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## Antiepileptic drugs and migraine

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### 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.<sup>1</sup> Among the pain syndromes for which AEDs are used, migraine headache is a common application. In the USA, 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.<sup>2-6</sup> Various open-label observational studies and small randomized controlled trials of topiramate and two large multicentre randomized controlled trials have established the effectiveness of topiramate in migraine prevention.<sup>7,8</sup> The US 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 beta-blockers and amitriptyline. Evidence from double-blind randomized placebo-controlled studies also support the effectiveness of gabapentin in migraine prophylaxis<sup>9,10</sup> and it is considered a third-line agent by BASH. Less robust clinical studies have indicated that carbamazepine,<sup>11</sup> lamotrigine,<sup>12-15</sup> zonisamide,<sup>16,17</sup> and levetiracetam<sup>18</sup> may also be effective in the treatment of migraine. A meta-analysis by the Cochrane Collaboration confirmed that as a class AEDs reduce migraine frequency and are relatively well tolerated.<sup>5</sup>

AEDs are generally useful for the treatment of disorders of excessive, synchronous cellular excitability.<sup>19</sup> They are broadly effective in suppressing excessive or ectopic activity in neural cells and in some instances in muscle.<sup>1</sup> 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 (CSD) 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.

## Migraine as an episodic disorder

The syndromes for which AEDs are used are characteristically episodic in nature. Episodic phenomena are common symptoms of disease.<sup>20,21</sup> 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.’ As 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 leads to a net increase in circuit excitability (as in severe myoclonic epilepsy in infancy<sup>22</sup>). 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.<sup>23,24</sup> As discussed by Ottman and Lipton,<sup>25</sup> 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% greater in relatives of migraineurs than in relatives of controls.<sup>26,27</sup> This suggests that complex genetic factors contribute to the risk for migraine, as is the case for epilepsy.<sup>28</sup> 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 (FHM), 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.

## 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  $\text{Ca}_v2.1$  of neuronal P/Q-type calcium channels.<sup>29</sup> 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  $\text{Ca}_v2.1$  current density in neurons.<sup>30</sup> Thus, precisely how the FHM mutations influence cellular excitability is obscure. Interestingly, mutations in *CACNA1A* are also associated with the episodic ataxia syndrome EA-2, the spinocerebellar ataxia syndrome SCA-6, and also idiopathic generalized epilepsy.<sup>31</sup> Moreover, mutations in homologues of the gene can cause absence-like seizures in rodents.<sup>32</sup>

The second FHM gene to be described was *ATP1A2*, which encodes the  $\alpha 2$  subunit of  $\text{Na}^+\text{-K}^+\text{-ATPase}$ .<sup>33</sup> 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.<sup>34</sup> Other allelic conditions include alternating hemiplegia of childhood, basilar-type migraine, and migraine without aura.<sup>35</sup> FHM mutations in *ATP1A2* lead to complete inactivation of the protein.<sup>36</sup> Seizures can be produced by inhibition of  $\text{Na}^+\text{-K}^+\text{-ATPase}$ ,<sup>37,38</sup> 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  $\text{Na}_v1.1$ .<sup>39</sup> 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.<sup>40</sup> 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+.<sup>41</sup> 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 influences ion channel gating and function.

### Cortical spreading depression

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<sup>42</sup> 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 3–5 mm/min. Recovery of the initial pattern of spontaneous activity occurred over 5–10 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<sup>43,44</sup>. Recording from small isolated slabs of cortex in *cereveau 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<sup>+</sup>'. 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 scotom as with a characteristic distribution of fortification figures. The disturbance usually starts at the centre of the visual field and propagates to peripheral zones within 10–15 min. Function returns to normal within another 10–15 min.<sup>45</sup> 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<sup>46</sup> 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.<sup>47,48</sup> 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.<sup>49</sup>

Given these various lines of evidence, there is general consensus that spreading depression accounts for migraine aura. However, as there are no pain fibres 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.<sup>50</sup> 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 the 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 brainstem, form synapses with neurons in the thalamus. Hippocampal spreading depression is also able to activate the trigeminal nucleus,<sup>51</sup> 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 as 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.<sup>52</sup>

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  $\text{Na}^+/\text{K}^+$ -ATPase.<sup>53</sup> 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,<sup>54</sup> 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 millimetres 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 non-synaptic 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.<sup>55</sup> 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.<sup>56</sup> 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.<sup>57</sup> At present, the contribution of astrocytes to spreading depression is incompletely defined; additional evidence is needed to characterize how and when they play a part, 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 part in migraine. It is probably too simplistic to presume that suppression of the high frequency firing noted by Grafstein<sup>43</sup> 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.

### 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.<sup>58,59</sup> 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 examples 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 provide insight into the neurobiological similarities and differences between migraine and epilepsy.

