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Review article

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ACTIONS OF SODIUM VALPROATE ON THE CENTRAL NERVOUS SYSTEM

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The branched chain fatty acid, valproate, has a number of distinct pharmacological effects on the central nervous system. In experimental animals it showed clear anticonvulsant activity, an observation which led to its major clinical use as an antiepileptic agent, especially in petit mal seizures. More recently, valproate has shown its usefulness in treating mood disorders and migraine headaches. The basis for its clinical efficacy might be related to its ability to enhance central GABAergic neurotransmission or perhaps to its inhibition of Na^+channels. Whether each of the distinct therapeutic effects of valproate has the same molecular basis is not known.

Key words: *valproate, epilepsy, migraine headaches, mood disorders, GABA, Na^+ channels.*

INTRODUCTION

Valproic acid (also known as 2-propylpentanoic acid or *n*-dipropylacetic acid) is a branched chain fatty acid (*Fig. 1*), and is a liquid at room temperature. Indeed, it is because of its physical properties that we now know this is an important antiepileptic drug. Meunier and colleagues (1) were studying compounds for their effects against drug-induced seizures in experimental animals. These compounds were dissolved in valproic acid before injection. Each of the drugs exhibited anticonvulsant properties and subsequently the investigators showed that it was the vehicle which provided the pharmacological effects. Sodium valproate, the sodium salt, is equally efficacious at suppressing seizures.

In addition to its inhibitory effects on epileptic seizures, sodium valproate is also a useful drug in the suppression of the development of migraine

headaches (2) and as a means of treating patients with emotional disorders such as manic depressive illness or panic disorder (3, 4).

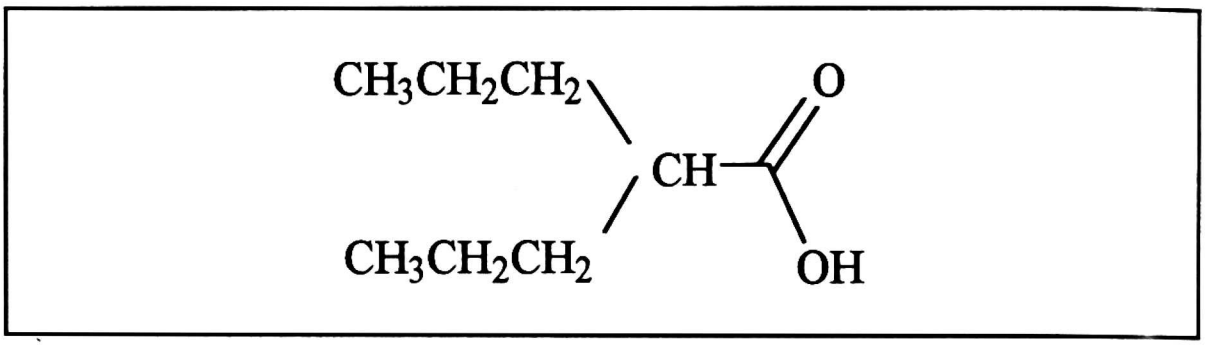

Fig. 1. Chemical structure of valproic acid

PHARMACOLOGY

Antiepileptic Activity

Valproate is unusual as an anticonvulsant since it is effective against most forms of epilepsy, particularly generalized seizures. Moreover, in experimental animals it requires relatively high doses to be effective (plasma levels: 1.4—3.5 mM) yet in humans a much lower dose is adequate (plama concentration range: 350—700 μM) (5). In animal models of epilepsy valproate is the most effective against pentylenetetrazol-induced seizures, a model for absence seizures, but it also provides good protection against electroshock-induced convulsions, a model of grand mal epilepsy (6).

Mechanism of Anticonvulsant Effect

The two broad types of mechanisms to be considered are (a) those involving intracellular events, e.g., inhibition of enzyme activity or effects on nucleic acid function, and (b) those involving events at the plasma membrane, e.g., alterations of ion channel or receptor function. These mechanisms are not necessarily mutally exclusive.

