sponse of the atmosphere-ocean circulation during times of low continental ice volume is particularly difficult to model. During the warm period at 55 Ma, high-latitude temperatures increased substantially (>10°C), but tropical temperatures may have been almost constant or even slightly lower than today (*19*). [This interpretation has been challenged, however, on the grounds of possible diagenetic alteration of the oxygen isotope temperature signal (*20*).] A similar explanation could apply to the mid-Mesozoic discrepancies discussed by Veizer *et al.* Such altered zonal gradients are often attributed to increased ocean heat transport, but to our knowledge, no coupled climate model simulations have ever produced the observed patterns.

The first-order agreement between the CO_2 record and continental glaciation continues to support the conclusion that CO_2 has played an important role in long-term climate change. The Veizer *et al.* data, if correct, could be considered a Phanerozoic extension of a possible dilemma long known for the early and mid-Cenozoic.

To weigh the merits of the CO_2 paradigm, it may be necessary to expand the scope of climate modeling. For factors responsible for the presence or absence of continental ice, the CO_2 model works very well. In contrast, there are substantial gaps in our understanding of how climate models distribute heat on the planet in response to CO_2 changes on tectonic time scales. Given the need for better confidence in some of the paleoclimate data and unanticipated complications arising from altered tectonic boundary conditions, it may be hazardous to infer that existing discrepancies between models and data cloud interpretations of future anthropogenic greenhouse gas projections.

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PERSPECTIVES: NEUROSCIENCE

Unwrapping Glial Cells from the Synapse: What Lies Inside?

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The central nervous system houses two main kinds of cells—neurons, which move information around the brain in the form of electrical signals, and glia, which until relatively recently have been considered to fulfill only a supportive role. However, an exciting possibility is emerging—the major type of glia, the astrocyte, seems actually to be required for synapse formation and maintenance, and for synaptic efficacy (*1*, *2*).

The long, thin processes of astrocytes ensheathe the synaptic connections between neurons and are therefore well positioned anatomically to contribute to synaptic transmission. Furthermore, these glial cells express a wide variety of neurotransmitter receptors and voltage-gated ion channels, which are important in receiving and integrating neuronal signals (*3*). Two reports in this issue of *Science* by Iino *et al.* on page 926 (*4*) and Oliet *et al.* on page 923 (*5*) use two different animal models and experimental approaches to illuminate astrocytic participation in the workings of the synapse.

Glutamate receptors called AMPA receptors, triggered by the neurotransmitter glutamate, mediate the majority of fast synaptic transmission in the central nervous system (CNS). These receptors are formed by combinations of glutamate receptor subunits, GluR1 through GluR4 (*6*). The GluR2 subunit is of particular functional importance because it confers Ca^{2+} impermeability on the AMPA receptor complex. About a decade ago, soon after the AMPA receptor subunits were cloned, Kettenmann's and Sakmann's laboratories reported that Bergmann glial cells (cerebellar astrocytes) did not express GluR2 and hence their AMPA receptors are Ca^{2+}-permeable (*7*, *8*). Since this discovery, the physiological function of Ca^{2+}-permeable receptors in Bergmann glia has remained a mystery.

The study by Iino *et al.* (*4*) provides the first piece of evidence for a functional role of these receptors. They demonstrate that AMPA receptor–mediated Ca^{2+} influx is important in generating and maintaining the appropriate structural and functional association between the neuronal elements of glutamatergic synapses in the cerebellum and Bergmann glia. They focus on synapses that have been well studied both from a neurocentric as well as a gliocentric perspective.

Parallel fiber and climbing fiber terminals establish synaptic contacts with Purkinje cell dendrites in the cerebellar cortex. Bergmann glia become part of these functional units by extending processes whose thin membrane sheets wrap around these synapses. Glutamate released at these synapses activates both AMPA receptors on Purkinje cells and Bergmann glia, and glutamate transporters on the glia. These thin processes of the Bergmann glia define anatomical and functional three-dimensional compartments termed microdomains near and around the synapse, which define the area of functional interaction of the neurons and glia (*9*). Stimulation of cerebellar synapses between parallel fibers and Purkinje cell neurons leads to an AMPA receptor–mediated increase in the intracellular Ca^{2+} concentration in Bergmann glia.

Iino *et al.* (*4*) modified the molecular composition of AMPA receptors in the Bergmann glia by infecting Purkinje cells with a recombinant adenovirus containing the coding region of the GluR2 gene. As expected, the virally induced introduction of GluR2 into Bergman glia led to the expression of AMPA receptors that display Ca^{2+} impermeability. Conse-

