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Antiepileptic Drugs and Migraine

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1. Introduction

Antiepileptic drugs (AEDs) have broad utility in neurology and psychiatry. Apart from epilepsy, they are commonly used for the treatment of pain syndromes, mood disorders and various neuromuscular conditions (Rogawski and Löscher, 2004b). Among the pain syndromes for which AEDs are used, migraine headache is a common application. In the United States, the AEDs approved for use in the prophylaxis of migraine are divalproex sodium (valproate) and topiramate. There is extensive evidence from randomized controlled clinical trials that valproate is effective in preventing migraine attacks or reducing their frequency, severity and duration (Rothrock, 1997; Hering and Kuritzky, 1992; Freitag et al., 2002; Chronicle and Mulleners, 2004; Buchanan and Ramadan, 2006). Various open-label observational studies, and small randomized controlled trials of topiramate and two large multicenter randomized controlled trials have established the effectiveness of topiramate in migraine prevention (Brandes et al., 2004; Silberstein et al., 2004). The U.S. Food and Drug Administration approved valproate for migraine in 1996 and topiramate in 2004. The British Association for the Study of Headache (BASH) considers valproate and topiramate to be second line prophylactic agents after the first line β -blockers and amitriptyline. Evidence from double blind randomized placebo-controlled studies also support the effectiveness of gabapentin in migraine prophylaxis (Di Trapani et al., 2000; Mathew et al., 2001) and it is considered a third line agent by BASH. Less robust clinical studies have indicated that carbamazepine (Rompel et al., 1970), lamotrigine (Steiner et al., 1997; D'Andrea et al., 1999; Lampl et al., 2005; Gupta et al., 2007), zonisamide (Drake et al., 2004; Pakalnis and Kring, 2006) and levetiracetam (Brighina et al., 2006) may also be effective in the treatment of migraine. A metaanalysis by the Cochrane Collaboration confirmed that as a class AEDs reduce migraine frequency and are relatively well tolerated (Chronicle and Mulleners, 2004).

AEDs are generally useful for the treatment of disorders of excessive, synchronous cellular excitability (Rogawski and Löscher, 2004a). They are broadly effective in suppressing excessive or ectopic activity in neural cells and in some instances in muscle (Rogawski and Löscher, 2004b). A key characteristic of AEDs is that they are able to suppress pathological patterns of excitation with only minimal interference with normal cellular activity. In this chapter, I describe current concepts in the pathophysiology of migraine, which posit that a reduced threshold for activation in the migraineur leads to excessive neural activity. This, in turn, induces cortical spreading depression that is the precursor to migraine pain. With this general theoretical schema as a backdrop, I then consider how diverse AEDs useful in migraine prophylaxis protect against the appearance of pathological neural discharges. Much of the information on AED mechanisms is derived from studies aiming to define the action of the AEDs in epilepsy. However, given the similarities between the triggering mechanisms in epilepsy and migraine, the mechanistic studies are likely applicable to an understanding of migraine as well. Remarkably, each of the agents acts through a unique molecular target and reduces hyperexcitability in a distinctive way. However, the end result is a reduction in the frequency of migraine attacks.

2. Migraine as an Episodic Disorder

The syndromes for which AEDs are used are characteristically episodic in nature. Episodic phenomena are common symptoms of disease (Ptáček, 1998; Haut et al., 2006). They include seizures, headaches, cardiac arrhythmias, episodic movement disorders, and periodic paralyses. Although they affect diverse organ systems and have different outward manifestation, the disorders that exhibit episodic symptoms have a number of common features. They are chronic disorders that often occur in otherwise normal individuals and the attacks may be precipitated by factors such as stress, fatigue or diet. Disorders exhibiting episodic symptoms often have a genetic component and are first experienced in infancy, childhood or adolescence. As the genetic bases of the syndromes have been identified, it has become clear that many episodic disorders are due to defects in membrane ion channels, or, more broadly, ion (or neurotransmitter) transport molecules. Disorders associated with defects in ion channels have become known as “channelopathies.” Since ion channels are the principal mediators of cellular excitability properties, it can be presumed that the underlying pathophysiological basis of diverse channelopathies is altered cellular excitability. For some episodic disorders—for example some genetic epilepsies, long QT syndromes, and periodic paralyses—it has been possible to define the specific nature of the change in cellular excitability that results from the mutations that cause the disorders. Often this is a gain-of-function increase in excitability, but in some instances there may be a reduction in excitability in a specific cell population (for example in inhibitory interneurons) that lead to a net increase in circuit excitability (as in severe myoclonic epilepsy in infancy; Yu et al., 2006). Additional evidence for a common pathophysiological basis among the episodic disorders is that they may occur together. In particular, there is strong evidence of comorbidity between migraine and epilepsy (Ottman and Lipton, 1994; Ludvigsson et al., 2006). As discussed by Ottman and Lipton (1996), this comorbidity may not be due to a common genetic susceptibility. Rather, it may be the case that a state of altered brain excitability from whatever cause—environmental as well as genetic—might increase the risk of both migraine and epilepsy. (Alternative explanations of comorbidity that were considered less likely given the available evidence are that migraine attacks or seizures cause brain injury leading to the other disorder, or that there are shared environmental risk factors.)

Migraine is an episodic disorder that shares many clinical characteristics with other episodic disorders known to be channelopathies. Importantly, migraine aggregates in families, so that the risk of migraine is 50 percent greater in relatives of migraineurs than in relatives of controls (Stewart et al., 1997; Stewart et al., 2006). This suggests that complex genetic factors contribute to the risk for migraine, as is the case for epilepsy (Ferraro and Buono, 2006). Many epilepsy syndromes that are inherited in a Mendelian fashion have been found to be due to mutations in ion channels and there is reason to believe that epilepsy susceptibility may be broadly due, at least in part, to variations in ion channels that predispose to altered neuronal excitability. The commonality of migraine and epilepsy is supported by the identification of ion channel mutations in some types of familial hemiplegic migraine, a subtype of migraine with aura. These various considerations provide a basis to speculate that migraine generally, like epilepsy, may be a disorder of excessive cellular excitability. If this is the case, it is not surprising that AEDs have found utility in migraine treatment.

