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Nutrient control of neural stem cells

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The physiological status of an organism is able to influence stem cell behaviour to ensure that stem cells meet the needs of the organism during growth, and in response to injury and environmental changes. In particular, the brain is sensitive to metabolic fluctuations. Here we discuss how nutritional status is able to regulate systemic and local insulin/IGF signalling so as to control aspects of neural stem behaviour. Recent results have begun to reveal how systemic signals are relayed to neural stem cells through local interactions with a glial niche. Although much still remains to be discovered, emerging parallels between the regulation of *Drosophila* and mammalian stem cells suggest a conserved mechanism for how the brain responds to changes in nutritional state.

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Introduction

Throughout their lifetimes organisms modulate their physiological state in response to their changing environment. This is achieved by signalling between organs that can sense the environment, and those that are able to respond to changing conditions and thereby maintain an animal's physiology in a stable state ('homeostasis'). For example, to achieve 'energy homeostasis' an animal's energy needs must be closely matched with their food intake and mobilisation of internal energy stores (reviewed in [1,2]).

The brain is affected by changes in energy metabolism

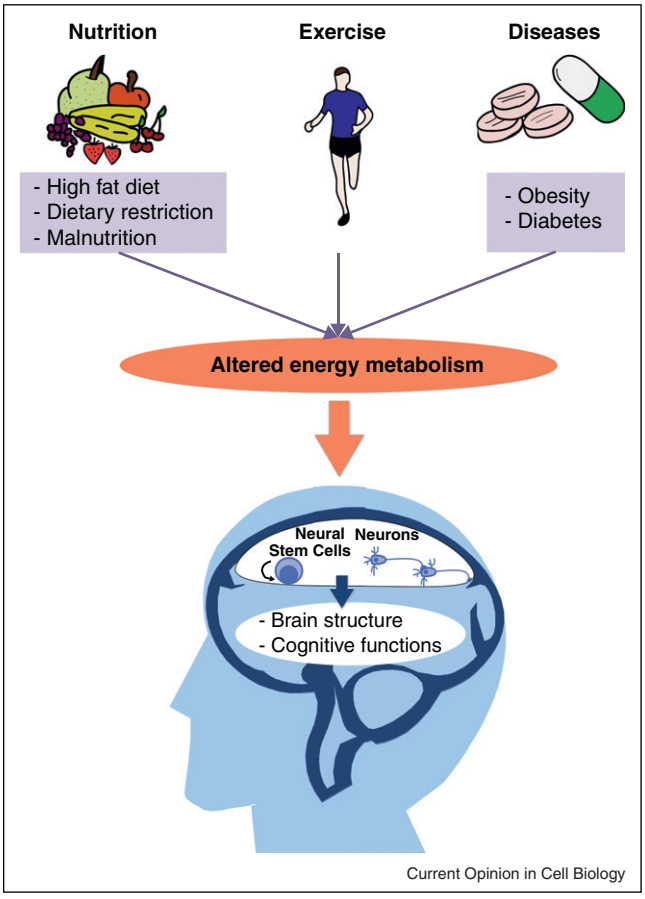
The brain, like other nutrition-sensitive organs such as the liver and the pancreas, can be influenced by changes in metabolic state [3–5] (see Figure 1). Overeating or consumption of a high-fat diet has been shown to impair neurogenesis in the hippocampus of rodents [6,7], while dietary restriction enhances neurogenesis [8,9]. In adult rodents subjected to three months of caloric restriction, newly born neurons in the dentate gyrus, a region of the brain instrumental in memory and learning, show increased survival. Exercise is associated with enhanced cognitive function in humans [10] while in rodents, voluntary exercise promotes neurogenesis and the proliferation of neural stem cells in the hippocampus [11] and is associated with improved performance in various learning tasks [12,13]. On the contrary, diseases that lead to an imbalance in sugar levels, such as diabetes, have been correlated with cognitive decline in humans [14]. Rodent models of diabetes exhibit compromised memory and learning ability [7,15]. The underlying cause of this cognitive impairment may be the reduced neurogenesis observed in these animals [16]. How is the brain able to respond to metabolic changes? What are the mechanisms at work in sensing energy levels? What are the physiological and cellular responses in the brain?

