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Basic Pharmacology of Valproate

A Review After 35 Years of Clinical Use for the Treatment of Epilepsy

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Abstract

Since its first marketing as an antiepileptic drug (AED) 35 years ago in France, valproate has become established worldwide as one of the most widely used AEDs in the treatment of both generalised and partial seizures in adults and children. The broad spectrum of antiepileptic efficacy of valproate is reflected in preclinical *in vivo* and *in vitro* models, including a variety of animal models of seizures or epilepsy.

There is no single mechanism of action of valproate that can completely account for the numerous effects of the drug on neuronal tissue and its broad clinical

activity in epilepsy and other brain diseases. In view of the diverse molecular and cellular events that underlie different seizure types, the combination of several neurochemical and neurophysiological mechanisms in a single drug molecule might explain the broad antiepileptic efficacy of valproate. Furthermore, by acting on diverse regional targets thought to be involved in the generation and propagation of seizures, valproate may antagonise epileptic activity at several steps of its organisation.

There is now ample experimental evidence that valproate increases turnover of γ-aminobutyric acid (GABA) and thereby potentiates GABAergic functions in some specific brain regions thought to be involved in the control of seizure generation and propagation. Furthermore, the effect of valproate on neuronal excitation mediated by the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors might be important for its anticonvulsant effects. Acting to alter the balance of inhibition and excitation through multiple mechanisms is clearly an advantage for valproate and probably contributes to its broad spectrum of clinical effects.

Although the GABAergic potentiation and glutamate/NMDA inhibition could be a likely explanation for the anticonvulsant action on focal and generalised convulsive seizures, they do not explain the effect of valproate on nonconvulsive seizures, such as absences. In this respect, the reduction of γ-hydroxybutyrate (GHB) release reported for valproate could be of interest, because GHB has been suggested to play a critical role in the modulation of absence seizures.

Although it is often proposed that blockade of voltage-dependent sodium currents is an important mechanism of antiepileptic action of valproate, the exact role played by this mechanism of action at therapeutically relevant concentrations in the mammalian brain is not clearly elucidated.

By the experimental observations summarised in this review, most clinical effects of valproate can be explained, although much remains to be learned at a number of different levels about the mechanisms of action of valproate. In view of the advances in molecular neurobiology and neuroscience, future studies will undoubtedly further our understanding of the mechanisms of action of valproate.

Valproic acid or valproate, a major and well established first-line antiepileptic (anticonvulsant) drug (AED), is one of the most widely used AEDs in the treatment of different types of epilepsy.[1,2] Valproate is the trivial name for 2-n-propylpentanoic acid (also called n-dipropylacetic acid). As a simple branched-chain fatty acid, it differs markedly in structure from all other AEDs in clinical use.

1. Historical Background

Valproate was first synthesised in 1882 by Burton,[3] 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, as published by Meunier et al.[4] At that time, valproate was used as a vehicle to dissolve the active ingredient in testing the anticonvulsant activity of new compounds.[5] The positive results, whatever the drug and the dose tested, led to the testing of valproate itself and to confirmation that it was effective against drug-induced seizures. The first clinical trials of the sodium salt of valproate were reported in 1964 by Carraz et al.,[6] and it was first marketed in France in 1967.

2. Overview of Clinical Use

Valproate has been used for the treatment of epilepsy for nearly 35 years and is currently marketed in over 100 countries. Since its introduction into clinical use, valproate has become established

worldwide as a major AED with a wide spectrum of activity against a broad range of seizure disorders. Controlled clinical trials have demonstrated that it has similar efficacy to ethosuximide in the treatment of absence seizures and to carbamazepine, phenytoin and phenobarbital (phenobarbitone) in the treatment of both tonic-clonic and partial seizures.[7-11] Furthermore, valproate compares favourably with newer AEDs, such as vigabatrin[12] and oxcarbazepine,[13] in both efficacy and tolerability.[14]

Results from numerous clinical trials suggest that valproate probably has the widest spectrum of antiepileptic activity of all established AEDs in both children and adults with epilepsy.[15,16] In addition to partial and generalised seizures, valproate has demonstrated efficacy in the treatment of syndromes known to be very refractory, such as Lennox-Gastaut syndrome[17,18] and West syndrome.[19] This gives valproate special significance for the treatment of patients with mixed seizure types who have highly refractory symptoms.[14] Furthermore, as a consequence of its broad spectrum of antiepileptic activity and as opposed to many other AEDs, there is no contraindication to the use of valproate in any type of seizure or epilepsy.[14]

