Antiepileptic Drugs: How They Work in Headache

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Antiepileptic drugs (AEDs) are promising agents for the prevention of migraine and other head pain. Migraine and epilepsy share several clinical features and respond to many of the same pharmacologic agents, suggesting that similar mechanisms may be involved in their pathophysiology. The mechanisms of action of AEDs are not fully understood, and a single drug may have more than one mechanism, both in epilepsy and in migraine. Valproate, topiramate, and gabapentin are likely to affect nociception by modulating gamma-aminobutyric acid- (GABA-) and/or glutamate-mediated neurotransmission. All three AEDs enhance GABA-mediated inhibition. Valproate and gabapentin interfere with GABA metabolism to prevent its ultimate conversion to succinate, and topiramate potentiates GABA-mediated inhibition by facilitating the action of GABA receptors. In addition, topiramate acts directly on non-*N*-methyl-D-aspartate, alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid/kainate glutamate receptors. Valproate, topiramate, and possibly gabapentin inhibit sodium ion channels. All three drugs modulate calcium ion channel activity. Valproate blocks T-type calcium ion channels; topiramate inhibits high-voltage-activated L-type calcium ion channels; and gabapentin binds to the $\alpha_2\delta$ subunit of L-type calcium ion channels. AEDs may be useful in migraine prevention through such mechanisms as modulating the biochemical phenomena of aura or acting directly on the nociceptive system. Further evaluations of AEDs in migraine models will provide a better understanding of the pathophysiology and prevention of migraine.

Key words: GABA, gabapentin, glutamate, migraine, topiramate, valproate

Abbreviations: AED antiepileptic drug, MOA mechanism of action, GABA gamma-aminobutyric acid, NMDA *N*-methyl-D-aspartate, AMPA alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid

In recent years, antiepileptic drugs (AEDs) have shown considerable promise in the prevention of migraine and other severe forms of headache. Physicians in the 19th century believed that migraine was actually a form of epilepsy,[1] and although they are likely to be two distinct disorders, migraine and epilepsy share several clinical features and in many cases respond to similar pharmacologic strategies.[2]

Since Sørensen first reported the effectiveness of valproate (the sodium salt of valproic acid) for migraine prevention in 1988, AEDs as a class have emerged as important options in migraine prevention.[3] Preclinical studies, as well as early clinical trials, indicate that some of the newer AEDs, including gabapentin and topiramate, may also be effective in the prevention of migraine and other head pain based on their mechanisms of action (MOAs).[4-6]

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KNOWN MOAS OF AEDS

Our understanding of the MOAs of AEDs is based on their anticonvulsant profiles in animal models of epilepsy, yet these mechanisms have not been fully explained.[9] AEDs appear to target one or more molecular sites in the brain, with the ability to alter neurotransmission through their effects on ion channels, neurotransmitter receptors, and neurotransmitter metabolism.

GABA-Mediated Inhibition.—The neurotransmitter system most commonly associated with AEDs is an inhibitory system involving gamma-aminobutyric acid (GABA), an amino acid widely distributed throughout the central nervous system.[10] GABA is synthesized in neurons from glutamate by the enzyme glutamic acid decarboxylase (Figure 1).[11] It is then degraded by another enzyme, GABA transaminase, to succinate semialdehyde, which, in turn, is

metabolized by succinate semialdehyde dehydrogenase to succinate. When released from the presynaptic axon terminal, this inhibitory neurotransmitter crosses the synapse and binds to one of at least two, and possibly more, subtypes of neuronal receptor complexes.[10] The $GABA_A$ receptor subtype is a pentameric transmembrane chloride ion channel with binding sites for several substances, including endogenous GABA, barbiturates, benzodiazepines, neurosteroids, and ethanol. The release of GABA also activates the $GABA_B$ receptor, a G-protein coupled receptor on the postsynaptic membrane.

GABA binding to its receptors causes an influx of chloride ions and an efflux of potassium ions, resulting in hyperpolarization and inhibition of the postsynaptic neuron. Reuptake of GABA may occur in the presynaptic terminal or from the extracellular space by glial cells.

