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Review

The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees?

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Abstract. After more than 40 years of clinical use, the mechanisms of action of valproate in epilepsy, bipolar disorder and migraine are still not fully understood. However, recent findings reviewed here shed new light on the cellular effects of valproate. Beyond the enhancement of γ-aminobutyric acid-mediated neurotransmission, valproate has been found to affect signalling systems like the Wnt/β-catenin and ERK pathways and to interfere with inositol and arachidonate metabolism. Nevertheless, the clinical relevance of these effects is not always clear. Valproate treatment also produces marked alterations in the expression of multiple genes, many of which are involved in transcription regulation, cell survival, ion homeostasis, cytoskeletal modifications and signal transduction. These alterations may well be relevant to the therapeutic effects of valproate, and result from its enhancement of activator protein-1 DNA binding and direct inhibition of histone deacetylases, and possibly additional, yet unknown, mechanism(s). Most likely, both immediate biochemical and longer-term genomic influences underlie the effects of valproate in all three indications.

Keywords. Valproate, antiepileptic, migraine, bipolar disorder, histone deacetylase, neuroprotection, signal transduction.

Introduction

Valproate, a simple branched-chain fatty acid (2-propylpentanoic acid) (Fig. 1), is a broad-spectrum anticonvulsive drug with well-established efficacy in both partial and generalized seizures. Since 1962, when valproate was serendipitously found to be an anticonvulsant, it has become available for the indication of epilepsy in more than 100 countries [1]. Valproate is also commonly prescribed for bipolar mood disorder and is recommended by several national and international societies of psychiatry and pharmacology as a first-line drug for both the treatment of acute mania and as maintenance therapy for mania prevention, alone or in combination with other agents [2]. Valproate is sometimes recommended as part of the treatment for bipolar disorder depression [2] although its antidepressive effect is smaller and not as well substantiated as its antimanic one [3]. In addition, valproate is recognised as a first-line prophylactic drug for migraine headache [4].

As an acute biochemical effect, valproate has been shown to increase brain levels of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) probably by inhibiting succinic semialdehyde dehydrogenase, consequently increasing brain levels of succinic semialdehyde, a metabolite that inhibits GABA transaminase thus preventing GABA catabolism [5]. Evidence also suggests a direct inhibitory effect of valproate on voltage-gated Na^+ channels, suppressing

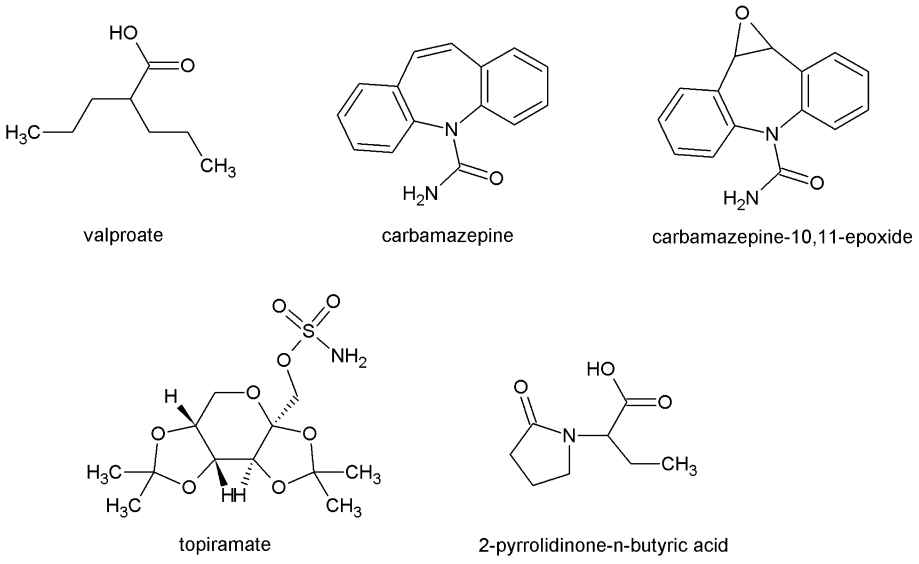

Figure 1. Chemical structures of antiepileptic drugs, or their major metabolites, that are HDAC inhibitors.

high-frequency firing of neurons, and possibly indirect effects on non-GABAergic neurotransmission [5, 6]. Nevertheless, the mechanisms of action of valproate in neuropsychiatric disorders are far from fully understood. A 1999 review entitled 'The pharmacologic basis of antiepileptic drug action' attributed its antiepileptic effect principally to elevation of brain GABA concentration and inhibition of neuronal voltage-gated Na^+ channels, although the involvement of additional 'actions, not yet clearly defined' was also pointed out [6]. However, a similar review published in 2005 ranked the GABA enhancement as only a 'secondary' action of valproate and the Na^+ channel inhibition as 'controversial', and proposed that 'other actions' form the primary basis for the antiepileptic activity of valproate [7]. Likewise, in bipolar disorder, the relevance of the facilitation of GABAergic transmission to the beneficial effect of valproate remains unclear. Although it is assumed that the pro-GABAergic influence of valproate causes initial sedative and anxiolytic effects that may be helpful in these patients [8, 9], research has focused on other avenues through which valproate may have a mood-stabilising effect in bipolar disorder [9, 10]. In migraine prophylaxis, despite a possible role for GABA enhancement in the attenuation of migraine-related neuroinflammation [11], the mechanism of action of valproate is uncertain, since although valproate can reduce neuronal excitability via the inhibition of voltage-gated Na^+ channels, this alone seems insufficient to inhibit the cortical spreading depression implicated in migraine pathogenesis [12]. Furthermore, little is known about the way in which valproate interacts with its cellular targets: it has been shown that valproate (and its metabolites) can bind covalently and irreversibly to tissue proteins [13], but the nature of the resulting changes in their conformation and/or charge remains obscure.

