2003). It is also worth noting that in the adult brain, neurons and neural stem cells express numerous chemokine receptors in addition to Cxcr4, suggesting that they may be responsive to diverse chemokines whose synthesis is upregulated in the context of neuroinflammatory disease and brain repair (Tran et al., 2004). As a result, chemokines may be involved in regulating the migration of neural stem/progenitor cells during adult neurogenesis as well, thereby recapitulating events observed during embryogenesis. Furthermore, the expression of chemokine receptors by mature neurons in the adult nervous system may act as a conduit for decoding the effects of the diseased, inflamed brain on neuronal activity as well as on neuronal death and survival. Thus, chemokine signaling may be of great importance in the nervous system from its early development until its ultimate demise.

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Inactivity Sets XL Synapses in Motion

Neurons adapt their synaptic responses to the activity of the underlying network. In this issue of *Neuron*, Thiagarajan and colleagues report on specific subcellular mechanisms of homeostasis after prolonged neuronal inactivity. The results have important implications not only for neuronal homeostasis but also for further understanding of metaplasticity.

A remarkable property of most excitatory synapses in the central nervous system is their ability to undergo activity-dependent long-lasting changes in synaptic strength. In this context, phenomena like long-term potentiation (LTP) and long-term depression (LTD) have been most intensively studied as cellular models for learning and memory (Malenka and Bear, 2004). However, nonsupervised Hebbian forms of plasticity tend to run out of balance and consequently lead to unstable neuronal networks. This quandary is referred to as the "plasticity-stability dilemma." Thus, a mechanism is needed that maintains an appropriate level of total excitation within a network but still allows Hebbian plasticity to occur.

Theoretical and experimental work suggest that sliding plasticity-induction thresholds (BCM model), synaptic redistribution, and spike-timing-dependent plasticity might help to overcome some of these problems (Abbott and Nelson, 2000). Recent studies have also found homeostatic mechanisms to be of importance for synaptic gain control (Burrone and Murthy, 2003; Turrigiano et al., 1998). First, work on the neuromuscular junction suggested that synapses respond to prolonged inactivity or hyperactivity with up- or downregulation of synaptic inputs, respectively. Furthermore, data on spinal and cortical neurons demonstrated that alterations in overall network activity rescale synapses in a multiplicative or fractional manner (Turrigiano and Nelson, 2004). Such mechanisms allow cells to balance between inhibition and excitation and thereby prevent hyper- or hypoexcitability of the network. Little is known, however, about the detailed subcellular mechanisms underlying the principles of neuronal homeostasis.

In this issue of *Neuron*, Thiagarajan et al. (2005) have performed in vitro measurements on hippocampal pyramidal neurons with an extensive repertoire of experimental tools to study induction and expression mechanisms of homeostasis in response to chronic network inactivity. Their first set of experiments confirmed earlier results (Thiagarajan et al., 2002) that prolonged blockade of AMPARs (with NBQX) increases synaptic strength by enhancing both amplitude and frequency of miniature EPSCs (mEPSCs). The authors then had a closer look at the mEPSCs kinetics and uncovered a quickening of the decay of synaptic events. Because synaptic kinetics can be determined by receptor channel subtypes, the altered time constant suggested a change in AMPAR-subunit composition after chronic synaptic inactivity. Indeed, acute application of philantotoxin, a specific blocker of Ca^{2+}-permeable, GluR1-containing AMPARs (but not Ca^{2+}-impermeable AMPARs containing GluR2), reversed all the effects seen with NBQX incubation. How does prolonged AMPAR blockade then lead to all the above described changes in synaptic properties?