Insulin signalling is sensitive to nutritional status

Insulin and insulin-like growth factors (IGF) are important regulators of growth and metabolism. The insulin/IGF pathway is well conserved from invertebrates to mammals. Insulin/IGFs bind to receptors on the cell surface, which activate the canonical PI3K-Akt signalling cascade (reviewed in [17]). This pathway impinges upon two downstream effectors: i) TOR kinase, which is activated by Akt (and separately by nutrients) and promotes protein translation, and ii) FOXO, a transcription factor that is phosphorylated by Akt and prevented from entering the nucleus.

Dietary restriction leads to reduced levels of circulating insulin/IGF in both invertebrates and vertebrates (reviewed in [18]). Studies carried out both *in vitro* and *in vivo* suggest that insulin/IGF, or at least their well-established downstream effectors, promote neurogenesis through effects on neural stem cell proliferation or differentiation [19–24,25•] and survival [26•]. Recent results suggest a role for IGF-1 in the control of neural stem cell division in mammals [27]. IGF-1 drives proliferation in both the embryo and the adult (reviewed in [28,29]. Similarly loss of PTEN, an antagonist of PI3K, disrupts the homeostatic control of proliferation and increases neural stem cell self-renewal [30], whereas inhibition of the PI3K-Akt pathway reduces DNA synthesis and entry into S-phase. Therefore, insulin signalling plays a key role in translating the general nutritional status of an organism into a signal to which neural stem cells can respond (Figure 2). Systemic regulation thus ensures that

Figure 1



The brain senses and adapts to changes in organismal energy metabolism.
Nutrition, exercise and disease are all factors that can influence energy homeostasis. Changes in energy metabolism influence the behaviour of neural stem cells and their progeny. This can impact brain physiology and function affecting, for example, learning and memory.

stem cells meet the needs of an organism during growth, and in response to changing environmental conditions.

Regulation of neural stem cell quiescence and reactivation by nutritional stimuli

