the precision with which tLTD could sculpt barrel map topography.

To determine whether an activated astrocyte could induce LTD independently of pre- or postsynaptic activity, Min and Nevian[4] directly activated astrocytic Ca^{2+} signaling by applying depolarizing pulses to the astrocyte and monitored the effect on synaptic transmission at neighboring L4-to-L2/3 synapses. Surprisingly, they found that direct stimulation of astrocytes elicits LTD, but only if it is combined with stimulation of presynaptic afferents. Notably, this form of LTD is prevented by blocking NMDA receptors and occludes subsequent induction of tLTD, indicating that direct stimulation engages the same mechanisms as tLTD, but only if combined with presynaptic stimulation. Thus, induction of tLTD is dependent on a second level of coincidence detection at the presynaptic terminal: activation of presynaptic NMDA receptors must coincide with presynaptic action potential firing. This second level of coincidence detection is predicted to prevent LTD from occurring at totally quiescent synapses that are contacted by an activated astrocyte (**Fig. 1b**), but leaves open the possibility that heterosynaptic LTD would occur at contacted synapses exhibiting presynaptic action potentials, but without coincident postsynaptic firing (**Fig. 1c**). This possibility is particularly intriguing because the role of presynaptic NMDA receptors in triggering tLTD is lost during development, with adult tLTD requiring only activation of postsynaptic NMDA receptors[11]. If astrocyte activation of presynaptic NMDA receptors does enable broader heterosynaptic tLTD in the developing barrel cortex, then the loss of this mechanism during development may result in more synapse-specific tLTD in adults. Future studies should determine whether heterosynaptic tLTD is more prevalent during development and how such changes affect the functional outcome of tLTD.

In addition to determining the functional effect of the identified presynaptic coincidence requirement, it will be important to determine how coincident activation of presynaptic NMDA receptors and action potential firing are detected and translated into presynaptically expressed tLTD. Ca^{2+} influx through NMDA receptor channels is a classic inducer of plasticity, but what is the downstream effector mechanism and what is the function of presynaptic action potentials? Notably, if developing presynaptic NMDA receptors contain the Mg^{2+}-insensitive NR3A subunit, then the traditional requirement of membrane depolarization to alleviate the Mg^{2+} blockade of Ca^{2+} influx through activated NMDA receptor channels may not function[13].

Min and Nevian's findings[4] highlight yet another important action of astrocytes in the tripartite synapse. Identifying their central function in mediating tLTD in developing somatosensory cortex should substantially facilitate efforts to determine the specific roles and mechanisms of tLTD in establishing cortical topographic maps, a fundamental process in neocortical development and function.

COMPETING FINANCIAL INTERESTS
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Fat incites tanycytes to neurogenesis

Marcelo O Dietrich & Tamas L Horvath

Tanycytes in the hypothalamic median eminence have now been found to form a metabolically sensitive neurogenic niche in the brain. In adult mice, tanycytes give rise to hypothalamic regulatory neurons in response to a high-fat diet.

Hypothalamic circuitries responsible for coordinated energy balance have been the focus of extensive research, driven, at least in part, by a perceived obesity epidemic. Neurogenesis in the hypothalamus has been described previously and its function has been associated with energy balance in adult mice[1,2]. In this issue of *Nature Neuroscience*, Lee *et al.*[3] present evidence that tanycytes in the median eminence form a neurogenic niche in the hypothalamus that is responsive to metabolic cues and that the newly born cells seem to participate in the regulation of energy metabolism.

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Tanycytes are radial glia–like cells located in the walls of the third ventricle[4]. These cells are strategically positioned to respond to factors arising in the periphery owing to their exposure to the bloodstream through the fenestrated capillaries in the median eminence and their exposure to the cerebrospinal fluid in the ventricle[5]. Lee *et al.*'s[3] results, when interpreted together, suggest that tanycytes in the median eminence give rise to neurons that regulate energy balance during postnatal life. These newly born neurons are potentially involved in the metabolic response to high-fat diets and could serve as part of the process that leads to obesity.

