Original Article

MOLECULAR METABOLISM

Adult neural stem cell fate is determined by thyroid hormone activation of mitochondrial metabolism

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ABSTRACT

Objective: In the adult brain, neural stem cells (NSC) located in the subventricular zone (SVZ) produce both neuronal and glial cells. Thyroid hormones (THs) regulate adult NSC differentiation towards a neuronal phenotype, but also have major roles in mitochondrial metabolism. As NSC metabolism relies mainly on glycolysis, whereas mature cells preferentially use oxidative phosphorylation, we studied how THs and mitochondrial metabolism interact on NSC fate determination.

Methods: We used a mitochondrial membrane potential marker *in vivo* to analyze mitochondrial activity in the different cell types in the SVZ of euthyroid and hypothyroid mice. Using primary adult NSC cultures, we analyzed ROS production, SIRT1 expression, and phosphorylation of DRP1 (a mitochondrial fission mediator) as a function of TH availability.

Results: We observed significantly higher mitochondrial activity in cells adopting a neuronal phenotype *in vivo* in euthyroid mice. However, prolonged hypothyroidism (3 weeks) reduced not only neuroblast numbers but also their mitochondrial activity. *In vitro* studies showed that TH availability favored a neuronal phenotype and that blocking mitochondrial respiration abrogated TH-induced neuronal fate determination. DRP1 phosphorylation was preferentially activated in cells within the neuronal lineage and was stimulated by TH availability.

Conclusions: These results indicate that THs favor NSC fate choice toward a neuronal phenotype in the adult mouse SVZ through effects on mitochondrial metabolism.

Keywords Adult neurogenesis; Mitochondrial metabolism; Thyroid hormone; Neural stem cell fate

1. INTRODUCTION

Neurogenesis persists in the brain of adult mammals in two, well-defined niches, the hippocampus and the sub-ventricular zone (SVZ) [1,2]. In both areas, NSCs can differentiate to form neurons or glial cells (oligodendrocytes and astrocytes) [3]. NSCs produce transit amplifying progenitors that predominantly differentiate to neuroblasts, which migrate to the olfactory bulb forming interneurons [4]. Progenitors can also acquire an oligodendroglial phenotype, becoming oligodendrocyte precursor cells (OPCs) that mature to oligodendrocytes (OLs) [5]. Diverse internal and external signals modulate NSC differentiation, with thyroid hormones (THs) having a crucial role in promoting neuroblast determination [6]. Understanding homeostatic controls of neuron/glial cell fate decisions is necessary to address how adult neurogenesis is modified in physiological and pathological conditions.

It is well established that NSCs principally rely on aerobic glycolysis before differentiation, contrasting with mature cells, for which metabolism is mainly based on mitochondrial oxidative phosphorylation (OXPHOS) [7,8]. Though generating less ATP, high glycolysis can provide proliferating cells with increased production of nucleotides and lipids [9]. Hypoxia also contributes to maintaining an undifferentiated state, influencing proliferation and cell-fate commitment [10,11]. In turn, changes in metabolic status influence NSCs pluripotency and differentiation [12,13]. According to energy production needs, mitochondria change shape, number and connections, through mitochondrial biogenesis, fission, and fusion. These processes modulate mitochondrial creation, growth, interconnections, intracellular dissemination, and destruction of damaged mitochondria [14]. Factors enhancing OXPHOS will involve an increase in these processes. Amongst factors regulating mitochondrial dynamics, DRP1 induces mitochondrial fission. When phosphorylated, DRP1 interacts with FIS1