Valproate is tolerated well in most patients.[20] Most adverse effects are mild to moderate in intensity, and hypersensitivity reactions are rare. A comparison with other widely used AEDs showed that valproate causes fewer neurological adverse effects and fewer skin rashes than phenytoin, phenobarbital and primidone, and its tolerability and safety appear to be similar to that of carbamazepine.[20] Main areas of concern with valproate are teratogenicity and idiosyncratic liver toxicity. With respect to teratogenicity, recommendations on the use of valproate in women who plan to conceive, such as monotherapy with the lowest effective dose, have lowered this risk, so that with these recommendations valproate does not appear to induce birth defects with any greater frequency than other AEDs.[20] With respect to idiosyncratic liver toxicity, identification of high-risk patients such as children under 2 years with severe epilepsy and mental retardation receiving polytherapy has considerably reduced its incidence.[20]

The present review summarises the major pharmacological effects of valproate that appear to be of importance for its unique antiepileptic efficacy. For a more comprehensive survey of the multiple effects of valproate, including its adverse effects and pharmacokinetics, several previous reviews and monographs are available.[1,2,15,21,22] Furthermore, the major aspects of the clinical use of valproate, its advantages and limitations and their correlation with pharmacological findings are covered in the review by Perucca[23] that also appears in this issue of *CNS Drugs*.

3. Epilepsy and Epileptic Seizures

Epilepsy, a common neurological disorder characterised by recurrent spontaneous seizures, is a major, worldwide health problem that affects about 1 to 2% of the population.[24] Despite progress in understanding the pathogenesis of seizures and epilepsy,[25] the cellular basis of human epilepsy is only incompletely understood. In the absence of a specific aetiological understanding, approaches to drug therapy of epilepsy must necessarily be directed at the control of symptoms (i.e. the suppression of seizures). Long-term administration of AEDs is the treatment of first choice in epilepsy.

The selection of an AED is based primarily on its efficacy for specific types of seizures according to the international classification of epileptic seizures.[26] The major categories within this classification are partial and generalised seizures, based on whether a seizure begins locally in a part of one hemisphere, most commonly the temporal lobe, for partial seizures, or is bilaterally symmetrical without local onset for generalised seizures. In addition to this classification of seizures, various types of epilepsy or epileptic syndromes can be identified as characterised by different seizure types, aetiologies, age of onset and EEG features.[24] More than 40 distinct epileptic syndromes have been identified, making epilepsy a remarkably diverse collection of disorders. Localisation-related

(focal, local, partial) epilepsies account for roughly 60% of all epilepsies, while generalised epilepsies account for approximately 40% of all epilepsies.[24]

An epilepsy or epileptic syndrome can be idiopathic (with a presumed genetic basis), symptomatic (i.e. secondary to a known acquired brain pathology) or cryptogenetic (without a known causation). Known potential causes of epilepsy account for about one-third of incidences of epilepsy and include brain tumours, CNS infections, traumatic head injuries, developmental malformations, perinatal insults, cerebrovascular disease, febrile seizures and status epilepticus.[27]

4. Animal Models of Epilepsy

In epilepsy research, animal models of epilepsy or epileptic seizures serve a variety of purposes.[28] First, they are used in the search for new AEDs. Second, once the anticonvulsant activity of a novel compound has been detected, animal models are used to evaluate the possible specific efficacies of the compound against different types of seizures or epilepsy. Third, animal models can be used to characterise the preclinical efficacy of novel compounds during long-term administration. Such long-term studies can serve different objectives, for instance evaluation of whether drug efficacy changes during prolonged treatment (e.g. because of the development of tolerance) or examination of whether a drug exerts antiepileptogenic effects during prolonged administration (i.e. is a true AED). Fourth, animal models are employed to characterise the mechanism of action of older and newer AEDs. Fifth, certain models can be used to study mechanisms of drug resistance in epilepsy. Sixth, in view of the possibility that chronic brain dysfunction, such as with epilepsy, might lead to altered sensitivity to drug adverse effects, models with epileptic animals are useful to study whether epileptogenesis alters the adverse effect potential of a given drug. Finally, animal models are needed for studies on the pathophysiology of epilepsies and epileptic seizures (e.g. the processes involved in epileptogenesis and ictogenesis).

