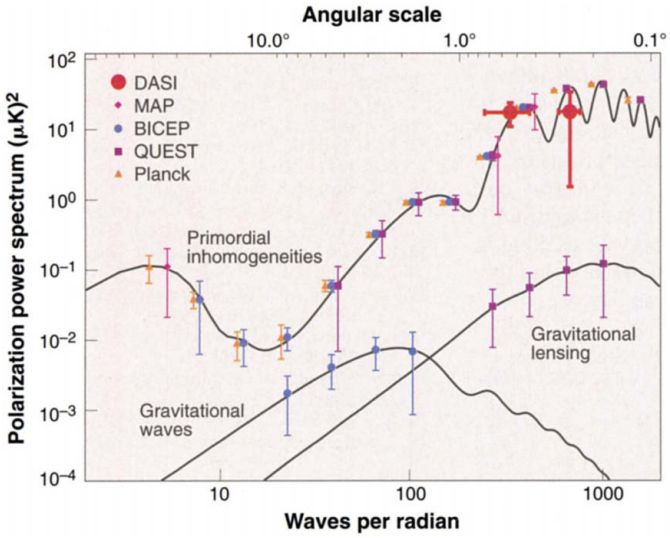

Current and future polarization data. The polarization power spectrum determines the correlation of polarization over patches of sizes indicated on the top axis. (Top curve) Prediction for the polarization from primordial inhomogeneities produced by inflation. The large-angle bump in this curve is the enhancement from early star formation. (Lower curves) Inflationary gravitational-wave and gravitational-lensing signals. These can be distinguished from the larger mass-inhomogeneity signal with geometric properties of the polarization. DASI data points are shown in red. Future experiments will go beyond DASI in sensitivity to detect some of these other signals. We show the data points that experimentalists hope to achieve with some of these new experiments (*17*).

The current DASI results (see the figure) are not nearly precise enough to test these predictions fully, but they are a dramatic first step. They detect the polarization with high confidence (5σ), and the measured amplitude is consistent with that expected.

Far more will be learned with more precise polarization maps. First, the polarization will provide much more precise velocity maps because it is due primarily to the velocity at the surface of last scatter. In contrast, the temperature pattern is due to a combination of the mass inhomogeneity and velocity. Second, the polarization will provide a test for inflation theories, which predict a unique polarization pattern (*12*, *13*). Third, polarization might map the mass distribution in the more recent universe through the effects of weak gravitational lensing (*14*). The galaxies between us and the surface from which the CMB radiation was emitted induce a gravitational bending of light that leads to an identifiable distortion to the CMB polarization pattern. Finally, polarization with large coherence patches is generated by rescattering of CMB radiation from intergalactic debris produced by the onset of star formation.

DASI has ended a 34-year quest to detect the CMB polarization, sounding the starting gun for a new race to peer further back in time, with more precision than ever before. Many more CMB polarization experiments are in progress or planned. NASA's recently launched Microwave Anisotropy Probe (MAP) (*15*) should detect the large-angle polarization induced by early star formation. This should be followed by increasingly precise ground and balloon experiments leading to launch of the European Space Agency's Planck satellite (*16*) in 2007. If the recent past is any indication, studies of the CMB will continue to advance cosmology, even after Planck.

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PERSPECTIVES: NEUROSCIENCE

GABA Becomes Exciting

Rüdiger Köhling

Epilepsy is one of the most common neurological diseases, affecting 1 to 2% of the world's population (*1*). It is caused by a state of neuronal hyperexcitability, or more precisely, by massive hypersynchronous discharges from large numbers of neurons in the brain (*2*). Numerous studies have sought to unravel the mechanisms underlying epileptic seizures. Despite a consensus view that voltage-gated ion channels controlling cell excitability and synaptic processes responsible for communication among neurons are involved (*3*), the specific events leading up to epileptic discharges are largely unknown. On page 1418 of this issue, Cohen *et al.* (*4*) shed light on the underlying causes of epileptic seizures with their in vitro study of brain tissue from 21 patients with temporal lobe epilepsy. Their findings suggest that interneurons producing the inhibitory neurotransmitter GABA together with aberrantly behaving excitatory pyramidal neurons in the hippocampal region can precipitate epileptic seizures.

