activated by $Ca^{2+}$-dependent signalling.[234] This assumption is based on a strong sequence homology with a $Ca^{2+}$/calmodulin dependent kinase in both mice and humans, and remains to be verified. Altogether, these data suggest that TH-induced $Ca^{2+}$ intake could play a major role in neuronal determination of progenitor cells by promoting DCX activation and microtubule formation, together with mitochondrial fission and dissemination along microtubules, which also depend on calcium.[235]

THs also directly induce the expression of *Pgc1α* (peroxisome proliferator-activated receptor gamma coactivator 1α), a master regulator of mitochondrial biogenesis.[236] PGC1α activation indirectly induces the expression of mitochondrial transcription factor A (TFAM), that in turn activates the expression of many genes required for mitochondrial activity.[237] The impact of THs on both TFAM and PGC1α has mostly been studied in the postnatal rat brain. Pups born from hypothyroid dams show severely decreased expression levels for both proteins in the cerebellum, as well as significantly lower mitochondrial protein expression.[238] However, the functional impact of TH-mediated induction of PGC1α and TFAM has not been explored specifically in the context of neurogenesis so far.

## 4.3 | Implication of reactive oxygen species in NSC fate decisions and differentiation

Reactive oxygen species (ROS) generated as side products of mitochondrial activity can trigger stem cell differentiation.[239-242] Experimental evidence indicates that increased ROS production is involved in NSC and progenitor differentiation in both the developing and adult brain, as shown in rodents and in human cells.[205,212,243-247] NSC differentiation in the adult SVZ also requires TH-dependent activation of mitochondrial metabolism and ROS production in cells committing towards a neuronal fate.[20] In turn, ROS production is impacted by mitochondrial dynamics. Khacho et al[212] showed that mitochondrial fragmentation observed during embryonic NSC commitment is a key trigger for increasing mitochondrial ROS production. ROS signalling activates nuclear respiratory factor 2 (NRF2), which in turn activates genes involved in inhibiting proliferation (*Notch*), and activating differentiation (*Isl1, Nkx2.1, Lhx5* and *Sim1*). Interestingly, NADPH oxidase 2 (NOX2)-derived ROS production appears necessary for cell proliferation in adult mouse activated NSCs.[248] Similar effects are observed in newt, where inhibiting ROS production by NOX reduced NSC proliferation, whereas inhibiting mitochondrial function did not.[249] These results reveal a distinct impact of mitochondrial ROS vs ROS produced by NOXs on cell proliferation and differentiation.

ROS production, by modifying a cell's oxidative state, also impacts NSC fate choice. For instance, hindering NOX2-derived ROS production in cultured adult mouse SVZ-NSCs increased the number of neurospheres composed exclusively of glial cells by about 30% compared to wild-type cultures.[248] Accordingly, in vitro exposure to the superoxide indicator hydroethydine showed that SVZ-derived NSCs committed to a neuronal fate produce more ROS than those differentiating towards an oligodendroglial fate.[20] In contrast, an increase in intracellular ROS following glutathion synthetase inhibition induced embryonic cortical progenitor cells to generate astrocytes, at the expense of neurons.[250] This process implicates an induction of the protein deacetylase SIRT1, a pivotal regulator of cell metabolism and mitochondrial biogenesis,[251,252] which is also involved in maintaining the undifferentiated state of NSCs and progenitors.[253,254] Furthermore, SIRT1 can promote neuronal differentiation in embryonic progenitors by interacting with the N-CoR corepressor,[255] involved in TH-target gene inhibition on positively regulated genes. In the adult SVZ, SIRT1 is expressed by a majority of cells engaged in the neuronal differentiation pathway, and only in a minority of cells engaged in glial differentiation,[20] suggesting that its involvement in adult NSC commitment mirrors the embryonic conditions. Lastly, acute $T_3$ exposure also increased ROS production in the neuronal lineage of the adult mouse SVZ, but not in the glial lineage.[20] The cellular oxidative state could therefore play an important role in NSC fate choice, with a crucial, fine-tuned control of glycolytic/mitochondrial metabolism, ROS production and ROS detoxification.

## 4.4 | Implications of iron metabolism in NSC fate decisions and differentiation

TH-dependent regulation of mitochondrial activity also involves iron metabolism. In particular, prolyl hydroxylase (PHD) enzymes use iron to catalyse HIF1α inactivation,[256,257] thus in turn potentially modifying *Dio3* expression (Figure 4). Moreover, the mitochondrial electron transport chain depends on iron-sulphur clusters.[258] In the blood stream, iron ($Fe^{3+}$) is mainly bound by the glycoprotein transferrin (Tf). THs can directly induce *Tf* transcription, as shown in human hepatocellular carcinoma cells.[259] Furthermore, hypothyroidism decreases *Tf* expression in the brain of postnatal mice,[260]

