Mechanism of Action of Valproic Acid and Its Derivatives

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Abstract

The mechanism of action of valproic acid is complex, calling for a decrease in neuronal hyperexcitability both by strengthening GABAergic transmission and by inhibiting sodium and especially calcium ion channels. Valproic acid activates or inhibits the various targets by direct routes or by unknown mechanisms. Cellular targets of acid valproic histone deacetylase are HDACs, ion channels, the level of GABA; phospholipase A2 signaling pathway, synthesis of inositol and resulting phospholipids, the pathway of MAP Kinases and GSK3. These complex mechanisms of action may account for the many therapeutic uses of valproic acid.

Keywords: Valproic acid; Valproate; GABA; Ion channels; Glutamine; Inositol; ERK; MAPK; GSK3.

Introduction

There are several derivatives of valproic acid. These molecules have been used for almost 40 years, but the mechanism(s) of action remains unclear. Early studies linked their mechanism to GABAergic activity, since they have been shown to play on a wide variety of signaling pathways, but a small number of direct targets. The analysis of structural characteristics made it possible to distinguish therapeutic and cellular effects, including adverse reactions such as teratogenicity and hepatotoxicity. The focus of this paper is to explain the various mechanisms of action of valproate derivatives.

Potentiation of GABAergic inhibitory activity

Valproate and derivatives increase regional neuronal concentrations of neurotransmitter GABA by inhibiting its degradation (direct inhibition of GABA transaminase and succinic semi-aldehyde dehydrogenase) and by increasing its synthesis [1]. (Stimulation of glutamic acid decarboxylase). There is also an indirect action on the GABA-A postsynaptic receptor, inducing an increase of GABA in the synaptic cleft [2].

Inhibition of ion channels

Valproic acid blocks neuronal excitability, especially high action potentials frequency, by inhibiting voltage dependent sodium channels [3]. This inhibition of currents sodium causes repolarization of the membrane, altering their conductance; it is an effect stabilizing membrane. A decrease in neuronal hyperexcitability also occurs by blockage of the calcium channel voltage-dependent T-type [4].

Inhibition of glutamatergic transmission

It can be indirect, by inhibiting the voltage-gated Na+ channels localized as presynaptic on glutamatergic neurons (membrane stabilizing effect), but also at the level of postsynaptic neurons responsible epileptic discharges [5]. This mechanism of action seems not, however; agree to explain that molecules base of valproate, but it remains a hypothesis because this mechanism corresponding to that of many other antiepileptic drugs. This blockage of neuronal excitability by enhancing the inhibitory activity of GABA and blockage of voltage-gated Na+ and Ca2+ channels partly explains its effectiveness for epilepsy, but the relevance of the link between these mechanisms and the clinical effects of valproate is not always clear. For its other indications the mechanism of action remains unclear. A hypothesis in the pathophysiology of migraine offers a state of hyperexcitability due to cortical depression propagated, wherein the valproic acid normalize neuronal firing and increase the threshold action potential, an effect that can occur by inhibiting ion channels like in other treatments indicated in epilepsy and migraine. Many other targets have been identified in various studies (conducted in largely rodent) to be to explain the efficacy of valproate in bipolar disorder; here are the different assumptions found.

Action on the signaling pathway of inositol

The signaling pathway of inositol is involved in many cellular processes, including the phenomenon of neurotransmission. An increase in myo-inositol levels has been observed in the frontal lobe and especially in the cingulate cortex of patients with bipolar disorder in manic episode [6]. The anti-manic effect of lithium is also attributed to its inhibition of inositol monophosphates (IMPase), the enzyme used to produce myo-inositol [7]. A hypothesis a common mechanism has therefore been issued for valproate (VPA) and carbamazepine (CBZ), with depletion of cellular inositol by reducing its de novo synthesis [8]. Cerebral inositol synthase (Ino-1) is thus inhibited by valproic acid, this inhibition might be indirect and not competitive [9]. There is also inhibition of the entry of extracellular inositol into the cell via inhibition of the specific transporter sodium / myo-inositol (SMIT). This hypothesis, although highly relevant for the treatment bipolar disorder, is discussed and is yet to be elucidated.
Activation of the extracellular signal-regulated kinase pathway (ERK)

Valproate has been observed to activate the ERK pathway at therapeutic doses in vitro [10]. This signaling pathway involves many signaling factors as well as transcription (Elk1 and c-Fos), ERK and the resulting signaling cascade have a central role in neurogenesis, dendritic arborization, survival and neuronal plasticity. The hypothesis action on this target opens up new perspectives to explain the effects of valproate.

