Current Trends in Neurology
Vol. 11, 2017

Review

Valproic acid and autism spectrum disorder: from clinical observations to animal studies

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental pathology clinically characterized by persistent deficits in social communication and social interactions associated with restricted repetitive patterns of behavior, interests or activity. ASD is actually one of the most common childhood neurological disorders. Despite a genetic origin, environmental factors are determinant in the etiology of autism. Based on observations that exposure to valproic acid (VPA) during pregnancy increases the risk of autism in children, *in utero* exposure of rodents to VPA was performed to produce animal models of autism. VPA-treated rodents exhibit social interaction deficits and repetitive behaviors, and display similar brain structure abnormalities to those observed in human cases of ASD. These rodent VPA models support the hypothesis that an imbalance between excitation and inhibition and/or a hyperconnectivity-hyperplasticity in those brain regions implicated in social interactions, learning and perception is at the root of ASD, and thus provide valuable tools for screening novel therapeutics.

KEYWORDS: autism, valproate, prenatal exposure, neurodevelopment, connectivity, excitation/inhibition balance.

INTRODUCTION

Autism spectrum disorder (ASD) is classified as a neurodevelopmental pathology defined by persistent deficits in social communication and social interactions in multiple contexts associated with restricted, repetitive patterns of behavior interests or activity. Although symptoms may be/are present in the early developmental period, they only fully manifest when social demands exceed limited capacities (DSM 5, Diagnostic and Statistical manual of Mental disorders published by the American Psychiatric Association, Fifth Edition Washington, DC: 2013). Typically, ASD is diagnosed within the first three years of life. The increase in the prevalence of ASD cases, reaching more than 1/100 children worldwide, places this disorder as one of the most common pervasive neurodevelopmental disorders [1]. The etiology of ASD remains elusive, and most ASD cases are classified as idiopathic. Nevertheless, a genetic origin including single gene mutations, copy number variations and polygenic risk factors may explain approximatively 20-30% of ASD cases [2]. Prenatal exposition to various environmental factors such as maternal immune activation, maternal stress, heavy metal, air pollution, pesticides, endocrine disruptors and drugs have been proposed as risk factors for ASD [3]. In this line, it is generally admitted that the epigenetic effects of environmental factors may affect normal neurodevelopment and lead to ASD [4].

Postmortem neuropathologic explorations of human tissue have revealed cellular and cytoarchitecture alterations in several regions of the brain from individuals with ASD [2]. Cortical regions such as the prefrontal cortex, known for its role in cognitive control, the fusiform gyrus, that plays a role in our

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capacity to interact appropriately in social situations, and cortical areas (frontoinsular and cingulate cortex) implicated in the processing of emotions and their integration are consistently altered in ASD patients. The limbic system, including hippocampus (spatial memory) and amygdala (emotional learning) are also altered in ASD patients. Finally, the cerebellum that is involved in motor coordination and learning, as well as in more complex tasks such as the regulation of emotion [5] and the perception of environment [6] presents alterations in ASD patients.

The most consistent structural finding yielded by magnetic resonance imaging (MRI) is the increased growth of total cortical volume in early ASD infants. The same observation is also reported for some subcortical brain regions (e.g., amygdala and hippocampus) and the cerebellum. However, studies comparing ASD adolescents or adults with controls did not reveal such differences and have even reported a decrease of total brain volume in ASD patients [7].

Hyperconnectivity and underconnectivity, as well as a combination of both have been revealed by functional MRI in the autistic brain [8]. Although fascinating, these studies are complex and difficult to interpret given the mosaic of behavior abnormalities in ASD patients.

The current animal models of ASD which mimic ASD behaviors have been developed in the rodents [9] and zebrafish [10] to investigate the neuropathological processes of ASD. Based on the well-characterized forms of ASD linked to monogenic mutations in humans, monogenic mouse models of ASDs have been developed and provide strong converging evidence for the important contribution of synaptic dysfunction to the pathophysiology of autism [11]. Animal models of idiopathic ASD have also been developed using environmental constraints such as maternal stress [12], maternal immune activation [13], and prenatal exposure to paraben [14] and to valproic acid (VPA) [9].

