of benzodiazepines in this population over the past 10 years[15]. The need for additional research, both basic and clinical, is apparent. Regardless, whether in mouse or in man, if you're a teenager, there is good reason to be anxious, and perhaps those raging hormones should be welcomed as a beneficial governor.

COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests

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Synapses go nucle(ol)ar

Joel D Richter & Justin R Fallon

Jordan and colleagues report that activity causes the shuttling of a synaptic protein AIDA-1d from dendritic spines to the nucleus. This work sheds light on how nuclear protein synthesis is regulated in response to synaptic activity.

The formation of long-term memories requires protein synthesis that is trigged by synaptic activity[1]. This activity-regulated synthesis has drawn considerable interest, as it holds clues for understanding both the mechanisms of enduring synaptic modification and how their derangement can result in neurological diseases such as Fragile X and Rett syndrome[2,3]. Some of these new proteins are made locally from mRNAs resident in dendrites and synaptic spines[4,5], whereas others are derived from fresh mRNAs transcribed in response to synaptic activity[6]. However, we know relatively little about how events at the synapse are reported back to the nucleus[7], and how nuclear protein synthesis is regulated by activity at the dendrites. In this issue, Jordan and colleagues[8] report progress on both of these fronts. They show that activity results in the shuttling of a synaptic protein, EB-1/AIDA-1d, to the nucleus. Surprisingly, once there, AIDA-1d does not head for the transcriptional machinery, but rather is targeted to Cajal bodies and the nucleolus, where it seems likely that it regulates ribosome biogenesis and perhaps RNA dynamics.

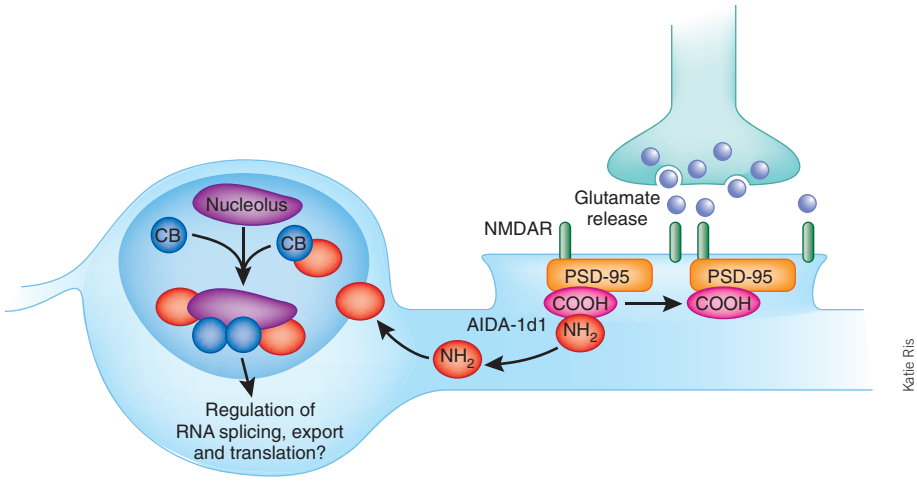

Figure 1 AIDA-1, a PSD component, is cleaved into amino and carboxy portions following NMDA receptor activation. While the carboxy portion remains anchored to the PSD, the amino portion is transported to the nucleus, where it associates with Cajal bodies (CB) and causes them to become juxtaposed to the nucleolus. This rearrangement of subnuclear organelles may regulate RNA metabolism such as splicing, nuclear export or translation.

The story begins with a proteomic analysis of postsynaptic density (PSD) fractions. Of the >450 polypeptides identified, the authors focused on AIDA-1d, which harbors nuclear localization sequences. The presence of this signature in a PSD protein suggested that AIDA-1d could function both at synapses and in the nucleus. Biochemical characterization lent further support to such a dual role. AIDA-1d associates with PSD-95, a major synaptic scaffolding protein that also binds glutamatergic NMDA receptors. AIDA-1d (or a piece of it—more on that below) is also present in nuclear fractions.

Are synaptic and nuclear AIDA-1d functionally related, and does activity regulate their interplay? A nice series of cell biological experiments showed that GFP-tagged AIDA-1d accumulated at synapses in cultured neurons, but was found in relatively few nuclei. However, when the neurons were stimulated with KCl or NMDA, the tagged AIDA-1d became localized to the nucleus (**Fig. 1**). Two features of this translocation pathway are notable. First, although AIDA-1d translocation depends on NMDAR activation, neither intra- nor extracellular calcium appears to be required. This calcium independence suggests that an unusual signaling pathway may be at work. Second, only the amino-terminal half of AIDA-1d translocates to the nucleus: the carboxyl-terminal portion is retained in the PSD fractions. Therefore, NMDAR activation must be linked in some way to AIDA-1d proteolytic processing.

