Previews

in a culture dish resulted in scaling up of synaptic inputs received by that cell within 1–2 hr. It is unlikely that blocking the spiking of a single cell would have a significant impact on the levels of glutamate in the dish, causing increased TNFα release. Furthermore, this scaling required a decrease in intracellular Ca^{2+} levels.

How do we reconcile these observations with the TNFα model? As with other types of synaptic plasticity, it is probable that there will turn out to be different types of homeostatic plasticity, functioning at different timescales and induced under different conditions (Figure 1). For example, one type of synaptic scaling may result from relatively rapid changes in the spike output of an individual neuron and would serve as a real-time adjustment of the firing rate of individual cells. This type of scaling would rely on cell-autonomous, intracellular mechanisms, such as Arc or CamKIV. Another type of scaling mechanism could be used to detect global changes in the activity of a network of neurons. These global changes would occur over a slower timescale and involve diffusible factors, such as TNFα or BDNF, that would affect multiple cells in the network. It would be advantageous to a neuron to be able to have separate mechanisms that allow it to adjust its own firing rate independently of other neurons, as well as sense the overall state of network excitability. It is interesting to note that the levels of membrane-associated β3 integrins increase within a few hours of TTX exposure but are also sensitive to TNFα, which normally doesn't increase until after 1–2 days of TTX exposure. This means that multiple mechanisms may be able to regulate β3 integrin function, suggesting that integrin signaling could be a point of convergence of these different types of synaptic scaling. Future experiments addressing the functional and mechanistic roles of these other molecules, as well a more detailed understanding of β3 integrin regulation, are likely to allow our knowledge in this field to "scale" new heights.

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Seeing the Light: Insulin Receptors and the CNS

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Although insulin clearly affects brain function, the role of insulin receptor (IR) signaling in the establishment and function of circuits in vivo remains largely unknown. In this issue of *Neuron*, Chiu et al. show a role for IRs in regulating synapse density and dendritic plasticity required for visual responses in *Xenopus*.

Insulin is well known for its critical role in controlling metabolism through the uptake of glucose into cells in most parts of the body—with the notable exception of the brain. Insulin is a peptide hormone, normally secreted by the pancreas in response to increasing levels of blood glucose. Until about 15 years ago, the brain was considered "insulin-insensitive" based on early observations that glucose uptake into CNS neurons is not insulin dependent. However, recent reports suggest that insulin can promote the utilization of glucose in some brain areas (Park, 2001). These observations, combined with the discovery of insulin receptor (IR) expression in the brain (Havrankova et al., 1978), lead to the hypothesis that the brain may be an insulin target. Recently, numerous reports have shown that brain IRs regulate diverse aspects of neuronal development, survival, function, plasticity, and perhaps even cognitive function and aging. Despite these exciting reports, the role of IRs in regulating the establishment and function of neuronal circuits in vivo has remained unknown—until the report by Chiu et al. (2008) in this issue of *Neuron*.

Excitement about the role of insulin in the CNS stems from human studies

showing an effect of systemic insulin on cognitive function. Results from these studies are controversial because of the difficulty in elucidating the direct actions of insulin from hypoglycemic effects. Nevertheless, insulin administration, under conditions that reportedly do not increase blood glucose, facilitates attention and memory (Plum et al., 2005). Conversely, individuals with Type 2 diabetes have a higher risk of learning and memory problems and cognitive decline (Starr and Convit, 2007). Finally, individuals with Alzheimer's disease have reduced brain IR expression and lower CSF insulin concentrations; administration of insulin to these patients improves memory and performance (Zhao et al., 2004).

IRs are irregularly distributed throughout the brain and are present in high levels in several regions, including the hippocampus and cerebral cortex (Schulingkamp et al., 2000). IRs are developmentally regulated, higher during neurogenesis and lower in the adult. At the cellular level, IRs are enriched in neurons relative to glia and are found specifically in synaptosomal membranes (Schulingkamp et al., 2000). Taken together, these results place IRs in the right place at the right time to regulate the initial development as well as the function and plasticity of CNS synapses.

