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The Role of $GABA_B$ Mechanisms in Animal Models of Absence Seizures

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Abstract

Generalized absence seizures in humans are a unique type of epilepsy characterized by a synchronous, bilateral 3-Hz spike and wave discharge emanating from a cortical and thalamic network within the brain. The availability of a number of pharmacological and genetic animal models has provided us with the means with which to investigate the cellular and molecular mechanisms underlying these seizures. Over the last few years a significant amount of research in these models has focused on the role of the inhibitory $GABA_B$ receptors, which have been previously described in a number of brain areas as being responsible for a long-lasting hyperpolarization and depression in neurotransmitter release. Initial studies provided evidence that the $GABA_B$ receptor was capable of generating the low threshold calcium spike required for initiation of the burst firing, leading researchers to hypothesize that the $GABA_B$ receptors played a significant role in these seizures. Subsequent research took advantage of the new generation of $GABA_B$ antagonists that became available in the early 1990s and demonstrated that in a number of models the seizures could be abolished by the administration of one of these compounds. Further biochemical, molecular, and electrophysiological experiments have been carried out to determine the exact involvement of $GABA_B$ receptors and their mechanism of action. The current evidence and interpretations of this work are presented here.

Index Entries: Generalized absence seizures; $GABA_B$ receptors; animal models; pre- and postsynaptic mechanisms; *lh/lh*; GAERS; GHB; low threshold calcium spikes.

Introduction

Genetic and pharmacological animal models have provided us with an increased understanding of the cellular and molecular mechanisms of generalized absence seizures in humans. This type of seizure is easily distinguished from other types of epilepsy, displaying a bilateral, synchronous 3-Hz spike and wave discharge recorded on the EEG. The onset/offset is sudden and accompanied by an abrupt decrease in responsiveness to environmental stimuli. This usually occurs between the ages of four and adolescence, and in some

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cases, may also be accompanied by other types of seizure/abnormalities (Sato, 1983; Berkovic, 1993; Porter, 1993) Generalized absence seizures are also unique in their response to anticonvulsants, responding to the antiabsence drugs ethosuximide, trimethadione, valproic acid, or benzodiazepines and being refractory to or even exacerbated by phenytoin, barbiturates, or carbamazepine (Berkovic, 1993). Recent data (discussed below) also indicate that these seizures are exacerbated by $GABA_B$ agonists.

Numerous earlier data from humans and animal models (Jasper and Droogleever-Fortuyn, 1946; Williams, 1953; Prince and Farrell, 1969; Gloor, 1979; Pellegrini and Gloor, 1979; Avoli and Gloor, 1982; Avoli et al., 1983; Avoli, 1987; Gloor and Fariello, 1988) implicated the involvement of thalamic and neocortical populations of neurons in the generation of absence seizures. Whereas there has been extensive debate over which neuronal populations initiated the absence seizures, the sum of these findings clearly show that synchronized oscillatory burst-firing of the type that occurs during an absence seizure requires the integrity of a thalamocortical network.

More recent research has determined that this critical neuronal network underlying generalized absence seizures is made up of neocortical pyramidal neurons, relay cells of the thalamus, and GABAergic neurons of the nucleus reticularis thalami. This "thalamocortical loop" in conjunction with the intrinsic properties of the neurons is capable of generating and sustaining the oscillatory behavior observed during generalized absence seizures (Steriade and Llinas, 1988; Coulter et al., 1989a; Crunelli and Leresche, 1991; von Krosigk et al., 1993; Steriade et al., 1993; Huguenard and Prince, 1994). A number of mechanisms underlying these intrinsic properties are relevant as current or future areas of therapeutic treatments, including the T-type calcium channels (ethosuximide; Coulter et al., 1989c), $GABA_B$ receptors in neurons *(see below)*, and $GABA_A$ receptors in thalamic nucleus reticularis thalami (NRT) neurons (clonazepam; Huguenard and Prince, 1994). The scope of this article, however, will be limited to the role of $GABA_B$ receptors in these seizures.