Certain drugs, such as barbiturates and benzodiazepines, enhance GABA binding to receptor sites in the postsynaptic membrane and can therefore be used to modulate GABA-mediated inhibition.[10] This is probably important for their therapeutic effectiveness in epilepsy.

Glutamate-Mediated Excitation.—Glutamate is an amino acid found in high concentrations in the brain.[10] In contrast to GABA, glutamate exerts powerful excitatory, rather than inhibitory, effects throughout the central nervous system. Valproate and topiramate affect glutamate-mediated excitation,[11] an action which may be important in both epilepsy and migraine.[12]

Following its release from the presynaptic terminal, glutamate normally moves through the synapse to receptors at postsynaptic binding sites.[11] This excitatory neurotransmitter system, however, is modulated by sodium and calcium ion channels in the presynaptic terminal (Figure 2). An influx of sodium causes depolarization of the presynaptic membrane, resulting in an increased influx of calcium into the axon and release of stored glutamate into the synapse. Glutamate then binds to both *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors on the

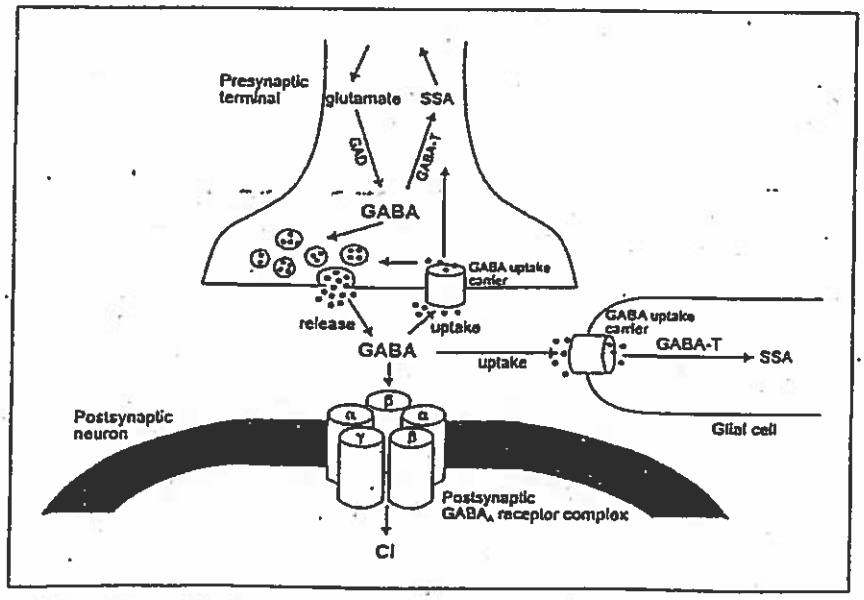

Fig 1.—Gamma-aminobutyric acid (GABA)-mediated inhibition. Glutamate is synthesized in the presynaptic terminal, and GABA is synthesized from glutamate by the enzyme glutamic acid decarboxylase (GAD). GABA is degraded by the enzyme GABA transaminase (GABA-T) to succinic semialdehyde (SSA). GABA is contained in synaptic vesicles and released into the synapse upon presynaptic depolarization. Reuptake occurs in the axon or by glial cells from the extracellular space. Postsynaptically, GABA activates the pentameric $GABA_A$ receptors, which stimulate the influx of chloride ions through the GABA-gated chloride channel, and $GABA_B$ receptors (not pictured), which stimulate the efflux of potassium, resulting in hyperpolarization or inhibition of the postsynaptic neuron. Reprinted from *Progress in Neurobiology*, Vol 58, Löscher W, Valproate: a reappraisal of its pharmacodynamic properties and mechanisms of action, pages 31-59, ©1999, with permission from Elsevier Science.

postsynaptic membrane, where binding at the non-NMDA receptor causes an influx of sodium ions into the dendrites and excitation of the postsynaptic neuron. This excitatory action subsequently displaces magnesium ions from the NMDA receptor pore, causing an influx of calcium and sodium ions through the NMDA receptor/ion channel complex and depolarization of the postsynaptic neuron.