Most Hebbian forms of plasticity like LTP and LTD require the activation of postsynaptic N-methyl-D-aspartate (NMDA) receptors and subsequent Ca^{2+} entry (Malenka and Bear, 2004). Thiagarajan et al. tested this

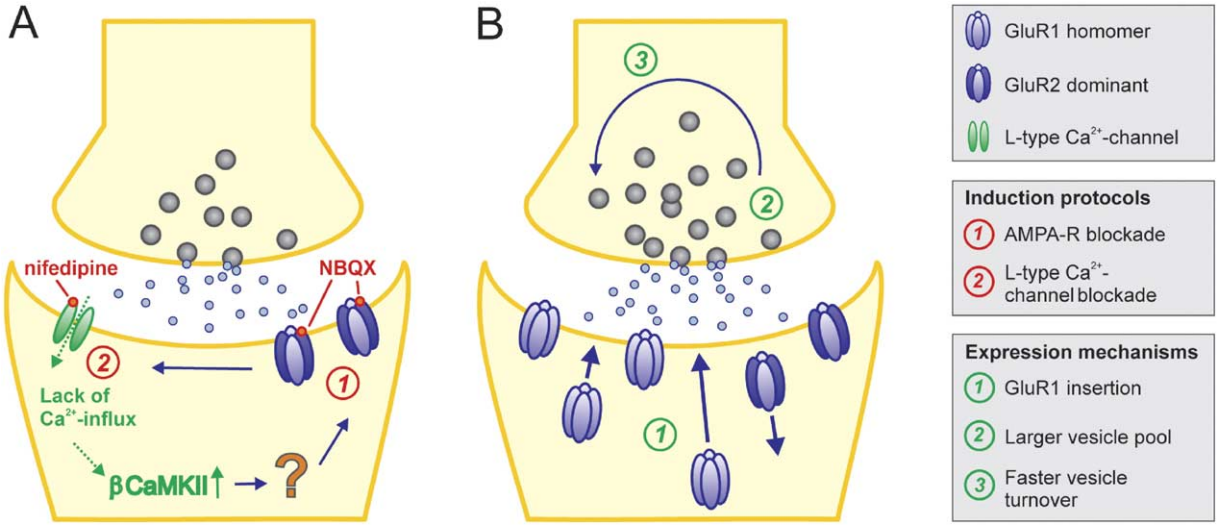

Figure 1. Induction and Expression Mechanisms of Synaptic Adaptation to Neuronal Inactivity

(A) Chronic network inactivity induced by blockade of AMPARs leads to blockade of L-type Ca^{2+} channels and a lack of postsynaptic Ca^{2+} influx. This reduction in Ca^{2+} level potentially acts on βCaMKII (compare Thiagarajan et al., 2002), which then triggers a yet unknown signaling cascade.

(B) Adaptation to reduced neuronal activity is expressed via pre- and postsynaptic mechanisms: At the postsynapse, GluR1-homomers are inserted and also replace GluR2-containing AMPARs. The presynaptic vesicle pool is both enlarged and shows an increased turnover rate.

pathway but could not find a role for NMDARs in this particular form of homeostasis. The authors then investigated other potential sources of Ca^{2+} influx and indeed chronic blockade of L-type Ca^{2+} channels not only mimicked but also occluded all the effects of AMPAR antagonism, thereby suggesting a shared pathway (Figure 1A). This finding is notable because conventionally an increase in and not the lack of Ca^{2+} influx is the key signaling element.

Further illuminating the expression mechanisms (Figure 1B), Western blot analysis indicated an upregulation of GluR1-protein levels, but not GluR2, thus confirming the philantothoxin results on mini-EPSC amplitude and kinetics. Triple stainings for synapsin, activity-dependent uptake of synaptotagmin, and GluR1 homomers suggest that homomeric GluR1-containing AMPARs are preferentially added to already existing, large synapses rather than being incorporated into new and/or previously silent synapses. Finally, there also seems to be a small but significant degree of direct swapping of GluR1 for GluR2 subunits. An additional presynaptic element in the expression of homeostasis was indicated by the electrophysiological measurements. These could be substantiated by monitoring presynaptic vesicle cycling: The authors performed internalization measurements of an antibody for the luminal epitope of the vesicle protein synaptotagmin, which revealed an increase in the exocytosis-endocytosis rate after NBQX treatment. Beside the increased vesicle turnover rate, an upregulation of the vesicle pool was also reported, thereby adding to the changes in presynaptic properties in response to chronic network inactivity.