One of the intrinsic cellular mechanisms believed to be critical in this type of seizure activity involves the low threshold (T-type) calcium channels (Coulter et al., 1989a). Opening of these channels in thalamic neurons triggers a low-threshold calcium spike that is capable of generating a burst of action potentials characteristic of the spike-wave discharge observed during absence seizures. These channels are quickly inactivated and require a long hyperpolarization to deinactivate them, leaving them primed once more for activation (Coulter et al., 1989b). Based on this evidence and the known physiological properties of the $GABA_B$ receptor, it was proposed and subsequently demonstrated that the long-lasting (>200 ms) hyperpolarization mediated by $GABA_B$ receptors was sufficient to deinactivate the T-channels, evoking a low-threshold calcium spike that was potentially capable of promoting burst firing (Crunelli and Leresche, 1991). Following this, a number of groups set out to test the effect of known $GABA_B$ antagonists in established animal models of generalized absence seizures, each subsequently reporting a block of seizure activity by the antagonist (Snead, 1992a; Marescaux et al., 1992b; Hosford et al., 1992).

To begin to address the role of $GABA_B$ receptor mechanisms in generalized absence seizures it is appropriate to first review the thalamocortical circuitry and the oscillatory rhythms generated within this area that are believed to underlie the seizures. In addition, a brief overview of the physiology and pharmacology of $GABA_B$ receptors in the central nervous system (CNS) will be included.

Thalamocortical Circuitry: Extrinsic and Intrinsic Mechanisms Underlying Seizure Activity

Generalized absence seizures arise as a result of a rhythmic thalamocortical burst firing as a

result of the intrinsic properties of populations of neurons in the thalamus and cortex. It must also be noted, however, that a powerful influence also exists in the form of extrinsic pathways that project to these areas (*see* Snead, 1995). Relay neurons within the thalamus are capable of switching between oscillatory/burst firing and tonic firing, which in turn determines the behavioral state of the animal. Under alert or awake conditions thalamic relay neurons undergo tonic firing, reflected in a desynchronized EEG and faithful transmission of information to the cortex. However, this activity can be switched to a burst firing mode, altering transmission to the cortex (Steriade and Llinas, 1988; Steriade et al., 1993). This ability to switch into an oscillatory mode is regulated in part by a group of neurons within the NRT. NRT neurons are GABAergic (Houser et al., 1980) and extend connections to the thalamic relay nuclei and cortex. In addition, they are reciprocally connected within NRT. They receive excitatory input from both thalamocortical and corticothalamic fibers, presumably glutamatergic. By acting like a pacemaker, they are capable of "imposing" their oscillatory firing behavior on neurons in the thalamus and cortex (Fig. 1).

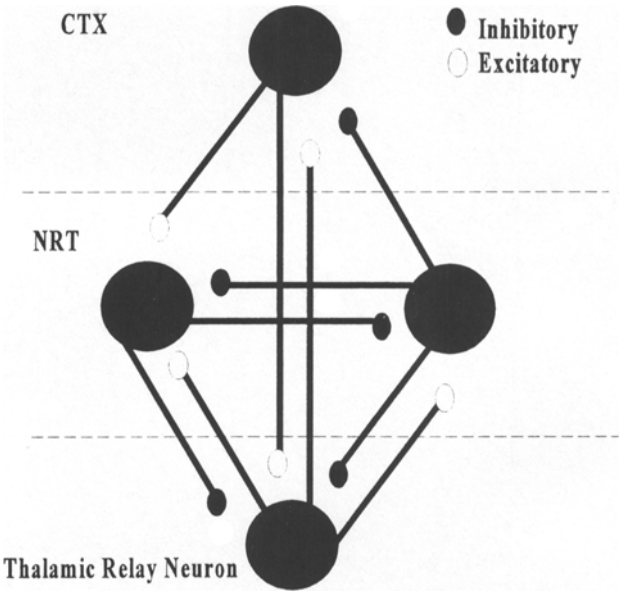

Fig. 1. GABAergic neurons in the nucleus reticularis (NRT) receive excitatory input from the cortex (CTX) and thalamus. Activation of NRT results in inhibitory postsynaptic potentials (IPSPs) mediated by both $GABA_A$ and $GABA_B$ receptors on relay neurons of the thalamus/cortex. The resulting hyperpolarization deinactivates the low threshold calcium current (I_T), which generates calcium spikes that in turn underlie bursts of sodium action potentials. These bursts are capable of re-exciting the NRT through reciprocal connections, thereby continuing the cycle of oscillations.

