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VALPROATE: A REAPPRAISAL OF ITS PHARMACODYNAMIC PROPERTIES AND MECHANISMS OF ACTION

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Abstract—Valproate is currently one of the major antiepileptic drugs with efficacy for the treatment of both generalized and partial seizures in adults and children. Furthermore, the drug is increasingly used for therapy of bipolar and schizoaffective disorders, neuropathic pain and for prophylactic treatment of migraine. These various therapeutic effects are reflected in preclinical models, including a variety of animal models of seizures or epilepsy.

The incidence of toxicity associated with the clinical use of valproate is low, but two rare toxic effects, idiosyncratic fatal hepatotoxicity and teratogenicity, necessitate precautions in risk patient populations. Studies from animal models on structure-relationships indicate that the mechanisms leading to hepatotoxicity and teratogenicity are distinct and also differ from the mechanisms of anticonvulsant action of valproate.

Because of its wide spectrum of anticonvulsant activity against different seizure types, it has repeatedly been suggested that valproate acts through a combination of several mechanisms.

As shown in this review, there is substantial evidence that valproate increases GABA synthesis and release and thereby potentiates GABAergic functions in some specific brain regions, such as substantia nigra, thought to be involved in the control of seizure generation and propagation. Furthermore, valproate seems to reduce the release of the epileptogenic amino acid γ-hydroxybutyric acid and to attenuate neuronal excitation induced by NMDA-type glutamate receptors.

In addition to effects on amino acidergic neurotransmission, valproate exerts direct effects on excitable membranes, although the importance of this action is equivocal. Microdialysis data suggest that valproate alters dopaminergic and serotonergic functions.

Valproate is metabolized to several pharmacologically active metabolites, but because of the low plasma and brain concentrations of these compounds it is not likely that they contribute significantly to the anticonvulsant and toxic effects of treatment with the parent drug.

By the experimental observations summarized in this review, most clinical effects of valproate can be explained, although much remains to be learned at a number of different levels of valproate's mechanisms of action.

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ABBREVIATIONS

cAMP	Cyclic adenosine monophosphate
cGMP	Guanosine 3′,5′-monophosphate
CNS	Central nervous system
CSF	Cerebrospinal fluid
DOPAC	3,4-Dihydroxyphenylacetic acid
EEG	Electroencephalogram
GABA	γ-Aminobutyric acid
GABA-T	GABA aminotransferase
GAD	Glutamic acid decarboxylase
GHB	γ-Hydroxybutyric acid
HVA	Homovanillic acid
5-HIAA	5-Hydroxyindoleacetic acid
KDHC	α-Ketoglutarate dehydrogenase complex
NMDA	*N*-Methyl-D-aspartate
SN	Substantia nigra
SNR	Substantia nigra pars reticulata
SRF	Sustained repetitive firing
SSA	Succinic semialdehyde
SSADH	Succinic semialdehyde dehydrogenase
SSAR	Succinic semialdehyde reductase

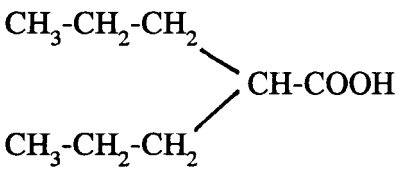
1. INTRODUCTION

Valproate (valproic acid; usually used as its sodium salt), also referred to as di-*n*-propylacetic acid, is a simple eight-carbon branched-chain fatty acid with unique anticonvulsant properties. Valproic acid was first synthesized in 1882 by Burton (1882), but there was no known clinical use until its anticonvulsant activity was fortuitously discovered by Pierre Eymard in 1962 in the laboratory of G. Carraz, which was published by Meunier *et al.* (1963). The first clinical trials of the sodium salt of valproate were reported in 1964 by Carraz *et al.* (1964). It was marketed in France in 1967 and was released subsequently in >100 other countries (in the USA in 1978) for the treatment of epilepsy. Since then, valproate has established itself worldwide as a major antiepileptic drug against several types of epileptic seizures. Clinical experience with valproate has continued to grow in recent years, including use of valproate for diseases other than epilepsy, for example, in bipolar disorders and migraine.

The present review is not meant to be an exhaustive survey on valproate; detailed summaries on various aspects of valproate's actions are already available (Pinder *et al.*, 1977; Meldrum, 1980; Turner and Whittle, 1980; Chapman *et al.*, 1982; Hammond *et al.*, 1981; Kerwin and Taberner, 1981; Johnston, 1984; Morre *et al.*, 1984; Löscher, 1985; Macdonald and McLean, 1986; Cotariu *et al.*, 1990; Löscher, 1991, 1993a; Davis *et al.*, 1994; Fariello *et al.*, 1995; Löscher, 1998b). This review concentrates on preclinical studies with particular emphasis on valproate's actions that appear to be of importance for its diverse therapeutic effects.