This review focuses on the “valproate model of ASD” that follows epidemiologic observations of human ASD cases and summarizes its main contribution to our understanding of ASD neuropathology.

In utero exposure to VPA: a risk factor for autism in humans

VPA is an antiepileptic agent commonly used as adjunctive therapy in patients that have failed to respond adequately to other medications. One of its main modes of action is to potentiate the inhibitory effects of gamma-aminobutyric acid (GABA) on neuronal firing [15]. Nevertheless, although VPA is an efficient therapeutic agent for epilepsy and bipolar troubles, it is particularly toxic for the fetus. Indeed, exposure to VPA in the first trimester of pregnancy is associated with three-fold increase in the rate of major anomalies such as spina bifida, cardiac and craniofacial skeletal and limb defects associated with a cluster of anomalies including behavioral delays that are clinically defined as the fetal valproate syndrome (FVS) [16]. Based on case reports, prenatal exposure to VPA was also suspected to be a risk factor for infantile autism [17]. Although this was subsequently confirmed by several studies and clinical observations, the link between *in utero* VPA exposure and autism was finally proven in 2013 [18]. In that study, clinical observations from a large population of children demonstrated that maternal use of VPA during pregnancy increases the risk of autism by a factor 4. The FSV and autism are the consequence of the teratogenic effect of VPA, with drastic effects for the infant if VPA is administrated when the neural tube of the fetus is closing during pregnancy [16, 19]. Nevertheless, later exposure to VPA could not be excluded as a cause of autism. At the cellular level, VPA acts as a non-selective inhibitor of histone deacetylases implicated in the regulation of gene transcription and phenotype differentiation [20].

Exposure to VPA generates an animal model for autism

Based on human cases of autism showing that exposure to teratogens during the pregnancy period corresponding to closure of the neuronal tube causes/leads to lesions of motor cranial nerve nuclei, Rodier and colleagues [21] have looked for similar lesions in rats exposed to VPA (350 mg/kg) during the closure of the neural tube (embryonic day (E) 11.5, 12 and 12.5). All treatments with VPA affected motor nuclei leading to the conclusion that the initiating autism injury occurs around

the time of the neuronal tube closure. Interestingly, the same group [22] also showed that a single dose of VPA (600 mg/kg) at E12.5 causes Purkinje cell loss, the cerebellar anomaly associated with autism in humans. Furthermore, rats exposed prenatally (E9) to VPA present high levels of serotonin in several brain regions similar to those in autistic patients [23]. These pioneering experiments strongly suggest that rats prenatally exposed to VPA were potential animal models of autism. However, a precise phenotypic characterization of these VPA rats was necessary to confirm that such animal models reproduce the core symptoms of autism i.e deficits in social interactions and communication associated with repetitive behaviors. Subsequently, Schneider and Przewlocki [24] clearly demonstrated that a single injection of VPA (600 mg) at E12.5 decreased a number of social behaviors, increased latency of social interactions and locomotor repetitive stereotypic-like hyperactivity combined with low exploring activity in male offspring. In addition, the VPA rats showed delayed maturation, lower body weight, delayed motor development, attenuated integration of coordinated series of reflexes and lower sensitivity to pain [24]. Comparing different embryonic periods of VPA exposure revealed that VPA exposure at E12 produced the most significant behavioral changes: i.e reduced sociability and social preference [25]. Similarly, prenatal exposures to VPA (E13, 600 mg/kg) in mice produced developmental deficits and reduced social interactions and repetitive behaviors [26-29]. Experiments conducted by many groups have thus confirmed that a prenatal exposure of rodents to VPA reproduces the core signs of human autism. Consequently, VPA rodents have been adopted as environmental models to study several aspects of autistic neurodevelopmental diseases [9, 30].

The zebrafish (larval and adult) presents numerous advantages as a model organism to study brain function and dysfunction [31]. Zebrafish are a highly social species and exhibit a range of social behaviors that could be analyzed and quantified. Recently, VPA exposure at early developmental stages was shown to induce deficits in social interactions, anxiety, and hyperactivity in the adult zebrafishes [32]. Consequently, the VPA-treated zebrafish is another possible model to analyze the deficits relevant to ASD [33]. Similarly, *Xenopus laevis* tadpoles exposed to VPA display abnormal sensorimotor and schooling behaviors suggesting that the effects of VPA are conserved across the vertebrates [34].

