Inhibition and Epilepsy

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Recurrence of paroxysmal neurological and/or behavioral manifestations, commonly termed seizures, is the hallmark of epilepsy. Epileptic seizures are generally considered hyperexcitable phenomena resulting from a chronic imbalance between excitatory and inhibitory events. Hence, since GABA is the major inhibitory transmitter in the CNS, impairment of GABA function should lead to seizures, while enhancing its efficacy may exert an anticonvulsant action. Reviews of the role played by GABA in seizure generation and epileptogenesis have appeared in the last few years (3, 23).

Today, it is well established that postsynaptic activation of GABA\textsubscript{A} receptors mediates fast inhibition caused by a Cl\textsuperscript{−} conductance, while GABA\textsubscript{B} receptor activation leads to a relatively slow form of inhibition due to a G-protein-linked, increase in K\textsuperscript{+} conductance (Figure 1A). In both cases GABA acts by increasing the membrane conductance for ions that have an equilibrium potential near or more negative than the resting membrane potential. In this way neurons hyperpolarize, thus preventing action potential firing. GABA\textsubscript{B} (and perhaps GABA\textsubscript{A}) receptors are also found on the nerve endings of cortical neurons where they inhibit transmitter release by reducing Ca\textsuperscript{2+} entry. When they are localized at excitatory terminals, activation of GABA\textsubscript{B} receptors inhibits glutamate release and thus the overall effect is a decrease in excitation (Figure 1B). However, when they are situated at inhibitory terminals (these receptors are also known as autoreceptors) their activation causes a decreased release of GABA (Figure 1C), which may in turn result in neuronal network excitation.
The oldest demonstration of a relation between GABA and seizures rests on the occurrence of convulsions in infants fed with a formula accidentally made deficient in pyridoxine during processing (17). Pyridoxine, known also as vitamin B6, is the coenzyme for the formation of GABA from glutamic acid by means of the enzyme glutamic acid decarboxylase (GAD). Several studies have later confirmed that substances capable of interfering with GABA synthesis, release or postsynaptic effects cause convulsions in vivo or epileptiform synchronization in vitro. Moreover, weakening and/or blockade of GABA-mediated inhibition have been reported to occur shortly before the onset of seizure activity in several animal models of epileptiform discharge both in vivo and in vitro (3).

The relevance of these data within the context of chronic epileptic disorders remains debatable. In fact most of this evidence has been obtained in normal brains subjected to 'acute' manipulations. Some studies have shown that particular types of cortical (neocortex and hippocampus)
GABAergic cells are not damaged in animal models of mesial temporal lobe epilepsy and in epileptic patients (14). However, other authors have observed a loss of GABAergic neurons and axon terminals in human sclerotic epileptic hippocampus, being basket cells and chandelier cells two of the interneuronal types affected (1). It has been also reported that decreased inhibitory control within the epileptic limbic system results from the functional disconnection of interneurons from excitatory inputs (11, 27, 29). Functional changes in inhibitory mechanisms in patients with mesial temporal lobe epilepsy may also relate to deficits in GABA transporter function (30) or alterations in GABA_A receptor subunit composition (13, 18, 24). Indeed, GABA_A receptor function in the dentate gyrus of epileptic animals is altered by Zn^{2+} (6, 7). This represents an interesting mechanism as the reorganized mossy fibers in the dentate gyrus contain this metal.

Emerging evidence indicates that GABA may promote epileptiform synchronization. For instance, GABA receptor-mediated inhibition can facilitate the thalamocortical processes leading to the occurrence of generalized spike and wave discharges that occur during absence seizures in primary generalized epilepsy. The synchronous activity generated by thalamocortical relay cells is regulated by the inhibitory inputs that originate from neurons of the thalamic nucleus reticularis (9, 15). These inputs elicit both fast GABA_A and slow GABA_B receptor-mediated hyperpolarizing IPSPs that cause rebound action potential bursts in thalamocortical relay neurons, thanks to de-inactivation of a T-type Ca^{2+} current. The thalamocortical volleys in turn excite cortical cells that re-excite nucleus reticularis neurons via corticothalamic connections. Hence, hypersynchrony within the thalamocorticothalamic loop can be insured through GABA receptor-mediated mechanisms that re-configure the thalamocortical network operation into patterns of activity characteristic of spike and wave discharge. Data obtained from slices obtained from beta_3 knockout mice has confirmed that the excitability of nucleus reticularis neurons modulates thalamocortical oscillatory synchrony (16). Moreover, intraperitoneal injection of GABA mimetics induces a dose-dependent increase in the duration of the spike and wave discharges in several genetic models of absence seizures (10, 12, 21). Early studies performed in the model of feline generalized penicillin epilepsy have also indicated that GABA_A receptor-mediated potentials are still operant in neocortical cells that participate in spike and wave discharges (5).