Activation of MAPK (Mitogen Activated Protein Kinases)

Bipolar disorders are associated with a loss of volume in certain brain regions, the activation of MAPK giving rise to a neuroprotective effect, it could explain the effect therapeutic valproate [11]. The activation of the MAPK pathway is also found in other mood stabilizers. The mechanism of this activation remains unclear; a study on a simple biomedic model suggests that valproate may cause activation MAPK by inhibiting the PKA pathway (protein kinase A) [12].

Decrease of arachidonic acid / inhibition of PLA2 (phospholipase A2)

Arachidonic acid and its metabolites influence many brain mechanisms, such as certain neurotransmissions, membrane excitability, gene transcription, membrane fluidity, neurite production, cerebral blood flow, influencing our sleep, memory and behavior [13]. Many metabolites of arachidonic acid are considered to be pro-inflammatory. Arachidonic acid is released from the phospholipids of the synaptic membrane. This release takes place during neurotransmission through activation by the enzyme PLA2 (Phospholipase A2) coupled to a post-synaptic neuroreceptor. It is physiological, but higher amounts are also released during process disease such as neuroinflammation, excitotoxicity, ischemia, convulsions. Other treatments used in bipolar disorder reduce the release of acid arachidonic, making this way a potential target for valproic acid [14].

The different possible levels of inhibition of the arachidonic acid cascade are [15]:
- at the level of the neuroreceptor coupled to PLA2 itself,
- at the level of the coupling mechanism with cPLA2
- inhibition of acyl-CoA synthetase (Acsl), which blocks the reincorporation of the acid arachidonic and thus slows its synthesis
- inhibition of the formation of PGE2 (Prostaglandin E2) by decreasing the activity of Cox2 (Cyclooxygenase 2) by inhibiting its transcription (inhibition of NF-kB)

Inhibition of GSK3 (glycogen synthase kinase)

The enzyme GSK3ε (one of the two isoforms of GSK3 which is a serine / threonine protein kinase) is involved in cell cycle progression, the structure of neuron cell survival [16]. It is suggested as a target in the treatment of bipolar disorder [17]. Indeed, a study on mice GSK3β-knockout mice or treated by inhibiting GSK3β showed a reduction of depression and reduction of manic behavior. This enzyme is also sensitive to lithium. Inhibition of GSK3 by valproic acid is believed to occur through direct and indirect, but this hypothesis is quite controversial [18]. Studies on nearby molecules valproic acid show no direct inhibitory effect of GSK3 any tested compound, others show strong inhibitory effects but not correlated with the anticonvulsant effect. On the other hand, GSK-3β plays a critical role in the CNS by regulating many cytoskeletal processes as well as long-term neural events and is a common target for both lithium and VPA; inhibition of GSK-3β in the CNS may thus underlie some of the long-term therapeutic effects of mood-stabilizing agents.

Intervention in gene expression

Considering that it takes about 10 days of oral administration of valproate before its effect mood stabilizer becomes effective [19] and this effect persists well after the judgment was assumed that its mechanism of action involves not only acute biochemical effects and short term but also changes at the genomic level. Valproate does appear to alter the expression of many genes, and although mechanisms were not attached for the moment efficacy in bipolar disorder, they however, allow new hypotheses [20].

First, as discussed above we saw a likely effect on the transcription of COX2 and NF-kB. But another way of change in gene expression was observed by the activation of the binding of the protein AP-1 to DNA. AP-1 (activator protein 1) is a transcription factor for several important brain functions [21], such as development, plasticity and neurodegeneration. It is involved in the expression of multiple genes such as those encoding for neurotrophins, receptors and enzymes involved in the synthesis of neurotransmitters. AP-1 is a heterodimer, its subunits are proteins involved in many cellular signaling pathways, like proteins belonging to the c-Jun, c-Fos, and other families activating transcription factors (ATF) [22]. The activation of AP-1 valproate is observed in many studies and could play a role in its therapeutic effects.