Contribution of VPA animal models to our understanding of ASD and development of targeted treatments

As a major role of VPA in the etiology of ASD was demonstrated in several animal species, this compound should be prohibited for pregnant women at any time of gestation. An important issue for pharmaceutical companies is to validate an alternative treatment for VPA-sensitive epilepsy.

VPA and epigenetics

VPA inhibits histone deacetylase (HDAC) and consequently impairs the modulation of gene transcription. A link between autistic-like behaviors and VPA effect on HDAC has been clearly established in mice. Indeed, whereas a prenatal exposure to VPA induced social deficits, a prenatal exposure to valpromide, a VPA analogue lacking histone deacetylase inhibition activity had no effect [35]. Furthermore, prenatal exposure of mice to trichstatine A, a potent HDAC inhibitor, reproduces the sociability deficits induced by prenatal exposure to VPA [36]. Importantly, SHANK2 and SHANK3 [37, 38] which encode a family of postsynaptic scaffolding proteins that are present at glutamatergic synapses and growth cones of developing neurons [39] are genes which show impaired transcription after prenatal exposure to VPA. Mutations in the SHANK family genes are also linked to ASD in humans and animal models [40]. In addition, mRNA expression of Neuroligin3, a member of the Neuroligins family that are postsynaptic cell-adhesion molecules involved in synaptic maturation, is downregulated in some brain regions in the VPA mice [41]. Furthermore, prenatal exposure to VPA induced a transient increase in brain-derived neurotrophic factor (BDNF) mRNA and protein in the fetal brain [42]. In the medial prefrontal cortex, VPA exposure altered the expression of a subset of genes implicated in the circadian rhythm and acting in extracellular matrix [43].

Brain structures affected by prenatal VPA exposure

Neuroanatomical and functional investigations of ASD patients have mainly revealed alterations in neocortical structures, limbic system and cerebellum. Similarly, neocortical regions are affected in VPA rodent models of autism. Whereas the typical cortical organization of the prefrontal cortex is preserved, the interneuronal space is wider in VPA-treated than in control animals [44]. A loss of Nissl positive cells in the middle and lower layers of the prefrontal cortex and lower layers of the sensory cortex has been reported in VPA male mice [35]. However, a longer exposure to VPA (prenatal plus postnatal) increased the number of neocortical neurons [45] associated with autistic-like behaviors, suggesting a differential effect of VPA on neocortical structures depending on the duration of the VPA treatment. Morphological alterations in VPA rodent models include complexity of the apical dendrites of cortical motor neurons [46], decreased dendritic branching of neurons in the orbitofrontal and medial prefrontal cortices, decreased spine density of neurons of the prefrontal cortex [47, 48], and synaptic structure deficits in cortical neurons [49].

Several alterations have been identified in the hippocampus after prenatal exposure to VPA, such as a reduced size of CA1 of the dorsal hippocampus [50], increased neuronal density in CA1, CA2, CA3, dentate gyrus and subiculum [51], induced spatial disorganization of the pyramidal CA3 layer and dentate granular cell layers [44], retracted neuronal arborization in the ventral and dorsal hippocampus, reduced number of spines in the dorsal hippocampus and increased dendritic spine density in the ventral hippocampus [48]. The amygdala was also affected by prenatal VPA exposure as the size of the basolateral amygdala [50], as well as the spine density [48] were reduced. A link between morphological rearrangements in limbic regions and the typical exploratory behavior and enhanced spatial memory of VPA animals is under debate [48, 51].

In the cerebellum, prenatal exposure to VPA reproduces the anomalies associated with autism: a reduced volume of the vermis associated with a decrease in Purkinje cell number [22]. In addition, Purkinje cells are smaller with shorter and less complex dendritic arbors [52]. The morphology of the deep cerebellar nuclei was also modified after prenatal exposure to VPA [53]. Accordingly, animals prenatally exposed to VPA performed significantly worse in cerebellum-dependent motor tasks [52].