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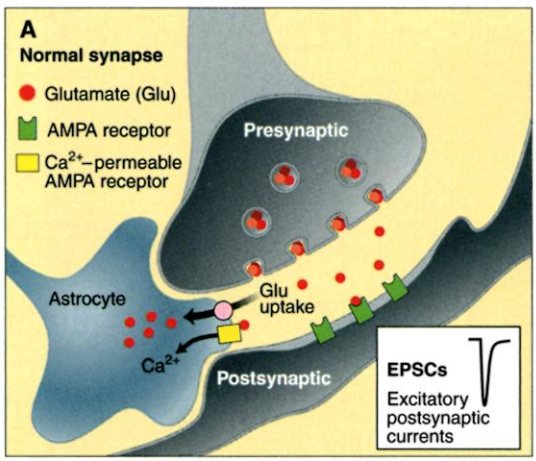
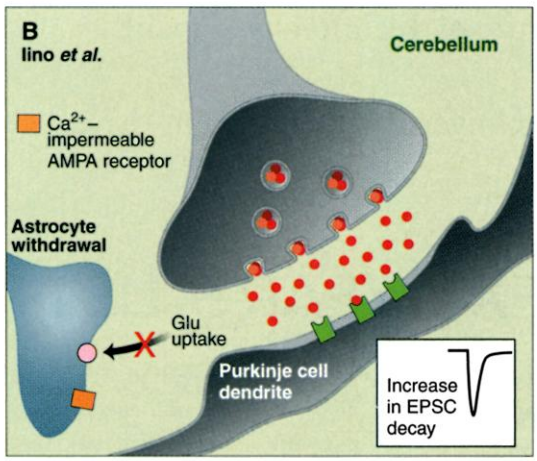
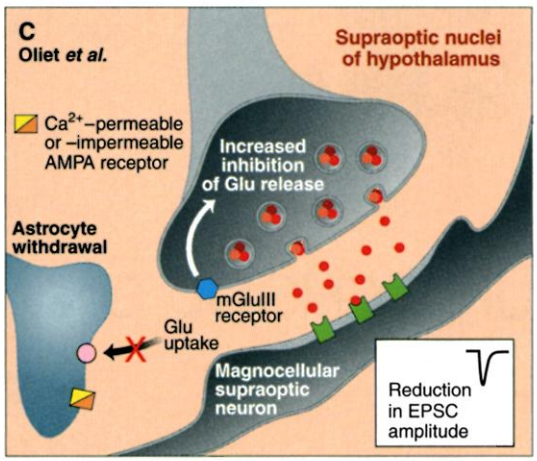
quently, unexpected anatomical and morphological modifications were observed. Bergmann glia retracted their fine, morphologically complex processes from the synapses on Purkinje cell dendrites to form less-complex structures. In addition, the Purkinje cells, now stripped of their glial processes, showed increased innervation by the climbing fibers.

The authors hypothesize that glutamate released from neurons triggers an AMPA receptor–mediated Ca^{2+} signal that is necessary to maintain the partnership between Bermann glia and the synaptic elements, and to regulate innervation of Purkinje cells by climbing fibers. This might be a developmental neuronal-glial signal (*11*), because multiple innervation of Purkinje cells by climbing fibers is detected early in postnatal development, but not in the adult (*12*).

The physiological function of glial cells in neuronal signaling is further investigated by Oliet *et al.* (*5*), who examine the role of astrocytic glutamate uptake mechanisms in regulating excitatory synaptic transmission. A key role of astrocytes is the clearance from the synaptic cleft of neurotransmitters that have been released from neurons (*10*). This process is central in terminating the effects of released neurotransmitters, increasing the temporal resolution of information transfer, preventing excitotoxicity, and ensuring input specificity by limiting cross talk between synapses. Without this transmitter clearance, the kinetics of the excitatory postsynaptic currents (EPSCs) are slower, because removal of glutamate from the synaptic cleft is delayed.







Glial cells—a third element within the synapse. (**A**) The processes of glia are intimately associated with the neuronal elements of the synapse (pre- and postsynaptic neuronal structures), where they can easily participate in neuronal signaling. (**B**) The molecular mechanisms that underlie the formation of these tripartite synapses are largely unknown, although an AMPA receptor–mediated Ca^{2+} influx into the glia is required to maintain the functional connection between astrocytes and the synapse (*4*). (**C**) As described in (*5*), lactation-induced withdrawal of astrocytic processes from supraoptic nuclei in the hypothalamus leads to an increase in the group III mGluR-mediated inhibition of glutamate release, and thus an inhibition of the evoked EPSC.

The authors take advantage of a previously characterized morphological plasticity of the supraoptic nuclei of the hypothalamus, in which the close association between astrocytic processes and synapses is severely compromised in lactating rats as compared with that seen in virgin or postlactating rats. By exploiting this anatomical modification, they demonstrate that the absence of astrocytic glutamate uptake in lactating rats leads to a reduction of the evoked EPSC amplitude in magnocellular supraoptic neurons. From the results of a series of pharmacological manipulations, they attribute this decrease to an enhanced activation of presynaptic inhibitory group III metabotropic glutamate (mGlu) receptors. This increased activation is due primarily to a less-efficient removal of glutamate from the synaptic cleft by the uptake protein, GLT-1, found exclusively in astrocytes.

As discussed above, the clearance of glutamate from the synaptic cleft by glia is important in influencing the kinetic profile of the postsynaptic receptor–mediated currents (*4*). Oliet *et al.* (*5*) reveal an additional role for glutamate uptake by astrocytes in synaptic transmission—fine-tuning the existing tonic presynaptic mechanisms that serve to modulate release. Together, the two studies elegantly demonstrate the importance of astrocytic uptake in shaping the synaptic transmission between neuronal cells.

A complex functional integration between astrocytes and neurons is emerging which suggests that defining signal processing in the CNS as a purely neuronal phenomenon may be an oversimplification. It is becoming evident that, in response to neuronally released glutamate, astrocytes can themselves release glutamate. Such a mechanism causes feedback onto both pre- and postsynaptic elements to modify transmission (*3*). Thus, in any given synapse, various aspects of the interplay between neurons and glia contribute to signaling within the CNS. Future studies that further integrate the functions of glial glutamate uptake and release will lead to a more complete understanding of the role that these cells play in synaptic activity.

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