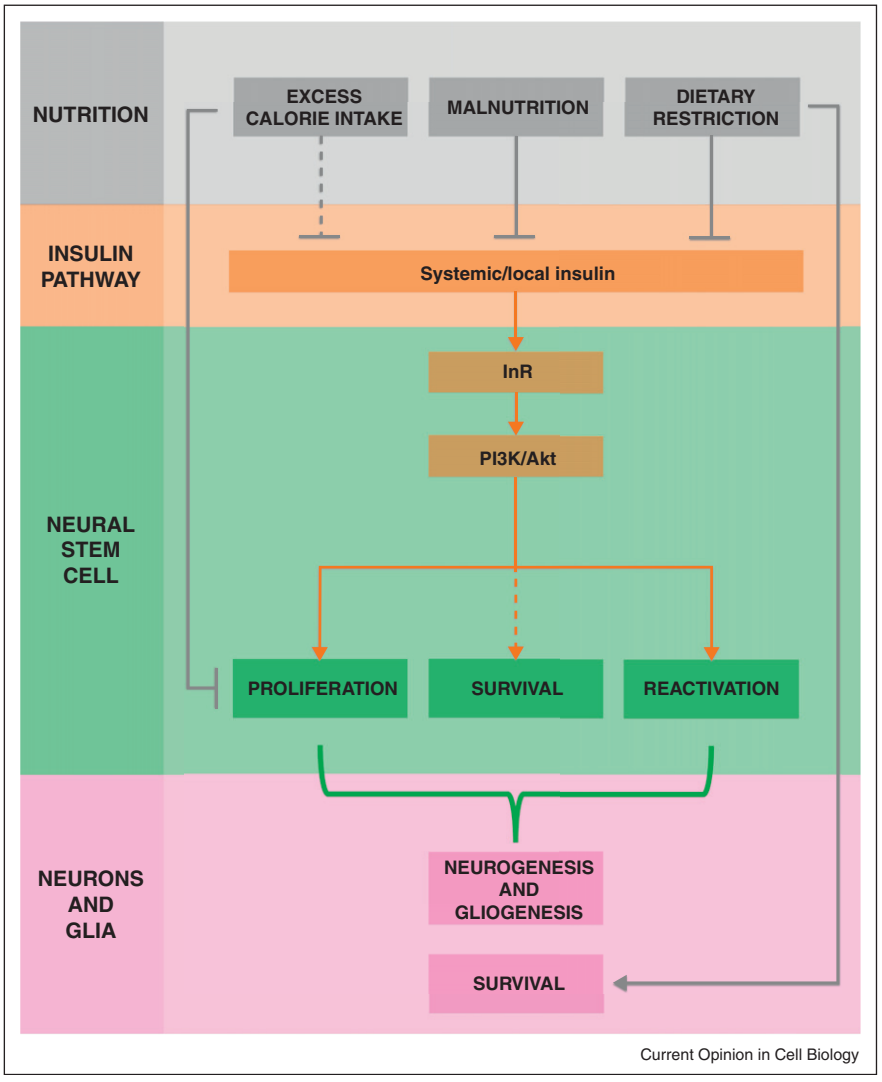
Neural stem cells in the mammalian subventricular zone and hippocampal subgranular zone generate neurons throughout life, alternating between periods of quiescence (a mitotically dormant state) and proliferation [31–34]. An important point of stem cell regulation, therefore, is the decision whether to remain quiescent or to exit quiescence and proliferate. *Drosophila* neural stem cells (or neuroblasts) transit through a period of quiescence separating distinct embryonic and post-embryonic phases of proliferation [35–38]. Britton and Edgar found that the exit from quiescence is physiologically coupled to larval growth and development through a nutritional stimulus transmitted via an organ called the fat body [39]. The fat body acts as a sensor of global amino acid levels linking nutritional state to organismal growth [39,40]. It is able to store both glycogen and fat, and thus serves a similar function to the vertebrate liver and white adipose tissue [1,2] The fat body is thought to emit a signal that acts on the CNS to bring about neuroblast proliferation [39]. This signal, originally called the fat body-derived mitogen (FBDM), initiates cell growth in quiescent neuroblasts, and promotes (or at least permits) cell cycle re-entry. For example, quiescent neuroblasts isolated from starved animals can be induced to reactivate when co-cultured *in vitro* with fat bodies from fed animals, suggesting that fat bodies alone are able to emit the reactivation signal. Blocking the fat body's ability to sense amino acids by mutating the amino acid transporter, Slimfast, or inhibiting TOR causes a systemic decrease in larval growth and a concomitant reduction in neuroblast reactivation [40,41••].

Endocrine and paracrine influences on stem cell reactivation

How do neuroblasts perceive the signal from the fat body and respond to it? What is the link between systemic regulation by the fat body and the local reactivation of neuroblasts? Upon exit from quiescence neuroblasts must first enlarge before proliferation, increasing their diameter nearly two fold before recommencing cell division [38,42••]. Interestingly, in the developing mammalian cortex, neural stem cell exit from quiescence also coincides with an increase in cell size [30,43]. Transcriptome analysis of *Drosophila* nerve cords revealed that expression of the insulin-like peptides, *dILP2* and *dILP6*, parallels stem cell reactivation and that this expression is lost upon amino acid deprivation [44]. The insulin/IGF-like peptides in *Drosophila*, seven in total (for an extensive analysis, see [45]), bind a single receptor (dInR), activating the PI3K-Akt pathway that leads to cellular growth and proliferation (reviewed in [46]). Activation of the insulin/IGF pathway was shown to be essential for neuroblasts to exit quiescence [44,47]. Furthermore, constitutive activation of PI3K-Akt signalling in neuroblasts, drove neuroblast proliferation in the absence of dietary protein, uncoupling neuroblast reactivation from systemic control.