Many new insights into the biological activities of valproate have emerged in the past several years, changing our understanding of how this drug works. Plausible biochemical mechanisms which may underlie, for example, the effect of valproate in bipolar disorder [14] or the persistence of some therapeutic effects after drug administration has ceased [15], are starting to emerge. Likewise, the mechanisms behind valproate teratogenicity [16–18] and certain adverse events [19, 20] are becoming clearer. This review attempts to highlight recent major findings regarding the biochemical and genomic effects of valproate while assessing their relevance to human disease.

Effects on the extracellular signal-regulated kinase pathway

The central role of the extracellular signal-regulated kinase (ERK) pathway in supporting neurogenesis, neuronal survival, dendritic arborisation and synaptic plasticity in the adult mammalian brain has recently been reviewed elsewhere [21]. These effects seem to be mediated by ERK-induced expression of trophic and protective factors such as the antiapoptotic product of the B cell lymphoma/leukaemia-2 gene (Bcl-2) [21]. Animals with induced impairments in this pathway exhibit behavioural alterations that resemble some features of mood disorders (especially hyperactivity) and respond to therapies employed in these disorders [21, 22].

Over the past several years valproate, at clinically relevant concentrations, has been demonstrated to activate the ERK pathway: *in vitro*, this activation requires the topmost components of this pathway, namely Ras, Raf and mitogen-activated protein kinase kinase (MEK), and results in increased levels of the phosphorylated forms of ERK1/2 [23]. ERK phosphorylation, in turn, can activate the transcription factor Elk1, and the latter enhances the expression of c-Fos [24], a potentially significant element in the mechanism of action of valproate (see below). Another target of the ERK pathway whose expression is increased *in vitro* after valproate exposure is growth cone-associated protein (GAP-)43, which is important for neural plasticity [23]. *In vivo*, valproate can increase the levels of Bcl-2 in the frontal cortex of rats [25], as indeed may be expected of an activator of the ERK pathway [21]. In subsequent studies, not only was valproate-induced ERK1/2 phosphorylation – and thus activation – demonstrated in the rat brain, but a significant increase in protein levels of brain-derived neurotrophic factor (BDNF), a known target of the ERK pathway, was found in the rat hippocampus and frontal cortex [22, 26]. This concurred with an earlier observation that chronic valproate administration to rats results in increased BDNF levels in the frontal cortex [27]. Although in this study changes in BDNF mRNA abundance were not measured, the authors attributed the increased BDNF protein to enhanced expression of the BDNF gene, which may indeed be an effect of ERK activation. Importantly, both *in vitro* and *in vivo* [23, 26] valproate can promote neurite outgrowth and cortical neurogenesis, and MEK inhibition prevents these valproate-induced processes. Activation of the ERK pathway by valproate can contribute not only to trophic changes but also to changes in receptor expression: valproate has been shown to potentiate the transcriptional efficacy of several nuclear hormone receptors at least partially through its function as an activator of the ERK pathway [28].

What might be the significance of these valproate-mediated effects, assuming they also occur in the human brain? Post-mortem and imaging studies in bipolar disorder patients have demonstrated reductions in glial and neuronal cell density, along with reduced synaptic and dendritic densities, particularly in the prefrontal cortex (and especially in its medial region), as well as in the hippocampus and subcortical brain areas [29, 30]. It is hypothesised that these organisational, and presumably circuitry, alterations are at least partially neurodegenerative in nature and contribute to the phenotype of this mood disorder. Chronic neuropsychiatric drug therapy can produce morphometric changes in disease-relevant cortical areas along with clinical improvement [31, 32]. It is therefore not unreasonable to suggest that valproate, through its effect on the ERK pathway and upregulation of trophic and protective factors such as BDNF and Bcl-2, can similarly help to reverse the neurodegenerative changes seen in bipolar mood disorder, possibly not through neurogenesis – which is unlikely in the adult human prefrontal cortex – but perhaps through the enhancement of neuropil building [21]. Whether a similar trophic mechanism contributes to the long-term effects of valproate in epilepsy is unknown. However, an association between the pathophysiological progression of affective disorders and epilepsy has been proposed [33], and progressive hippocampal and extrahippocampal atrophy have been demonstrated in some epilepsy patients [34]. Therefore, the trophic support of valproate, mediated partially by ERK pathway activation, should be studied as one of the mechanisms of action of the drug in epilepsy. Indeed, repeated exposures to valproate *in vitro* (at clinically relevant concentrations) increases GABAergic differentiation of rat cortical stem cells and is accompanied by a concurrent increase in Bcl-2 expression [35]. Similarly, even though the overall harmful or protective role of BDNF in epilepsy needs to be further elucidated [36], BDNF has been shown to promote the maturation of GABAergic neurons *in vitro* and to enhance the expression of $GABA_A$ [37], a receptor with a role in neuronal synchrony control [38].

Nevertheless, the exact role of ERK pathway activation in the mechanism of action remains to be clearly defined and valproate is not a 'cure-all'. For example, Hsieh et al. [39] assessed whether valproate-mediated neuronal differentiation of adult hippocampal neural progenitors *in vitro* is directly caused by the activation of the ERK pathway: although valproate did activate ERK, application of a MEK inhibitor did not hinder the cell fate commitment initiated by valproate, indicating that the ERK pathway was not solely, or not at all, responsible for the valproate-induced differentiation of these progenitor cells.