GABA_A receptor-activated channels can also depolarize cortical neurons. Indeed, GABA_A-mediated depolarizations can be recorded following intense synaptic activation or during application of 4-aminopyridine, and they often result from the activation of GABA_A receptors located on dendrites (Figure 2). This might imply that [Cl^-]_i in the dendrites of cortical neurons is much higher than in the soma, where hyperpolarizations are recorded. However, GABA_A receptor-mediated depolarizations also occur because GABA_A receptor-activated channels can become permeable to HCO_3^-, an anion with equilibrium potential more positive than Cl^- (19, 28). GABA_A receptor-mediated depolarizing postsynaptic responses are also contributed by an increase in [K+]_o that may be largely dependent on the HCO_3^- conductance (4). Moreover, intense synaptic activation of GABA_A receptors in the adult hippocampus leads to Ca^{2+} neuronal uptake through the activation of voltage-gated Ca^{2+} channels by the HCO_3^- dependent depolarization (2). GABA_A receptor-mediated depolarizations have been recorded in the guinea-pig hippocampus from inhibitory interneurons of the dentate hilus where they contribute to interneuron synchronization (22).
Figure 2: GABA-mediated long-lasting depolarizations (asterisks) generated by a hippocampal neuron during application of low concentrations of the K⁺ channel blocker 4-aminopyridine (Control) in response to stratum (s.) radiatum stimulation or spontaneously, but not following alvear stimuli. Note that the long-lasting depolarizations are preceded by an early (GABAＡ-receptor-mediated) hyperpolarizing potential and followed by a long-lasting (GABAＢ-receptor-mediated) hyperpolarization. Local application of bicuculline methiodide (BMI) to the apical dendrites causes a selective depression of both evoked and spontaneous long-lasting depolarizations whereas the antidromic recurrent IPSP is still recorded. From Avoli 2000.

Activation of GABAＡ receptors leading to elevation in [K⁺]₀ can paradoxically initiate ictal activity in the CA3 area of the young rat hippocampus (Figure 3A) and in the adult rat or mouse entorhinal cortex (Figure 3B).
Figure 3: GABA-mediated synchronization leads to the onset of epileptiform discharge during application of 4-aminopyridine. A: Simultaneous field potential (Field) and intracellular (Intra) recordings performed in the CA3 area of a 22-day-old rat. The onset of the ictal discharge is illustrated at an expanded time base to show details of the initial GABA-mediated potential and subsequent ictal discharge. B: Simultaneous field potential (Field) and \([K^+]_o\) recordings performed in the adult rat entorhinal cortex show the occurrence of spontaneous negative potentials that are associated with increases in \([K^+]_o\) (a). In b, an ictal discharge is initiated by a negative-going potential. Note that \([K^+]_o\) increases during this negative potential (arrow) and attains values that are larger than those associated with the isolated negative-going potentials. From Avoli 2000.

Hence, GABA receptor-mediated synchronization may serve as a powerful implement for the initiation of epileptiform activity. It is well known that increasing \([K^+]_o\) induces a positive shift of GABA-mediated postsynaptic inhibition, depolarizes neurons and disinhibits excitatory postsynaptic interaction. The facilitatory effects of GABA receptor mechanisms in implementing ictal discharges is supported by the ability of pharmacological procedures that interfere with GABAergic transmission (e.g. activation of \(\mu\)-opioid receptors causing interneuron hyperpolarization and thus a decreased GABA release) to abolish GABA-mediated synchronous potentials along with the ictal-like discharges (Figure 4).
Figure 4: Pharmacological demonstration of the role played by the synchronous GABA-mediated potential in the initiation of ictal discharges in juvenile hippocampus (A) and in the adult entorhinal cortex (B). A: Activation of μ-opioid receptors by DAGO ([D-Ala₂,N-Me-Phe⁴,Gly-ol⁵]enkephalin), which abolishes GABA release from interneuron terminals, blocks both GABA-mediated field potentials and ictal discharges recorded with field potential and [K⁺]₀ recordings during application of 4-aminopyridine in the CA3 subfield of a hippocampal slice obtained from a young rat hippocampus. From ref 63. B: Similar effects are seen during DAGO application to a combined hippocampal-entorhinal cortex slice that was also treated with 4-aminopyridine. In this experiment field potential recordings were obtained from the entorhinal cortex (EC) and the CA3 subfield. Note that interictal discharges continue to occur in both experiments. From Avoli 2000.

Synchronous GABA_A receptor-mediated depolarizing potentials are also generated spontaneously by hippocampal neurons early in life (8). It has been proposed that these depolarizing events represent a key element for controlling several Ca²⁺-dependent developmental phenomena that include cell proliferation, migration and targeting (20, 26). The molecular and cellular mechanisms responsible for the generation of these GABA_A-mediated depolarizations in each of these specific conditions remain unclear. However, recent findings indicate that the ontogenetic changes in GABA_A receptor-mediated responses from depolarizing to hyperpolarizing is coupled to a developmental expression in neurons of a Cl⁻-extruding K⁺/Cl⁻ co-transporter, that may also represent the main promoter of fast hyperpolarizing postsynaptic inhibition in the mature brain (25).

Over fifty years of research on GABA functions have made possible to identify several actions that are mediated by this neurotransmitter. Indeed, when expressed in the complexity of the brain function, the role of GABA receptors goes far beyond the original inhibitory role described in early studies. As a result we face today scenarios that are at times in antithesis with the simple view that seizures stem from a decrease in GABA receptor-mediated inhibition. Nonetheless, one must recognize that epileptiform discharges, whether caused by a mechanism related to GABA function or not, can be controlled by GABA strategies that include the use of traditional pharmacological approaches that increase the efficacy of GABA receptor-mediated mechanisms.
References

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