Pharmacological interventions for the treatment of epilepsy rely principally on drugs that reduce cellular excitability (for example, by blocking voltage-gated channels) or that modulate synaptic communication, usually by enhancing the activity of inhibitory GABA receptors. However, a dampening of intrinsic neuronal activity or a restriction of synaptic communication may impinge upon the normal functioning of the brain, resulting in unacceptable side effects. Thus, it is critical that therapeutic interventions be targeted to specific neuronal subpopulations, such as "pacemaker" neurons that initiate spontaneous discharges, or to a particular subtype of excitatory or inhibitory synapse. In this context, two important questions must be addressed: Are there distinct neuronal populations that initiate epileptic discharges? And if so, what type of synapse coordinates synchronization of these discharges?

Three principal factors are thought to contribute to the initiation of epileptic discharges. The first is a population of excitatory neurons with the ability to generate so-called intrinsic bursts, that is, barrages of action potentials. The second is an increase in glutamatergic (excitatory) synaptic transmission particularly via recurrent connections; the third is a decrease in the efficacy of GABA-mediated (inhibitory) connections (*2*, *3*). It has been proposed that an "imbalance" between excitatory and inhibitory synaptic transmission that

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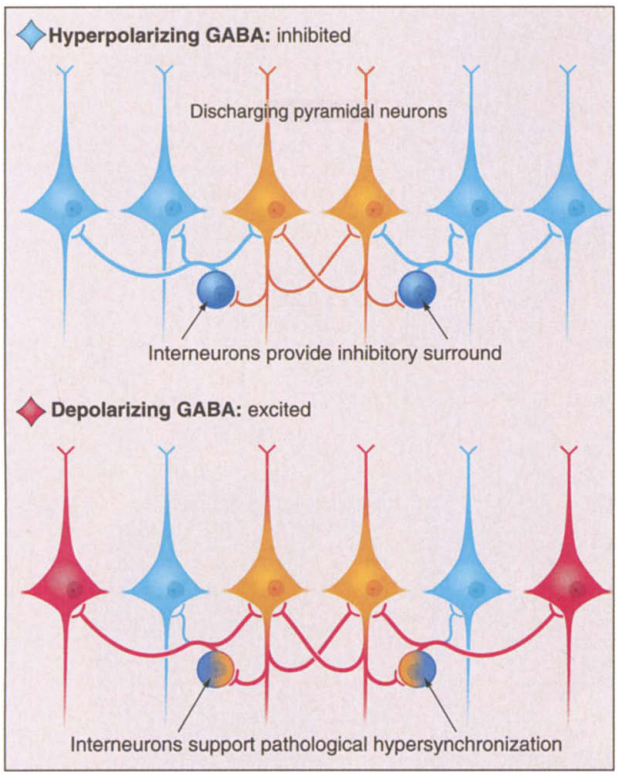
favors excitation leads to the initiation of epileptic discharges. In this respect, a subpopulation of neurons called interneurons that release GABA are thought to create an inhibitory shield around the excitable neurons that form the focus of the epileptic seizure (see the figure).