2. CHEMISTRY AND PHYSICOCHEMICAL PROPERTIES OF VALPROATE

Valproic acid or valproate is the trivial name for 2-propylpentanoic acid (also called *n*-dipropylacetic acid). As a simple branched-chain carboxylic acid it differs markedly in structure from all other antiepileptic drugs in clinical use. Its structural formula is as follows:



Valproic acid (molecular weight, 144.21; melting point 120–121°C) is a colourless liquid with a pK_a value of 4.56 (Löscher, 1985). The partition coefficients of valproic acid between organic solvents and buffer at pH 7.4 have been reported as 0.013 for heptane, 0.064 for benzene and 0.21 for chloroform (Löscher and Frey, 1984). Thus, because of its high degree of ionization at pH 7.4, valproic acid is much less lipid-soluble than any other standard anticonvulsant drug (Löscher and Frey, 1984). This explains why the volume of distribution of valproic acid is so low (see Section 3), because only the non-ionized, lipid-soluble part of a drug can distribute from blood to tissues by passive diffusion. However, the rapid entry of valproate in the brain is not compatible with its physicochemical properties and is thought to be mediated by active transport mechanisms (see Section 3).

Valproic acid is usually used as its sodium salt, which has a molecular weight of 166.198. Sodium valproate is a hygroscopic white powder which dissolves readily in polar solvents (e.g. water, ethanol, methanol) but is poorly soluble in solvents of lower polarity. In the body, however, sodium valproate is rapidly dissociated to valproic acid with the physicochemical properties described above. In addition to sodium valproate, the drug is available in several forms, including the parent compound, its magnesium salt and a combination of the parent compound and its sodium salt (divalproex sodium). In this review, the term valproate will be used for all of these formulations. For clinical use, valproate is available in capsule, tablet, enteric-coated tablet, sprinkle, liquid, intravenous, suppository and controlled-release formulations. Pharmacokinetic and tolerability differences between formulations have been reviewed recently (Davis *et al.*, 1994).

3. PHARMACOKINETICS OF VALPROATE IN DIFFERENT SPECIES

The main pharmacokinetic data for valproate in different species are summarized in Table 1. Valproate is rapidly absorbed after different routes of administration, provided that conventional formulations (e.g. no slow release or retard formulations) are used. Bioavailability after oral administration depends on the species. While it is up to almost 100% in humans, it is much lower at the high doses often given in rodents. While volume of distribution is similar in most species (being about equal to the extracellular fluid volume), there are

Table 1. Pharmacokinetics of valproate in different species

Species	Apparent volume of distribution ($l\ kg^{-1}$)[a]	Half-life [$t_{0.5}$ (β)] (h)	Bioavailability after oral application	Plasma protein binding[b] (%)	Brain/plasma ratio[b]	CSF/plasma ratio[b]
Man	0.13–0.19	9–18	70–100	80–95	0.07–0.28	0.08–0.25
Rhesus monkey	0.17	0.66		80	0.22	0.3
Dog	0.21–0.77	1–4	80–90	70–80	0.28–0.39	0.2–0.4
Cat	0.38	9			0.2–0.7	
Rat	0.66	2–5[c]		63	0.18–0.32	
Mouse	0.33	0.8	34–47	12	0.15–0.2	

[a] $V_d(\beta)$ or $V_d(ss)$. [b] At "therapeutic" plasma concentrations of 50–80 $\mu g\ ml^{-1}$. [c] Nonlinear kinetics. Adapted from Löscher (1985) and Levy and Shen (1995).

