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Metabolism and neurogenesis

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The generation of neurons in the developing and adult mammalian brain by neural stem/progenitor cells (NSPCs) depends on a tight control of NSPC activity and neuronal differentiation that is regulated by a plethora of intrinsic and extrinsic molecular cues. Besides well-studied morphogenic signaling pathways and transcriptional codes that govern the distinct developmental steps from the dividing NSPC to a functional neuron, a critical role of cellular metabolism to determine the functional properties of NSPCs and newborn neurons has been recently identified. Here, we review advances in our understanding of how metabolism affects NSPC behavior and subsequent neuronal differentiation and suggest how metabolism may serve as a common signal integrator to ensure life-long addition of new neurons in the mammalian brain.

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Introduction

The brain is the most complex organ in mammals. The numbers of neural cells, their positioning within brain areas, the subtype specification of neurons, and the connectivity of individual neurons and subregions need to be tightly controlled to ensure the proper functioning of neural circuits [1,2]. During embryonic development dividing neural stem/progenitor cells (NSPCs) generate the vast majority of neurons that will populate the adult mammalian brain. The formation of the central nervous system has been extensively studied and key cellular and molecular principles have been identified that regulate the expansion of NSPCs, the induction of the generation of neurons, and subtype specification of neuronal as well as glial cells [1–3]. Notably, the process of generating neurons, called neurogenesis, does not stop with the end of embryonic and early postnatal development but continues throughout life in distinct regions, such as the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ) [4]. Thus, identifying the mechanisms governing NSPC behavior is not only needed to understand the formation of the brain but is also required to understand the principles of neurogenesis that occurs throughout life in the mammalian brain. Given the complexity of the end product, it is not a surprise that each step during embryonic and adult neurogenesis is regulated by a variety of intrinsic mechanisms and cell-extrinsic cues, for example, regulated through defined transcriptional codes and key morphogenic signaling pathways [1,5,6].

Until recently a core component of each cell, its metabolism, has been largely neglected for the role it may play during neurogenesis. However, it seems quite obvious that cellular metabolism determining for example the cell's energy status will be linked to NSPC activity and neuronal differentiation processes, as cell division and differentiation are associated with an increase in cell volume and biomass production and require substantial amounts of energy for DNA replication and organelle synthesis [7••]. Indeed, extensive analyses of the transcriptomes of distinct NSPC stages as well as transgenesis-based *gain-of-function* and *loss-of-function* studies indicated that distinct metabolic states play a critical role to govern developmental steps in the course of embryonic and adult neurogenesis (e.g., [6,8–11,12••,13•]). Here, we will concisely review recent evidence of how cellular metabolism affects NSPC activity and subsequent neuronal differentiation. Further, we will discuss how metabolism may serve as a molecular hub to integrate a variety of signaling pathways regulating neurogenesis during embryogenesis and in the adult mammalian brain.