Using peripheral injections of BrdU, Lee *et al.*[3] identified the median eminence as a highly neurogenic area relative to other hypothalamic nuclei. The resultant newly born cells were responsive to metabolic stimuli (for example, fasting) and hormonal signaling (for example, leptin). Furthermore, short-term feeding of a high-fat diet was able to stimulate neuronal proliferation in the median eminence in adult mice. Fate-mapping studies confirmed that these new cells arose from β2-tanycytes. Finally, the authors used a newly developed computed tomography–guided focal irradiation technique to ablate neurogenesis in the median eminence. Irradiation of the ventrobasal hypothalamus led to less weight gain and increased energy expenditure and activity in adult mice that were fed a high-fat diet. These data highlight the putative importance of cell proliferation in the ventrobasal hypothalamus as a component of the central regulation of metabolism. These findings are consistent with previously published reports

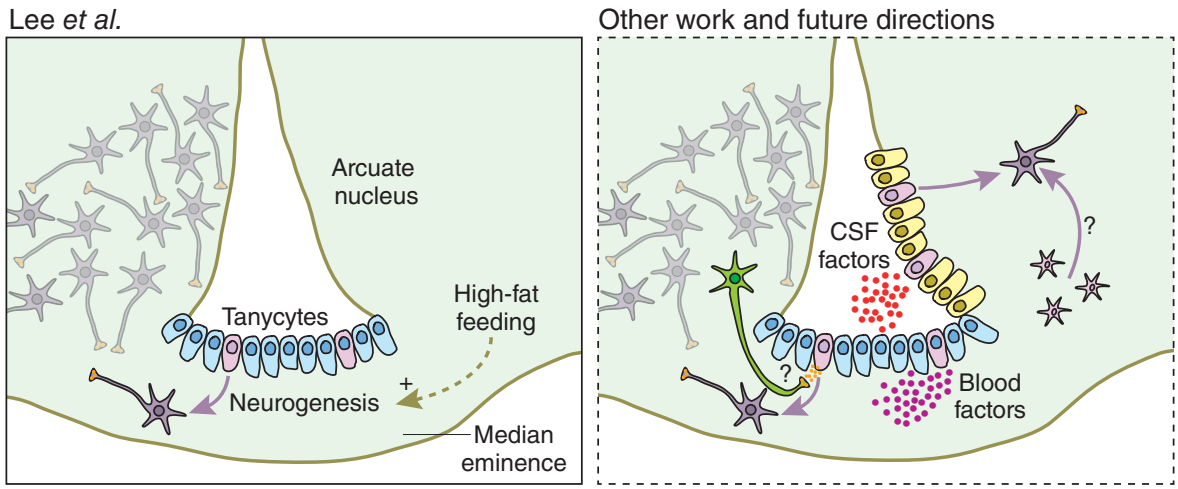

Figure 1 Neurogenic niches in the hypothalamus. Left, Lee *et al.*[3] describe the role of tanycytes (purple) in the median eminence as a proliferative niche in the postnatal brain. These cells give rise to neurons that are responsive to metabolic variations, including high-fat feeding. Blue represents nonproliferative ependymal cells. Right, proliferative tanycytes were known to be present in the median eminence and in the medial part of the third ventricle wall, where these cells are intermingled with ciliated nonproliferative cells (yellow)[7–9]. Ependymal cells are strategically positioned to respond to blood-borne and cerebrospinal fluid (CSF) factors that can lead to changes in neurogenesis in the hypothalamus. An alternative hypothesis is that neurons (green) in the hypothalamus signal the tanycytes to change their proliferative status. Other groups of dividing cells in the hypothalamic parenchyma cannot be excluded as a source of new neurons.

on the effect of pharmacological inhibition of cell proliferation in the brain[1,2].

Neurogenesis in the postnatal brain has been observed in many regions, mainly in the subventricular zone of the lateral ventricle and in the subgranular zone of the dentate gyrus of the hippocampus. Other brain areas also have the capacity for neuronal proliferation. Indeed, multipotent and self-renewing neural progenitor cells have been identified in the hypothalamus[6]. In addition to constitutive proliferation of neural progenitors in the hypothalamus, these stem cells also respond to trophic factors, such as CNTF[2] and IGF-1 (ref. 7). An elegant study identified neural progenitor cells in the hypothalamus that were derived from the ependymal layer of the third ventricle and found that some of these ependymal progenitor cells were tanycytes[8]. The same report presented evidence that these newborn cells form mature neurons that migrate to the hypothalamic parenchyma and form synapses in the network[8].