The intrinsic cellular mechanism that underlies the shift into burst-firing mode of the thalamic relay neurons is the low-threshold calcium current (T-current). Indeed, T-currents may be one target of therapeutic treatments, such as ethosuximide and trimethadione, compounds that act selectively against generalized absence seizures (Coulter et al., 1989a,b, 1990; Huguenard and Prince, 1992). Of note, in recent work it has been suggested that there may be an increase in the amplitude of the T-current in NRT in the GAERS genetic model of generalized seizures (Tsakiridou et al., 1995); this has not been demonstrated as of yet in other models. Activation of the voltage-dependent T-channels at relatively hyperpolarized potentials (–65 to –55 mV; Crunelli et al., 1989; Coulter et al., 1989c; White et al., 1989) results in a low-threshold calcium spike that then elicits a high frequency burst of sodium action potentials. T-channels are inactivated quickly and then require a relatively long hyperpolarization to become deinactivated, priming them for further activation. It is thought that one of the functions of the $GABA_B$ receptors is to provide this deinactivation (Crunelli and Leresche, 1991). Stimulation of the inhibitory fibers from NRT can elicit a biphasic inhibitory potential within relay neurons, followed by a low threshold calcium spike underlying a burst of action potentials (Fig. 2). It must also be pointed out that in addition to the low-threshold T-current, there are a number of concurrently activated voltage and calcium-dependent potassium currents that will clearly influence the threshold of burst firing (Huguenard et al., 1991).

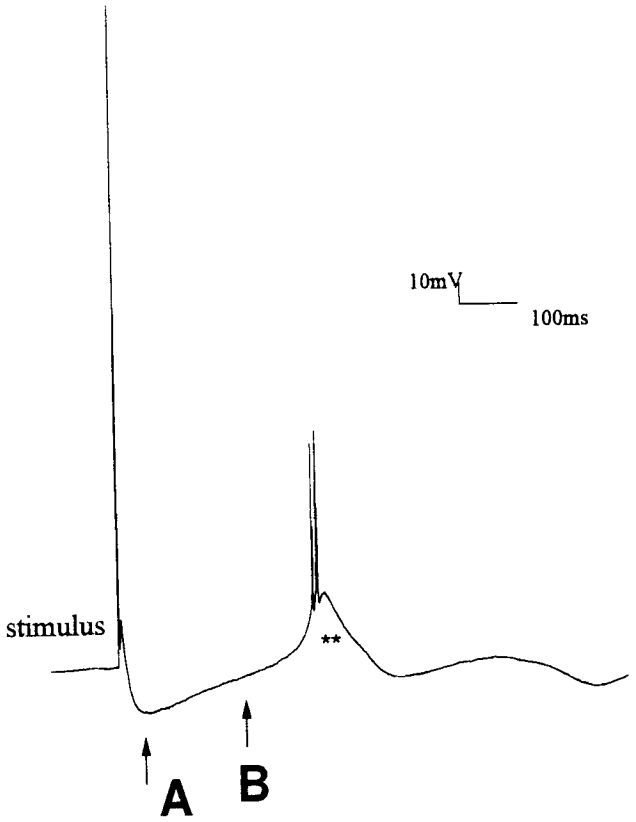

Fig. 2. Stimulus-evoked, biphasic IPSP, recorded in current clamp from a relay cell in the ventrobasal thalamic nuclei. The arrows/letters Indicate the portion of the IPSP mediated by the $GABA_A$ and $GABA_B$ receptors. The large initial spike is the stimulus artifact, immediately followed by a small excitatory potential. This particular experiment was not carried out in the presence of excitatory amino acid antagonists because the excitatory afferents are largely absent in this preparation and an EPSP if observed is very small. The low threshold calcium spike arises on the tail end of the $GABA_B$ IPSP (**) and gives rise to Na^+ spikes before repolarizing. The resting membrane potential for this cell was -58 mV.