1. Effects on intracellular events

Since γ-aminobutyric acid (GABA) is the main inhibitory chemical transmitter in the brain (7), it is intuitive to speculate that it might be associated with seizure activity. Indeed, there is considerable evidence from animal studies that a reduction in GABA function leads to convulsive activity (8, 9). Such strong evidence, though, is lacking in human epilepsy (10). Nevertheless, in principle a drug that can enhance central GABA

neurotransmission should possess antiepileptic properties. The mechanism of action of several clinically useful therapeutic agents support this idea, e.g., phenobarbital, diazepam, and vigabatrin. Consequently, it is not surprising that studies of the potential effects of valproate on the GABA system have received much attention.

The first attempt at elucidating the mechanism of action of valproate by studying effects on GABA was reported by Godin *et al.* (11). They injected 200 mg/kg into rats and after 1 hr the GABA content of whole brain had increased approximately 30%. The rise in GABA levels was attributed to the inhibition of GABA aminotransferase, an effect they also showed to occur *in vitro*, albeit at high inhibitor concentrations. Further experiments (12) confirmed the elevated brain GABA concentrations following valproate treatment and the weak inhibitory action of valproate on GABA aminotransferase. The nature of this inhibition was found to be competitive with respect to GABA. Others observed that sub-chronic treatment of rats with valproate for 10 days led to an increase in GABA concentrations in several brain regions (13); and in human epilepsy GABA levels were elevated in cerebrospinal fluid after valproate administration (14). A detailed kinetic analysis of the inhibition of rabbit brain GABA aminotransferase by valproate supported the competitive nature of the inhibition, yielding a K_i of 42 mM and confirming the low sensitivity of the enzyme to the inhibitor (15). After administering high doses of valproate to audiogenic seizure-susceptible mice, Anlezark *et al.* (16) reported a total lack of response to auditory stimulation, together with a 57% increase in brain GABA levels and a modest reduction in GABA aminotransferase activity 45 min later. Löscher (17) measured GABA aminotransferase activity in synaptosomes isolated from various brain regions after the intraperitoneal injection of valproate, and noted that enzyme activity decreased by about 25% in substantia nigra, with smaller reductions in the pons and medulla. When whole tissue was used, however, no such decreases in enzyme activity were apperent. Interestingly, from an investigation employing neurons and astrocytes in culture, it was found that neuronal GABA aminotransferase was much more sensitive to valproate than the glial enzyme (18). Other studies, though, have failed to show an effect on GABA aminotransferase activity *in vivo* after valproate treatment (19—21).

Hearl and Churchich (22) have presented convincing evidence that GABA aminotransferase and succinic semialdehyde dehydrogenase (SSADH) form a catalytic protein complex which is responsible for the metabolic conversion of GABA to succinate, allowing the carbon skeleton of GABA to enter the citric acid cycle. Compared with its weak effect on GABA aminotransferase, valproate is much more effective at inhibiting SSADH — about 30-times, in fact (23). This has led to the suggestion that the elevation of GABA levels in the brain are the indirect result of the inhibition of SSADH. The actual mechanism

might be a slow-down in GABA aminotransferase activity caused by an accumulation of its product, succinic semialdehyde, and by an actual reversal of the reaction (24). Maitre *et al.* (25) used a series of SSADH inhibitors in order to see if GABA synthesis from succinic semialdehyde could be detected. No synthesis could be measured, but since these were *in vitro* experiments, the relevance of the observations have to be questioned. Even if a reversal of GABA aminotransferase did occur under such conditions, it would not be expected that the concentrations of succinic semialdehyde in the brain would contribute significantly to the reported increases in GABA levels. However, it has been calculated that the plasma concentrations of valproate required for it to be an effective antiepileptic agent are in the range 0.1-0.8 mM (26), and it could be anticipated that levels in the brain would be below these values. Indeed, one study claims that this concentration is about 50 μM (27). Accordingly, it seems improbable that a direct inhibition of GABA aminotransferase occurs. Even the idea of an inhibition of SSADH *in vivo* to explain the anticonvulsant effects of valproate is difficult to sustain since relatively high K_i values have been reported (0.5 mM to 1.5 mM) (23, 24).

Some studies have indicated that another mechanism to explain the elevation of cerebral GABA concentrations by valproate might be an increase in glutamate decarboxylase activity (28—30). Other investigations have supported this idea. For example, Löscher (31) reported an increase in GABA turnover in certain brain regions after valproate administration, and experiments by Taberner *et al.* (32) demonstrated that the incorporation of ^{14}C from radiolabelled glucose into GABA was increased in rats receiving valproate. On the other hand, two studies in which the incorporation of ^{14}C from glutamate into GABA was measured clearly show that [^{14}C]GABA formation was *inhibited* by valproate (33, 34). Moreover, Godin *et al.* (11) noticed a weak inhibition of glutamate decarboxylase *in vitro*. Hence the notion that the observed increases in GABA levels after valproate dosing are due to an increased synthesis of the amino acid is still open to doubt.