Calcium-Mediated Excitation.—Several roles for calcium ion channels have been described.[13] For example, high-voltage-activated calcium ion channels in the presynaptic membrane participate in the regulation of neurotransmitter release (Figure 2). Potential sites of action for calcium channel blocking drugs are L-type and T-type calcium ion channels. L-type calcium ion channels are involved in generating action potentials and in converting the membrane potential change to an intracellular Ca^{++} signal.[13] T-type calcium ion channels contribute to synchronization of the thalamocortical circuits that appear to underlie the spike-and-wave pattern of absence seizures.[14]

DRUG-SPECIFIC MOAS

Most AEDs appear to act through several cellular mechanisms (Table).[9,11,15-17] Their efficacy in the treatment of epilepsy may be due to this combination of mechanisms, since epilepsy is probably a disease with multiple etiologies.[11]

Valproate and Divalproex Sodium.—Valproate is a simple, eight-carbon branched-chain fatty acid with unique antiepileptic properties.[11] It is used widely for the treatment of partial and generalized seizures and is thought to have at least three potential MOAs.[9] Valproate increases GABA levels in the brain and potentiates GABA-mediated responses. One possibly important action of valproate is the blockade of the degradation of GABA by GABA transaminase, thereby increasing GABA concentrations in both axon and in glial cells (Figure 3). Its effect on GABA levels was observed at high doses; thus, the functional role of increased GABA levels following treatment with valproate is uncertain.

A number of in vitro and animal studies suggest other MOAs of valproate; however, the antiepileptic effects achieved in these studies were observed at levels considerably higher than therapeutic doses in humans.[11] In vitro, valproate has been found to block voltage-dependent sodium ion channels, thereby modulating the release of excitatory amino acids, and to block low-threshold T-type calcium ion channels. Valproate can also reduce levels of aspartate, glutamate, and other excitatory amino acids in cell cultures and

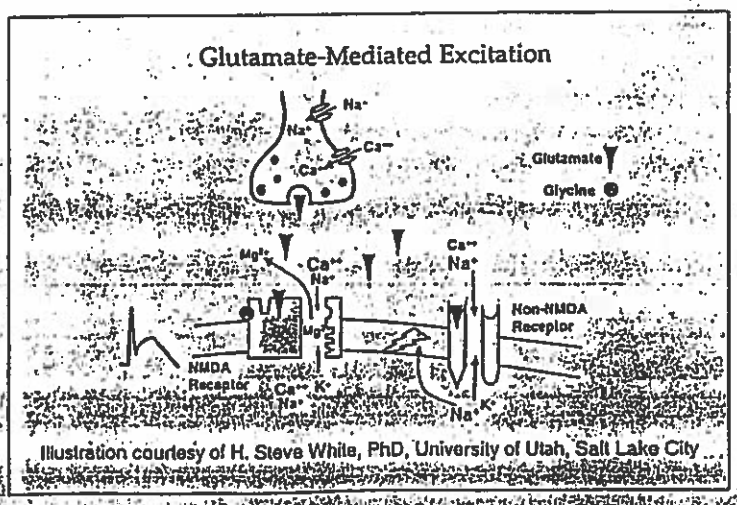

Fig 2.—Glutamate-mediated excitation. Glutamatergic neurotransmission is regulated by sodium and calcium ion channels in the presynaptic axon. An influx of sodium causes depolarization of the presynaptic membrane, resulting in an increased influx of calcium into the presynaptic terminal and release of stored glutamate into the synapse. Glutamate binding to AMPA receptors causes an influx of sodium ions into the postsynaptic neuron and excitation. Postsynaptic depolarization displaces magnesium ions from the NMDA receptor pore, causing an influx of calcium and sodium ions and further depolarization of the neuron.