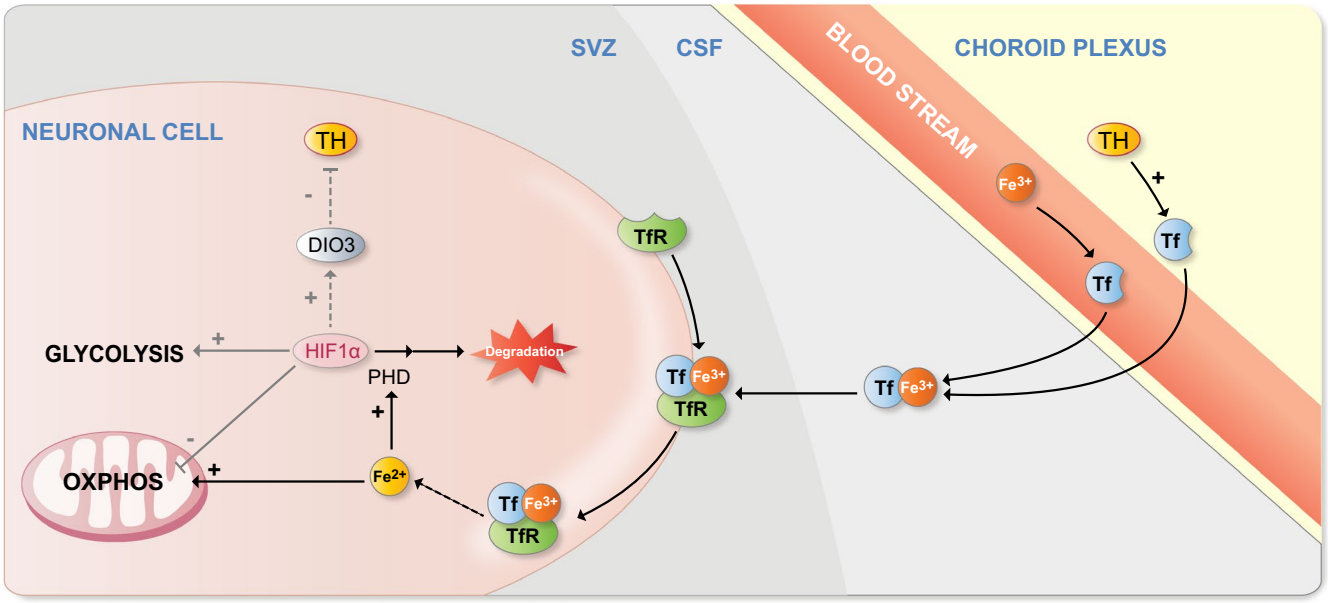


**FIGURE 4** Implication of iron in regulating the metabolic switch during neurogenesis. THs activate transferrin (Tf) transcription in choroid plexus cells. Tf is transferred to the cerebrospinal fluid (CSF) from the choroid plexus cells themselves, as well as from the blood stream, carrying iron in its $Fe^{3+}$ form. The Tf/ $Fe^{3+}$ complex binds to the cell-surface Tf receptor (TfR), facilitating their internalization. $Fe^{3+}$ is then reduced to $Fe^{2+}$ in the cytoplasm. Prolyl hydroxylases (PHDs) need both oxygen and $Fe^{2+}$ to be activated and to provoke HIF1α degradation. $Fe^{2+}$-Sulphur clusters are necessary for mitochondrial electron transport chain functioning in mitochondria, making iron necessary for OXPHOS activation. HIF1α degradation may be involved in preventing DIO3 activation, as shown in many cell types (eg, hepatocytes and cardiomyocytes). TfR expression in neuronal precursors has not been demonstrated yet, but has been shown in neurons, while absent from oligodendrocytes. Therefore, TfR expression could be initiated early during neuronal cell commitment

suggesting that THs also regulate *Tf* expression in vivo. From capillary vessels, Tf can cross the BCSFB[261,262] and the BBB,[263] but the mechanisms involved are not clear.[264] Iron-loaded Tf can also interact with specific cell surface receptors (TfR, Transferrin receptor). Then, the complex is internalized by endocytosis and $Fe^{3+}$ is reduced to $Fe^{2+}$ and released in the cytoplasm.