In summary, the work by Thiagarajan et al. comprehensively describes novel aspects of the subcellular mechanisms underlying homeostasis. Their model is appealing and straightforward with chronic blockade of AMPARs leading to a loss of postsynaptic Ca^{2+} influx via L-type Ca^{2+} channels and thereby adding GluR1-containing AMPARs to already existing synapses. The postsynaptic alterations are accompanied by presynaptic changes in vesicle pool size and turnover rate.

As is often the case with new provocative findings, the reader's initial excitement triggers plenty of related questions. To start right at the beginning of the cascade, what might be the downstream players after the loss of Ca^{2+} influx, which then lead to the change in postsynaptic receptor composition? It will be of interest to investigate whether homeostatic mechanisms share signal transduction pathways with other plasticity phenomena like LTD and/or LTP. There is good evidence that the calcium/calmodulin-dependent protein kinase II (CaMKII) is required for NMDAR-dependent forms of LTP, and likewise, the same group has found a role for the β-isoform of CaMKII in homeostasis (Thiagarajan et al., 2002). Obviously, synaptic homeostasis and plasticity manifest themselves on strikingly different timescales, and it is yet unclear how a lack of Ca^{2+} influx might lead to altered gene expression.

The next question is related to the locus of expression mechanism and is of profound significance not only for the curiosity and publication record of scientists but also functionally for the synapse (Abbott and Nelson, 2000): Postsynaptic expression, for example, the insertion of new receptors (Bredt and Nicoll, 2003), causes a uniform increase in synaptic efficacy, whereas presynaptic alterations redistribute the available synaptic efficacy and thereby represent a mechanism to change the content of signals conveyed between neurons. In the present study, it is reported that post- and presynaptic function are altered in a coordinated way, dominated by changes at the largest (XL) synapses. The simplest model involves first a postsynaptic loss of

Ca^{2+} influx, causing insertion of new GluR1-containing AMPARs into the postsynapse after which unidentified subsequent events adapt the presynaptic elements. However, such a model is in contrast to recent findings in other systems in which pre- or postsynaptic modifications had been described (for review see Burrone and Murthy, 2003). The discrepancy may be due to differences in developmental stages, the type of neurons investigated (e.g., cortex versus hippocampus), and the specific interventions used.

To further complicate this issue, here, acute application of philantotoxin not only changed mini-EPSC amplitude and kinetics but also the frequency of minis to control levels. In classical terms, a change in mEPSC frequency is interpreted as a sole alteration at the presynaptic element, but we now know that pure postsynaptic modifications can also change the frequency of detected mini events. Well aware of the caveat of such an interpretation, the authors argue that postsynaptic modifications (e.g., AMPAR insertion) can only explain a small part of the NBQX-induced increase in mini frequency. Therefore, one might speculate that philantotoxin has direct effects at the presynaptic terminal (unlikely, because controls are not changed), that acute application of philantotoxin antagonizes the release of a retrograde messenger, or that the toxin preferentially mutes XL synapses, the most GluR1-rich and presynaptically active synapses. Further experiments will hopefully help to differentiate between these different models.

Another important issue is whether the observed effects are developmentally regulated. Interestingly, a recent paper showed that the silencing of individual neurons within a neuronal network caused bidirectional effects dependent on the developmental stage of the network (Burrone et al., 2002). When activity was reduced before synapse formation, a competitive loss of synaptic inputs to the silenced neuron occurred, whereas a homeostatic increase in synaptic input could be seen when activity was lowered after most synapses had already formed.

Last but not least, the finding that synaptic inactivity provokes the insertion of GluR1 homomers has direct implications for metaplasticity. Metaplasticity generally describes modulatory changes that modify the ability of synapses to undergo subsequent episodes of plasticity. Evidently, insertion of GluR1-containing AMPARs introduces a new source for Ca^{2+} entry and may thereby alter the threshold for any after plasticity events (Abraham and Tate, 1997; Jia et al., 1996). An experimental proof for this hypothesis should be on the agenda of inquisitive neuroscientists in the near future.

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