Cellular Mechanisms of Action of Selected Antiepileptic Drugs [9,11,15–17]

Drug	Modulatory Effect on GABA System	Modulates Glutamate-Mediated Excitation	Reduced Activity of Voltage-Gated Na^+ Channels	Reduced Activity of L-Type Ca^{++} Channels
Valproate	+	±	+	NE*
Gabapentin	+	±	±	±†
Topiramate	+	+	+	+

NE indicates not effective.
*At high concentrations, valproic acid has been shown to reduce activity of T-type Ca^{++} channels.[16]
†Binds to the $\alpha_2\delta$ subunit of voltage-sensitive L-type Ca^{++} channels.[17]

rat models to suppress excitation. Other in vitro models have demonstrated valproate-mediated suppression of protein kinase C, a substance known to regulate the glutamatergic system, as well as direct suppressive effects on neuronal membranes.[18,19]

Divalproex sodium is a stable coordination product composed of sodium valproate and valproic acid, created by a partial reduction using sodium hydroxide. Currently, it is the only AED approved by the US Food and Drug Administration for migraine prevention. Divalproex sodium is also indicated for the treatment of complex partial seizures, as well as simple and complex absence seizures.[20]

Gabapentin.—Gabapentin is approved as adjunctive therapy in adults and children (>3 years) with partial seizures with or without secondary generalization.[21] It is a cyclohexane acetic acid/GABA analog that has no effect at $GABA_A$ or $GABA_B$ receptors. Although the MOA of gabapentin in epilepsy is not thoroughly understood, it appears to have multiple antiepileptic effects.[6] Gabapentin increases the concentrations of, and possibly the rate of synthesis of, GABA in the brain (Figure 4). Increased concentrations of GABA are then released into the synapse following activation of the presynaptic neuron. The released GABA binds to postsynaptic receptors,

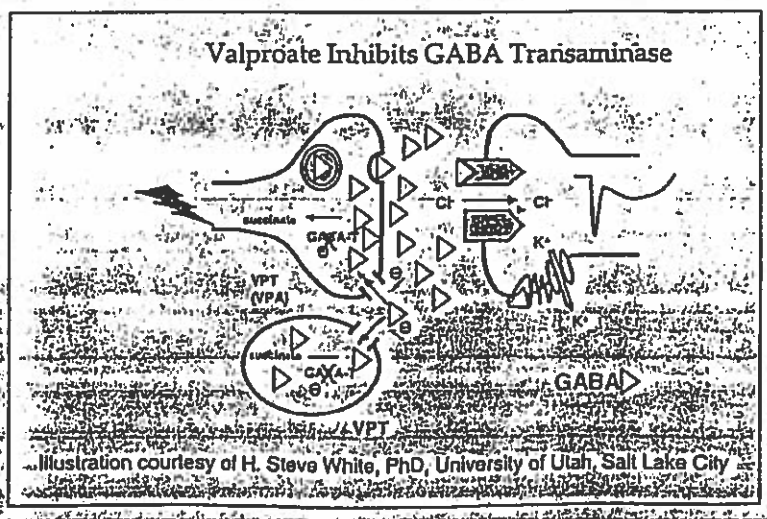

Fig 3.—Valproate-mediated gamma-aminobutyric acid (GABA)-transaminase inhibition. Valproate (VPT) inhibits GABA transaminase, preventing the metabolic breakdown of GABA and increasing GABA concentrations in the axon and in glial cells.

causing an influx of calcium ions into the presynaptic terminal. Gabapentin is also thought to enhance GABA release through nonvesicular mechanisms.[6,9] In a porcine model, gabapentin has been shown to interact with a specific subunit ($\alpha_2\delta$) of the calcium ion channel to modulate calcium ion current. It also reduces the release of several monoamine neurotransmitters. With prolonged administration in a murine model, gabapentin limits sustained repetitive firing through action at voltage-sensitive sodium ion channels.[9,17]

Gabapentin may exert its antiepileptic effect by increasing GABA in the presynaptic axon and suppressing GABA metabolism (Figure 4).

Topiramate.—Topiramate is a sulfamate-substituted monosaccharide derived from D-fructose that is structurally distinct from other AEDs.[7,21] It is used in the treatment of partial-onset and primary generalized tonic-clonic seizures and is being evaluated for migraine prevention.