In what way(s) can valproate interact with the ERK pathway? There are no clear answers to this question. Hao et al. [26] hypothesised that valproate-induced inositol depletion (discussed below) affects the synthesis of phosphatidylinositol, a molecule used by several signalling pathways that cross talk with the ERK pathway, such that this pathway is eventually activated. Yuan et al. [23] speculated that either valproate induces, through non-ERK pathways, the expression of secreted neurotrophic factor(s) that in turn activate the ERK pathway via cell surface tyrosine kinase receptors, or valproate – which is incorporated into neuronal phosphatidylcholines *in*

vitro [40] – disturbs the normal catabolism of the latter and causes accumulation of lysophosphatidylcholine, which is an activator of ERK through the tyrosine kinase-Ras pathway [41]. Since the incorporation of valproate into neuronal phosphatidylcholines *in vivo* has been repeatedly questioned [42], the former explanation remains at present more likely.

Effects on the phosphoinositide cycle and the phosphokinase C family

Increased cortical myo-inositol levels have been implicated in the pathophysiology of bipolar disorder: magnetic resonance imaging studies suggest an increase in myo-inositol levels in the frontal, and especially in the cingulate cortex of manic patients, and the antimanic effect of lithium has thus been attributed to its inhibition of inositol monophosphatase, the enzyme that dephosphorylates inositol monophosphates to produce myo-inositol [recently reviewed in 43]. Valproate, at clinically relevant concentrations, has been shown to be a non-competitive indirect inhibitor of human cortical myo-inositol-1-phosphate synthase, the enzyme that mediates *de-novo* synthesis of the substrate for inositol monophosphatase, implying that, like lithium, valproate may have an inositol-depleting effect on the brain [44, 45]. This was indeed observed *in vivo* after acute valproate treatment, yet a 14-day repeated administration of valproate to mice failed to produce a similar reduction in brain inositol [44].

However, doubts have been expressed about the therapeutic relevance of the inhibition by lithium of inositol monophosphatase, and in general the role of inositol changes in bipolar disorder remains hypothetical and requires further research [10, 43, 46, 47]. Myo-inositol is required for the synthesis of phosphatidylinositol 4,5-bisphosphate (PIP_2). Ligand binding to G_q protein-coupled receptors stimulates phospholipase C to hydrolyse PIP_2 into inositol 1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG), and these two, in turn, mediate mobilization of intracellular calcium and activate protein kinase C (PKC), respectively [43]. It has been proposed that inositol depletion and subsequent intracellular reduction of IP_3 and DAG and their downstream effectors are therapeutic through cytoskeletal and gene expression alterations; however, these alterations can be induced by valproate (and lithium) through alternative, non-inositol related, mechanisms, hence some of the doubts about the therapeutic significance of inositol depletion [47]. Nevertheless, valproate-induced alterations in PKC activity, mediated by inositol depletion or by other factors, has attracted significant attention [10].

The PKCs are a family of serine/threonine protein kinases that phosphorylate proteins such as receptors for neurotransmitters and neuropeptides, signalling molecules, transcriptional factors and cytoskeletal proteins [48]. In the brain, PKCs are found primarily pre-synaptically, and upon activation translocate from the cytosol to the cell membrane, where they are anchored to the membrane by the receptor for activated C kinase-1 (RACK1) and participate in neurotransmitter release (particularly isoforms PKC-α and PKC-ε) [10, 47]. A possible linkage between PKC activation and bipolar disorder is supported by the increased cell surface presence of PKC in the frontal cortex and blood platelets of bipolar patients compared to controls [49–51]. Chronic lithium therapy leads to a reduction in membrane-associated PKC in the rat hippocampus, an effect that is thought to be relevant to the anti-manic activity of this drug [52]. It was suggested that PKC-ε also plays a role in seizure generation, at least in primary generalised epilepsies [53]: PKC-ε is selectively upregulated in rat hippocampal granule cells after kainate-induced seizures [54] and its activation attenuates $GABA_A$ receptor sensitivity [55]. PKC-ε knock-out mice are supersensitive to allosteric $GABA_A$ receptor modulation, leading to the proposal that pharmacological attenuation of PKC-ε should also result in similar $GABA_A$ receptor hypersensitivity and increased GABAergic neuronal inhibition in epilepsy [55].

Although valproate does not directly interact with PKC [56], several days of *in vitro* exposure of C6 glioma and hippocampal cells to valproate at clinically relevant concentrations (<0.6mM [57]) produce a significant reduction in the protein content and activity of PKC, especially PKC-α and PKC-ε, in both cytosol and membrane [56, 58]. Valproate also downregulates the expression of the PKC substrate myristoylated alanine-rich C kinase substrate (MARCKS) [58, 59], a protein that cross-links actin and participates in membrane-cytoskeleton remodelling and synaptic modification [60]. Of note, it takes MARCKS up to a week to recover to control levels after valproate is withdrawn [58]. In bipolar manic patients, a 2-week course of valproate therapy attenuated the excessive baseline PKC activity in platelets [48]. Interestingly, in this study, valproate also suppressed the interaction between serotonin and thrombin receptors and various G_α proteins without affecting the expression of these G proteins [48], which may indicate an entirely novel mode of action of valproate. Based on the temporal profile of the valproate-induced changes in PKC activity, it was proposed that valproate enhances intracellular formation of active complexes of PKC with its co-factors and substrates, leading eventually to increased proteolysis

of PKC [58]. Indeed, the degradation of PKC isoenzymes by the ubiquitin-proteasome system depends on the phosphorylated state and catalytic function of these enzymes [61]. However, valproate, at least in epithelial cells, significantly suppresses proteasomal activity even after short-term exposure [62], so mechanisms other than enhanced catabolism should be considered for the downregulation of PKC activity by valproate, e.g. transcriptional suppression. Notably, the inhibition of proteasomal activity may point to another mechanism by which valproate can increase the presence (but not necessarily the activity) of various cellular proteins.