dramatic species differences in elimination half-life. Some species, for example, the rat, exhibit dose-dependent nonlinear elimination kinetics. The markedly lower elimination half-life of most species compared to humans explains why higher doses of valproate are needed in most species to obtain comparable 'active' plasma levels as in man. A further marked species difference is plasma protein binding, ranging from extensive binding in humans to almost absent binding in mice. Despite this difference in protein binding, brain/plasma ratios of valproate are almost the same in all species investigated in this regard. About 20% of the plasma concentration of valproate is present in the brain, and similar figures are present in cerebrospinal fluid (CSF). Experiments on the kinetics of penetration of common antiepileptic drugs into CSF of dogs have shown that valproate enters the central nervous system (CNS) rapidly, which is in contrast to its physicochemical properties (see Section 2) and can best be explained by a saturable and probenecid-sensitive transport carrier at the blood–brain and blood–CSF barrier (Frey and Löscher, 1978; Löscher and Frey, 1984). As shown by experiments with probenecid, valproate is also rapidly transported out of the brain, which explains the relatively low brain/plasma ratios. A further explanation is that valproate does apparently not bind to brain proteins. Accordingly, acute and subacute studies in rodents showed no retention of valproate in the brain (cf. Löscher, 1985). However, a gradual accumulation of radioactivity was observed in the olfactory bulb in mice and rats following intraveneous (i.v.) injection as well as in monkeys after long-term infusion of radiolabeled valproate (Schobben *et al.*, 1980; Hoeppner, 1990). Whether this radioactivity was due to covalent bound valproate, a valproate metabolite, or other degradation products is not clear. Interestingly, destruction of the olfactory bulb markedly reduces the anticonvulsant efficacy of valproate (Ueki *et al.*, 1977). In this regard, it may be important that the principal target of olfactory bulb efferent projections is the piriform (primary olfactory) cortex, a region that seems to be critical to the amplification and generalization of seizures (Löscher and Ebert, 1996).

Biotransformation is the major route of elimination of valproate in humans and animals. Valproate undergoes metabolism by a variety of conjugation and oxidative processes, which has been reviewed in detail recently (Baillie and Sheffels, 1995). Several of the resulting unsaturated and oxygenated metabolites of valproate exert anticonvulsant activity (see Section 7.6), although the brain concentrations of these metabolites are too low to contribute to any significant extent to the anticonvulsant activity of the parent drug. However, it has often proposed that metabolites may be involved in the toxicity of valproate (see Section 6). Some of the major metabolites of valproate are shown in Fig. 1.

With respect to pharmacokinetic drug interactions, valproate may alter the plasma and brain levels of other drugs, due to interactions at the level of drug metabolism and plasma protein binding (cf. Löscher, 1985; Perucca and Richens, 1985; Davis *et al.*, 1994). Similarly, other drugs may affect plasma and brain levels of valproate, thereby changing its pharmacodynamic potencies.

4. CLINICAL USE OF VALPROATE

4.1. Epilepsy

The major use of valproate is in the pharmacological therapy of epileptic seizures, although its use in other indications, such as psychiatric disorders and migraine, is steadily increasing. Epilepsy is one of the most common diseases of the brain, affecting at least 50 million persons worldwide (Scheuer and Pedley, 1990). Epilepsy is a chronic and often progressive disorder characterized by the periodic and unpredictable occurrence of epileptic seizures which are caused by an abnormal discharge of cerebral neurons. Many different types of seizures can be identified on the basis of their clinical phenomena. These clinical characteristics, along with their electroencephalographic (EEG) features, can be used to categorize seizures (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). Seizures are fundamentally divided into two major groups: partial and generalized. Partial (focal, local) seizures are those in which clinical or electrographic evidence exists to suggest that the attacks have a localized onset in the brain, usually in a portion of one hemisphere, while generalized seizures are those in which evidence for a localized onset is lacking. Partial seizures are further subdivided into simple partial, complex partial and partial seizures evolving to secondarily generalized seizures, while generalized seizures are categorized into absence (nonconvulsive), myoclonic, clonic, tonic, tonic–clonic and atonic seizures. In addition to classifying the seizures that occur in patients with