What is the source of insulin/IGF? The *dILP6* promoter was found to drive expression in a set of stellate surface glial cells overlying the neuroblasts, suggesting that these glial cells might be the source of the signal that reactivates neuroblasts [44]. Forced expression of insulin/IGF-like peptides in glia is also able to drive neuroblast proliferation in the absence of dietary protein, whereas disrupting vesicle trafficking in glia reduces neuroblast reactivation [44,47]. Therefore neuroblasts respond to a local, not systemic, source of insulin/IGFs. Exit from quiescence appears to depend upon a nutrient-sensitive signal from the fat body, an organ that acts as a systemic sensor [39]. The nutrient-sensitive TOR signalling pathway in the fat body is required to emit this signal, once amino acids are transported into fat body cells by Slimfast [40,41]. The as

Figure 2



Insulin signalling is a key effector in conveying nutritional status to the brain.
Alterations in nutritional status can lead to the systemic, or local, release of insulin-related factors, which activate the insulin receptor/PI3K/Akt pathway in neural stem cells. Insulin/IGF signalling has been shown to modulate stem cell reactivation, proliferation and differentiation, and possibly also survival. It is noteworthy that the survival of stem cell progeny can also be directly affected by nutritional changes.

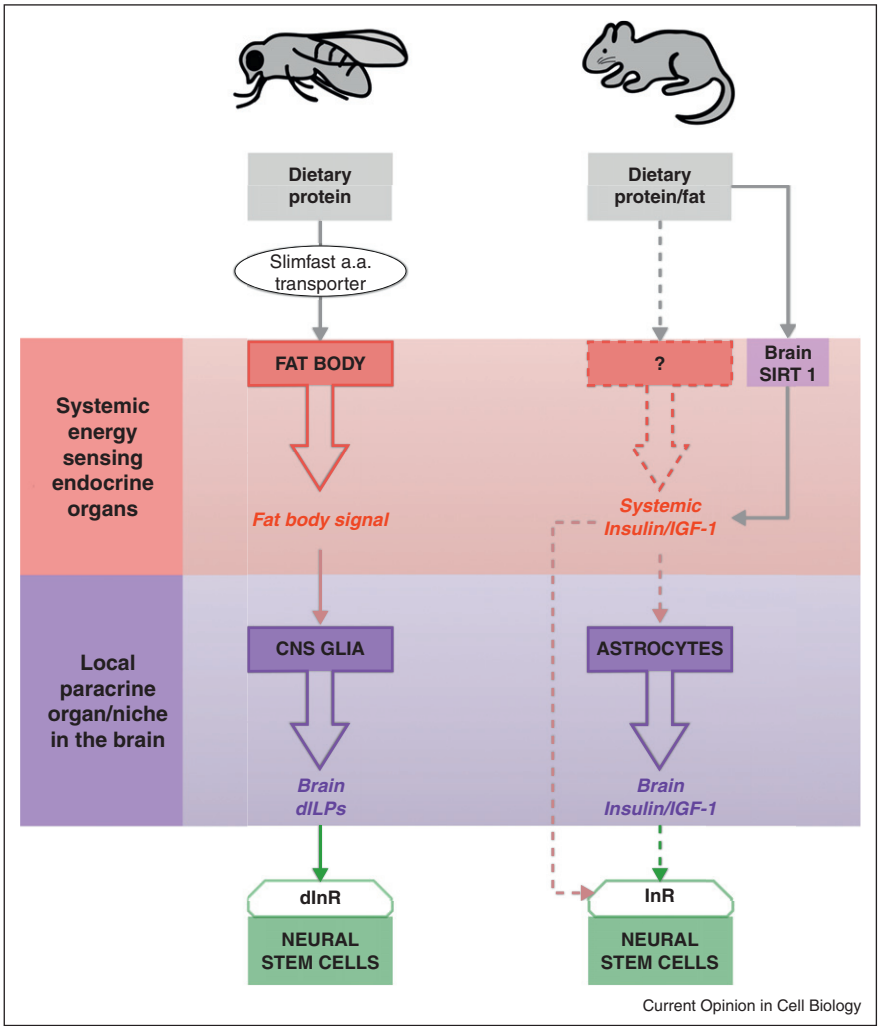
yet unidentified endocrine signal may then be responsible for inducing glial cells to secrete dILPs, a paracrine signal that acts locally on neighbouring neural stem cells. Therefore, in *Drosophila*, the nutritional status of the organism is relayed to the nervous system via a systemic sensor and a local, niche-like, transducer. The nutritional signal ultimately results in induction of the insulin signalling pathway and reactivation of neural stem cells (Figure 3).