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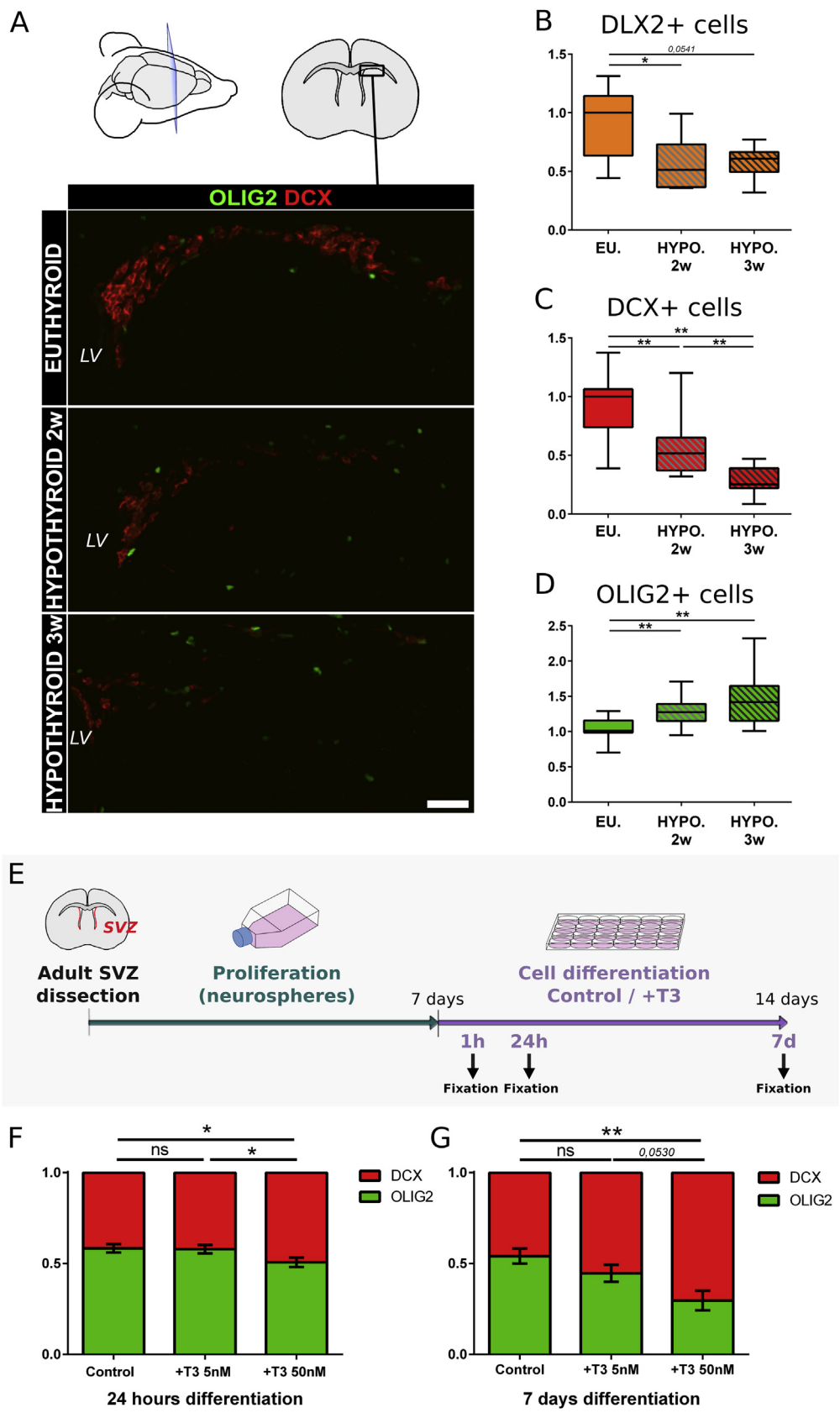

Figure 1: Thyroid hormones favor neuronal over glial fate decision *in vivo* and *in vitro*. (A) Coronal sections of dorsal SVZ in euthyroid versus hypothyroid adult mice (two and three weeks, see materials and methods) treated by IHC (OLIG2, in green and DCX, in red). Representative images. Scale bar: 50 μm. LV: Lateral ventricle. (B–D) Quantification of DLX2+, DCX+ (integrative density) and OLIG2+ cell numbers in the adult SVZ of euthyroid and hypothyroid mice. Four experiments were pooled, n = 12 euthyroid and hypothyroid