Effects on glycogen synthase kinase-3 and the Wnt/β-catenin pathway

Wnts are a family of secreted, cysteine-rich, glycosylated protein ligands that influence cell growth, differentiation, polarization, migration and fate through several pathways, including the Wnt/β-catenin pathway: binding of Wnts to their cell membrane receptor leads to the phosphorylation and inhibition of glycogen synthase kinase-3 (GSK-3), which cannot then phosphorylate β-catenin. β-Catenin accumulates in the cytosol, translocates to the nucleus, binds to transcription factors of the Tcf (T cell factor)/Lef (lymphoid-enhancer factor) family, and activates transcription of Wnt-dependent target genes [63, 64]. In other words, the serine/threonine kinase GSK-3 plays a pivotal inhibitory role in this pathway through phosphorylation of β-catenin, labeling the latter for destruction by the ubiquitin-proteasome system [64]. There are two structurally similar GSK-3 mammalian isoforms encoded by distinct genes, GSK-3α and GSK-3β, and both can phosphorylate β-catenin (although they may not be functionally identical otherwise) [64]. Both isoforms target a wide variety of intracellular substrates other than β-catenin, including cytoskeletal targets and transcription factors. Finally, inhibition of GSK-3β has been shown to protect neurons from programmed cell death [65].

Following the initial report that, like lithium, clinically relevant concentrations of valproate directly inhibit both GSK-3 isoforms (and particularly GSK-3β) [66], a debate emerged on three questions: (1) is valproate truly a direct inhibitor of GSK-3? (2) if not, does valproate have any effect on this enzyme and on the Wnt/β-catenin pathway? and (3) are GSK-3 and the Wnt/β-catenin pathway relevant at all to the pathophysiology of bipolar mood disorder (GSK-3 has not been implicated in epilepsy or migraine)?

Using immunoprecipitated or recombinant enzyme at different Mg^{2+} concentrations (Mg^{2+} is a potentiator of GSK-3 activity), a number of studies have demonstrated that valproate directly inhibits GSK-3β [66–68]. On the other hand, several other studies [17, 18, 69, 70], using recombinant GSK-3β and a similar range of Mg^{2+} concentrations, could not detect such a direct inhibition of this enzyme by valproate or by valproate derivatives. Conflicting data also emerge from studies in a range of cellular systems. Whereas Hall et al. [69] found that valproate decreased GSK-3 phosphorylation of microtubule-associated protein 1B in cerebellar granule cells, and Tatebayashi et al. [71] attributed valproate-induced attenuation of tau phosphorylation in PC12 cells to GSK-3 inhibition, Phiel et al. [18] and Jin et al. [72] could not detect any valproate-mediated inhibition of GSK-3β phosphorylation of tau in Neuro2A and cerebellar granule cells, respectively. Similarly, while Chen et al. [66] found that valproate produced a marked increase in both cytosolic and nuclear β-catenin levels in SH-SY5Y neuroblastoma cells, which they attributed to GSK-3β inhibition, Williams et al. [57] and Ryves et al. [70] did not observe any changes in cellular β-catenin levels after exposing dorsal root and embryonic neocortical neurons, respectively, to valproate. Indeed, Phiel et al. [18] reported a valproate-induced increase in β-catenin in Neuro2A cells, but as this took 10 h to develop and since direct GSK-3 inhibition by valproate was not detected, the increase was attributed to enhanced β-catenin transcription through the inhibition of valproate of histone deacetylase, which was confirmed by demonstrating an increase in β-catenin mRNA levels. De Sarno et al. [73], working in SH-SY5Y cells with somewhat above-therapeutic concentrations of valproate, also attributed the phosphorylation (activation) of Akt and resultant serine9 phosphorylation (inactivation) of GSK-3β to the inhibition by valproate of histone deacetylase, and not to a direct effect of the drug on GSK-3β. Effectively, the last two studies point to a process whereby valproate affects the Wnt/β-catenin pathway regardless of GSK-3 inhibition, as has also been proposed by others [17]. In summary, consistent effects of valproate on substrates of GSK-3 in cellular systems have not been demonstrated. Whereas this inconsistency could have resulted from using different cell lines and employing diverse experimental methods in these studies [70, 72], it may also indicate that inhibition or inactivation of GSK-3 is not a universal consequence of valproate exposure [72].

Limited information exists on the effects of valproate on GSK-3 and β-catenin *in vivo*, but the available data seem to support an indirect inactivation of GSK-3 by the drug. Following 11-day treatment of adult rats with valproate, Kozlovsky et al. [74] found no changes in the frontal cortex content of GSK-3β or in the activity

of total GSK-3. Nevertheless, in a subsequent study employing a similar treatment paradigm, the same researchers found a significant 40% increase in the fontal cortex content of the inactivated (serine9 phosphorylated) form of GSK-3β [75], which concurs with the cellular findings of De Sarno et al. [73]. The observation that prophylactic valproate administration to mice attenuates hypoxia-induced dephosphorylation of brain GSK-3α and GSK-3β (without altering GSK-3 protein content) [76] further emphasises the role of valproate in keeping GSK-3 inactivated, even if this enzyme is not directly inhibited by the drug. In the rat, 9-day administration of valproate (achieving clinically relevant serum levels) yielded a significant increase in the frontal cortex, but not hippocampal, content of β-catenin, without any change in β-catenin mRNA abundance [77]. While the latter experiment leaves obscure the mechanism behind the increase of β-catenin by valproate (and contradicts the cellular results of Phiel et al. [18]) its findings can be explained by valproate-enhanced inactivation of GSK-3.