Nutrition-responsive glia control neural stem cell reactivation

In mammals, glia form part of the adult neural stem cell niche (reviewed in [48]), and astrocytes are thought to play a key role in regulating neural stem cell proliferation [49]. Astrocytes can promote neural stem cell proliferation *in vitro* [50] and they express the pro-proliferative factors FGF-2 and IGF-1 [51,52]. IGF-1 expression is induced in stellate astrocytes (astroglia) [53,54] in response to CNS injuries, and is believed to account for the rise in neural stem cell division following cortical ischemia [53]. *Drosophila* stellate glial cells, much like mammalian astrocytes, control the proliferation of neural stem cells and exhibit many of the properties that define a niche [44,55].

Do mammalian glia act as a local, paracrine relay for a systemic signal, as has been described in *Drosophila*, or are they able to sense changes in nutrition and metabolic

Figure 3



Nutritional status is translated into neural stem cell behaviour through a cascade of systemic and local relays.
In both vertebrates and invertebrates insulin/IGF signalling appears to be involved in relaying changes in systemic metabolic state to neural stem cells and their progeny.
In *Drosophila*, amino acid levels are sensed by the fat body, the functional equivalent of the vertebrate liver and white adipose tissue, through the amino acid transporter *slimfast*. In response to nutrition the fat body is thought to emit a systemic signal that, directly or indirectly, induces glial cells to secrete insulin-like peptides (dILPs) locally. dILPs bind to the insulin receptor on underlying neural stem cells, activating the insulin/IGF signalling pathway and triggering stem cells to exit quiescence. The identity of the fat body-derived signal and how it affects glial cells remain to be determined.
In mammals, the signalling pathway from nutrition to neural stem cells has not been as extensively characterised. It has been shown that nutritional changes can modulate the levels of systemic insulin/IGF-1 through changes in the levels of histone deacetylase SIRT1 in the brain. In addition, astrocytes can secrete insulin/IGF-1. However, a direct link between the two has yet to be demonstrated.

state directly? In mammals, dietary restriction leads to increased expression in the brain of the histone deacetylase, SIRT1 [56,57]. Conversely, excessive caloric intake resulting from a diet high in fat and sucrose leads to decreased SIRT1 in the hippocampus and cerebral cortex [58]. Thus the protein level of SIRT1 correlates with nutritional status. Interestingly, the decrease in systemic IGF-1 observed in response to dietary restriction is dependent upon increased SIRT1 in the brain [59]. This suggests that the brain itself may be able to sense systemic changes in energy levels, and in turn regulate the levels of insulin/IGF-1. Deciphering the sequence of events between the local expression of SIRT1 in the brain and the systemic release of insulin/IGF1 will be instrumental in understanding the relationship between nutrition and neural stem cells in mammals (Figure 3).

Conclusions

Recent research has advanced our understanding of how organs communicate with one another to coordinate their response to nutritional signals ('integrative physiology'), however much remains to be learned. With respect to the

regulation of neural stem cells in *Drosophila*, the elusive TOR-dependent fat body signal emitted in response to nutrition has yet to be identified. Nor is it known whether this signal acts directly on stellate glial cells, or if it initiates a relay through one or more uncharacterised factors. Finally, it will be of great interest to discover if a similar relay system operates in the mammalian brain and, by identifying the organs and molecules that are involved, to understand how highly conserved are the mechanisms regulating stem cell behaviour in the invertebrate and the mammalian brain.

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