## Cellular mechanism of antiepileptic drugs widely used for migraine prophylaxis

### 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.<sup>60</sup> It has therefore been proposed that valproate acts through a combination of actions. Among these various actions, Löscher<sup>61,62</sup> 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 *N*-methyl-*D*-aspartate or kainate receptor-mediated synaptic transmission;<sup>63,64</sup> whether these actions could contribute to the efficacy of valproate in migraine prophylaxis is not known. As noted previously, valproate seems to potently 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.<sup>65,66</sup> However, recently Ayata *et al.*<sup>66</sup> found that prolonged treatment with valproate along with many other drugs useful in migraine prophylaxis, including beta-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.

### Topiramate

Several studies have shown that topiramate can suppress CSD in rats and cats at doses comparable with those that protect against seizures.<sup>66,67</sup> 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.<sup>68</sup> Pain in migraine is hypothesized to be due to activation of trigeminal nerve axons (presumably by CSD), which then release calcitonin gene-related peptide (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.<sup>69</sup> 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<sub>A</sub> 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.<sup>60,70</sup> The effects on sodium channels, high voltage-activated calcium channels, and GABA<sub>A</sub> 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.<sup>71</sup> Similarly, the carbonic anhydrase inhibition is not likely to be relevant to the antimigraine activity of topiramate.<sup>72</sup> 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 on retigabine below). These openers, which are analogues 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 *N*-methyl-*D*-aspartate receptors.<sup>73</sup> Thus, in cultured neurons, topiramate was found to inhibit responses to kainate, an agonist of AMPA and kainate receptors.<sup>73</sup> 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.<sup>74</sup> 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 neurobehavioural 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 linked with the 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<sup>75,76</sup> and GluR5 kainate receptor subunits and functional GluR5 kainate receptors are expressed in trigeminal neurons.<sup>77</sup> Moreover, GluR5 antagonists are active in migraine models<sup>78,79</sup> 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.<sup>80</sup> 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.<sup>81</sup> 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 trial 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.<sup>74</sup> 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,<sup>82</sup> 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.<sup>83</sup> 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.

## Antiepileptic drugs that are possibly effective for migraine prophylaxis

### Gabapentin and pregabalin

In the USA, gabapentin and its analogue 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 analogue 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<sub>A</sub> receptors. The drugs also do not interact with other sites on GABA<sub>A</sub> receptors, including the benzodiazepine recognition site.<sup>84</sup> 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.<sup>85</sup> The binding affinities of gabapentin, pregabalin, and related structures to  $\alpha 2\delta$  subunits correlates in a stereoselective fashion with their

analgesic activity.<sup>86</sup> 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 their analgesic activity without influencing the analgesic activity of morphine.<sup>87,88</sup> 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 accounts 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 approximately 150 kDa (997–1150 amino acid residues). There are four homologous forms, but only subtypes 1 and 2 bind gabapentin and pregabalin with high affinity.<sup>89</sup>  $\alpha 2\delta$ -1 and  $\alpha 2\delta$ -2 subunits are believed to form complexes with many voltage-dependent calcium channel types.<sup>90</sup> 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.<sup>85</sup> 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.<sup>91–94</sup> 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 as release under normal conditions is maintained.

Recent studies indicate that the ability of gabapentin and pregabalin to influence release of neuroactive substances may not be dependent upon calcium entry through voltage-sensitive calcium channels.<sup>85</sup> 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,<sup>88</sup> possibly by affecting physical interactions between presynaptic calcium channels and proteins mediating exocytosis.<sup>95</sup>

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.<sup>96</sup> 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.<sup>97</sup> 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.<sup>98</sup> 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.

## Zonisamide

There is limited information, largely from open label clinical trials, suggesting that zonisamide may be effective in migraine prophylaxis in adults and children.<sup>16,17,99–102</sup> 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 sulphonamide side chain. Topiramate also contains a sulphur atom in an *O*-sulphamate moiety that is structurally similar to the sulphonamide in zonisamide. Thus, zonisamide and topiramate are the only sulphur-containing AEDs. Carbonic anhydrase inhibitors such as acetazolamide also have a sulphonamide side chain, and indeed, both AEDs inhibit carbonic anhydrase.<sup>103</sup> 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. As 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<sup>60</sup>. 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 as there is no compelling evidence that more potent carbonic anhydrase inhibitors such as acetazolamide have antimigraine 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.<sup>104</sup> Studies with microdialysis in freely moving rats have indicated that zonisamide has complex effects on 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.

### Levetiracetam

Limited information from retrospective and open label trials suggests that levetiracetam may have utility in migraine prophylaxis.<sup>18,105–110</sup> Levetiracetam has been marketed for epilepsy therapy since 2000, but its molecular target in brain was only recently identified.<sup>111</sup> 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 analogues 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.<sup>112</sup> 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.