3. Familial Hemiplegic Migraine

Familial hemiplegic migraine (FHM) is a rare subtype of migraine with aura that is inherited in a Mendelian autosomal dominant fashion. Three different genes cosegregate with FHM. The first to be described was *CACNA1A* which encodes the pore-forming subunit $Ca_v2.1$ of neuronal P/Q-type calcium channels (Ophoff et al., 1996). Mutations in *CACNA1A* account for about one-half of all cases of FHM. FHM mutations in *CACNA1A* cause an increase in the calcium flux of single channels but there is paradoxically a decrease in the maximal $Ca_v2.1$ current density in neurons (Tottene et al., 1996). Thus, precisely how the FHM mutations influences cellular excitability is obscure. Interestingly, mutations in *CACNA1A* also are associated with the episodic ataxia syndrome EA-2, the spinocerebellar ataxia syndrome SCA-6 and also idiopathic generalized epilepsy (Chioza et al., 2001). Moreover, mutations in homologs of the gene can cause absence-like seizures in rodents (Tokuda et al., 2007).

The second FHM gene to be described was *ATP1A2*, which encodes the $\alpha 2$ subunit of $Na^+ - K^+$ -ATPase (De Fusco et al., 2003). One family has been described in which a mutation in the *ATP1A2* gene was not only associated with FHM, but also with benign familial infantile convulsions (BFIC) (Vanmolkot et al., 2003). Other allelic conditions include alternating hemiplegia of childhood, basilar-type migraine, and migraine without aura (De Vries et al., 2006). FHM mutations in *ATP1A2* lead to complete inactivation of the protein (Koenderink et al., 2005). Seizures can be produced by inhibition of $Na^+ - K^+$ -ATPase (Pedley et al., 1969; Stone and Javid, 1982), presumably because neuronal resting membrane potential is less well maintained at a hyperpolarized level so that neurons can be more easily brought to threshold and excited. A similar increased excitability mechanism is likely to account for the FHM attacks.

The third FHM gene is *SCN1A*, which encodes the pore-forming $\alpha 1$ -subunit of neuronal voltage-gated sodium channel $Na_v1.1$ (Dichgans et al., 2005). Mutations in this gene have been associated with generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI). The FHM mutation in *SCN1A* is believed to accelerate recovery from sodium channel fast inactivation, which would be expected to cause an increased tendency toward repetitive action potential firing (Torkkeli and French, 2002). Many AEDs reduce repetitive action potential firing and conversely sodium channel toxins that promote repetitive action potential firing (such as pyrethroids and veratradine) induce seizures. Therefore, it is believed that repetitive firing is critical to at least some types of seizures, including those occurring in GEFS+ (Spampanato et al., 2004). In the case of FHM associated with *SCN1A* mutations, it can be presumed that enhanced repetitive spike firing may also underlie the occurrence of migraine.

FHM is distinguished from typical migraine by its Mendelian inheritance and association with hemiparesis. Nevertheless, there are sufficient similarities in headache characteristics and triggers to suggest that an understanding of the pathophysiological basis of FHM can shed light on the underlying mechanisms of the far more frequently encountered non-hemiplegic migraine syndromes. It is remarkable that mutations in FHM genes can cause either migraine or epilepsy, or in some cases both, clearly demonstrating a commonality between FHM and epilepsy, and supporting the notion that migraine generally, like epilepsy, is a disorder of neuronal hyperexcitability. This concept is

supported by the observation that the known FHM genes encode protein complexes that play a direct role in neuronal excitability mechanisms. Thus, they are either ion channels, or in the case of ATP1A2, a molecule that regulates the level of membrane potential and thus indirectly influence ion channel gating and function.

4. Cortical Spreading Depression (CSD)

CSD is becoming increasingly accepted as the basis for the aura in migraine and the trigger for the subsequent headache pain. The phenomenon was first described by Leão (1944) who found that weak electrical or mechanical stimulation of the exposed cerebral cortex in the rabbit elicited a decrease in the spontaneous activity (depression of the EEG signal) at the stimulated region that slowly spread in all directions at 3 to 5 mm/min. Recovery of the initial pattern of spontaneous activity occurred over 5 to 10 min. Although Leão focused on the suppression of neuronal activity in CSD depression, Grafstein's subsequent work demonstrated that the depression is actually preceded by neural activation (Grafstein, 1956; see, Strong, 2005). Recording from small isolated slabs of cortex in *cerveau isolé* (midbrain transected) cats, Grafstein was able to confirm Leão's observation that spreading depression is associated with a slow negative DC shift and depressed neural activity. However, she observed that there is a brief (2–3 s) burst of action potential activity at the initiation of the DC negativity and she hypothesized that the intense neuronal activity caused potassium elevations in the interstitial space that led to the depolarization and excitation of adjacent neurons, which in turn are "thrown into intense activity and liberate more K^+ ." Spreading depression is thus a slowly propagating wave of neuronal depolarization that travels across the cortex and is followed by long-lasting suppression of neuronal activity.

The initial suggestion that spreading depression is responsible for the migraine aura was based on a comparison between the rates of progression of the aura and of spreading depression. Migraine aura is any transient neurological disturbance that appears shortly before or during the development of a migraine headache. Most commonly, the aura arises in the primary visual cortex and typically involves spreading scintillating scotomas with a characteristic distribution of fortification figures. The disturbance usually starts at the center of the visual field center and propagates to peripheral zones within 10 to 15 min. Function returns to normal within another 10 to 15 min (Lauritzen, 2001). The rate of development of the visual symptoms suggests that there is a front of hyperactivation in the visual cortex that moves at a speed of approximately 3 mm/min. Milner (1959) noted that the speed of propagation of the visual symptoms was the same as that of spreading depression, leading to the hypothesis that spreading depression is the physiological basis for the aura. Interestingly, in subjects experiencing somatosensory symptoms, the rate of spread of symptoms along the sensory homunculus occurs at a similar rate.

Numerous neuroimaging studies in humans have supported the concept that spreading depression-like phenomena in neocortex occur with migraine aura (Olesen et al., 1981, 1990). In particular, using functional magnetic resonance imaging, it has been possible to demonstrate slowly propagating neurovascular changes in visual cortex that occur together with visual symptoms of patients experiencing visual aura (Hadjikhani et al., 2001).