Like valproate, topiramate has several potential MOAs that may be relevant in epilepsy and in migraine. In preclinical studies, topiramate has been found to have at least four mechanisms possibly relevant to its antiepileptic activity[7,21]:

- Topiramate blocks voltage-sensitive sodium ion channels and limits sustained repetitive firing.
- Topiramate enhances neurotransmission of GABA by facilitating $GABA_A$ receptor action through nonbenzodiazepine and nonbarbiturate mechanisms (Figure 5). It increases the opening frequency of the chloride ion channels in $GABA_A$ receptors. Its action on chloride ion channels is not blocked by the benzodiazepine antagonist flumazenil. Unlike barbiturates, topiramate has no effect on the duration of chloride ion channel opening.
- Topiramate is a negative modulator of the excitatory neurotransmitter glutamate, which acts by binding to the non-NMDA alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate receptor, thereby decreasing the flow of sodium and calcium ions across the postsynaptic membrane. Topiramate has no effect on the NMDA receptor.
- Topiramate reduces the activity of L-type Ca^{++} channels.
- Topiramate is a weak inhibitor of carbonic anhydrase. It is unclear whether this mechanism is involved in its antiepileptic action.

Pathophysiology of Migraine.—A migraine attack develops through a cascade of clinical events. Therefore, it is likely that more than one potential site of action exists for AEDs in the treatment of migraine.[2] The migraine attack can be divided into four stages, beginning

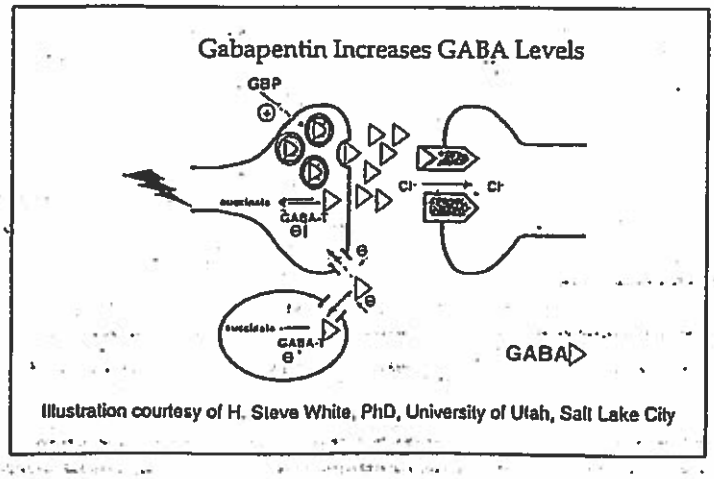

Fig 4.—Gabapentin-mediated increase in gamma-aminobutyric acid (GABA) levels. Gabapentin (GBP) increases the concentrations of, and possibly the rate of synthesis of, GABA in the brain, which may enhance GABA release through nonvesicular mechanisms.

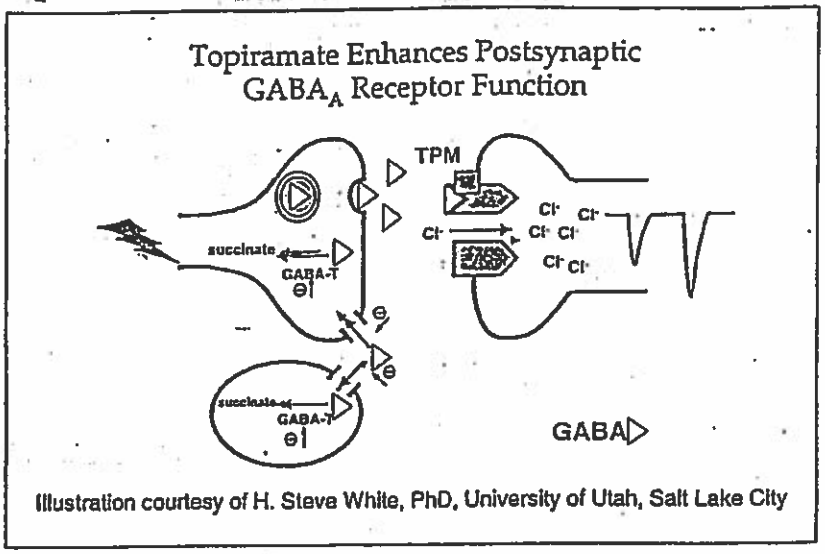

Fig 5.—Effect of topiramate (TPM) on postsynaptic GABA$_A$ receptor function. TPM facilitates GABA$_A$ receptor action by increasing the opening frequency of chloride ion channels through nonbenzodiazepine and nonbarbiturate mechanisms.