VPA animal models and the excitation/ inhibition imbalance in autism

Several observations have led to the idea that some forms of autism are caused by an increased ratio of excitation/inhibition in sensory, mnemonic, social and emotional systems [54]. In principle, this imbalance between excitation and inhibition may be a consequence of one or more of the following parameters: ratio between the number of excitatory and inhibitory neurons, neuronal excitability, connectivity, and synaptic strength (based on number of synaptic contacts, number of post synaptic receptors and concentration of neurotransmitter in the synaptic cleft).

As detailed above in VPA animal models, the morphological alterations in neurons (dendritic arbor and dendritic spines) that are susceptible to impact the excitatory/inhibitory ratio have been depicted. Prenatal VPA may alter the expression of transcription factors governing glutamatergic/ GABAergic differentiation during fetal neural development, in conjunction with the genetic preload [55]. Prenatal VPA exposure causes a loss of inhibitory GABAergic Purkinje cells in the rat cerebellum [22] and a loss of GABAergic interneurons in the hippocampal dentate gyrus [56]. VPA exposure also impairs the GABAergic synaptic transmission in the cortex [57]. Intriguingly, GABA has abnormally conserved an immature-like, depolarizing effect on pyramidal neurons in the hippocampus of adult VPA rats [58]. Prenatal VPA treatment was shown to alter GABAergic transmission in both young and adult rodents as the expression of two of its important regulators, the GABAAR β3 subunit and the K-Cl co-transporter KCC2 [59] was downregulated in the temporal cortex, parietal cortex, cerebellar cortex and hippocampus. Similarly, GABRA1, GABRA5 and GABRB2 subunits were downregulated in the cortices of VPA-induced autistic adult mice [60]. VPA is believed to cause an ectopic increase in glutamatergic synapses in the cortex and hippocampus [61] and a selective

overexpression of 2A and 2B subunits of NMDAR in the neocortex of young autistic rats [62]. However, a more recent study shows that NMDAR subunits 2A, 2B, 2C are downregulated in the cortices of VPA-induced autistic adult mice [60].

In the hippocampus, VPA treatment is likely to alter the clearance of glutamate by astrocytes [63] and increase metabotropic glutamate receptor 1A immunoreactivity [64] while drastically reducing the serotonin level [65]. The effect of VPA on the serotoninergic system has been confirmed in zebrafish which selectively fail to express central serotonin after VPA treatment early during development [66]. The implication of serotonergic and dopaminergic deficiencies in the etiology of human ASD is supported by hypofunction of the dopaminergic system in the mouse prefrontal cortex after VPA exposure [67].

VPA models: autism and the intense world theory

At the cellular level, the young rat (PND 12-16) VPA model of autism present hyperconnected, hyperreactive and hyperplastic neuronal microcircuits in different brain regions such as the somatosensory cortex [68], prefrontal cortex [69, 70] and amygdala [71, 72]. The local electric field potentials in the hippocampus and the olfactory bulb also suggest a distinct electrical activity of the brain of animals prenatally exposed to VPA [73]. Overexpression of the NMDA receptor subunits NR2 A and B could be involved in the hyperplasticity at least in somatosensory cortex [74]. Such modifications of the neuronal circuitry are associated with a hyperleaning and a hyperfear memory [70, 71]. Nevertheless, in contrast to young VPA-treated rats, the synaptic function was reduced in the medial prefrontal cortex [75] and expression of the NMDAR subunits was downregulated in the cortex of adult (PND 50) VPA-treated rats [62].

Based on these observations, at least young VPA animals exhibit amplified fear processing and memories along the line of the original notion of an Intense World Syndrome in autism proposed by Markram *et al*. [76, 77]. Their observations in the neocortex and amygdala suggest that hyperfunctional microcircuits become autonomous and memory-trapped leading to exacerbated perception, attention, memory and emotions. In autistic patients, the symptoms may depend on the brain areas concerned by alterations of microcircuit activity [78]. Interestingly, based on the analysis of the number of c-Fos-positive auditory neurons in response to tones, VPA-exposed rats have been postulated to display hyperresponsiveness to sound [79].