It should be noted that three studies from different laboratories conducted on post-mortem frontal cortex specimens from bipolar patients could not detect significant differences between patients and normal controls in the content of GSK-3β and/or β-catenin [78–80], GSK-3α and GSK-3β mRNA abundance or total GSK-3 activity [78]. Furthermore, no differences were observed between non-medicated patients and those on mood stabilisers [79] and between the frontal and occipital cortices [78]. Although the absence of Wnt/β-catenin or GSK-3 perturbations in human bipolar disorder does not rule out the possibility that valproate exerts its influence in this disorder through an interaction with these intracellular effectors, the post-mortem findings raise doubts as to the relevance of GSK-3 and the Wnt/β-catenin pathway to the pathophysiology of human bipolar disorder and to their role in the therapeutic effect of valproate.

Effects of brain lipids and their metabolism

As valproate is a small, branched fatty acid it is naturally intriguing to explore whether any of its effects may be due to alterations in the brain's lipid metabolism. As has already been mentioned above, *in vivo* evidence consistently counters the notion that valproate is incorporated into brain phospholipids [for further discussion see Ref. 81]. It was pointed out that valproate, through an unknown mechanism, decreases the incorporation of different substrates like glycerol, mevalonate and lactate into both sterols and glycerolipids in different regions of the central nervous system [82]. This may result in structural changes and decreased fluidity of neuronal membranes, thereby increasing the neuronal firing threshold and limiting the progression of epileptic discharges [82]. It should be noted, however, that this was inferred from findings in neonatal brains, whose lipid composition is different from that of the adult nervous system [83, 84], and it still remains to be demonstrated that valproate has similar effects on cellular membranes in the fully developed brain. Additionally, in lecithin liposomes employing the fluorescent probe 1,6-diphenyl-1,3,5-hexatriene (DPH), valproate (at a high concentration of 2mM) did not change the fluorescence anisotropy of DPH, which does not support the concept that changes in the microviscosity of cellular membranes play an important role in the mechanism of action of this drug [85].

Valproate was recently shown to be a direct non-competitive inhibitor of brain microsomal long-chain fatty acyl-CoA synthetase [42], an enzyme whose inhibition leads to reduced availability of arachidonoyl-CoA and subsequently to decreased turnover of arachidonic acid in phospholipids and diminished prostaglandin production. This study complemented an earlier observation from the same group that chronic valproate administration in the rat, such that produces clinically relevant plasma and brain levels, reduces the incorporation rate and turnover of arachidonic acid in brain phospholipids by 33% [86]. In the latter study, the effect of valproate on arachidonate metabolism was not accompanied by a reduction in the levels of cytosolic phospholipase A_2 ($cPLA_2$). However, a comparable study [87] demonstrated that valproate-induced reduction in intracellular levels of arachidonic acid products was accompanied by a decrease a in the protein levels of cyclooxygenase (COX)-1 and COX-2, a decrease whose nature (i.e. transcriptional or post-transcriptional) is unclear. It remains an open question whether valproate inhibits arachidonate metabolism through direct enzymatic inhibition, a transcriptional change, or both. Whatever the answer may be, the fact that lithium has a similar effect on arachidonic acid metabolism (apparently through a decrease in the gene expression of $cPLA_2$) [86] led to the hypothesis that both drugs act, at least in bipolar disorder, by reducing the formation of arachidonic acid products [88]. Support for this hypothesis comes primarily from pre-clinical studies [for review see Ref. 88], and from observations that dietary supplementation with n-3 polyunsaturated fatty acids, which can inhibit COX-2-mediated conversion of arachidonic acid to prostaglandins [87], is beneficial in extending mood-stable remissions in bipolar patients [89].

However, a recent review on this topic presented overall little to no clinical evidence supporting the existence of arachidonic acid metabolic perturbations in bipolar disorder [90]. If any, there are data to indicate that COX inhibitors (non-steroidal anti-inflammatory drugs, NSAIDs) can exacerbate manic symptoms [90], and in post-mortem brain specimens from bipolar subjects, prostaglandin E2 synthase levels are reduced in untreated patients and increase with therapy [91]. In experimental epilepsy, the epileptogenic contribution of COX-2 and arachidonate products has been demonstrated [92], but the significance of this metabolic pathway in clinical epilepsy is still unknown and there are no reports of a therapeutic effect of COX inhibition in human epilepsy [93]. Therefore, the claim that altering arachidonate metabolism is a major mode of action of valproate in either epilepsy or bipolar disorder requires further substantiation. In migraine, however, NSAID therapy is well established for both prevention and treatment of acute attacks [94], and prostaglandins, especially prostaglandin E_2, have been implicated in migraine pathophysiology [for a discussion see ref. 95]. It thus cannot be excluded that valproate acts in this condition, at least partially, through arachidonic acid metabolism inhibition.