Tf can also be directly synthesized by oligodendrocytes[265,266] and choroid plexus cells in rodents.[265,267] While *Tf* expression and secretion by the choroid plexus presumably favours iron transport to the CSF,[268] its role in oligodendrocytes remains unclear. In fact, they do not secrete the glycoprotein,[269,270] and, unlike adult neurons[271,272] or OPCs in rat neonates,[273] they do not express TfR.[274-276] However, iron could enter oligodendrocytes through other receptors.[276] It has been suggested that Tf allows intracellular iron storage.[277] Marziali et al.[260] studied the influence of THs and Tf on oligodendrocyte differentiation and maturation, showing that both hyperthyroidism and intracerebral injection of apo-Tf (Tf that does not bind iron) decrease OPC numbers, and increase mature oligodendrocytes in the corpus callosum in postnatal mice. Inversely, hypothyroidism during embryonic development (i) increased OPC numbers in postnatal mice, a phenotype reversed following an apo-Tf injection, and (ii) reduced the number of mature oligodendrocytes.[260] These results are in line with studies showing that short-term hypothyroidism favours NSC determination towards OPCs in the adult mouse SVZ.[19,20] They also reveal that TH can influence iron metabolism, through Tf induction, thus modulating NSC fate. This could constitute one of the TH-triggered pathways allowing mitochondrial activation during neurogenesis, and it would be particularly interesting to study the interplay between THs and iron metabolism in this context.

## 4.5 | Future research on metabolism and NSCs

It would be interesting to investigate other factors involved in TH-mediated regulation of mitochondria in the context of neurogenesis and NSC fate determination. For instance, TH activation of adenine nucleotide translocators (ANTs), transporters of ATP and ADP between cytoplasm and mitochondria,[278,279] and that of the mitochondrial glycerol 3P dehydrogenase (mGPDH), an activator of mitochondrial electron transfer directly activated by THs.[278,280] Additionally, $T_3$ can interact with 2 truncated mitochondrial TRα isoforms, p43 and p28.[281-283] Even though we are currently not aware how $T_3$ binds to p28 to affect mitochondrial function, p43 itself strongly in vitro stimulates mitochondrial biogenesis and activity in presence of $T_3$.[281,284-287]

### 4.5.1 | Notch and Wnt signalling pathways

Modulation of signalling pathways such as the Notch pathway could also be involved in mitochondrial changes during NSC commitment and differentiation. Activation of Notch signalling provokes the inhibition of mitochondrial fragmentation in vitro via the activation of Akt and MFN1/2.[288,289] As mentioned above, the Notch pathway maintains the NSC pool in the adult SVZ[290-292] and is also required for OPC generation in the embryo.[293] Moreover, Notch signalling responds to THs.[98,294] Thus, in the adult, Notch-induced inhibition of fission might be involved in the reduced activation of DRP1 in SVZ-OPCs.[20] Furthermore, activation of Wnt/β-catenin in tumour cells promotes aerobic glycolysis,[295,296] and modulates mitochondrial dynamics by decreasing DRP1 interaction with mitochondria and increasing expression of mitofusin, a key player of mitochondrial dynamics.[297] Since a crosstalk between THs and Wnt is well-demonstrated in many stem cell types in several organisms,[298-300] Wnt could be a key TH-target pathway playing a role in mitochondria dependent NSC fate decision.

### 4.5.2 | Lipid metabolism

Glycolytic metabolism favours the production of lipids, essential for cell proliferation, in NSCs and progenitors. During cell commitment to neuronal differentiation, lipid biosynthesis decreases following the expression of *Spot14*.[301] $T_3$ can directly induce *Spot14* expression,[302,303] and could thus be a key element in lipid biosynthesis decrease during cell differentiation. Hence, we can hypothesize that DIO3 in OPCs[19] may prevent a $T_3$-mediated inhibition of lipid production during commitment to the glial lineage.

Myelinating oligodendrocytes also produce an important quantity of lipids to generate myelin. Besides, oligodendrocytes use large amounts of lactate,[304,305] and several studies suggest that oligodendrocyte processes contain less mitochondria than neuronal projections.[306-308] Thus, metabolic differences between lineages initiated during early cell commitment may persist throughout cell maturation, possibly under the influence of TH signalling.

## 5 | CONCLUSION

THs play a central role in governing neurogenesis and gliogenesis in the embryonic, postnatal and adult brain. We have reviewed the evidence that TH components (eg, transporters, carrier proteins, deiodinases and receptors) participate in fine-tuning of cell type-specific regulation of intracellular TH levels. These cellular and molecular TH-dependent mechanisms are largely conserved through vertebrate evolution. In particular, TH signalling favours NSC commitment towards a neuronal fate in adult rodent neurogenic niches, while SVZ-OPC determination requires TH absence. Cell metabolic state also affects NSC proliferation, fate choice and differentiation. Increasing evidence shows that TH signalling triggers fate-specific metabolic changes, involving modifications in mitochondrial activity, mitochondrial dynamics and/or ROS production. More research is needed to explore whether the lower circulating TH levels observed during ageing could be involved in the onset of certain neurodegenerative diseases, known to be associated with important mitochondrial defects. Thus, investigating the role of TH signalling in neuro- and gliogenesis during development as well as in the adult and ageing brain will be critical to fully grasp the underlying cellular and metabolic mechanisms. Each of these basic research areas can generate new findings that could provide a solid foundation for novel therapeutic purposes for neurodegenerative diseases.

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## CONFLICT OF INTEREST

All the authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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