with a premonitory period up to 24 hours before the onset of headache (up to 60% of migraineurs experience the prodrome).[22] The next stage, the aura, is a complex of focal neurologic symptoms that can be characterized by visual, sensory, motor, or language disturbances. Visual disturbances of migraine aura often spread across the visual field. The aura phase can be followed by the headache phase; pain is typically unilateral and throbbing, and may persist up to 3 days. The migraine attack finally resolves (headache resolution phase) as the pain wanes, often leaving the patient fatigued and listless.

This cascade of clinical events is likely to reflect a series of biochemical brain events, many of which are not understood. There is increasing evidence that the cerebral cortex is involved early in the process in patients who experience aura, as evidenced by the slow, spreading decreases in cortical blood flow and activation capacity similar to that observed in animal models of spreading depression.[23] In these models, propagation of spreading depression requires the activation of NMDA glutamate receptors.[2]

Activation of the primary afferent neurons of the trigeminovascular system plays a pivotal role in the generation of migraine pain and its associated symptoms (Figure 6).[23] Primary afferent fibers within the trigeminal nerve carry nociceptive information through the trigeminal ganglion and terminate in the trigeminal nucleus caudalis, an area of pain processing in the brain stem. Through a parallel process, the pain may be perpetuated and gradually intensified. Depolarization of the trigeminovascular nociceptive neurons triggers the release of neuropeptides from the activated nerve terminals. These neuropeptides, including substance P, neurokinin A,[23] and calcitonin gene-related peptide, are protein fragments that are associated with a neurogenic inflammatory response, which may lead to vasodilation, extravasation, and activation of the local cellular immune response. These events may be associated with a lowering of the threshold for reactivation, which creates a positive feedback loop, resulting in a perception of increasing pain.

Mechanisms of AEDs in Headache Pain.—Animal models have provided clues to the mechanisms involved in the inhibitory effects of AEDs on pain. In one model of trigeminal pain, afferent meningeal nociceptive neurons were activated with a chemical irritant (capsaicin). The nociceptive information was then transmitted into the trigeminal nucleus caudalis, where the number of second-order neurons expressing the immediate early gene c-fos provided a semiquantitative measurement of the extent to which the pain system was activated.[24]