Effects at the genomic level

Considering that about 10 days of oral valproate administration are required before its mood-stabilizing effect becomes significant [3], and that this effect persists well after valproate cessation [96], it has been assumed that the mechanism of action of valproate involves not only acute and short-term biochemical effects but also changes at the genomic level [10, 96]. Observations in some patients and animal models of persisting antiepileptic, antimigrainous and other effects up to weeks after the discontinuation of valproate [6, 15, 97–100] further support this notion. Interestingly, it takes 16, but not 3, weeks of valproate treatment to suppress spreading cortical depression in a rat model of migraine prophylaxis [12], which concurs with the clinical observation that the prophylactic effect of valproate in migraine evolves to its full extent over 7–12 months of therapy (while the dose is kept unchanged) [101], findings that are incompatible with an acute biochemical effect. A similar increase in valproate efficacy with repeated administrations, while the brain levels of the drug remain unchanged, was also observed in experimental epilepsy [102]. This indicates that increased efficacy was not due to drug accumulation (and thus more pronounced short-term effects) but through another mechanism(s).

Indeed, many studies have demonstrated the ability of valproate to alter *in vitro* and *in vivo* the expression of various genes pertinent to neuropsychiatric disorders. Treatment of C6 glioma cells with valproate at a clinically relevant concentration resulted after 20 h, but not after 1.5 h, in a twofold increase in the density of the serotonin 2_A receptor (5-HT_{2A}R) as assessed by ketanserin binding [96]. Based on the time course of this change, and on the fact that the gene for this receptor contains an activator protein (AP)-1-binding site (see below), the authors suggested that valproate enhanced the expression of the 5-HT_{2A}R gene, although the abundance of 5-HT_{2A}R mRNA was not measured in this study. In view of post-mortem studies reporting reduced presence of 5-HT_{2A}R mRNA and protein in the frontal cortex of bipolar patients [103, 104], this finding may be relevant to the beneficial effect of valproate in this disorder. Indeed, in a sample of seven acutely manic patients, a relatively short exposure to valproate (<5 weeks) produced clinical improvement but only insignificant increases in the 5-HT_{2A}R brain binding of the positron emission tomography tracer [^{18}F]-setoperone [105]; however, longer exposures to valproate may yet result in greater increases in the presence of 5-HT_{2A}R in the brain, and if so, clarification will be needed as to whether such changes involve enhancement of this receptor's transcription. Repeated administration of valproate to rats increased the mRNA levels of tyrosine hydroxylase – the gene for which also contains an AP-1-binding sequence – in the locus coeruleus [106]. Chronic valproate treatment in rats led to increased expression of certain Ca^{2+}-binding stress proteins in the endoplasmic reticulum, especially in the frontal and parietal cortices, raising the possibility that valproate may in this way reduce neuronal damage secondary to increased intracellular Ca^{2+} levels that are presumed to develop in bipolar disorder [107]. The application of RNA microarray analysis to brains of rats treated for 30 days with valproate (200 mg/kg per day) revealed significant alterations (both up- and downregulation) in the expression of about 120 genes, many of which are involved in transcription regulation, ion channelling and transport, cytoskeletal modifications and signal transduction [108], targets potentially relevant to treating migraine, epilepsy and bipolar disorder. An indication that valproate exerts a similar effect in humans was provided by a study that employed oligonucleotide microarrays to compare whole blood from epileptic children treated chronically with valproate with blood from comparable drug-free or carbamazepine-treated patients: the

valproate-treated group exhibited expression changes (again, both up- and downregulation) in 461 genes compared to the two control groups [109]. In light of the above discussion on valproate and its interaction with PKC, ERK pathway signalling and arachidonate metabolism, it is interesting to note that a significant number of the down-regulated genes in the valproate-treated children code for serine threonine kinases, including PKCs and ERK1, and that COX-2 was also downregulated. It remains to be established whether any of these expression changes also occur in the brain, and if so, which are therapeutically relevant.

Recent research suggests two mechanisms through which valproate can simultaneously affect the expression of multiple genes: the enhancement of AP-1 binding to DNA and the inhibition of histone deacetylases (HDACs). AP-1 is a collective term used for dimeric transcription factors that are made of either a homodimer of jun gene products (commonly c-Jun) or a heterodimer comprising a Jun protein with an activator transcription factor (ATF) protein or a Fos family protein (often c-Fos) [110]. AP-1 transcription factors bind to the DNA at a specific regulatory site (the 12-O-tetradecanoylphorbol 13-acetate (TPA)-response element) and regulate the expression of multiple genes, including many for neurotrophines, transcription factors, receptors and enzymes involved in neurotransmitter synthesis [111]. In both glial and neuronal cell lines, valproate increased the DNA binding of AP-1 and enhanced AP-1-regulated gene expression in a time- and concentration-dependent manner and at clinically relevant concentrations, but probably not through a direct interaction with AP-1 [112, 113]. Mutations at the AP-1-binding site diminish the effect of valproate on AP-1-regulated gene expression [113]. Animal studies that evaluated changes in the brain expression of genes like tyrosine hydroxylase [106] or BDNF [27] after valproate treatment indicate that valproate-enhanced expression of AP-1-regulated genes also occurs *in vivo*. Interestingly, increased AP-1 DNA binding in the rat cerebral cortex and hippocampus was found even 7 days after valproate administration [112].