γ-Hydroxybutyrate (GHB) is a metabolite of GABA that possesses certain attributes of an inhibitory neurotransmitter (35). It is synthesized in brain by the catalytic action of succinic semialdehyde reductase. *In vitro* studies have indicated that valproate can inhibit this biosynthesis (36). However, a recent report suggests that a cloned version of the enzyme from rat is insensitive to valproate (37). Consequently, how much of the pharmacology of valproate is related to its effects on GHB is unknown.

Valproate might have an effect on gene regulation because when incubated with rat C6 glioma cells, it was found to increase the DNA binding activity of activator protein-1 (AP-1) transcription factors by up to two-fold. The effect was time- and concentration dependent (38). Similar results have been observed with human neuroblastoma cells (39). Glycogen synthase kinase can

phosphorylate the protein c-*jun*, an effect which can inhibt AP-1 DNA binding activity. Chen *et al.* (40) found that valproate can inhibit the kinase in a concentration-dependent manner, suggesting that the observed valproate-mediated increases in AP-1 binding to DNA are the results of a reduction in the amount of phosphorylated c-*jun*. Experiments using human neuroblastoma SH-SY5Y cells supported this concept (40).

Another possible genomic site of action of valproate might be the neuroprotective protein bcl-2. Chronic administration of valproate to rats led to a substantial increase in the number of bcl-2 immunoreactive cells in layers 2 and 3 of the frontal cortex (41). Bcl-2 seems to offer protection agains conditions that induce neuronal degeneration (42, 43). An earlier study had demonstrated that valproate can protect cultured cerebellar neurons in culture from degeneration (44).

Valproate has been shown to alter β-adrenergic receptor function in rat C6 glioma cells. Chronic exposure reduced both the number of receptors and the capacity of cell membranes to bind [^{3}H]forskolin. In addition, the ability of forskolin to stimulate cAMP production was impaired (45).

2. Membrane Effects

Sodium Channels

There is evidence that vlproate can interfere with both use-dependent and voltage-dependent Na^+ channels within the nervous system. Normally there is an increase in the rate of high frequency firing of action potentials during a train, but valproate can limit these increases. Moreover, the slow-down in the firing rate is further reduced by depolarizing from hyperpolarized potentials (46). The use- and voltage-dependency of the valproate effects are consistent with the pharmacology of the anticonvulsant which is known to inhibit repetitive discharges during convulsions but to have little effect on normal nerve cell activity.

Nosek (47) measured changes in action potentials in the crayfish stretch receptor in the presence of valproate. There was a reduction in axon excitability and a decrease in Na^+ and K^+ currents. Similar results were obtained when peripheral nerve fibers of *Xenopus* were used (48). Other workers have reported that valproate can significantly inhibit fast Na^+ currents (49, 50), although Taverna *et al.* (51) failed to observe an effect of valproate up to 200 μM on fast Na^+ currents in acutely dissociated neocortical neurons. However, low concentrations of valproate (10-30 μM) markedly reduced the persistent fraction of the Na^+ current.

Adrenal chromaffin cells, which are derived from neural crest, can be grown in culture. Bovine cells contain the α- and β_1-subunit of voltage-dependent Na^+ channels, as well as the nicotine-ion channel complex and voltage-dependent

Ca^{2+} channels. Yamamoto *et al.* (52) exposed bovine chromaffin cells to valproate for up to six days. There was a time-dependent increase in the binding of saxitoxin, a site 1 ligand, which could be abolished by the presence of cycloheximide, a protein synthesis inhibitor. The presence of valproate also potentiated the veratridine-induced influx of Na^+ and at the same time potentiated the veratridine-induced Ca^{2+} influx. The valproate treatment also increased the nicotine-induced Na^+ influx through the ion channel of the nicotinic receptor. The mRNA for both the α- and the β-subunits of the Na^+ channel was substantially increased by the valproate treatment. How can these increases in Na^+ channel expression after repeated valproate exposure be explained in light of the evidence that acute administration leads to a reduction in Na^+ influx? If there is a decrease in Na^+ entry into the cell via voltage-sensitive channels, the cell might respond by synthesizing more of the Na^+ channel protein, a process that could be considered an up-regulation. The reported decreases in use- and voltage-dependent Na^+ currents induced by valproate (46) are unlikely to be a direct effect of the drug on the Na^+-channel protein complex since valproate was unable to inhibit the binding of either [^{3}H] saxitoxin or [^{3}H] BTX-B (53, 54). These ligands recognize Na^+-channel receptor sites 1 and 2, respectively. Accordingly, the most likely explanation is that valproate, a hydrophobic fatty acid, perturbs the plasma membrane adjacent ot the channel, interfering with Na^+ fluxes.