Differences in the identification of proliferative zones in the brain may occur as a result of varying permeability of peripherally injected BrdU[6,9]. In the study by Lee *et al.*[3], BrdU was injected peripherally and it labeled the median eminence with high specificity with a very low labeling of cells elsewhere in the hypothalamus. However, the median eminence is known to lack a (or have a more permissive) blood-brain barrier[5,10]. This factor needs to be taken into account when considering the kinetics of the median eminence proliferative zone relative to the kinetics in other sites of the hypothalamus[3]. Indeed, other studies have found higher BrdU labeling of the hypothalamus when BrdU is delivered directly into the lateral ventricles than when it is injected peripherally[9]. Thus, other areas in the hypothalamus may also have their own proliferative niches. An extensive study[7] identified two proliferative zones in the wall of the third ventricle in the hypothalamus. The medial portion was highly responsive to growth factors and contained an intermediate architecture with tanycytes and ciliated ependyma being present. In the ventral zone, which is the same area reported by Lee *et al.*[3], these researchers found proliferative tanycytes[7] (**Fig. 1**).

Lee *et al.*[3] did not explore the molecular machinery involved in the tanycytic neurogenesis. In addition, it is not known what signals are important for the differentiation of tanycytes into different subtypes of neuronal or non-neuronal cells. For example, molecular targets that act as metabolic sensors in the hypothalamus could influence the differentiation of β2-tanycytes. One such example is Sirt1, a protein from the sirtuin family that senses the redox state of the cell. Sirt1 in the hypothalamus has been linked to energy metabolism[11], and its activation by mild oxidative conditions leads to decreased proliferation of neural precursors and directs their differentiation toward an astroglial lineage instead of a neuronal lineage[12].

Whether cell proliferation and differentiation in the hypothalamus might be a reasonable target for the treatment of obesity remains to be seen. In addition, tanycytes express type II iodothyronine deiodinase (DII)[13], an enzyme that converts inactive thyroid hormone, thyroxine, to its active form, triiodothyronine, inside the cell. This mechanism is under metabolic control[14]. Thyroid hormone is an important regulator of development and metabolism, and the presence of DII in tanycytes indicates that humoral thyroid hormone may account for the response of these cells to metabolic changes. Lee *et al.*[3] found that short-term high-fat feeding in young adults is sufficient to maintain cellular proliferation and neurogenesis in the median eminence, and ablation of cell proliferation by focal irradiation impairs the metabolic response of these animals to a high-fat diet. It could be that thyroid hormones and other metabolic hormones and metabolites signal the energetic change to tanycytes, leading to the increase in proliferation.

Local signals from neurons in close proximity to tanycytes could also signal to these cells to change their proliferation and differentiation status. Tanycytes and their processes are present in the arcuate neurons, where neurons responsible for coordination of energy balance are located. Tanycytes express glutamate receptors[15] and dopamine-responsive elements[4], indicating that these cells can respond to dynamic changes in local neurotransmitters. It is therefore likely that local changes in neuronal activity regulate the proliferative and differentiation fate of tanycytes in the median eminence. Tanycytes are also a source of trophic factors that may

affect not only neuronal function, but also the differentiation of proliferating cells. Indeed, tanycytes express nerve growth factor[4] and insulin-like growth factor I[4], both of which are involved with neurogenesis elsewhere in the brain.

In summary, the study by Lee *et al.*[3] elaborates on the functional relevance of a neurogenic niche in the median eminence that is controlled by tanycytes in association with metabolic regulation. Because this area of the brain is highly and selectively accessible for signals arising from the periphery, these processes may lend themselves to pharmacological interventions in the development of targeted therapeutic strategies for the treatment of metabolic disorders.

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On the scent of mitochondrial calcium

Frank Zufall

Odorants are now shown to elevate mitochondrial Ca^{2+} in sensory neurons; moreover, blocking this Ca^{2+} sequestration impairs dynamic range. Acute stimulation rapidly recruits mitochondria from the soma to the dendritic knob.

Odor perception begins with the binding of odor molecules to specific G protein–coupled receptors located in the cilia of canonical olfactory sensory neurons (OSNs). This process causes a rise in cyclic AMP that leads to the opening of cAMP-gated, Ca^{2+}-permeable cation channels that, in turn, produce a transient elevation of intracellular Ca^{2+}. Thus, Ca^{2+} signaling is intimately related to odor sensing, and a detailed understanding of the mechanisms underlying Ca^{2+} regulation in OSNs is required for a complete understanding of olfactory function. A study by Fluegge *et al.*[1] in this issue of *Nature Neuroscience* opens a new chapter in this story and shows that mitochondrial Ca^{2+} regulation contributes to this feat.