To test the possibility that IR signaling mediates the formation of circuits during brain development, Chiu et al. (2008) blocked IR function in individual neurons of the *Xenopus* tectum and assessed the resulting visual responses in vivo. One of the benefits of using tadpoles as a model system is their translucent bodies that enable manipulation, electrophysiological recording, and visualization of dendritic dynamics in labeled neurons in vivo. The other advantage of this approach is the ability to decrease IR signaling in single neurons, presumably without affecting overall CNS glucose metabolism. Chiu et al. (2008) blocked IR function using a dominant-negative point mutant of the IR (dnIR) and morpholinos to the IR and found that IR signaling is required for normal visual responses in the tectum (Chiu et al., 2008). They then measured AMPAR-mediated EPSCs and found that dnIR expression significantly decreased mEPSC frequency but had no effect on amplitude. Finding no change in release

probability or in the AMPAR/NMDAR ratio, they utilized electron microscopy which revealed a significant decrease in synapse density following dnIR expression.

Based on these results, IRs can now be added to an ever-increasing list of secreted and transmembrane molecules that regulate synaptogenesis (McAllister, 2007). Most of these molecules have been termed "synaptogenic" since they increase synapse density when added to neurons and/or decrease synapse density when removed. Yet, it is important to note that synapse density at any age is the net result of synapse formation and synapse elimination. Thus, a decrease in synapse density caused by dnIR could be the result of decreased synaptogenesis or increased synapse elimination. Because synapse formation and elimination involve completely different molecular mechanisms, it will be important in the future to define which phenomenon is primarily affected by IR signaling to start to determine the molecular mechanisms used by this receptor.

Chiu et al. (2008) also imaged in vivo dendritic arbor growth rates in response to visual stimulation in neurons with decreased IR signaling. Their results suggest that IRs stimulate the growth rate of dendrites and prevent light-induced dendritic plasticity. This effect could occur through activation of members of the RhoGTPase family since the IR substrate 53 (IRSp53) links activated Rac1/Cdc42 to downstream effectors for actin regulation required for structural changes (Choi et al., 2005; Govind et al., 2001). Consistent with this idea, RhoGTPases modulate the effects of visual stimulation on dendritic arbor dynamics in this system (Sin et al., 2002). Dendritic arbor plasticity in response to visual stimulation also requires NMDAR activation (Sin et al., 2002), and chronic NMDAR blockade decreases dendritic arbor elaboration through decreasing dendritic branch stabilization and elongation (Rajan and Cline, 1998; Rajan et al., 1999). If insulin increases NMDAR function in *Xenopus* as it does in the mammalian hippocampus (Zhao et al., 2004), then dnIR expression would be expected to mimic the effects of chronic NMDAR blockade. Despite subtle differences in these manipulations, blockade of IR signaling does prevent light-

induced dendritic plasticity and branch elongation as predicted (Chiu et al., 2008). Whether IRs partner with NMDARs or utilize the same downstream kinase cascades is an important topic for future investigation.

Although insulin is the most compelling candidate to activate IRs in the CNS, insulin-like growth factors (IGFs) are also ligands of IRs, albeit with lower affinity (Kitamura et al., 2003). It will be important in the future to determine if insulin or IGFs are the primary ligands of IRs in the retinotectal system. Presuming that insulin activates at least some of the tectal IRs, it is important to determine the source of insulin. Although neuronal insulin synthesis has been reported, it is currently inconclusive if brain-derived insulin contributes to IR signaling (Woods et al., 2003). Thus, the primary source of brain insulin is thought to be from pancreatic cells. Although the amount of insulin that can cross the blood-brain barrier is controversial, insulin transport into the CNS appears to be increased in the neonatal period (Plum et al., 2005), consistent with the possibility that peripheral insulin levels may influence the formation of circuits in the developing brain.