The link between hyperreactivity of local neuronal circuitry and the excitatory/inhibitory imbalance and/or hyperconnectivity is still debated [78]. Whereas hyperconnectivity is established in the neocortex [68], the synaptic excitatory/inhibitory balance is believed to be disrupted in the amygdala [72] where the NMDA glutamatergic synaptic plasticity is dysfunctional [80] and the GABAergic system is disturbed [81, 82].

VPA models and sexual dimorphism of ASD

In humans, ASD is reported to be more prevalent in males than in females with a ratio of about 4/1. Interestingly, the rodent VPA models of autism present more pronounced behavioral alterations in males than in females [83-86]. Nevertheless, most studies on VPA animals have been performed on males and only very few studies concern cellular and molecular consequences of this sexual dimorphism. However, female VPA rats appear to lose Nissl-positive cells in the prefrontal cortex, but not in the sensory cortex [87], and postsynaptic maturation is only disturbed in male VPA rats [84]. Interestingly, a recent study reveals sex-specific metabolic and connectivity changes in VPA rats suggesting that difference in patterns of connectivity may underlie autistic-like behavior [86]. Finally, after prenatal VPA exposure, a preferential expression of exon 1- and exon 4-BDNF transcripts has been depicted in females compared to males and may contribute to sex differences in ASDs by protecting females from the adverse effects of genetic variants or environmental factors such as VPA on the developing brain [88]. Investigating sex-related differences in the effects of prenatal exposure to VPA could yield important information about the pathophysiology of ASD.

VPA models and preclinical studies for ASD treatments

One important issue about animal models of human pathologies is their use as a platform for

preclinical studies. In the case of VPA models of ASD, therapies should target core ASD behaviors: the deficits in social interactions and the stereotypes. One classical research axis is testing compounds able to restore the excitatory/ inhibitory balance by acting on the GABAergic and glutamatergic systems. Bumetanide restores the chloride gradient in dysfunctional GABAergic neurons and attenuates the behavioral phenotypes of VPA rats [89] and improves the core symptoms of ASD in children and adolescents [90]. Nematine [91] and Agmatine [92] are two NMDAR antagonists which rescued impaired social behaviors, as well as repetitive behaviors in the VPA-induced mice models of autism. VPA animal models have confirmed the therapeutic effect of ocytocin in ASD. Indeed, intranasal treatment with ocytocin attenuates the deficits in social interaction in prenatal VPA-exposed mice [93] and ameliorates the core symptoms of autism in ASD patients [94]. Elucidating the mechanism of this ocytocin effect on behavior is expected to provide new insights into ASD pathogenesis. Prenatal and early postnatal oxidative stress and neurodegeneration are possible causes of ASD in humans. In agreement, several anti-oxidant and neuroprotective agents has been recently shown to ameliorate behavioral disorders in rodents prenatally exposed to VPA [95-100] and may be effective candidates for pharmacological treatments of ASD.

CONCLUSION

It is clearly established that valproate is a risk factor associated with ASD in humans [17]. Converging data indicates that prenatal exposure of rodents to VPA provides relevant models for analyzing the mechanisms underlying autism**.** Recently developed VPA-treated zebrafish models may also clarify key events leading to neurodevelopmental perturbations associated with ASD. Although the VPA rodents are validated animal models of ASD as shown by the effects of bumetanide and ocytocin on behavioral abnormalities in both ASD patients and VPA rodents, it is now crucial to verify in VPA-treated rodents the correspondence of the core symptoms of ASD identified in human cases and the similarity of the impacted brain regions in human ASD patients and VPA-treated rodents. Furthermore, whereas behavioral therapies produce beneficial effects on ASD patients, environmental enrichment has been shown to reverse behavioral alterations in rats prenatally exposed to VPA [101, 102]. Thus, VPA models of autism provide valuable tools to investigate the brain region-specific neurodevelopmental and cellular defects underlying autistic behaviors and to screen for novel therapeutics.

ACKNOWLEDGMENTS

The authors thank Nancy Grant and Yannick Bailly for critical reading of the manuscript.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

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