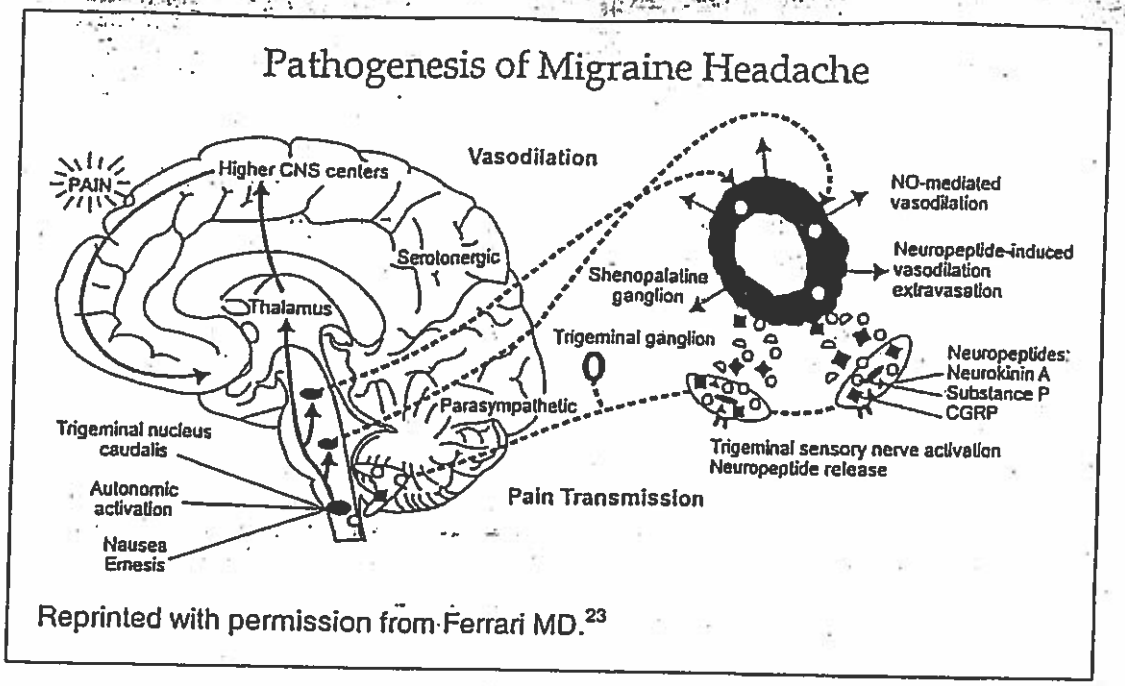

Fig 6.—Pathogenesis of migraine headache. Activation of the trigeminovascular system is pivotal to headache and its associated symptoms. Afferent fibers transmit nociceptive information to the trigeminal nucleus caudalis in the lower brain stem. Depolarization of the trigeminal ganglion activates the trigeminovascular system, in which released neuropeptides (substance P, neurokinin A, CGRP) produce a neurogenic inflammatory response leading to vasodilation and extravasation.

In this model, the GABAergic drug butalbital, a barbiturate component of a compound widely used for migraine treatment, exerts a significant ($P<.01$) dose-related, suppressive effect on c-fos expression within the nucleus caudalis at doses of 100 and 1000 μg/kg. Furthermore, the effect can be reversed by pretreatment with 30 μg/kg of the $GABA_A$ antagonist bicuculine ($P<.01$), suggesting that butalbital has a direct effect on pain through the $GABA_A$ system and that this may be one of its mechanisms in migraine or other head pain.

The same model was used to determine whether valproate, which enhances GABA synthesis and blocks GABA degradation, may have a similar mechanism in migraine. When administered in doses of 1, 3, 10, and 20 mg/kg, valproate also exhibits dose-dependent suppression of c-fos expression in this animal model, and the effect of the two highest doses was significant when compared with controls ($P<.05$).[24]

Pretreatment with bicuculine blocked the suppressive effects of valproate.[24] These findings suggest that models of trigeminal pain may be useful in assessing other drugs with high affinity for the $GABA_A$ receptor as potential antimigraine agents.

SUMMARY

Several AEDs have demonstrated efficacy in the prevention of migraine. Each of these drugs may have more than one mechanism of action.

Valproate, topiramate, and gabapentin modulate GABA- and/or glutamate-mediated neurotransmission. All three AEDs enhance GABA-mediated inhibition. Valproate and gabapentin interfere with GABA metabolism to prevent its ultimate conversion to succinate, and topiramate enhances $GABA_A$ receptor activity. In addition, topiramate acts directly on non-NMDA AMPA/kainate glutamate receptors.

Valproate, topiramate, and possibly gabapentin inhibit sodium ion channels. All modulate calcium ion channel activity: valproate by blocking T-type calcium ion channels, topiramate by inhibiting high-voltage-activated calcium ion channels, and gabapen-

tin by binding to the $\alpha_2\delta$ subunit of L-type calcium ion channels.

From what is known of the effects of glutamate, sodium ion channels, and GABA modulation in the aura phase of migraine, it is reasonable to speculate that the initiation of migraine may be affected by modulation of the biochemical phenomena of aura. AEDs may also be able to modulate the nociceptive system directly through their actions on glutamate and GABA. This is an exciting era in migraine research, as AEDs are not only evaluated for their potential in preventing migraine, but also used as experimental tools to better define the pathophysiology of this often debilitating illness.

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