The Chiu et al. (2008) paper offers exciting new insights into the in vivo role of IR signaling in circuit formation. These results also provide a possible mechanism by which peripheral insulin signaling could modulate cognition and disease. When IR signaling is decreased, such as in Alzheimer's disease, synapse maintenance could be decreased enough to limit experience-dependent plasticity and contribute to the deficits in learning and memory characteristic of these disorders.

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Causes and Consequences of Oscillations in the Cerebellar Cortex

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Cerebellar high-frequency oscillations have been observed for many decades, but their underlying mechanisms have remained enigmatic. In this issue of *Neuron*, two papers indicate that specific intrinsic mechanisms in the cerebellar cortex contribute to the generation of these oscillations. Middleton et al. show that GABA$_A$ receptor activation and nonchemical transmission are required for nicotine-dependent oscillations at 30–80 Hz and 80–160 Hz, respectively, while de Solages et al. provide evidence that recurrent inhibition by Purkinje cells is essential for oscillations around 200 Hz.

The olivocerebellar system and cerebral cortex are strongly connected through reverberating loops that are probably involved in sensorimotor control and cognitive processing (Figure 1A). So far, the vast majority of studies aimed at elucidating the mechanistic causes and functional consequences of the oscillations that occur within these systems have focused on the cerebral cortex (Sejnowski and Paulsen, 2006). Yet, the cerebellum also shows various sorts of oscillatory activities covering both the lower-frequency and the higher-frequency ranges (Table 1). At the lower frequencies these oscillations vary from slowly oscillating complex spike activities of Purkinje cells or slowly bursting activities of granule cells occurring at 2 to 10 Hz (delta band and theta band) to oscillating local field potentials that occur at 10 to 30 Hz (beta band). At the higher frequencies they vary from field oscillations at 30 to 80 Hz (gamma band) or 80 to 160 Hz (high-gamma band or very fast oscillations [VFOs]) to low-amplitude field potentials that oscillate at even higher

frequencies of 160 to 260 Hz (here called very-high-frequency oscillations [VHFOs]). While it is clear that the preferred frequencies of the slowly oscillating complex spike activities and slow theta and beta rhythms originate in the inferior olive and granular layer, respectively (D'Angelo et al., 2001; Courtemanche and Lamarre, 2005; Van Der Giessen et al., 2008), the potential mechanisms that may underlie the high-frequency oscillations in the cerebellar cortex are largely unknown.

In this issue of *Neuron*, Middleton et al. (2008) and de Solages et al. (2008) show that these high-frequency rhythms can be generated without fast glutamatergic inputs to the cerebellum (cf. Cheron et al., 2008). Middleton et al. (2008) show in vitro in both murine and human tissue that one can induce field oscillations at the gamma and high-gamma band in coronal slices of crus I and II following application of physostigmine or nicotine, but not in coronal slices of other cerebellar regions or in sagittal slices in general. Using pharmacological blockage

of GABA$_A$ receptors, these authors suggest that a combined input from GABAergic interneurons and Purkinje cells may be required to generate the gamma field potentials. The VFOs, on the other hand, may specifically require electrotonic coupling within a zonal region; the authors used five different types of gap junction blockers, and all of them affected the power of the VFOs. Moreover, they were able to show (in both molecular layer interneurons and a subset of Purkinje cells) so-called spikelets, which are subthreshold postjunctional potentials that usually reflect prejunctional full action potentials through a coupling mechanism. Combined with dye-coupling experiments, their data thus suggest that at least a subpopulation of Purkinje cells is directly coupled to molecular layer interneurons. Meanwhile, de Solages et al. (2008) investigated the potential mechanism underlying VHFOs. Using tetrode and multisite recordings in vivo, they show that VHFOs can occur in both anesthetized and awake rats and that they are probably largely