The "imbalance" theory of epileptogenesis has been challenged by the finding that GABA does not always inhibit neuronal activity. Although in the adult brain GABA usually induces hyperpolarization of neuronal membranes (which decreases neuronal excitability), in the juvenile brain GABA is depolarizing, that is, it brings the neuronal membrane closer to the firing threshold, often enabling action potentials to be triggered (*5*). In addition, the "imbalance" theory of epileptogenesis has been challenged by the discovery that petit mal (absence) epileptic seizures depend on the interplay between excitatory and inhibitory neurons in the thalamus and cortex (*3*, *6*), such that GABA or GABA-enhancing compounds can promote epileptic discharges. This is also the case in some animal models (*7*–*9*) where GABA has been found to have depolarizing activity. Thus, the depolarizing actions of GABA are seen not only in early brain development, but also in the adult brain. As in juvenile tissue, GABA-induced depolarizations in adult tissue can have dual effects: both inhibitory (short-circuiting the neuronal membrane) and excitatory. When GABA is excitatory, it promotes synchronous neuronal discharges and so can be proepileptic. Earlier reports suggested that a proepileptic role for GABA may underlie not only petit mal seizures but also focal seizures. Indeed, the spontaneous activity recorded in brain slices of human epileptic hippocampus and neocortex in vitro depends on GABAergic transmission (*10*, *11*). Collectively, however, these reports do not identify GABA's depolarizing activity or, more importantly, the specific subpopulations of neurons displaying this property.



GABA—friend or foe? (**Top**) In response to the inhibitory neurotransmitter GABA released by interneurons (blue circles), the membranes of excitatory pyramidal neurons in the subiculum of the hippocampal region usually become hyperpolarized (blue trapezoids). The GABAergic interneurons forming synapses with pyramidal neurons provide an inhibitory shield that surrounds and blocks off subpopulations of epileptically active pyramidal cells (brown trapezoids). (**Bottom**) Sometimes, the GABA released by interneurons (blue-brown circles) has excitatory effects on aberrantly behaving pyramidal neurons, depolarizing them and lowering their threshold for firing action potentials. In this case, interneurons switch behavior and recruit some pyramidal cells (red) into pathologically synchronous activity.

This challenge has been undertaken by Cohen *et al.* (*4*). They pinpoint a subpopulation of excitatory pyramidal neurons displaying depolarizing GABA responses in the subicular zone of the brain's hippocampal region as the likely pacemaker neurons that initiate epileptic discharges. These investigators prepared brain slices from the hippocampal region of temporal lobe epilepsy patients who had undergone surgery to alleviate their symptoms. Multielectrode recordings from these brain slices revealed spontaneous field potential discharges (synchronous activity of neuronal subpopulations), which closely resembled the discharges seen on the electroencephalograms of these patients. Cohen *et al.* discovered that these discharges started in the subiculum, a major output pathway of the hippocampus that projects to the temporal cortex. They observed that initiation sites within this region could change, indicating that there was no specific, structurally defined pacemaker population. Their principal finding was that these discharges are dependent on GABAergic synaptic transmission. Even more important, although most excitatory pyramidal neurons in the subiculum merely showed hyperpolarizing events, some fired bursts of action potentials in synchrony with interneurons before or during the discharges. Interestingly, the GABA released by interneurons was only depolarizing for this subgroup of pyramidal neurons. These results suggest that it is the interplay between pyramidal neurons depolarized by GABA and interneurons that initiates epileptic activity. Thus, aberrantly behaving excitatory pyramidal neurons in which GABA triggers a depolarizing response impose a dual role on GABA-releasing interneurons. On the one hand, when connected to "normal" pyramidal cells, interneurons provide a protective inhibitory shield around excitatory neurons, and on the other hand, they support pathological synchronization when connected to pyramidal cells responding aberrantly to GABA with depolarization and excitation (see the figure).

These findings open up several exciting possibilities for further exploration. Are the depolarizing effects of GABA linked to the low expression of the neuron-specific K^+/Cl^- cotransporter KCC2 in pyramidal neurons? This transporter protein supports a gradient of Cl^- ions across the membrane, which enables Cl^- ions to flow into neurons and hyperpolarize them when GABA receptors are activated. A decrease in expression of KCC2 has been reported during early rodent brain development (*12*) and, perhaps more importantly, in the adult brain tissue of an animal model of epilepsy (*13*). How does this decrease relate to seizure activity? Are there specific subpopulations of interneurons that depolarize the "aberrant" pyramidal neurons? Do these pyramidal neurons express a particular subtype of GABA receptor that could be targeted by specific drugs? Answering these questions might ultimately lead to the development of more specific, and hence more effective, antiepileptic therapeutics.

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