Given these various lines of evidence, there is general consensus that spreading depression accounts for migraine aura. However, since there are no pain fibers in the brain parenchyma, it has been difficult to understand how the alterations in brain tissue excitability of spreading depression induce the intense pain that follows. A recent study of blood flow in the rat cortex following the induction of spreading depression has been interpreted as providing the link (Bolay et al., 2002). These studies have shown that CSD in the rat is associated with changes in extracerebral cephalic blood flow as a result of vasodilation within the middle meningeal artery. It is hypothesized that the intrinsic neurophysiological events occurring in brain during spreading depression irritate axon collateral nociceptors in pia and dura mater leading to trigeminal and parasympathetic activation. Trigeminal pain afferents originating in the meningeal vessels pass through the trigeminal ganglion and synapse on second order neurons in the trigeminocervical complex. These nociceptive neurons, in turn, project through the trigeminal nucleus, and after decussating in the brain stem, form synapses with neurons in the thalamus. Hippocampal spreading depression is also able to activate the trigeminal nucleus (Kunkler and Kraig, 2003), but the role of the hippocampus in migraine has not been well characterized. It is conceivable that spreading depression in areas such as the hippocampus or other regions of the limbic system could be a cause of migraine without aura, especially since these headaches can be associated with disturbances in memory, abnormal perceptual experiences (olfactory or gustatory hallucinations and distortions of body image), or changes in mood (Morrison, 1990).

Following on the work of Leão and Grafstein, there have been numerous investigations into the physiological basis of spreading depression. It has been found that in addition to the classical triggers, the phenomenon can be induced by elevated extracellular potassium, glutamate, and inhibition of Na^+/K^+ -ATPase (Sanchez-Del Rio et al., 2006). Although Grafstein proposed that intense neural activation and elevations in extracellular potassium are responsible for the propagation of CSD, this has recently been questioned by Herraras (2005), at least as far as its central role in the spread of the depressed neural activity. Indeed, tetrodotoxin blockade of neuron firing fails to interfere with spreading depression in some situations, so intense neuronal activity does not seem to be required. Seconds before the neuronal activity is recorded and millimeters ahead of it, subthreshold pacemaker field oscillations can be detected that are resistant to synaptic transmission blockade. Thus, as an alternative to the potassium hypothesis, Herraras has suggested that neuronal synchronization and field oscillations that precede the front of depolarization play a critical role in extending the zone of depressed activity. The synchronization has been hypothesized to be due to nonsynaptic interactions between neurons possibly mediated by the excitatory neurotransmitter glutamate or through gap junctional interactions. Recently, glia have been implicated as the source of glutamate (Larrosa et al., 2006). These ideas are intriguing given the recent demonstration that calcium signalling in astrocytes may lead to the induction of epileptiform hypersynchronous activity in adjacent neuronal networks as a result of glutamate released from the astrocytes (Tian et al., 2005). Several AEDs, including valproate and gabapentin, with demonstrated activity in migraine prophylaxis, effectively suppress calcium signalling in astrocytes. The activity of valproate and gabapentin is more robust than that of phenytoin, which has not been demonstrated to have activity in migraine. Thus, it seems plausible that astrocytes are an important target for AEDs in migraine

prophylaxis. However, it is noteworthy that spreading depression can occur even when intracellular calcium waves are eliminated (Basarsky et al., 1998). At present, the contribution of astrocytes to spreading depression is incompletely defined; additional evidence is needed to characterize how and when they play a role, if any. Therefore, notwithstanding the interesting possibility that astrocytes could be a target for AEDs in migraine, in this chapter I focus on neurons where the actions of these agents are much better understood. Even if neuronal hyperactivity is not *required* for CSD, this does not eliminate the fact that such activity can trigger CSD and very likely plays a role in migraine. It is probably too simplistic to presume that suppression of the high frequency firing noted by Grafstein to be associated with the onset of spreading depression accounts for the activity of AEDs in protecting against migraine attacks. Rather, those AEDs that are effective in migraine may suppress the synchronizing mechanisms that Herraras has proposed are critical to CSD. Interference with synchronizing mechanisms may similarly be responsible for the effectiveness of AEDs in epilepsy, although how this might occur is still largely a matter of speculation.

5. Enhanced Cortical Responsiveness in Migraine

As is the case for many episodic disorders, the precise trigger for the migraine attack is enigmatic. Many clinical factors such as diet, alterations in sleep or stress are known to predispose to attacks. How these factors bring on a migraine attack is not known. However, there is evidence for enhanced cortical responsiveness to diverse stimuli in migraineurs (Palmer et al., 2000; Mulleners et al., 2001). The techniques that have been used include psychophysical studies; visual, auditory and somatosensory evoked potentials; magnetoencephalography; and transcranial magnetic stimulation (TMS) of the motor cortex. In all cases, there is evidence of heightened reactivity between migraine attacks. Results from TMS of the occipital (visual) cortex have been particularly compelling. Most but not all studies have observed a reduced threshold for induction of phosphenes in migraineurs than in controls. This phenomenon appears to be equally present in subjects that experience migraine without aura as those with migraine with aura.

In the remainder of this chapter, I consider the current understanding of the mechanisms of AEDs that are used for migraine prophylaxis or for which there is some supportive clinical evidence of efficacy. While many AEDs have activity in migraine, it is certainly not the case that all AEDs have such activity. Therefore, I close with some selected example of AEDs that are not likely to be effective in migraine. Consideration of the mechanisms of these agents can be useful in narrowing the set of targets to be considered in the development of antimigraine therapies and may eventually lead to an understanding of the neurobiological differences between migraine and epilepsy.

6. Cellular Mechanism of AEDs Widely Used for Migraine Prophylaxis

6.1 Valproate

Valproate has many pharmacological actions, none of which by itself can completely account for its clinical activity in epilepsy and the other conditions for which

it is used, including migraine (Macdonald and Rogawski, 2008). It has therefore been proposed that valproate acts through a combination of actions. Among these various actions, Löscher (2002ab) has concluded that increases in GABA turnover that are produced in specific brain regions is of particular importance in the ability of valproate to control seizure generation and propagation. However, agents that act on GABA systems have not in general been found to influence spreading depression or to be effective in the treatment of migraine. Therefore, it seems likely that other known or unknown actions of valproate might account for the clinical efficacy in migraine prophylaxis. There is limited evidence that valproate may inhibit NMDA or kainate receptor-mediated synaptic transmission (Gean et al., 1994; Gobbi and Janiri, 2006); whether these actions could contribute to the efficacy of valproate in migraine prophylaxis is not known. As noted previously, valproate seems to potentially inhibit astrocytic calcium signalling. It will be of interest to determine the underlying basis of this action and whether it has relevance for the antimigraine activity of valproate.

Acute treatment with valproate has generally not been found to influence spreading depression (Kaube and Goadsby, 1994; Ayata et al., 2006). However, recently Ayata et al. (2006) found that prolonged treatment with valproate along with many other drugs useful in migraine prophylaxis including β -blockers, topiramate, methysergide and amitriptyline reduced the number of potassium-induced CSD events and increased the electrical stimulation threshold for CSD in rats. These results suggest that all of the effective drugs could be acting in a common fashion to induce a plastic change in brain excitability mechanisms that lead to resistance to spreading depression.