Potentation of GABA Responses

In cultured spinal cord neurons GABA-mediated inhibitory responses can be measured, effects which were found by Macdonald and Bergey (55) to be potentiated by valproate in a dose-depended manner (*Fig. 2*). The effects on GABA were specific since valproate had no influence on either glycine or glutamate responses. Further, valproate alone was found to exhibit no inhibitory action. Harrison and Simmonds (56), on the other hand, saw a potentiation of the responses to GABA only at very high concentrations when they used a rat cuneate afferent fiber preparation. Similar augmentation of GABA responses have been obtained in the intact central nervous system. For instance, after an intravenous injection of valproate or after iontophoretic application, the inhibitory effects of GABA were enhanced (57). Kerwin *et al.* (58) reported similar findings. Hayashi and Negishi (59) studied the effects of GABA and valproate on carp retinal ganglion cells and observed that both suppressed spike discharges, actions that could be antagonized by bicuculline. Further, the actions of valproate and GABA were additive. Similar results were obtained by Baldino and Geller (60) after they applied valproate and GABA simultaneously to cortical neurons and recorded greater inhibitory responses than with GABA alone. However, when these investigators used hypothalamic

neurons, valproate exhibited inconsistent actions, leading to the suggestion that the effects of the drug are regionally specific within the brain (61). The inhibitory effects of both GABA and muscimol on locus coerulus neurons were enhanced by valproate (62). Similarly in the preoptic ara of the brain the inhibitory action of GABA was heightened by valproate (63). In addition, valproate increased the GABA-ipsp slope 54% in rat hippocampal slices, indicating that the mechanism of action of the anticonvulsant might include an augmentation of neuronal inhibition by GABA (64).

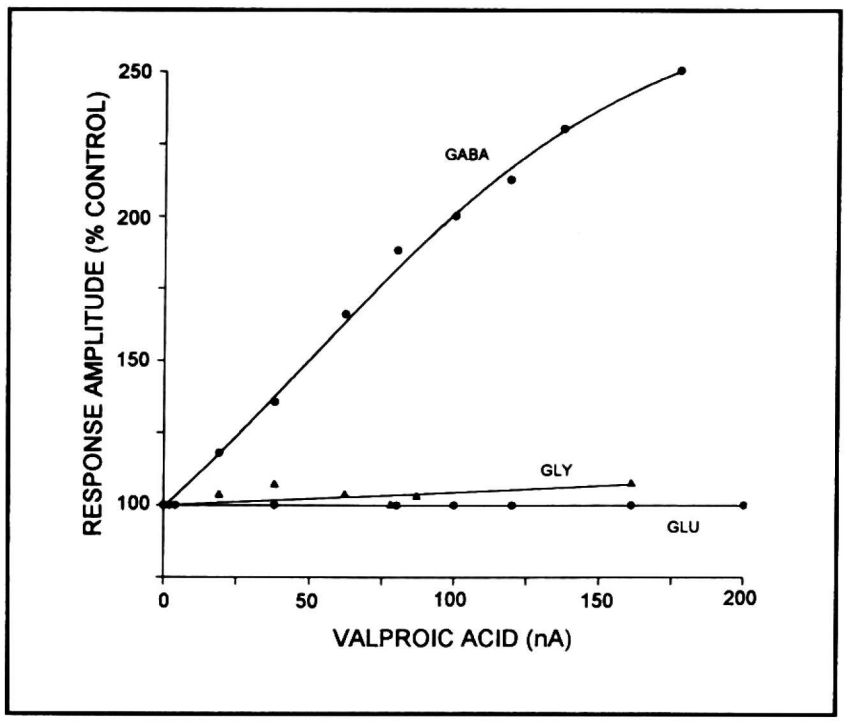

Fig. 2. Valproate selectively augmented GABA responses in cultured spinal cord neurons in a dose-dependent manner.
GLY = glycine;
GLU = glutamate.
Redrawn from Macdonald and Bergey (55).