$GABA_B$ Receptors: General Physiology and Pharmacology

In order to understand more clearly the actions of the $GABA_B$ receptor in generalized absence seizures, it is appropriate at this point to briefly summarize the general properties of this protein. First identified as being distinct from the $GABA_A$ receptor in the early 1980s (Bowery et al., 1980; Hill and Bowery, 1981), the $GABA_B$ receptor is a G-protein-coupled receptor (Fig. 3) that is capable of activating K^+ channels and inhibiting Ca^{2+} channels on the neuron. In addition, it is known to have a number of modulatory effects on other intracellular mechanisms (*see below* for review). Following a stimulus of the GABAergic fibers, a biphasic inhibitory potential is observed in many mammalian neurons; this is made up of a fast, short latency $GABA_A$-mediated hyperpolarization followed by the slower, longer latency $GABA_B$-mediated hyperpolarization. This latter effect is via the activation of K^+ channels and peaks at around 150–200 ms following the stimulus. $GABA_B$ receptors are also capable of depressing voltage-sensitive calcium channels on the presynaptic terminals of the neuron, resulting in a subsequent depression of neurotransmitter release (for comprehensive review *see* Mott and Lewis, 1994). One of the most widely used agonists selective for the $GABA_B$ receptor is the GABA analog baclofen (β-ρ-chlorophenyl GABA). In addition, there are now a number of selective antagonists based on the phosphinic analogs of GABA, including the compounds CGP 35348 (Olpe et al,, 1990), CGP 36742, CGP 55845A, and SCH 50911 (Bittiger et al., 1992; Froestl et al., 1992; Bolser et al., 1995).

Animal Models of Generalized Absence Seizures: The Role of $GABA_B$ Receptors

As referenced in the introduction, the current focus on $GABA_B$ receptors in absence seizures can be credited to the hypothesis put forth by Crunelli and Leresche (1991). It should be noted, however, that earlier, somewhat indirect studies looked at the effect of the $GABA_B$ agonist baclofen in other models, where it was noted to elicit proabsence effects (Meldrum and Horton, 1974; Golden and Fariello, 1984; Vergnes et al, 1984). Direct evidence that $GABA_B$ receptors played a role in absence seizures was provided by tests using $GABA_B$ receptor antagonists.