6.2 Topiramate

Several studies have shown that topiramate can suppress CSD in rats and cats at doses comparable to those that protect against seizures (Akerman and Goadsby, 2005; Ayata et al., 2006). In addition, topiramate is able to inhibit evoked activity in dorsal horn neurons in the cervical spinal cord (C2) that are believed to mediate headache pain (Storer and Goadsby, 2004). Pain in migraine is hypothesized to be due to activation of trigeminal nerve axons (presumably by CSD), which then release CGRP and other peptide mediators from terminals near the meningeal vessels to cause vasodilation. Whether or not the vasodilation is responsible for the pain, it is a useful marker of activation of the trigeminal system. Topiramate inhibited neurogenic dural vasodilation but did not inhibit vasodilation induced by CGRP, leading to the conclusion that topiramate might act presynaptically on trigeminal nerve terminals to inhibit the release of CGRP (Akerman and Goadsby, 2005b). Thus, topiramate appears to have a dual mechanism in migraine. The drug may inhibit activation of the attacks by raising the threshold for CSD and could also specifically interfere with pain mechanisms through effects on the trigeminovascular system.

Several cellular mechanisms have been proposed to underlie the therapeutic activity of topiramate: (1) activity-dependent attenuation of voltage-dependent sodium currents; (2) inhibition of high voltage-activated calcium channels; (3) potentiation of GABA_A receptor-mediated currents; (4) inhibition of AMPA/kainate receptors; (5) inhibition of types II and IV carbonic anhydrase isoenzymes; and (6) activation of a steady potassium current (White, 2005; Macdonald and Rogawski, 2008). The effects on

sodium channels, high voltage-activated calcium channels and GABA_A receptors are unlikely to contribute in a substantial way to the antimigraine action because there is little evidence that drugs that target these mechanisms are effective in migraine prophylaxis (Olesen, 1990). Similarly, the carbonic anhydrase inhibition is not likely to be relevant to the antimigraine activity of topiramate (Vahedi et al., 2002). However, the report that topiramate can activate a potassium current is intriguing inasmuch as potassium channel openers with activity on KCNQ channels have shown modest activity in an experimental model of spreading depression (see section 8.2 below). These openers, which are analogs of the investigational AED retigabine, reduce the number of spreading depression events induced in rat cortex by KCl. Additional studies are required to confirm an effect of topiramate on potassium channels.

Among the diverse pharmacological actions of topiramate, the interaction with ionotropic glutamate receptors is perhaps the most likely action to be relevant to its antimigraine activity. Topiramate is not a simple receptor antagonist although there is considerable evidence that it can influence the functional activity of AMPA/kainate-type glutamate receptors; there is no evidence that topiramate blocks NMDA receptors (Gibbs et al., 2000). Thus, in cultured neurons, topiramate was found to inhibit responses to kainate, an agonist of AMPA and kainate receptors (Gibbs et al., 2000). More recently, topiramate was reported to be a more potent and efficacious inhibitor of GluR5 kainate receptor currents in basolateral amygdala principal neurons than of AMPA receptor currents (Gryder and Rogawski, 2003). AMPA receptors are crucial for excitatory synaptic transmission throughout the central nervous system, and drugs that substantially block AMPA receptors are expected to produce dramatic neurobehavioral impairment. Thus, the finding that topiramate is weak and has low efficacy as an AMPA receptor antagonist corresponds with the clinical observation that the drug is reasonably well tolerated. Blockade of GluR5 kainate receptors is not associated with the side effects associated with blockade of AMPA receptors and, in fact, mice genetically engineered to lack GluR5 are grossly normal neurologically. However, GluR5 kainate receptors represent an interesting target for migraine therapy. GluR5 kainate receptors regulate pain transmission in the spinal cord (Li et al., 1999; Xu et al., 2006) and GluR5 kainate receptor subunits and functional GluR5 kainate receptors are expressed in trigeminal neurons (Sahara et al., 1997). Moreover, GluR5 antagonists are active in migraine models (Filla et al., 2002; Weiss et al., 2006) and intravenous LY293558 (tezampanel), an antagonist of AMPA and GluR5 kainate receptors, was found to dramatically improve headache in a small controlled clinical trial in acute migraine (Sang et al., 2004). Although the response rate for LY293558 (69%) was somewhat less than for subcutaneous sumatriptan (86%), LY293558 was better tolerated. In normal volunteers, LY293558 was found to cause “hazy vision,” a reversible side effect that is believed to be mechanism-related and due to effects in the retina (Sang et al., 1998). This concerning side effect was not spontaneously reported by the migraineurs, possibly because they had already experienced various visual symptoms in the setting of the acute migraine attack. The clinical trial results with LY293558 are compatible with the concept that GluR5 kainate receptors are an attractive target in migraine. However, because LY293558 is not selective for AMPA receptors, additional studies with more selective antagonists are required. An additional phase II clinical of subcutaneous LY293558 for the abortive treatment of migraine is currently ongoing under the sponsorship of Torrey Pines

Therapeutics. An oral prodrug form of LY293558 is also under investigation for migraine.

The inhibitory action of topiramate on GluR5 kainate receptors develops slowly, suggesting that it acts indirectly (Gryder and Rogawski, 2003). The effects on ion channels are complex and are unlikely to occur through direct effects on channel gating, but are more likely to be mediated indirectly, possibly through inhibition of channel phosphorylation. Recently, it has been found that topiramate inhibits phosphorylation of serine 845 of the AMPA receptor GluR1 subunit (Ängehagen et al., 2005), suggesting that the effect of the drug on AMPA and perhaps also kainate receptors could be due to an alteration in the phosphorylation state of the protein. The ability of topiramate to functionally inhibit GluR5 kainate receptors *in vivo* was confirmed in experiments in mice with selective glutamate receptor antagonists, where anticonvulsant doses of topiramate blocked clonic seizures induced by a selective GluR5 kainate receptor antagonist but not by an agonist of AMPA receptors (Kaminski et al., 2004). Taken together, the results with LY293558 and topiramate provide a compelling justification for further studies to investigate GluR5 kainate receptors as targets for migraine therapy.