The AP-1 dimers are, at least partly, regulated by the mitogen-activated protein kinase pathways of p38, ERK and c-Jun N-terminal kinase (JNK) [110]. Relevant to our discussion, the JNK pathway phosphorylates and activates c-Jun while the ERK pathway induces the phosphorylation of the monomeric ternary complex factor Elk-1 thus enhancing c-fos transcription [110]. Additionally, c-Jun can be phosphorylated by GSK-3, resulting in decreased AP-1 DNA binding [64], and the c-jun gene is subject to positive autoregulation through an AP-1-binding site on its promoter [113]. As valproate seems not to act via the JNK or p38 pathways [23] and has no effect on protein dephosphorylation [112] (dephosphorylation of c-Jun increases AP-1 DNA binding), and in light of its biochemical interactions discussed earlier, it could be hypothesised that the effect of this drug on AP-1 is, at least to some degree, mediated through the inactivation of GSK-3 and/or the activation of the ERK pathway. Indeed, in SH-SY5Y neuroblastoma cells, valproate at therapeutically relevant concentrations increases c-Fos immunoreactivity acutely and after 1 week of exposure (concomitantly increasing AP-1 DNA binding) [114], and acute valproate treatment in the rat results in an increased hippocampal content of c-Fos but not c-Jun [115], all findings consistent with ERK activation. The picture, however, is not entirely clear: chronic valproate treatment does not result in an increased c-fos expression [115], and a 3-day prophylactic treatment with valproate blunted, rather than enhanced, hippocampal and cortical post-seizure increases in c-fos mRNA levels [116]. In addition, since valproate has no effect on DNA binding of the transcription factor CREB (cAMP-responsive element binding protein) [112, 115], a substrate of GSK-3 whose phosphorylation enhances its transcriptional activity [64], the contribution of valproate inactivation of GSK-3 and putative prevention of c-Jun inactivation to the enhancement of AP-1 DNA binding should also be questioned. In summary, whatever its effects on c-fos and c-jun via ERK pathway activation and possibly GSK-3 inactivation may be, other mechanisms through which valproate increases AP-1 activity must be sought.

Clearly, not all the genes whose expression is altered by valproate have an AP-1–binding site, and ever since the landmark study by Phiel et al. [18] many of the genomic effects of valproate have been attributed to its inhibition of HDAC [18, 117]. The nucleosome, the basic unit of chromatin, comprises four pairs of histone proteins (H2A, H2B, H3 and H4) around which 147 base pairs of DNA are wrapped [118]. Lysine residues on the C-terminal tails of these histones control the degree of DNA coiling and thus the accessibility of the transcriptional machinery to DNA: increased acetylation of the lysine residues by histone acetyltransferases leads to DNA relaxation and enhanced transcriptional activity whereas hypoacetylation by HDAC results in gene silencing [118, 119]. Histone acetylation has been shown to be an important regulatory mechanism, controlling the transcription of about 2% of transcribed genes [120]. The HDACs are usually grouped into three classes: I, II and sirtuins; histone deacetylase inhibitors currently in clinical use or under development inhibit only the first two classes [119]. Valproate directly inhibits various HDACs at therapeutically relevant IC_{50} values

[18, 121, 122], but valproate metabolites seem to be weaker HDAC inhibitors [121]. Valproate-induced histone hyperacetylation has been demonstrated *in vivo*, and at clinically relevant concentrations: Yildirim et al. [123] showed that treatment of mice with repeated valproate injections increased the hippocampal acetylation of H3, putatively leading to an increase in the protein content of 5-lipoxygenase in that region. Recently, the histone-hyperacetylating effect of valproate has also been verified in bloodstream lymphocytes of bipolar and schizophrenia patients who had been treated with valproate for 4 weeks [124]. In these patients, valproate therapy was associated with an increase in H3, and to a lesser degree H4, acetylation, which was more pronounced in the bipolar patients. Importantly, symptomatic improvement in these patients correlated with an increase in both H3 acetylation and valproate serum concentrations. Indeed, several researchers have suggested that the therapeutic effect of valproate in bipolar mood disorder is at least partly mediated through inhibition of HDAC [18, 73, 118].

Can inhibition of HDAC by valproate explain its interaction with the various cellular processes in which it has been implicated? Is it possible, for example, that the activation of the ERK pathway is merely an epiphenomenon of the genomic effects of valproate? Theoretically it may be so, but empirically this does not seem to be the case: histone hyperacetylation is associated with increased BDNF expression [125, 126] (as is valproate treatment [22, 27]) and BDNF can activate ERK [127], but studies in neuronal and non-neuronal cell lines do not support a correlation between HDAC inhibition and ERK activation by valproate [26, 128]. It is also questionable whether HDAC inhibition can explain how valproate enhances the DNA binding of AP-1: at least in epithelial cells, HDAC inhibitors (valproate itself was not evaluated) lead to decreased expression of AP-1-dependent genes [129], although the response of neurons to HDAC inhibition may be different. Inhibition of axonal branching by valproate depends on the inhibition of HDAC, but the inhibition of neuronal growth cone collapse through inositol-depletion does not [17, 57], again indicating that only some of the effects of valproate can be accounted for by HDAC inhibition.

Although HDAC inhibition cannot explain many of the biochemical effects of valproate, it may nevertheless help to elucidate at least some of them: increases in Akt activation (with GSK-3 inactivation) [73] and in β-catenin expression [18] have been associated with HDAC inhibition. Additionally, while no data are available to associate HDAC inhibition with valproate-induced downregulation of brain PKCs, it should be noted that in epithelial cells, HDAC inhibitors have been shown to reduce the expression of PKC-α and PKC-ε [130]. Adverse effects associated with valproate therapy, like hepatic disturbances, weight gain and teratogenicity, have been clearly associated with HDAC inhibition [16–20].