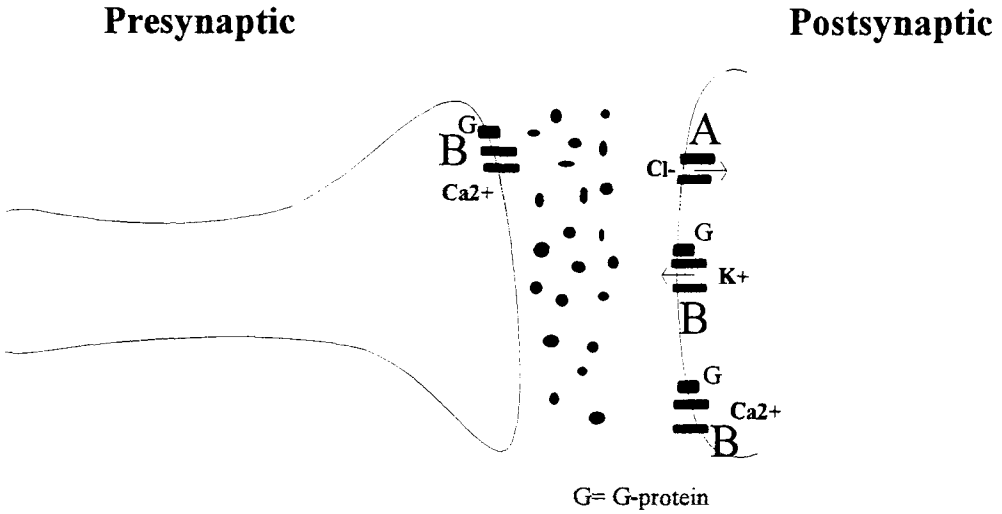

Fig. 3. A schematic drawing of a synapse within the thalamocortical circuit and the locations of the GABA receptors and ion-channel effecters. $GABA_B$ receptors are located both pre- and postsynaptically and exert effects via G-proteins; well-known actions are depression of Ca^{2+} channels or activation of K^+ channels, respectively. The $GABA_A$ receptor acts via a ligand-gated Cl^- ion channel. The effects of activation of the GABA receptors on the system is dependent on their location within the loop *(see text)*.

$GABA_B$ Receptor Antagonists: The Initial Findings

$GABA_B$ receptor antagonists were first tested and shown to have antiabsence effects in three previously established models of generalized absence seizures; the γ-hydroxybutyrate (GHB) model (Snead, 1992a), the genetic absence epilepsy rat from Strasbourg (GAERS) model (Marescaux et al., 1992b), and the lethargic mouse *(lh/lh)* model (Hosford et al., 1992). These initial findings gave further credence to the hypothesis that $GABA_B$ receptors were required for the expression of generalized absence seizures. In the GHB model, spike wave discharges are induced by administration of the GABA metabolite γ-hydroxybutyrate (Godschalk et al., 1976; Snead et al., 1976; Snead, 1978). This model has been validated and shown to produce absence seizures that in many ways are comparable to those seen in humans (Snead, 1992b). Application of the $GABA_B$ antagonist CGP 35348 (100–400 mg/kg IP) resulted in a significant dose-dependent decrease in spike-wave discharge duration, with the higher doses leading to a complete suppression of seizure activity. In the same study the antagonist was also tested in another pharmacological model, the pentylenetetrazole (PTZ) model, in which similar effects were observed (Snead, 1992a). The GAERS model (Vergnes et al., 1982) was developed after selectively breeding a strain of rats that displayed spontaneous generalized absence seizures, with characteristic bilateral spike-wave discharges that can be abolished with traditional antiabsence drugs (*see* Marescaux et al., 1992a). Systemic administration of CGP 35348 dose-dependently suppressed spontaneous spike-wave discharges, as recorded on the EEG in addition to those induced by GHB and GABA mimetics (Marescaux, 1992b), demonstrating the involvement of $GABA_B$ receptors in this particular model. The *lh/lh* model, discovered by Jackson Laboratories (Bar Harbor, ME) and representing a gene mutation on mouse chromosome 2 (Sidman et al., 1965; Noebels, 1986), displays spontaneous generalized absence seizures in addition to an ataxic gait (Sidman et al., 1965). Application of CGP 35348 in this model also abolished the spike-wave discharge in a dose-dependent manner, impli-

cating the $GABA_B$ receptor in the seizures observed in this model (Hosford et al., 1992). In more recent studies, the next generation of $GABA_B$ antagonists (CGP 36742, CGP 46381) has been tested in the *lh/lh* model and found to dose-dependently attenuate the seizures (Hosford et al., 1994). In addition to these, the $GABA_B$ antagonist SCH 50911 was found to abolish seizures in three models; *lh/lh*, GHB, and PTZ (Hosford et al., 1995a). The location of the $GABA_B$ receptors within the thalamocortical loop will obviously determine their effect on specific cell function. Understandably, then, a disruption of the receptors in any one given area will have considerably different outcomes at the network level. Therefore, these findings may not necessarily indicate that the dysfunction lies in the $GABA_B$ receptors *per se*, but instead in their relative densities or functional capability to activate intracellular mechanisms at each individual synapse within the network. Clearly they are relevant contributors to the mechanisms of generalized seizures. The capacity in which they perform this role may be more difficult to determine.