7. AEDs that Are Possibly Effective for Migraine Prophylaxis

7.1 Gabapentin and Pregabalin

In the U.S., gabapentin and its analog pregabalin are not approved for use in migraine although gabapentin is indicated for postherpetic neuralgia and pregabalin is indicated for this pain condition as well as for diabetic neuropathy. Gabapentin, the lipophilic 3-cyclohexyl analog of GABA, was originally synthesized in an attempt to develop a brain-penetrant GABA agonist. Although both gabapentin and pregabalin [(*R*)-3-isobutyl-GABA] are based on a GABA backbone, bulky aliphatic substituents in the molecules preclude binding to the GABA recognition site on GABA_A receptors. The drugs also do not interact with other sites on GABA_A receptors, including the benzodiazepine recognition site (Suman-Chauhan et al., 1993). High affinity binding sites for gabapentin and pregabalin in brain have been identified as $\alpha 2\delta$ proteins, which are believed to be auxiliary subunits of voltage-activated calcium channels (Dooley et al., 2007). The binding affinities of gabapentin, pregabalin and related structures to $\alpha 2\delta$ subunits correlates in a stereoselective fashion with their analgesic activity (Field et al., 2000). In addition, knock-in of a mutation (R217A) in the $\alpha 2\delta$ -1 subunit in mice, which results in markedly reduced binding of gabapentin and pregabalin, eliminates its analgesic activity without influencing the analgesic activity of morphine (Field et al., 2006; Rogawski and Taylor, 2006). Thus, there is strong support for the notion that the analgesic activity of gabapentin and pregabalin is mediated through the interaction with $\alpha 2\delta$. Whether this account for the prophylactic activity in migraine remains to be determined. In this regard it is noteworthy that as yet there is no evidence that gabapentin or pregabalin can influence the neural mechanisms that trigger migraine (spreading depression).

The $\alpha 2\delta$ subunits are highly glycosylated proteins of molecular mass ~150 kD (997 to 1150 amino acid residues). There are four homologous forms, but only subtypes 1 and 2 bind gabapentin and pregabalin with high affinity (Marais et al., 2001). $\alpha 2\delta$ -1 and

$\alpha 2\delta$ -2 subunits are believed to form complexes with many voltage-dependent calcium channel types (Davies et al., 2007). It is not yet clear which calcium channels are important for the therapeutic activity of gabapentin and pregabalin, nor is the functional role of the $\alpha 2\delta$ subunit complex fully understood. However, for some calcium channel types, $\alpha 2\delta$ subunit complex has been shown to allosterically enhance current amplitude and also promote channel trafficking to the membrane (Dooley et al., 2007). Functional studies of the effects of gabapentin on calcium channel activity have yielded divergent results; however, there is a general consensus that gabapentin and pregabalin reduce the release of neurotransmitters from neural tissue, with effects on CGRP, substance P and glutamate release being of particular relevance to migraine prophylaxis (Fehrenbacher et al., 2003; Dooley et al., 2000; Cunningham et al., 2004; Patel et al., 2000). It is noteworthy that the effect of gabapentin and pregabalin on these mediators is generally only observed in the presence of nerve injury associated with inflammation and hyperalgesia. Thus, $\alpha 2\delta$ ligands have minimal effects on physiological transmitter release but significantly inhibit sensitized or abnormal release. Although the mechanism underlying this selectivity is not understood, it may explain the relatively benign side-effect profiles of gabapentin and pregabalin since release under normal conditions is maintained.

Recent studies indicate that the ability of gabapentin and pregabalin to influence release of neuroactive substances may not dependent upon calcium entry through voltage-sensitive calcium channels (Dooley et al., 2007). Rather, $\alpha 2\delta$ subunit proteins might influence synaptic release directly, possibly through interactions with the release machinery that are independent of the main pore-forming $\alpha 1$ calcium channel subunits. It has been speculated that binding of the drugs to $\alpha 2\delta$ subunits directly influences the release machinery (Rogawski and Taylor, 2006), possibly by affecting physical interactions between presynaptic calcium channels and proteins mediating exocytosis (Spafford and Zamponi, 2003).

Gabapentin and pregabalin are absorbed in the gut and pass across the blood-brain barrier via the system L transporter, which is specialized for the transport of large neutral amino acids (Su et al., 2005). The fact that these drugs are substrates for this transporter is essential to their therapeutic activity because it allows them to gain access to the central nervous system (Bellioti et al., 2005). However, because the transporter can be saturated, the ability to achieve high blood and brain levels is limited. A gabapentin prodrug, XP13512 [(±)-1-[(α -isobutanoyloxyethoxy)carbonyl] aminomethyl)-1-cyclohexane acetic acid], is under development that may avoid these problems (Cundy et al., 2004). XP12512 is absorbed by high-capacity nutrient transporters and then rapidly converted to gabapentin, so the rate limiting absorption by the system L is circumvented.

7.2 Zonisamide

There is limited information, largely from open label clinical trials, suggesting that zonisamide may be effective in migraine prophylaxis in adults and children (Smith, 2001; Krusz, 2001b; Bigal et al., 2002; Drake et al., 2004; Pakalnis and Kring, 2006; Ashkenazi et al., 2006). Taken together with the available base of information on zonisamide, a case can be made that further study of the drug in controlled trials is warranted. Zonisamide has a unique chemical structure consisting of an aromatic fused

benzene-isoxazole ring and a sulfonamide side chain. Topiramate also contains a sulphur atom in an *O*-sulfamate moiety that is structurally similar to the sulfonamide in zonisamide. Thus, zonisamide and topiramate are the only sulphur-containing AEDs. Carbonic anhydrase inhibitors such as acetazolamide also have a sulfonamide side chain, and indeed, both AEDs inhibit carbonic anhydrase (Nishimori et al., 2005). There are intriguing similarities between zonisamide and topiramate in addition to their shared chemistry. Both drugs are associated with weight loss rather than the weight gain commonly observed with AEDs, and both drugs have been linked to nephrolithiasis and hypohidrosis, which could be due to their common action as carbonic anhydrase inhibitors. Since zonisamide has so many similarities to topiramate, it would not be surprising if zonisamide, like topiramate, has efficacy in migraine prophylaxis.

In animal seizure models, zonisamide has a profile of activity similar to that of sodium channel modulating AEDs, such as phenytoin, carbamazepine and lamotrigine (see Macdonald and Rogawski, 2008). Indeed, there is evidence that zonisamide can interact with voltage-activated sodium channels at low, therapeutically-relevant concentrations and that the effect on sodium channels is similar to that of other sodium channel modulating AEDs. However, zonisamide has several additional pharmacological actions that could contribute to its anticonvulsant activity including effects on T-type voltage-dependent calcium channels, presynaptic effects to inhibit or facilitate neurotransmitter release, and effects on neurotransmitter turnover and metabolism. As noted, zonisamide is also an inhibitor of carbonic anhydrase, although this alone is unlikely to be relevant to its putative efficacy in migraine since there is no compelling evidence that more potent carbonic anhydrase inhibitors such as acetazolamide have antimigrain activity. It is noteworthy that there is pharmacological evidence that carbonic anhydrase inhibition is not responsible for the anticonvulsant activity of zonisamide.