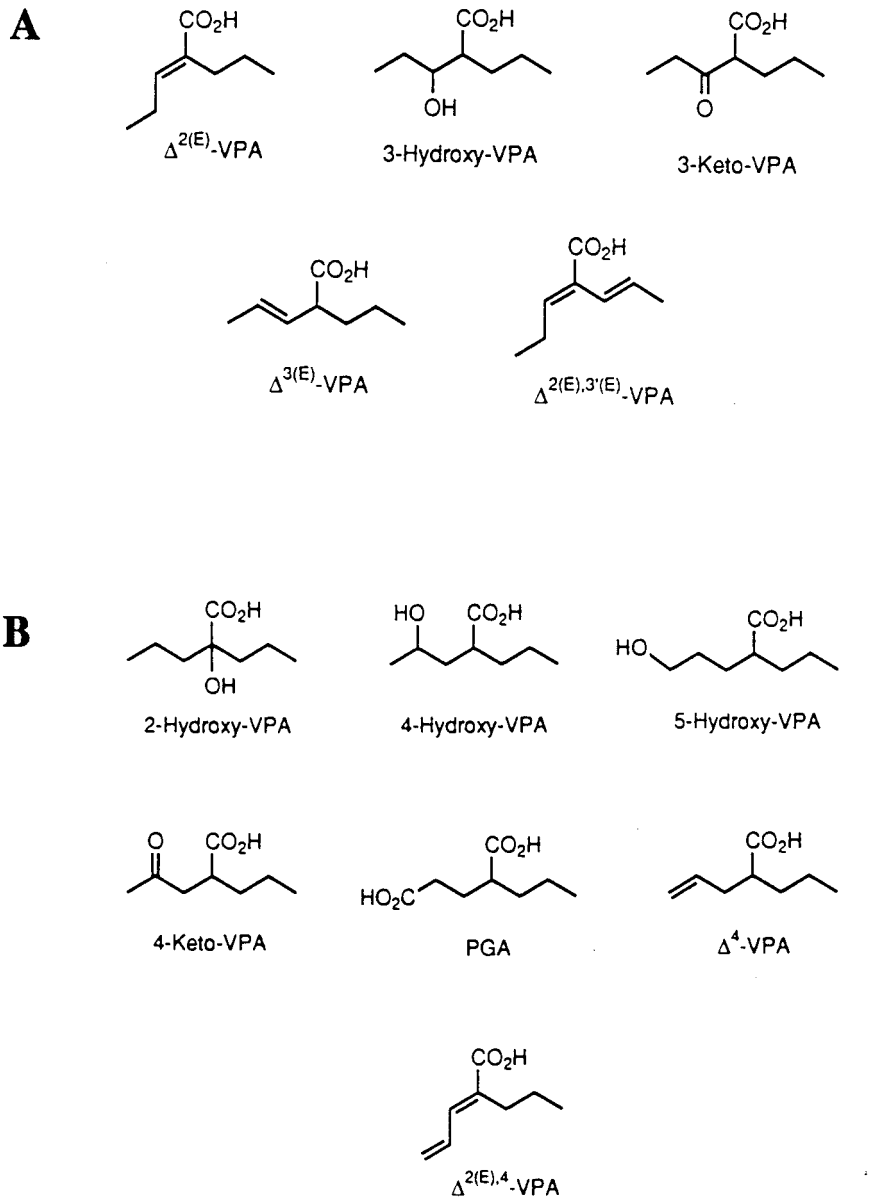


Fig. 1. Structure of some valproate metabolites. (A) Structures of metabolites of valproate believed to arise through mitochondrial β-oxidation. (B) Metabolites believed to derive from oxidative processes distinct from those of mitochondrial β-oxidation (Baillie and Levy, 1991). Most of the metabolites illustrated in this figure have been demonstrated to exert anticonvulsant activity in animal models, although all metabolites (except the E-2-en unsaturated one) were less potent than valproate.

epilepsy, patients are classified into appropriate types of epilepsy or epileptic syndromes characterized by different seizure types, etiologies, ages of onset and EEG features (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). More than 40 distinct epileptic syndromes have been identified, making epilepsy a remarkably diverse collection of disorders. The first major division of epilepsy are localization-related (focal, local, partial) epilepsies, which account for roughly 60% of all epilepsies, and generalized epilepsies, which account for *ca* 40% of all epilepsies. An epilepsy or epileptic syndrome is either idiopathic, which is virtually synonymous with genetic epilepsy, or symptomatic, that is, due to structural lesion or major identifiable metabolic derangements. Both types of seizure and epilepsy determine the choice and prognosis of therapy. For instance, the most common and most difficult-to-treat type of seizures in adult patients are complex partial seizures, while primary generalized tonic–clonic ('grand mal') seizures respond in most patients to treatment with anticonvulsants.

Various clinical studies and extensive clinical experience over the last decades have demonstrated that valproate is effective in the treatment of various

seizure types, including tonic–clonic, absence and partial seizures, both as add-on and monotherapy (cf. Davis *et al*., 1994). The drug has also demonstrated some evidence of efficacy in the treatment of infantile spasms (West syndrome), Lennox–Gastaut syndrome, febrile seizures and status epilepticus (Davis *et al*., 1994). Because of this wide-spectrum of anticonvulsant activity and its tolerability, valproate is a well-established first-line treatment for patients with a broad range of seizure types. Indeed, the discovery and therapeutic development of valproate can be considered a milestone in drug therapy of the epilepsies (Löscher, 1998b).