In isolated frog primary afferent fibers valproate has been shown to increase the responsiveness to GABA and to reduce the ability of K^+ and excitatory amino acids to depolarize membranes (65). During *in vivo* experiments, Rowley *et al.* (66) observed that treatment of rats with valproate enhanced hippocampal GABA release.

Despite these reports indicating that valproate might be able to augment GABAergic mechanisms, experiments by Blume et al. (67) were unable to confirm this and, in fact, appeared to suggest that valproate can sometimes have excitatory actions on neurons. Extracellular recordings were made from cortical and hippocampal neurons in rats. Microiontophoretic application of valproate increased the spontaneous firing of the majority of neurons. GABA was able to inhibit the effects of valproate application.

Excitatory Amino Acid Receptors

One type of excitatory amino acid receptor in the brain is the N-methyl-D-aspartate (NMDA) receptor, the activation of which can lead to clonic convulsions (68). Antagonists at this receptor often possess

anticonvulsant properties (69). Czuczwar *et al.* (70) showed that valproate could suppress NMDA-induced seizures but that other anticonvulsants were ineffective. In rat cerebral cortical slices valproate inhibited the NMDA-stimulated release of [^{3}H]noradrenaline (71). NMDA can induce transient depolararizations in rat cortical pyramidal neurons which can be inhibited by valproate (72). Valproate also decreased the NMDA-epsp slope by 14% in rat hippocampal slices (64).

Another type of excitatory amino acid neurotransmitter receptor is the ionotropic AMPA receptor, whose activation leads to an influx of Na^+ ions resulting in a depolarization of the neuron. Künig *et al.* (73), using slices of human hippocampus incubated in a buffer containing 40 nM [^{3}H]AMPA, reported that concentrations of valproate of 100 μM or greater inhibited the binding of the ligand to AMPA recetors. These observations might have clinical significance since therapeutic serum levels of valproate range between 350 and 700 μM (5).

Although whole-brain levels of glutamate were unaffected by the acute administration of valproate (11, 34, 74), most brain regions showed increases in glutamate following chronic treatment (75, 13). Moreover, since aspartate might play a role in excitatory neurotransmission, the observation that valproate decreases mouse brain aspartate concentrations (76), an effect which correlates with suppression of audiogenic seizures, might contribute to an explanation of the mechanism of action of this drug. A later study found a good correlation between the dose of valproate and the reduction in brain aspartate levels (77, 78). Valproate also has been reported to (79) to inhibit the release of aspartate from rat cortical slices (IC_{50} = 100 μM).

Other Membrane Effects

Some of the effects of valproate on neuronal activity are not as clearly dependent on GABA or excitatory amino acid respones. Zhang *et al.* (80), for example, reported that the drug suppressed both simple and complex thalamocortical burst complex activity in brain slices. These activities resembled absence seizure activity and tonic-clonic activity, respectively. Low concentrations of valproate rapidly inhibited spontaneously firing cerebral cortical neurons following intraperitoneal injections (81); and Salt *et al.* (82) found that oral administration of valproate led to a reduction in the duration of afterdischarges in the rat amygdala. Another study showed that valproate could produce a modest reduction in T-type Ca^+ currents in primary afferent neurons over a concentration range 0.1—1 mM (83).

Hippocampal slices can be made to yield rhythmic, synchronous field discharges if incubated under certaon conditions. Valproate reduced the occurrence of these discharge (84). Franceschetti *et al.* (85) also used

a hippocampal slice preparation and reported that valproate depressed frequency potentation. Moreover, the drug inhibited spontaneous epileptiform activity and after discharge effected by antidromic stimulation. Because of the delayed action, these results suggest valproate does not block Na^+ currents, as phenytoin does, but perhaps activates Ca^+-dependent K^+ flux.

Even in the invertebrate nervous system, valproate produced a hyperpolarization of *Aplysia* neurons which was accompanied by an increase in K^+ conductance (86).