As is the case for other sodium-channel modulating AEDs, the ability of zonisamide to modulate voltage-dependent sodium channels is expected to reduce action potential evoked release of glutamate through a presynaptic action. In fact, recordings from hippocampal neurons in rat brain slices have confirmed this action (Rogawski, 2002). Studies with microdialysis in freely moving rats have indicated that zonisamide has complex actions of the release of various neurotransmitters including GABA, dopamine, serotonin, and acetylcholine. How these effects could contribute to the activity of zonisamide in migraine is uncertain. Overall, the known pharmacological actions of zonisamide on voltage-dependent ion channels and other well-characterized targets are unlikely to explain the putative efficacy in migraine, raising the possibility that the drug could have actions on one or more as yet undefined targets.

7.3 Levetiracetam

Limited information from retrospective and open label trials suggests that levetiracetam may have utility in migraine prophylaxis (Drake et al., 2001; Krusz, 2001a; Cochran, 2004; Miller, 2004; Rapoport et al., 2005; Vaisleb et al., 2005; Brighina et al., 2006). Levetiracetam has been marketed for epilepsy therapy since 2000, but its molecular target in brain was only recently identified (Lynch et al., 2004). The discovery of this target—the synaptic vesicle protein SV2A—represents a milestone in AED research for two reasons. First, because SV2 is a component of the synaptic release

machinery, it focuses attention on the presynaptic nerve terminal as a site of action of AEDs. Second, the knowledge of the molecular target of levetiracetam has made it possible to screen for follow-on compounds with improved properties. Using this approach, two structural analogs of levetiracetam with 10-fold greater SV2A binding activity have been identified and advanced to clinical trials. These compounds are seletracetam (ucb 44212) and brivaracetam (ucb 34714); brivaracetam has been studied in epilepsy and neuropathic pain and is entering phase III clinical trials for epilepsy. The mechanism whereby binding to SV2A results in anticonvulsant activity is unknown. SV2A is an abundant protein component of synaptic vesicles that is structurally similar to 12-transmembrane domain transporters, although a transporter activity for SV2A has not yet been identified. SV2A is not essential for synaptic transmission, but mice in which the protein has been deleted by gene targeting exhibit seizures (Janz et al., 1999). It seems reasonable that the SV2A ligands could protect against states of excessive cellular excitability through effects on synaptic release mechanisms, although experimental support has not as yet been forthcoming.

8. AEDs in Development With Potential Utility in Migraine

8.1 Valproate-Like Agents

Valproate has a unique place in epilepsy therapy because of its broad spectrum of efficacy. In addition valproate is useful in the treatment of acute mania and, of course, migraine. However, valproate has several undesirable side effects including teratogenicity, weight gain and reproductive dysfunction, and it occasionally causes hepatic and pancreatic toxicity (Jager-Roman et al., 1986; Duncan, 2007). Therefore, much attention has been focused on the development of agents that have the same broad spectrum of clinical efficacy as valproate without these undesirable characteristics. Because the precise mechanism of action of valproate is unknown, it is difficult to predict—based on preclinical studies—whether an analog will have the same clinical efficacy. Nevertheless, several valproate-like compounds have been demonstrated to have a valproate-like profile in animal seizure and other behavioral models so that they have been advanced to clinical development (Rogawski, 2006; Bialer, 2006). In all cases, the compounds are amides, because it is believed that the acid forms predispose to teratogenicity. Indeed, the amide form of valproate, valpromide is more potent as an anticonvulsant than valproate and it is not teratogenic in mice susceptible to neural tube defects. However, in humans valpromide is biotransformed to valproate, so it does not offer advantages to valproate. The focus has been on obtaining compounds with reduced or no conversion to valproate or the corresponding acid. It is unknown whether these compounds have activity in preclinical models relevant to migraine. However, they do appear to have activity in models of neuropathic pain, which in some cases is greater than for valproate (Winkler et al., 2005ab).

Three valproate-like compounds (two existing in more than one stereoisomeric forms) that were discovered or extensively studied in the laboratory of Meir Bialer at the Hebrew University of Jerusalem are under active clinical development. The first to undergo human clinical trials was valroceamide (valproyl glycineamide; SPD493), which is now entering phase II development (Isoherranen et al., 2001). Valroceamide is more

potent than valproate in animal seizure models, possibly due to its increased accumulation in brain. In rats and dogs, valroceamide is converted to minimal amounts of valproate and embryotoxicity has not been observed in rats and rabbits. However, in humans, biotransformation of valroceamide to valproate is substantial. Therefore, although valroceamide could be safer than valproate, the risk of teratogenicity is not eliminated. Because of its relatively short half-life, three-times daily dosing will be required, unless a controlled release formulation is developed.

The resolved isomers of valnoctamide (2-ethyl-3-methylpentanamide) and diisopropyl acetamide (PID) are also under active development. Like valroceamide, these isomers exhibit greater anticonvulsant and valnoctamide has been shown to have greater antiallodynic potency than valproate (Winkler et al., 2005ab; Bialer, 2006). However, they are not converted to valproate, which could be an advantage from the perspective of teratogenicity and the other idiosyncratic toxicities of valproate. Valnoctamide has two stereogenic carbons, so that the molecule exists in four stereoisomeric forms. Only small differences were found between the anticonvulsant potencies and pharmacokinetic properties of the (2*S*,3*S*) and (2*R*,3*S*) isomers (Isoherranen et al., 2003a). The mixture of all four isomers was at one time marketed as an anxiolytic and sedative in Europe, but is not available at present. It appears that one or more of the isomers will be taken through a full development program for CNS indications that could include migraine. Despite the fact that it was marketed as a sedative, anecdotal evidence indicates that valnoctamide is well tolerated and not strongly sedative (Rogawski, 2006). Valnoctamide does not induce embryotoxicity in mice that are susceptible to valproate-induced spina bifida aperta (Radatz et al., 1998). However, the validity of this model as a predictor of risk for human spina bifida is uncertain.