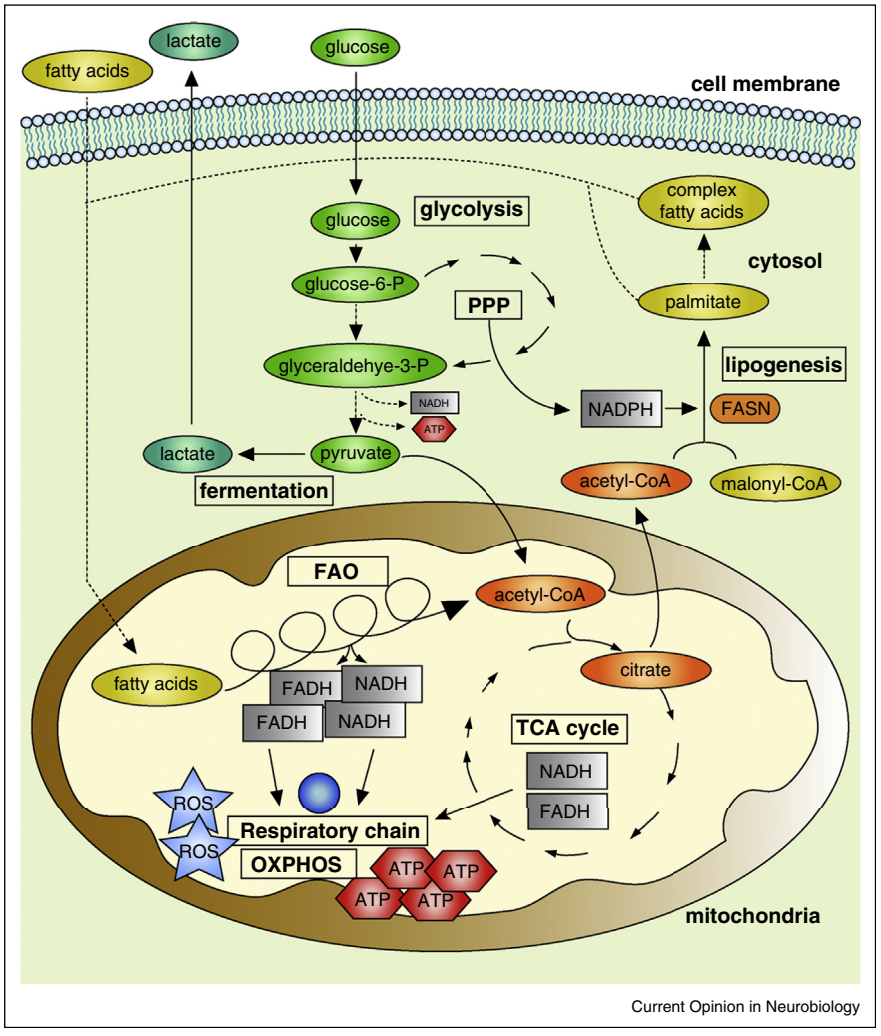
Metabolic control of NSPC activity

To ease understanding, a simplified scheme of the major cellular metabolic pathways is shown in Figure 1.

Lipid metabolism and NSPC activity

Distinct lipid metabolic pathways have been known for many years as the 'lipogenic phenotype' in cancer, providing proliferation and survival advantages [14]. Interestingly, similar lipid metabolic pathways are important for adult neurogenesis [12••]. Proliferating adult NSPCs upregulate the production of lipids through fatty acid synthase (FASN)-dependent *de novo* lipogenesis, and pharmacological or genetic manipulation of this pathway is associated with a drastic reduction in proliferation and neurogenesis, suggesting a crucial role for newly formed lipids in NSPCs [12••]. Further, *de novo* lipogenesis in

Figure 1



A simplified scheme of the major cellular metabolic pathways. Glucose is taken up and metabolized into pyruvate in a process called glycolysis, with a relatively small amount of energy equivalents, adenosine triphosphate (ATP) and reduced nicotinamide adenine dinucleotide (NADH), generated. Pyruvate can be either fermented into lactate, which is subsequently secreted, or can be shuttled into the mitochondria and used in the tricarboxylic acid (TCA) cycle to generate NADH and reduced flavin adenine dinucleotide (FADH) for energy production. In the mitochondrial respiratory chain, the NADH and FADH generated during the TCA cycle are used in a complex process called oxidative phosphorylation (OXPHOS), requiring oxygen (O_2) and resulting in the generation of energy in the form of ATP. As a side product, reactive oxygen species (ROS) can be generated during OXPHOS. NADH and FADH are also generated in large amounts by the breakdown of fatty acids in a process termed fatty acid oxidation (FAO), occurring in mitochondria as well as in peroxisomes (not shown in the scheme). The resulting acetyl-CoA can be fuelled into the TCA cycle for further energy production and as a carbon source or can be exported from mitochondria via citrate for other use. For instance, acetyl-CoA is one of the building blocks for the generation of new lipids (lipogenesis) in a process involving fatty acid synthase (FASN), yielding palmitate, which can be subsequently used to generate more complex fatty acids. The reduced nicotinamide adenine dinucleotide phosphate (NADPH) required for lipogenesis can be generated during the pentose phosphate pathway (PPP), a metabolic pathway parallel to glycolysis.

NSPCs is upregulated with running, a robust enhancer of adult NSPC proliferation, showing a direct influence of a pro-neurogenic stimulus on lipid metabolism in NSPCs [15]. The chronic pharmacological inhibition of FASN abolished the beneficial effects of exercise such as increased proliferation and cognitive enhancement [15], supporting the importance of lipid metabolism to control NSPC activity.

The amount of *de novo* lipogenesis also influences quiescence behavior as the production of new lipids is reduced in quiescent adult NSPCs through the action of a specifically expressed protein called Spot14 regulating the levels of Malonyl-CoA, one of the substrates for FASN [12••]. The dynamic response of Spot14-positive NSPCs to pro-neurogenic and anti-neurogenic stimuli further suggest that NSPCs can alter their lipid metabolism upon