## Antiepileptic drugs in development with potential utility in migraine

### 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.<sup>113,114</sup> 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 analogue 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 behavioural models so that they have been advanced to clinical development.<sup>115,116</sup> 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.<sup>117,118</sup>

Three valproate-like compounds (two existing in more than one stereoisomeric form) 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 glycinamide; SPD493), which is now entering phase II development.<sup>119</sup> 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 anti-allodynic potency than valproate.<sup>116–118</sup> 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.<sup>120</sup> 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 programme for central nervous system 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.<sup>115</sup> Valnoctamide does not induce embryotoxicity in mice that are susceptible to valproate-induced spina bifida aperta.<sup>121</sup> 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 stereocentre. 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.<sup>122–124</sup> PID was also 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.<sup>125</sup> Phase I clinical trials indicated that the compound is safe and well tolerated, but it is not currently being developed.

## Retigabine

Retigabine [*N*-(2-amino-4-[fluorobenzylamino]-phenyl)carbamic acid; D-23129], the desaza-analogue of flupirtine (a non-opiate analgesic approved in Europe for general nociceptive pain), is an effective inhibitor of CSD<sup>126</sup> and therefore has potential in migraine therapy. Retigabine has activity in a broad spectrum of animal epilepsy models.<sup>127–129</sup> 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 multicentre, 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.<sup>130</sup> 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.<sup>131–133</sup> 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.<sup>134,135</sup> 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.<sup>136</sup> 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.<sup>126</sup>

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<sub>A</sub> receptors.<sup>137</sup> Thus, retigabine enhances GABA-activated chloride current responses and GABAergic IPSCs at concentrations that are only modestly higher than those that influence KCNQ channels.<sup>138,139</sup> It has been suggested that the effects of retigabine on GABA<sub>A</sub> receptors could contribute to its efficacy in epilepsy and also to side-effects.<sup>115</sup> However, as GABA<sub>A</sub> receptor positive modulating activity is not associated with efficacy in migraine prophylaxis, KCNQ openers that lack activity on GABA<sub>A</sub> receptors could

potentially have better tolerability.<sup>140</sup> Several novel compounds, including acrylamides, have been identified to have KNCQ opening activity and to inhibit CSD.<sup>141–144</sup> Some of these compounds are more than two 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.

### 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.<sup>145</sup> 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.<sup>146</sup> Its mechanism of action is not well understood.<sup>115</sup> Recently, however, it has been proposed that two predominant actions could contribute to therapeutic efficacy.<sup>145</sup> 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, as epileptic depolarization of neurons is more prolonged than ordinary synaptic depolarization and is typically of the order of tens of seconds, the time-scale where slow inactivation is pertinent. It is not known whether this mechanism would similarly be relevant to neuropathic pain or migraine. 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.

### 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.<sup>147–149</sup> 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,<sup>150</sup> gap junction blockers do not eliminate CSD in all instances.<sup>151,152</sup> 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 targets for migraine therapy.

## Antiepileptic drugs unlikely to be of utility in migraine

### Carbamazepine and oxcarbazepine

Carbamazepine was the first AED studied in migraine, but there is only very limited clinical evidence of efficacy.<sup>11,153</sup> Carbamazepine is active itself and also serves as a prodrug for the active metabolite carbamazepine-10,11-epoxide. Oxcarbazepine, the 10-keto analogue 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<sup>19</sup>. Interestingly, there is essentially no positive data in the literature on oxcarbazepine in migraine<sup>153</sup>, suggesting that neither carbamazepine nor oxcarbazepine are clinically effective. Moreover, neither drug seems to be effective in blocking CSD. 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 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.

### 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.<sup>154</sup> 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.

### Ganaxolone

Ganaxolone (3 $\alpha$ -hydroxy-3 $\beta$ -methyl-5 $\alpha$ -pregnan-20-one) is the 3 $\alpha$ -methyl synthetic analogue of the endogenous neurosteroid allopregnanolone (3 $\alpha$ ,5 $\alpha$ -P), a metabolite of progesterone. Ganaxolone, like 3 $\alpha$ ,5 $\alpha$ -P, does not have classical steroid hormone activity. Whereas it is believed that 3 $\alpha$ ,5 $\alpha$ -P can be converted to metabolites with hormonal activity, ganaxolone cannot. Ganaxolone is a powerful positive allosteric modulator of GABA<sub>A</sub> receptors with potency and efficacy comparable with its endogenous congener 3 $\alpha$ ,5 $\alpha$ -P.<sup>155</sup> Neurosteroid actions on GABA<sub>A</sub> receptors occur at sites distinct from the benzodiazepine modulatory site<sup>156</sup> and neurosteroids fail to demonstrate tolerance (at least with respect to anticonvulsant activity) that limits the clinical utility of benzodiazepines.<sup>157</sup> Ganaxolone is currently undergoing clinical trials for partial seizures in adults and infantile spasms in children aged 4–24 months.<sup>158</sup> In the 1990s, 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 18–55, 203 of whom received active drug within 8 h 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 eight men and 22 women (three of whom were included in the 1042-0112 study) in which ganaxolone was also administered within 8 h of the onset of moderate or severe migraine, there was minimal correlation of pain relief at 2 h 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 h. Groups of 163 subjects ages 18–65 (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 h 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<sub>A</sub> 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,<sup>159,160</sup> the intriguing possibility exists that the drug would be useful as a prophylactic agent specifically in menstrual migraine.

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