PID, which is also expected to enter clinical development, has a single stereocenter. As in the case of valnoctamide, only small differences were found in the relative anticonvulsant potencies and pharmacokinetic properties of the enantiomers, with the (*R*)-enantiomer possibly being slightly more potent (Spiegelstein et al., 1999ab; Isoherranen et al., 2003b). PID also was free of teratogenicity in susceptible mice

Isovaleramide (3-methylbutanamide; NPS-1776) has a similar profile of activity to valproate in animal seizure models, but is weaker in potency (Bialer et al., 2001). Phase I clinical trials indicated that the compound is safe and well tolerated, but it not currently being developed.

8.2 Retigabine

Retigabine [*N*-(2-amino-4-[fluorobenzylamino]-phenyl)carbamic acid; D-23129], the desaza-analog of flupirtine (a nonopiate analgesic approved in Europe for general nociceptive pain), is an effective inhibitor of CSD (Wu and Dworetzky, 2005) and therefore has potential in migraine therapy. Retigabine has activity in a broad spectrum of animal epilepsy models (Tober et al., 1996; Rostock et al., 1996; Blackburn-Munro et al., 2005). Clinical testing in several phase II clinical trials, largely in patients with partial seizures with or without secondary generalization who were refractory to available therapies, suggested that the compound is efficacious for the treatment of epilepsy. This has been confirmed in a recent multicenter, randomized, double-blind, placebo-controlled trial as adjunctive therapy in patients with partial-onset seizures, where drug treatment

was associated with a dose-dependent reduction in seizure frequency (Porter et al., 2007). As yet, retigabine has not been evaluated in migraine.

There has been considerable interest in the molecular pharmacology of retigabine, which is the first in a new class of KCNQ (Kv7) potassium channel openers. Retigabine causes a specific enhancement of M-type potassium current, which is carried by KCNQ-type potassium channels (Rundfeldt and Netzer, 2000b; Main et al., 2000; Wickenden et al., 2001). M-current is a slowly activating current whose threshold is near resting potential. The principal action of retigabine is to shift the activation of KCNQ channels underlying the M-current to more hyperpolarized membrane potentials, and also to slow their deactivation and accelerate their activation (Tatulian et al., 2001, 2003). The critical action of the drug is to increase potassium current near resting potential, which reduces the excitability of neurons that express KCNQ2–5 subunits (Kv7.2–7.5). The cardiac-specific isoform KCNQ1 (KvLQT or Kv7.1) is not affected by retigabine. In addition to their localization in brain regions relevant to epilepsy, KCNQ/M channels are also present in elements of nociceptive sensory systems including dorsal root ganglia neurons, and retigabine inhibits responses in chronic pain models (Passmore et al., 2003). Retigabine could therefore have efficacy in migraine as a result of its novel analgesic activity on sensory systems in addition to the effects on CSD. Indeed, there is evidence that KCNQ2 channels are expressed in the trigeminal ganglia and the trigeminal nucleus caudalis and it has been proposed that sensitization of this pathway could be a factor in migraine (Wu and Dworetzky, 2005).

Although most attention has been focused on the unique ability of retigabine to activate KCNQ channels, the drug also acts as a positive modulator of GABA_A receptors (van Rijn and Willems-van Bree, 2003). Thus, retigabine enhances GABA-activated chloride current responses and GABAergic IPSCs at concentrations that are only modestly higher than those that influence KCNQ channels (Rundfeldt and Netzer, 2000a; Otto et al., 2002). It has been suggested that the effects of retigabine on GABA_A receptors could contribute to its efficacy in epilepsy and also to side effects (Rogawski, 2006). However, since GABA_A receptor positive modulating activity is not associated with efficacy in migraine prophylaxis, KCNQ openers that lack activity on GABA_A receptors could potentially have better tolerability (Wickenden et al., 2005). Several novel compounds, including acrylamides, have been identified to have KCNQ opening activity and to inhibit CSD (Wu et al., 2003ab, 2004; L'Heureux et al., 2005). Some of these compounds are more than 2 orders of magnitude more potent than retigabine, but equally efficacious. ICA-105665, a compound reported to have specific KCNQ opening activity, has entered phase I trials for epilepsy but also may be developed for neuropathic pain.

8.3 Lacosamide

Lacosamide [(*R*)-2-acetamido-*N*-benzyl-3-methoxypropionamide; SPM 927; harkoseride], is a functionalized amino acid currently in phase III clinical trials for the treatment of partial epilepsy and diabetic neuropathic pain. Additionally, lacosamide is under investigation for migraine prophylaxis, fibromyalgia, and osteoarthritis. Lacosamide has activity in a broad spectrum of acute seizure models, but is inactive in the pentylenetetrazol model (Beyreuther et al., 2007). It also has demonstrated

antihyperalgesic activity in a variety of acute and chronic inflammatory pain and neuropathic pain models, but does not have acute antinociceptive activity (Stöhr et al., 2005). Its mechanism of action is not well understood (Rogawski, 2006). Recently, however, it has been proposed that two predominant actions could contribute to therapeutic efficacy (Beyreuther et al., 2007). While lacosamide does appear to interact with voltage-gated sodium channels it does not have actions on fast inactivation as do conventional sodium channel modulating AEDs. Rather, it seems to selectively promote slow inactivation, a distinct and less well-understood form of sodium channel inactivation that occurs on a time scale of seconds to minutes, in contrast to fast inactivation, which occurs on a millisecond time scale. The enhancement of slow inactivation could theoretically lead to selective inhibition of epileptiform activity, since epileptic depolarization of neurons is more prolonged than ordinary synaptic depolarization and is typically of the order of 10s of seconds, the time scale where slow inactivation is pertinent. Whether this mechanism would similarly be relevant to pain or migraine is not known. Lacosamide has also been found to bind to collapsin response mediator protein-2 (CRMP-2), a cytosolic phosphoprotein mainly expressed in the nervous system, that promotes neurite extension and is involved in the signalling of growth inhibitory cues. Whether and how the interaction with CRMP-2 relates to the therapeutic activity of lacosamide remains to be determined.

