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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 gamma-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 gamma-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.

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