The most intriguing feature of AIDA-1d is where it goes once it gets to the nucleus. In 1903 Santiago Ramon y Cajal described a novel subnuclear structure now known

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as Cajal bodies[9]. This element is important in ribosomal RNA modification and RNA splicing. Cajal bodies are most easily detected by immunostaining for the protein coilin. They have also drawn attention because they harbor the survival of motor neuron (SMN) protein, mutations in which cause spinal muscular atrophy. Cajal bodies are often closely associated with nucleoli, which are sites of ribosomal DNA transcription and pre-ribosome assembly. However, the 700 or so proteins that comprise the nucleolus suggest that these organelles have more complex functions. Indeed, nucleoli are also places where mRNA editing by the adenosine deaminase enzyme ADAR occurs, where the chromosome end-lengthening telomerase ribonucleoprotein enzyme is stored in normal but not cancerous cells, and where the biogenesis of the signal recognition particle, the molecular assemblage that mediates the transfer of certain nascent polypeptides into the endoplasmic reticulum, takes place.

What could nucleolar and Cajal body localization signify for neurons and the circuits in which they participate? At this point, it is too early to say for sure—for example, the localization of endogenous AIDA-1d in either cultured cells or in the brain has yet to be visualized. However, from the known roles of these subnuclear structures, we can speculate on a number of potentially important functions. Jordan and colleagues tested one predicted outcome: the regulation of the protein synthetic capacity of the cell. Because nucleoli and Cajal bodies are important for ribosome biogenesis, regulating their number could affect the capacity of the cell to synthesize protein. Indeed, siRNA knockdown of AIDA-1d results in a modest decline in the levels of total protein synthesis observed following prolonged blockade of inhibitory synapses. Another potential action could be to charge newly made mRNAs onto ribosome-containing ribonucleoprotein particles destined for transport to the dendrites and synapse[10]. Such mechanisms could act in concert with signals that regulate transcription or could be independent of them. One outcome of such transport could be to tune the protein synthetic capacity of the cell to particular states. Indeed, the current report shows that nucleolar number and organization is a function of neuronal maturation as well as levels of synaptic excitation.

Finally, one could imagine that synaptic signaling to nucleoli, Cajal bodies and other subnuclear structures involved in RNA metabolism could also have a more selective role in orchestrating the synaptodendritic proteome. For example, mRNA editing, which occurs in these subnuclear elements, is important in generating neuronal-specific forms of key synaptic proteins, including ion channels and components of the vesicular trafficking machinery[11]. Neuronal activity can also regulate alternative splicing of NMDA receptor–subunit mRNAs[12]. Thus, synaptic signaling to these nuclear epicenters of the RNA world could have far-reaching consequences for information processing and storage in neurons.

COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests.

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It's about time for thalamocortical circuits

Court Hull & Massimo Scanziani

The timing of thalamocortical excitation and inhibition is critical to local microcircuits. Two new papers shed light on the development and performance of a somatosensory microcircuit that regulates the integration of thalamic inputs.

The timing of sensory stimuli is a fundamental parameter used by the neocortex to construct representations of the external world. In the somatosensory system, the timing of cortical spikes can accurately follow the pattern of stimuli generated while touching an object[1]. This temporal precision is likely to be essential for proper tactile discrimination. To enforce precise timing, the cortex uses a simple circuit that is activated by thalamic afferents[2]. These thalamocortical afferents provide the main input to the somatosensory cortex and form excitatory, glutamatergic synapses onto a subset of cortical neurons. In this issue, two papers examine the development and function of a microcircuit activated by thalamocortical afferents. Daw *et al.* show that the ontogeny of this thalamocortical microcircuit involves a set of rapid, coordinated steps that transform it into a precise coincidence detector[3]. Once the circuit is mature, Cruikshank and colleagues demonstrate that it relies on divergent kinetics and strength of excitation from thalamocortical afferents for reliable performance[4].

Upon entering the cortex, individual thalamocortical afferents contact both excitatory projection neurons (glutamatergic principal cells) and local inhibitory interneurons (GABAergic cells). Thus, somatosensory information is immediately distributed to both excitatory and inhibitory cells. Surprisingly though, thalamocortical synapses onto inhibitory interneurons are much stronger than those onto excitatory principal cells[2,5,6]. By contacting both inhibitory and excitatory cells, thalamocortical afferents lay the foundation for a simple disynaptic circuit that provides powerful, local feedforward inhibition (**Fig. 1**).

In the somatosensory cortex, thalamocortical afferents initiate feedforward inhibition by activating so-called fast-spiking interneurons, a subtype of GABAergic interneuron. Because these fast-spiking interneurons synapse onto the same excitatory principal cells that are directly contacted by thalamocortical afferents, thalamic activity results in both excitation and inhibition of cortical principal cells.

Because excitation is direct, whereas inhibition is delayed by one synapse, disynaptic feedforward inhibition lags

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