8.4 Tonabersat

Tonabersat [SB-220453; *cis*-(-)-6-acetyl-4*S*-(3-chloro-4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3*S*-ol] is a benzopyran with anticonvulsant properties that is a potent and effective blocker of CSD (Smith et al., 2000; Read et al., 2001; Bradley et al., 2001). It has similar pharmacological properties to carabersat (SB-204269), which demonstrated efficacy in a phase II clinical trial for epilepsy, but whose development was not continued because of concerns about the possible cardiotoxicity of a metabolite. Tonabersat was not effective as an abortive agent in migraine (N. Upton, personal communication). However, a phase IIa clinical trial in migraine prophylaxis demonstrated a significant reduction in migraine frequency and in rescue medication days, with good tolerability. Although the mechanism of action of tonabersat in migraine is not known, the fact that it is an effective inhibitor of CSD is intriguing. The clinical trial results with tonabersat may reflect the fact that inhibition of CSD can prevent migraine from being triggered, but once migraine is established and downstream mechanisms come into play, CSD is no longer a factor. There is evidence that tonabersat is a selective blocker of gap junctions (N. Upton, personal communication). The extent to which this action contributes to the effect on CSD is uncertain. While gap junction inhibitors have been observed to modify spreading depression (Theis et al., 2005), gap junction blockers do not eliminate CSD in all instances (Világi et al., 2001; Peters et al., 2003). Therefore, although it is clear that tonabersat inhibits spreading depression, whether this is due to the effect of the drug on gap junctions remains to be demonstrated. However, it does raise the intriguing possibility that gap junctions could be drug target for migraine therapy.

9. AEDs Unlikely to be of Utility in Migraine

9.1 Carbamazepine and Oxcarbazepine

Carbamazepine was the first AED studied in migraine, but there is only very limited clinical evidence of efficacy (Rompel and Bauermeister, 1970; Frediani, 2004). Carbamazepine is active itself and also serves as a prodrug for the active metabolite carbamazepine-10,11-epoxide. Oxcarbazepine, the 10-keto analog of carbamazepine, also is biotransformed to active metabolites, *S*(+)-licarbazepine and *R*(-)-licarbazepine. The parent and its metabolites probably act mechanistically in a similar fashion to carbamazepine (see Rogawski and Löscher, 2004a). Interestingly, there is essentially no positive data in the literature on oxcarbazepine in migraine (see Frediani, 2004), suggesting that neither carbamazepine nor oxcarbazepine are clinically effective. Moreover, neither drug seems to be effective in blocking cortical spreading depression. Carbamazepine and oxcarbazepine are believed to protect against seizures largely through effects on voltage-gated sodium channels, which lead to the suppression of high-frequency repetitive action potential firing. While this action confers protection against partial and primary generalized tonic-clonic seizures, it is apparently not capable of preventing migraine. Clearly, not all AEDs are effective in migraine prophylaxis. It is tempting to suggest that antimigraine activity is a feature of “broad spectrum” AEDs (effective in partial and at least one type of primary generalized seizures other than primary generalized tonic-clonic seizures). This may be the case, however, gabapentin and pregabalin, which are not known to be broad-spectrum agents, would seem to contradict the rule. (Perhaps the efficacy of gabapentin and pregabalin relates to their analgesic activity rather than in an ability to influence the hyperexcitability that triggers migraine.) In any case, sodium channel blockade is not likely to be a promising strategy for the development of migraine prophylactic agents.

9.2 Carisbamate

Carisbamate (RWJ333369; *S*-2-O-carbamoyl-1-ochlorophenyl-ethanol) is a monocarbamate with a broad spectrum of activity in a wide range of rodent epilepsy models. A phase IIb clinical trial for the treatment of partial onset seizures was recently completed demonstrating efficacy and good tolerability (Novak et al., 2007). The compound is currently completing a phase III clinical trial in partial seizures. A trial in migraine demonstrated that carisbamate does not have activity for migraine prophylaxis.

9.3 Ganaxolone

Ganaxolone (3 α -hydroxy-3 β -methyl-5 α -pregnan-20-one) is the 3 α -methyl synthetic analog of the endogenous neurosteroid allopregnanolone (3 α ,5 α -P), a metabolite of progesterone. Ganaxolone, like 3 α ,5 α -P, does not have classical steroid hormone activity. Whereas it is believed that 3 α ,5 α -P can be converted to metabolites with hormonal activity, ganaxolone cannot. Ganaxolone is a powerful positive allosteric modulator of GABA_A receptors with potency and efficacy comparable to its endogenous congener 3 α ,5 α -P (Carter et al., 1997). Neurosteroid actions on GABA_A receptors occur at sites distinct from the benzodiazepine modulatory site (Hosie et al., 2007) and

neurosteroids fail to demonstrate tolerance (at least with respect to anticonvulsant activity) that limits the clinical utility of benzodiazepines (Reddy and Rogawski, 2000a). Ganaxolone is currently undergoing clinical trials for partial seizures in adults and infantile spasms (Nohria and Giller, 2007). In the 1990's, ganaxolone was extensively investigated as an abortive migraine therapy in single dose studies but was never evaluated for migraine prophylaxis. The first study (1042-0112) was a double-blind, placebo-controlled dose-ranging trial in 252 premenopausal women ages 18 to 55, 203 of whom received active drug within 8 hours of the onset of moderate or severe migraine with or without aura. There was a suggestion that pain relief was correlated with plasma concentration. In the second study (1042-0116), an open-label trial of 8 men and 22 women (3 of whom were included in the 1042-0112 study) in which ganaxolone was also administered within 8 hours of the onset of moderate or severe migraine, there was minimal correlation of pain relief at 2 hours with ganaxolone plasma concentration. In the final study (1042-0117), the allowable time from moderate to severe migraine headache onset to dosing was reduced to 2 hours. Groups of 163 subjects ages 18 to 65 (132 women and 31 men in each group) received active drug or placebo. There was no statistically significant difference between treatment groups in migraine pain relief at 2 or 4 hours postdose. A subgroup analysis of the menstruating women (25 receiving ganaxolone and 20 receiving placebo) demonstrated a statistically significant reduction in migraine pain ($p=0.046$) in the drug-treated subjects. Overall, the clinical trials provided little evidence to support further studies of ganaxolone in acute migraine therapy in an unselected population and development for this indication has not progressed. The conclusion that ganaxolone lacks efficacy in migraine must be tempered by the fact that dosing in all studies occurred after pain onset. It cannot be concluded that the outcome would have been similarly unimpressive had the drug been administered on a prophylactic basis. In any case, however, the conclusion that ganaxolone lacks efficacy is consistent with the notion that the GABA_A receptor is not an appropriate target for migraine therapy. The suggestion of utility in hormonally dependent migraine warrants attention. Given the potential of ganaxolone in the treatment of hormonally-sensitive epilepsy (Monaghan et al., 1999; Reddy and Rogawski, 2000b), the intriguing possibility exists that the drug would be useful as a prophylactic agent specifically in menstrual migraine.

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