4.2. Other Clinical Indications

In addition to epilepsy, valproate is increasingly used for treatment of other diseases, including bipolar disorders, migraine and neuropathic pain (Balfour and Bryson, 1994; Petty, 1995). Valproate has been shown to be effective in patients with bipolar and schizoaffective disorders, including those resistant to lithium and carbamazepine. The drug is particularly effective against the manic episodes of bipolar disorders, although during long term prophylaxis both manic and depressive episodes may be reduced. Valproate also may have a wider spectrum of efficacy than lithium, with accumulating evidence of its use in atypical (dysphoric/mixed) mania, rapid cycling and secondary manias, in which lithium appears to be less clinically effective. The mood-stabilizing effect of valproate in psychiatric conditions is shared by some other anticonvulsant drugs, namely carbamazepine, lamotrigine, and possibly also gabapentin. Valproate, carbamazepine and gabapentin are also considered effective for treatment of chronic neuropathic pain. In migraine, valproate has been shown to be an effective prophylactic treatment in several controlled clinical trials (Balfour and Bryson, 1994; Silberstein, 1998).

5. PRECLINICAL PHARMACODYNAMICS OF VALPROATE

5.1. Anticonvulsant Effects of Valproate in Animal Models

As noted above, the anticonvulsant properties of valproate were serendipitously discovered in France in 1962 (Meunier *et al*., 1963). By using valproate as a lipophilic vehicle for dissolving water-insoluble khelline derivatives, a significant anticonvulsant effect against pentylenetetrazol (PTZ)-induced seizures was observed in the vehicle controls. Subsequent clinical trials substantiated the anticonvulsant activity of valproate in epileptic patients, and nowadays valproate is one of the major drugs for treatment of different types of epileptic seizures.

Experimentally, valproate exerts anticonvulsant effects in almost all animal models of seizure states examined in this respect (Tables 2–4), including models of different types of generalized seizures as well as focal seizures. The anticonvulsant potency of valproate strongly depends on the species, the route of administration, the type of seizure induction, and the time interval between drug administration and seizure induction. Because of the rapid penetration into the brain but the short half-life of valproate in most species (Löscher, 1985), the most marked effects are obtained shortly, that is, 2–15 min, after parenteral [e.g. intraperitoneal (i.p.)] injection. Depending on the preparation, onset of action after oral administration may be somewhat retarded. In most laboratory animal species, the duration of anticonvulsant action of valproate is only short so that high doses of valproate are needed to suppress long-lasting or repeatedly occurring seizures in animal models. In general, the anticonvulsant potency of valproate increases in parallel with the size of the animal. In rodents, the highest anticonvulsant potencies are obtained in genetically seizure susceptible species, such as gerbils and rats with spon-

Table 2. Anticonvulsant potency of valproate in different animal models of generalized clonic or tonic seizures with chemical seizure induction

Model			Efficacy of valproate			
Convulsant (mg kg^{-1})	Seizure type	Species	Time[a] (hr)	Route of application	ED_{50} (mg kg^{-1})	References (examples)
PTZ[c] (85–100 s.c.)	Clonic	Mouse	0.25	i.p.	120–150	Swinyard (1964); Shuto and Nishigaki (1970); Krall *et al*. (1978)
			0.5	p.o.	220–420	Swinyard (1964); Shuto and Nishigaki (1970); Frey and Löscher (1976)
PTZ[c] (85–100 s.c.)	Clonic	Rat	0.5	i.p.	74–260	Swinyard (1964); Kupferberg (1980)
			0.5	p.o.	180	Kupferberg (1980)
Picrotoxin (3.2 s.c.)	Clonic	Mouse	0.25	i.p.	390	Kupferberg (1980)
Bicuculline (2.7 s.c.)	Clonic	Mouse	0.25	i.p.	360	Kupferberg (1980)
3-MP[d] (66 s.c.)	Clonic	Mouse	0.5	i.p.	290	Löscher (1980b)
Allylglycine (400 i.v.)	Clonic	Mouse	0.5	i.p.	200	Worms and Lloyd (1981)
Isoniazide (200 s.c.)	Clonic	Mouse	0[e]	p.o.	280	Löscher and Frey (1977b)
DMCM[f]	Clonic/tonic	Mouse	0.5	i.p.	60	Petersen (1983)
Strychnine (1.2 s.c.)	Tonic	Mouse	0.25	i.p.	290	Kupferberg (1980)
NMDLA[g]	Clonic	Mouse	0.5	i.p.	340	Czuczwar *et al*. (1985)

[a]Time from application of valproate to injection of convulsant.[b]Dose which protects 50% of animals from seizures.[c]Pentylenetetrazol.[d]3-Mercaptopropionic acid.[e]Valproate and isoniazide were injected simultaneously.[f]Methyl-6,7-dimethoxy-4-ethyl-β-carbolin-3-carboxylate (an inverse agonist at central benzodiazepine receptors).[g]*N*-Methyl-D,L-aspartate (an agonist at the NMDA subtype of glutamate receptors).

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