Another route in which valproate would modify gene expression and which is supported in numerous studies, is that of histone deacetylases. Indeed, it was observed that the valproic acid is an inhibitor of histone deacetylase (HDAC) at doses used therapeutically [23]. Like other HDAC inhibitors, VPA activates transcription from various promoters [24]. This inhibition of HDAC induce expression dependent genes Wnt [25].

Wnt is a family of glycoproteins playing an important role in embryogenesis and homeostasis of adult tissues; it is involved in the cancer process. The protein kinase called GSK3 (Glycogen synthetase kinase 3) and beta-catenin, which is a transcription factor belonging to the Wnt signaling pathway [26]. Activation of the Wnt signaling pathway allows the beta-catenin to enter the nucleus and activate the expression of specific genes, which would increase the expression of catenin, which is a transcription factor. Lithium also activates this pathway, but by inhibition of GSK-3 in vivo; yet it seems that valproic acid activates the expression of Wnt-dependent genes by direct inhibition of histone deacetylase. Valproic acid mimics the natural histone deacetylase inhibitor, trichostatin A (TSA), causing hyperacylation of histones in cultured cells [27]. In addition to the similarity of action between valproic acid and TSA also are observed teratogenic effects on the development of similar mouse embryos [28]. Which indicates that inhibition of HDAC may be responsible for the mechanism of teratogenicity induced by valproic acid? Unlike the cellular targets exposed above, the modifications driven by valproate in the expression of multiple genes, induced at least partially by direct inhibition of HDAC.
have been demonstrated repeatedly. They could explain the therapeutic effects of this drug through various intracellular signaling pathways, such as blocking GSK-3, the effects neurotrophic and neuroprotective agents, promoting BDNF expression (brain-derived neurotrophic factor). The mechanism of its gene-inducing effect has been reported to involve transcription factors, Sp1 and activator protein-1.

Interaction in gene expression of valproic acid could have long-term effects term on brain plasticity; given the large number of genes which it modifies expression, it is reasonable to think that gene expression changes play a significant role in the long-term effects of this drug [29]. In conclusion, its genomic influence may provide insight into the therapeutics effects relevant to the three indications of epilepsy, migraine and disorder bipolar mood. A functional microarray analysis offers new information that could open novel avenues of research in biomarker discovery which may be useful for the early identification of children with a predisposition to epilepsy.

Conclusion

Valproic acid activates or inhibits the various targets by direct routes or by unknown mechanisms. Cellular targets of acid valproic histone deacetylase are HDACs, ion channels (X+), the level of GABA, phospholipase A2 (PLA2) signaling pathway, synthesis of inositol and resulting phospholipids [Ino & PI], the pathway of MAP Kinases (MAPK) and GSK3 (Glycogen synthase kinase 3). Unfortunately, as we have seen, the data for correlating each target of valproic acid with clinical effect in different pathologies are still quite limited. We observe a relative lack of data for the neuropharmacology of valproate compared to other mood stabilizers and anticonvulsants. Modern tools like basic and clinical neurology should shed light on its mechanism of action.

The anti-epileptic effects of valproic acid are complex and involve several mechanisms of action. Originally, the main mechanism of action of valproic acid put forward was the inhibition of voltage-gated sodium channels. Valproic acid modulates neuronal hyperexcitability, especially by blocking the T-type calcium channel. The anti-epileptic action of valproic acid also results from its ability to strengthen the inhibitory action of GABA by binding to the GABA-A receptor and by causing an increase in brain concentrations of GABA by a weak inhibition of the two enzymes, involved in the degradation of GABA (GABA-transaminase and succinyl-hemi-aldehyde dehydrogenase). However, pharmacodynamic studies suggest that these effects on GABA transmission are very moderate at therapeutic doses. Its mechanism of action remains largely unknown.

References