The most commonly employed animal models in the search for new AEDs are the maximal electroshock seizure (MES) test and the pentylenetetrazole (PTZ) seizure test.[28] The MES test, in which tonic hindlimb seizures are induced by bilateral corneal or transauricular electrical stimulation, is thought to be predictive of anticonvulsant efficacy against generalised tonic-clonic seizures. In contrast, the PTZ test, in which generalised myoclonic and clonic seizures are induced by systemic (usually subcutaneous) administration of convulsant doses of PTZ, is thought to represent a valid model for generalised absence and/or myoclonic seizures in humans, but its predictive validity is far from ideal. Thus, as shown in table I, although lamotrigine is ineffective in the PTZ test, it protects against absence and myoclonic seizures in patients with epilepsy. Vigabatrin and tiagabine are effective in the PTZ test but not against absence or myoclonic seizures in patients. Genetic animal models such as lethargic (*lh/lh*) mice, which have behavioural and electrographic features similar to those of human absence seizures, are clearly better suited to predict AED efficacy against this type of nonconvulsive seizure than the PTZ test.[28]

In addition to these models of primary generalised seizures, the kindling model is widely used as a model of partial (focal) seizures. The kindling model has correctly predicted the clinical effect of all AEDs that are currently used against partial seizures (see table I).

5. Effects in Experimental Models of Epilepsy and Epileptic Seizures

Valproate exerts anticonvulsant effects in almost all animal models of seizure states, including models of different types of generalised seizures as well as focal seizures.[2] Table I shows a comparison of the effects of valproate with those of other AEDs in the MES, PTZ and kindling models, as well as in clinical seizures. As shown by this comparison, the only other AEDs with a similar wide spectrum of activity as valproate are the benzodiazepines. However, the use of the benzodiazepines as AEDs is limited because of the loss of

Table I. Anticonvulsant effect of clinically established antiepileptic drugs (AEDs) against different types of seizures in the maximal electroshock seizure (MES), pentylenetetrazole (PTZ) and kindling models and in human epilepsy[29,30]

Drug	Anticonvulsant activity in experimental models			Clinical efficacy			
	MES test (mice or rats, tonic seizures)	PTZ test (mice or rats, clonic seizures)	amygdala-kindling test (rats, focal seizures)	partial seizures	generalised seizures		
					tonic-clonic	absence	myoclonic
Valproate	+	+	+	+	+	+	+
Carbamazepine	+	NE	+	+	+	NE	NE
Phenytoin	+	NE	+	+	+	NE	NE
Phenobarbital (phenobarbitone)	+	+	+	+	+	NE	+
Primidone	+	+	+	+	+	NE	+
Benzodiazepines[a]	+	+	+	+	+	+	+
Ethosuximide	NE	+	NE	NE	NE	+	±
Lamotrigine	+	NE	+	+	+	+	+
Topiramate	+	NE	+	+	+	±	+
Oxcarbazepine	+	±	?	+	+	?	?
Felbamate	+	+	+	+	+	±	+
Vigabatrin	NE	+	+	+	?	NE	NE
Tiagabine	NE	+	+	+	+	NE	NE
Gabapentin	±	±	+	+	?	NE	NE
Levetiracetam	NE	NE	+	+	?	?	?
Zonisamide	+	±	?	+	+	+	+

a Loss of efficacy (i.e. development of tolerance) during long-term administration.

NE = not effective; **+** indicates effective; ± indicates inconsistent data; **?** indicates no data available (or found).

efficacy during long-term treatment. No such loss of efficacy, and even an increase in efficacy, is seen during long-term treatment with valproate (see below).

In animal models, the anticonvulsant potency of valproate strongly depends on the animal species, the type of seizure induction, the seizure type, the route of administration and the time interval between drug administration and seizure induction.[2] Because of the rapid penetration into the brain but the short half-life of valproate in most species,[31] the most marked effects are obtained shortly (i.e. 2 to 15 minutes) after parenteral (e.g. intraperitoneal) injection. Depending on the preparation, the 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 high doses of valproate are needed to suppress long-lasting or repeatedly occurring seizures in animal models.[2] 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 spontaneously occurring spike-wave discharges, and against seizures induced by the inverse benzodiazepine receptor agonist methyl-6,7-diurethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM) in mice.[2]

In addition to animal models of generalised or focal seizures, valproate also has been evaluated in models of status epilepticus. As shown by Hönack and Löscher[32] in a mouse model of generalised convulsive (grand mal) status epilepticus, intravenous injection of valproate was as rapidly acting as benzodiazepines in suppressing generalised tonic-clonic seizures, which was related to the instantaneous entry of valproate into the brain after this route of administration. In view of the different mechanisms presumably involved in the anticonvulsant activity of valproate against different seizure types, the situation may be different for

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