In order to consider their role in the models investigated, it is perhaps appropriate to do so from a standpoint of the biochemical mechanisms by which they mediate their effects or the location of the receptors at synapses within the circuit. Subsequent sections will explore these questions.

Biochemical, Binding and Second Messenger Studies

Subsequent to the antagonist studies on seizures, much of the research became focused on the mechanisms underlying the $GABA_B$ receptor effects. Radioligand binding of ^{3}[H]-baclofen to thalamocortical membranes has been employed to determine any differences in the population of $GABA_B$ receptors with varying results. In the *lh/lh* model, a significant increase in the number of $GABA_B$ binding sites was observed in neocortical membranes of the epileptic strain as compared to their nonepileptic littermates (Hosford et al., 1992; Lin et al., 1993). Subsequent autoradiographic work showed increased $GABA_B$ binding sites in a diversity of thalamic nuclei in the *lh/lh* mice (Hosford et al., 1995b). This was seen to be a selective increase because no measurable differences were observed in NMDA or $GABA_A$ agonist binding sites (Lin et al., 1993). At the same time this increase in binding correlated with an increase in seizure frequency and could be suggestive of a causal role of $GABA_B$ receptors to absence seizures in this particular model (Lin et al., 1993). Similar experiments in the GAERS model showed no difference in $GABA_B$ receptor binding sites compared to controls (Knight and Bowery, 1992), although it had been previously shown that there was an increase in low affinity GHB binding sites in this model (Snead et al., 1990). The lack of difference in numbers of $GABA_B$ binding sites was also true in the GHB and PTZ models (Snead et al., 1993). Interestingly enough, studies looking at the distribution and ontogeny of GHB binding sites in the GHB model of absence (Snead, 1994) indicate a role for the receptor that may be independent of any $GABA_B$ effect. This will be discussed in light of more recent data later in this review. The results of the binding studies indicate that there may well be differences in the $GABA_B$-mediated mechanisms involved in absence seizures displayed by individual models.

Because of the correlation between the increased $GABA_B$ receptor binding and frequency of seizures in the *lh/lh* model further experiments were carried out to characterize the link between the receptors and the seizures. $GABA_B$ receptors are known to exert their effects primarily via G-proteins (Mott and Lewis, 1994), so further experiments focused on the coupling between the receptor and G-protein. No significant difference was observed between the two groups (Lin et al., 1993). Separate experiments carried out utilizing the GHB and PTZ models indicated a direct involvement of G-proteins in the mechanisms of the spike-wave discharge but did not provide any evidence for a difference in the coupling mechanisms (Snead, 1992c).

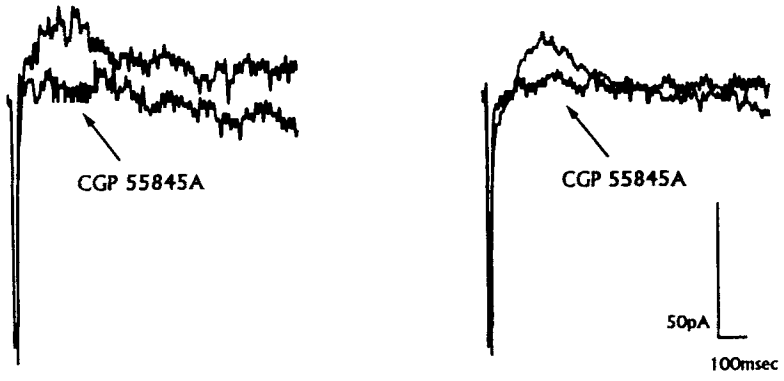

Fig. 4. Voltage clamp recordings of $GABA_B$-mediated IPSCs from a single VB neuron, isolated in the presence of DNQX, DL-APV, and bicuculline. No significant differences were observed between the two groups for any of the measured currents. The response could be subsequently blocked with CGP 55845A (Caddick and Hosford, 1996).