Valproate has been shown to alter β-adrenergic receptor function in rat C6 glioma cells. Chronic exposure reduced both the number of receptors and the capacity of cell membranes to bind [3H]forskolin. In addition, the ability of forskolin to stimulate cAMP production was impaired (87).

Antimigraine Activity

A major type of episotic headache is migraine. For many years the prevailing notion was that in patients undergoin a migrainous attack certain cerebral blood vessels underwent dilation, resulting in the characteristic pain. However, investigators no longer believe that migraines are simply vascular headaches. The raphe nucleus of the brainstem seems to play an major role in the genesis of this type of headache. Pharmacological treatment of migraine attacks usually means treating the pain, either with analgesics or with drugs from the newer class of serotonin antagonists like sumatriptan. Yet agents which prevent the development of migraines are also important in the overall treatment available. One such drug is sodium valproate.

The first study to demonstrate that valproate might possess the bility to prophylactically treat migraine headaches was carried out by Sorensen (88). This was an open trial in which seventeen of eighteen patients obtained a benefit from the administration of valproate. The first study to employ a placebo was reported by Hering and Kuritzky (89) in which 86% of patients responded favorable to valproate treatment. In 1994 Jensen *et al.* (90) performed a triple-blind, placebo-controlled trial during which 34 patients completed the study. Seventeen patients showed a clear reduction in migraine frequency following valproate treatment. An open prospective investigation was carried out by Lenaerts *et al.* (91) in which 56 patients suffering from various types of migraine were enrolled. Over a period of six months, patients received an average of 928.5 mg sodium valproate each day which led to 80% of these patients experiencing a reduced frequency of migraine by at least one-half. A larger, multicenter study, involving 90 patients found that 48% achieved a reduction in headache frequency if valproate was administered on a daily basis (92). An even larger trial two years later involved 176 patients and confirmed the effectiveness of chronic vlproate treatment on migraines (93).

The β-adrenergic receptor antagonist propanolol has been used successfully in the prophylactic treatment of migraine (94). Kaniecki (95) initiated a study to compare the relative effectiveness of valproate and propanolol as prophylactic agents in treating migraine. Thirty-two patients completed the randomized, single-blind, placebo-controlled trial which lasted 36 weeks. For valproate, most patients eventually received 1.5 g per day and for propanolol most patients eventually received 180 mg per day. Although migraine frequency was reduced in 19% of patients receiving placebo, 66% of patients receiving valproate and 63% of patients receiving propanolol reported a reduction in headache frequency. Thus valproate appears equally effective as propanolol at inhibiting the development of migraine headaches.

Valproate in Mood Disorders

Manic depression, or bipolar disorder, affects about one percent of the US population and these patients are at considerable risk for suicide. Lithium has been the drug of choice for the treatment of this disorder but serum levels have to be monitored carefully owing to its low therapeutic index. The relationship between the alleviation of bipolar symptoms and alterations in brain chemistry by lithium is far from clear. Further, many patients do not respond to lithium therapy (96), whereas others might show only partial longterm improvement (97).

A report by Lambert *et al.* (98) was one of the first to indicate valproate might be useful in treating mood disorders. Later, Emrich *et al.* (99) observed that out of five patients receiving valproate, four showed improvement in symptoms of acute mania. Since then much stronger evidence for the effective treatment of acute mania by valproate has been obtained by two clinical studies which properly employed placebo groups (94, 2, 100). The first was a randomized controlled trial in which 53% of a group of acutely manic patients experienced at least a 50% reduction in symptoms over the course of 3 weeks. Only 11% of the patients taking a placebo showed a similar improvement. The second of these randomized controlled trials yielded an improvement rate of 48% for patients on valproate compared to 25% of patients on placebo. Weaker evidence has been put forward for the alleviation of manic phase symptoms in bipolar disorder (101, 102). In a prospective clinical trial of patients with refractive bipolar disorder, valproate together with lithium was shown to have promise in treating the manic phase in one third of the eighteen patients studied (103). A subgroup of patients with bipolar disorder exhibit depression on occasion but these people are often unresponsive to lithium (104). In a parallel-group, double-blind study of acute mania certain patients who poorly responded to lithium treatment tended to exhibit symptoms of depression, whereas other patients showing signs of depression were better responders to valproate administration (105).