OSNs provide an excellent experimental model for studying the role of Ca^{2+} in neuronal signal transduction because these cells have a clear-cut function and they exhibit a highly compartmentalized organization (**Fig. 1**). The main electrical events in OSNs include an odor-evoked graded membrane depolarization produced by the ciliary cAMP second messenger cascade, which then spreads down a single dendrite, reaching the OSN soma and its axon, where it is thought to be converted into an action potential sequence. These discharges then travel along the olfactory nerve to the olfactory bulb in the forebrain, where they cause the release of neurotransmitter at the first synapse of the olfactory system. Ca^{2+} signaling probably has important functions in all OSN compartments, but only its function in primary

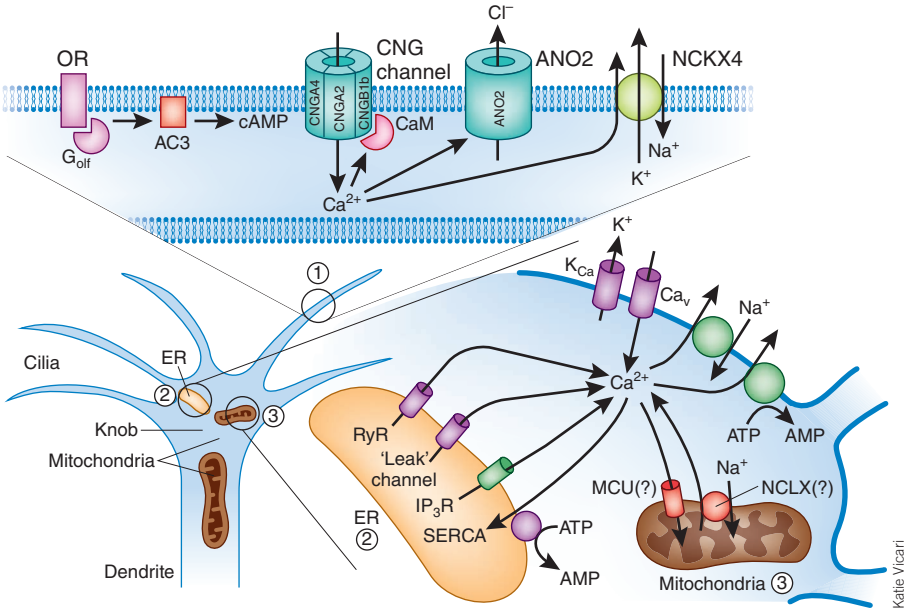

Figure 1 Schematic representation of Ca^{2+} signaling mechanisms in cilia and dendritic knob of an OSN. Much is known about the main Ca^{2+} influx pathway in the cilia (1), the role of Ca^{2+} in primary olfactory signal transduction, and the principal Na^+/Ca^{2+} exchanger (NCKX4) that allows rapid response termination and adaptation of an OSN[2–5,8,11]. Odor-evoked Ca^{2+} signaling in the dendritic knob and dendrite (2) involves additional Ca^{2+} regulation mechanisms, including caffeine-sensitive endoplasmic reticulum (ER) Ca^{2+} stores, Ca^{2+}-induced Ca^{2+} release and voltage-activated (Ca_V) Ca^{2+} channels[13]. However, an entire piece of the puzzle, an essential role of mitochondria (3) in OSN Ca^{2+} regulation, has been missing until now. NCLX, the mitochondrial Na^+/Ca^{2+} antiporter, and MCU, the pore-forming subunit of the mitochondrial Ca^{2+} uptake channel, may participate in mitochondrial Ca^{2+} flux[14], with the caveat that molecular proof of their presence in OSNs is still lacking. AC3, adenylyl cyclase 3; ANO2, Ca^{2+}-activated Cl^- channel; CaM, calmodulin; CNG, cyclic nucleotide gated; G_{olf}, G protein; IP_3R, inositol-1,4,5-trisphosphate receptor; K_{Ca}, Ca^{2+}-activated K^+ channel; OR, odor receptor; RyR, ryanodine receptor; SERCA, sarcoplasmic-endoplasmic reticulum Ca^{2+}-ATPase.

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