Further biochemical assays were employed to investigate the role of presynaptic $GABA_B$ receptors in the *lh/lh* model. Synaptosomes prepared from *lh/lh* mice and their wild-type littermates were used to look at the effect of $GABA_B$ receptor activation on GABA release, Ca^{2+} uptake, and cyclic AMP formation, all indicators of presynaptic function. The findings from these experiments demonstrate an increased efficacy of $GABA_B$ receptors in the cortical synaptosomes of *lh/lh* mice concurrent with a decreased efficacy in thalamic synaptosomes (Lin et al., 1995). One could hypothesize various ways in which these results would favor synchronous burst-firing in a thalamocortical network. However, the difficulty in determining the exact origin of the synaptosomes may prevent any definite comment on these results. Therefore, more direct electrophysiological tests were used to answer the questions arising from the earlier binding studies.

Electrophysiological Studies of the $GABA_B$ Receptor

Initial studies in our laboratory on the *lh/lh* model were aimed at looking to see if the increase in $GABA_B$ receptor binding reflected an increase in postsynaptic function on the relay neurons in the thalamus. Whole-cell voltage and current clamp techniques were employed to look at individual synaptic potentials and the K^+ conductance activated by $GABA_B$ receptors. Comparisons of both showed no significant differences between the *lh/lh* and nonepileptic littermates in this area (Fig. 4; Caddick and Hosford, 1996). This coupled with the results of the biochemical experiments may suggest that the difference is more likely to reside at a presynaptic locus, and experiments are being carried out at present to answer this question in all areas of the thalamocortical loop.

Presynaptic $GABA_B$ Receptors: Increasing Evidence of Their Role in Generalized Absence Seizure Mechanisms

The experiments described above all appear to be leading to implicating the presynaptic $GABA_B$ receptor as the important locus in these seizures in the *lh/lh* model. Studies carried out in the GAERS model looking at the effect of cadmium, a known blocker of Ca^{2+} channels and Ca^{2+}-activated K^+ channels, reported that its effect was primarily significant in NRT, rather than in the thalamic relay neurons

(Avanzini et al., 1993). This could be indicative of an increased efficacy of $GABA_B$ receptor activation on cortical or thalamic terminals synapsing onto NRT neurons. Further investigations of the mechanisms of action of GHB have also implied a putative role in the activation of presynaptic $GABA_B$ receptors. The actions of GHB on release of GABA and glutamate from thalamic nerve terminals can be blocked by $GABA_B$ antagonists and GHB may act at a presynaptic site that shares pharmacological properties with the $GABA_B$ receptor (Banerjee and Snead, 1995). However, it is not clear if this is a presynaptic $GABA_B$/GHB complex or a presynaptic $GABA_B$ receptor that can be activated by GHB. A recent study demonstrated that a tonic activation of $GABA_B$ receptors by GHB, which can be blocked by CGP 35348, but not NCS 382 (GHB antagonist), may be responsible for the pro-oscillatory actions of GHB in the thalamus (Williams et al., 1995).

Generalized Absence Seizures and $GABA_B$ Receptors: A Summary

Although it is apparent that in the last few years much has been accomplished toward understanding the role for $GABA_B$ receptors in generalized absence seizures, it is still as yet unclear whether the individual models share a common mechanism of action. Clearly the trend appears to be directed at a presynaptic locus of action, but further research needs to be done to ascertain whether this is general throughout the thalamocortical loop or selective for one of the synapses within the loop. As pointed out earlier, the location of the $GABA_B$ receptors will have a critical effect on determining the firing patterns of the whole network. It must also be taken into consideration that $GABA_B$ receptors might not be causal in the generation of these seizures, but as a result of their integral role in the maintenance they could be used as promising targets of therapeutic compounds. Future directions for research will involve specifying the exact mechanisms and loci of action of these receptors in the assorted models that have displayed an involvement of the receptor and using these data to evolve more efficacious therapies for the treatment of the disorder. Concurrently, research into other molecular and synaptic mechanisms will be of value in determining the overall mechanisms of generation of absence seizures.

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