The contribution of HDAC inhibition to the antiepileptic effect of valproate is unknown [122]. Since analogues of valproate that do not inhibit HDAC still protect against chemically induced seizures in rodents, the inhibition of HDAC cannot fully account for the anticonvulsive activity of valproate [18]. This is also true when considering the rapid onset of the anticonvulsive effect of valproate [131], which is not compatible with genomic changes that occur at a much slower pace. Nevertheless, HDAC inhibition may shed light on longer-term effects of valproate in epilepsy [15, 99, 102], effects that possibly involve interference with chronic seizure development (epileptogenesis) [125] or neuroprotection. HDAC inhibitors have been proposed as being antiepileptogenic by countering the post-seizure H4 hypoacetylation that leads to the detrimental downregulation of AMPA GluR2 (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor subunit 2) [122, 125], a downregulation which renders neurons more Ca^{2+}-permeable [132]. However, a recent study demonstrated that at least *in vitro*, valproate does not increase (but rather decreases) neuronal surface expression of GluR2 [133].

As a neuroprotective agent, valproate is effective in experimental brain ischaemia [134] as well as in *in vitro* models of neuroinflammation where it protects neurons by attenuating the production of pro-inflammatory factors such as tumor necrosis factor-α [135, 136] and interleukin-6 (IL-6) [135]. Although in manic patients, valproate had no significant effect on the plasma levels of IL-6 [137], it has been suggested that the anti-inflammatory and other neuroprotective properties of valproate may be beneficial in neurodegenerative disorders such as Parkinson's disease [136]. While failing to demonstrate an antiepileptogenic effect of valproate, a recent study has shown that valproate, administered chronically to rats in an epilepsy model of spontaneous recurrent seizures, has a neuroprotective effect both in terms of hippocampal neuronal viability and animal behaviour [138]. In the latter study, the neuroprotective effect was attributed, among other mechanisms, to the activation of Akt following inhibition of HDAC by valproate [138]. HDAC inhibition by valproate has also been implicated in the latter's *in vitro* neuroprotection from glutamatergic excitotoxicity:

in cerebellar granule cell culture, valproate treatment causes a time-dependent increase in acetylated H3, concomitant with a decrease in the levels of the pro-apoptotic enzyme glyceraldehyde-3-phosphate dehydrogenase, whose gene is associated with H3 [139].

Alterations in histone acetylation do occur after seizures and have been linked to potentially significant gene expression changes [125, 140]. For example, post-seizure H4 hyperacetylation is associated with increased BDNF expression [125, 126], a potentially neuroprotective measure [138] that may be sustained or augmented by the DHAC inhibition by valproate. Whereas the antiepileptogenic influence of valproate has not been demonstrated so far through any mechanism, this drug may well exert a long-term neuroprotective effect in epilepsy, an effect that possibly involves HDAC inhibition. The fact that not only valproate but other, unrelated, anticonvulsants like topiramate, levetiracetam (through its major metabolite 2-pyrrolidinone-n-butyric acid) as well as carbamazepine and its major active metabolite carbamazepine-10,11-epoxide are all HDAC inhibitors (Fig. 1) [122, 141] further supports the notion that HDAC inhibition may play an important role in epilepsy therapy. Interestingly, some of these antiepileptic agents also serve in bipolar disorder and in migraine [9, 12, 14].

Overall interpretation

A plethora of diverse data has been published over the past several years in an attempt to explain through a variety of mechanisms the efficacy of valproate in its different clinical indications. These data support the involvement of valproate in several pathways in which it had not been previously implicated. Yet, reviewing this information, it is remarkable that the number of cellular targets that have been proven to be directly affected by valproate is very small, and this number becomes even smaller when considering the relevance of some of these direct targets to epilepsy, bipolar disorder or migraine, at least as we understand their pathophysiology today.

There is little doubt that valproate directly interferes with GABA metabolism to increase GABA brain levels, and that this effect likely plays a significant role in the immediate control valproate exerts over epileptic seizures [5] and possibly also mediates some early therapeutic effects of valproate in bipolar disorder [8] and migraine [11]. The direct inhibition of GSK-3 by valproate, however, is at best controversial [70], and the inhibition of microsomal long-chain fatty acyl-CoA synthase [42] still awaits further reproduction and substantiation of its relevance to human disease. Likewise, what underlies valproate inhibition of brain myo-inositol-1-phosphate synthase activity, and whether this is at all relevant to bipolar disorder therapy, still needs elucidation [44].

In contrast to the latter cellular targets, valproate-induced changes in the expression of multiple genes, mediated at least partially through the direct inhibition of HDAC [18, 121, 122, 142], have been repeatedly demonstrated and may very well be relevant to the therapeutic effects of this drug through interference with intracellular signalling, e.g. the inactivation of GSK-3 [73], and neurotrophic and neuroprotective effects, e.g. through the promotion of BDNF expression [27]. Considering the large number of genes whose expression is altered by valproate [108, 109], it is reasonable to hypothesise that gene expression changes plays not an insignificant role in the long term effects of the drug. Future research should try and assess for every newly discovered valproate-induced cellular effect whether it is dependent or independent of HDAC inhibition or AP-1 DNA binding promotion by this drug. Nonetheless, many genomic effects of valproate cannot be explained with our current knowledge of its influences on AP-1 DNA binding and HDAC inhibition, and additional mechanisms through which valproate, or its metabolites, can affect gene expression should be sought.

In conclusion, influence of valproate at the genomic level may provide insights into therapeutic effects relevant to all three indications of epilepsy, migraine and bipolar mood disorder [12, 124, 138]. The 'unified field theory' for the mechanism of action of valproate in neuropsychiatric disorders possibly comprises acute effects mediated essentially through the enhancement of GABAergic transmission followed by a variety of longer-term effects primarily resulting from gene expression changes.

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