Recently valproate has begun to be used to treat both acute mania and manic depression in some patients. As valproate appears to enhance the GABAergic system and to interfere with Na^+ channel function, it is possible the mood stabilizing properties of the drug can be explained this way. However, glutamate function might be altered by valproate and account for its effectiveness in treating certain affective disorders. Interestingly, Dixon and Hokin (106) reported that both valproate and lithium stimulated glutamate release from cortical slices which was accompanied by an accumulation of inositol 1,4,5-triphosphate.

It has been estimated that up to 3% of the US population is susceptible panic attacks (107). Evidence points to the idea that susceptible patients might be helped with valproate treatment. In an open 7-week study by Primeau *et al.* (108), administration of valproate led to an improvement in a number of patients suffering from panic disorder. Keck *et al.* (109) reported that valproate is useful against lactate-induced panic attacks and against spontaneous attacks. Woodman and Noyes (110) have described a study involving twelve patients with panic disorder who were administered valproate over a 6-week period. Three-quarters of the patients exhibited a definite improvement in the frequency of attacks and in general anxiety levels. The remaining patients showed a moderate improvement. In a more recent trial, thirteen patients were enrolled but three eventually dropped out (111). Valproate treament produced a significant improvement in depression, anxiety and mood instability as well as a marked reduction in the number of panic attacks.

Huntington's disease is a genetic neurological disorder in which neurons in the basal ganglia undergo a progressive degeneration. Since both GABA concentrations and the activity of glutamate decarboxylase were markedly reduced in postmortem brains from patients, a clinical trial was initiated to test the idea that valproate could alleviate neurological symptoms (112). The double-blind study involved eight patients who received placebo or 1.5 g valproate daily for one week followed by valproate and GABA (24.5 g) for a further 18 to 21 days. No improvement in chorea severity, finger dexterity, gait or speech was observed over the period of the trial.

TOXICOLOGY

Valproate is a widely used drug and is known to be reasonably safe and often effective. Nevertheless, sometimes hepatotoxicity can occur and there has been a number of fatalities, mainly at high doses (113, 114). Some of these patients exhibited microvesicular steatosis of the liver and encephalopathy. The basis of the fatalities might be explained by the effect of valproate on mitochondrial biochemical processes in hepatocytes.

In both humans and experimental animals treated with valproate, a dicarboxylic aciduria was observed, indicating an effect on mitochondrial β-oxidation of fatty acids (11). Since valproate is a branched chain fatty, it might be expected to interfere with normal metabolic oxidations of fatty acids in mitochondria. Also implicating mitochondria involvement was the presence of a persistent hyperammonemia during valproate intoxication (116—118). When isolated liver cels were studied, valproate clearly inhibited fatty acid oxidationn (119, 120). Other studies using *in vitro* liver preparations were able to corroborate the inhibitory actions of valproate on β-oxidation (121—123). In addition to the effects on fatty acid oxidation, valproate inhibited fatty acid synthesis and gluconeogenesis (119, 124). Other researchers reported that valproate inhibited the urea cycle in hepatocytes (120, 125).

Some of the hepatotoxicity of valproate might be caused by metabolites of the drug. CoA esters of several valproate derivatives have been isolated (126, 127). In addition, a number of hydroxylation and dehydrogenation products have been described (128, 129) which could contribute to liver damage. Geber *et al.* (130) noticed a resemblance between the structure of 2-propylpent-4-enoate, a valproate metabolite, and the hepatotoxin methylene cyclopropylacetate.

Chronic treatment of rats with valproat led to decreased respiration in both liver and brain when either succinate or glutamate were substrates (131). Subsequent studies have shown that repeated valproate administration produces an inhibition of proton pumping ability by Complex IV of the inner membrane of liver mitochondria. This results in a reduction of oxidative phosphorylation (132).

CONCLUSIONS

Since it was shown to possess anticonvulsant properties almost forty years ago, valproate has become an important therapeutic agent to control several types of epilepsy. More recently the clinical uses of valproate have expanded to include its use in the treatment of migraine headaches and mood disorders. We are still not certain of its mechanism of action and, indeed, it is possible that its different clinical uses rely on different mechanisms. The two major targets for the action of valproate in the brain are the GABAergic neurotransmitter system and certain Na^+ channels involved in action potential propagation. It is obviously possible that the pharmacological profile of valproate depends on its action on both of these targets. At high doses valproate can result in hepatic damage. There is evidence that disturbances in mitochondrial metabolism within hepatocytes sometimes leads to irreversible alterations in liver function.

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