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Chapter 8

Valproic Acid in Autism Spectrum Disorder: From an Environmental Risk Factor to a Reliable Animal Model

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54824

1. Introduction

Autism spectrum disorders (ASD) have attracted public attention by its high prevalence, elevated social cost and large impact on the family [1]. Since the first descriptions of autism made by Hans Asperger in 1938 [2] and by Leo Kanner in 1943 [3, 4], much discussion has focused in the search for the triggering points of autism and identifying risk factors has become a high priority of scientists. Nevertheless, even after almost seventy years since the first reports, the etiology of autism remains unknown and its molecular basis is not well understood. Environmental factors (such as virus, bacteria, drugs, etc.) known to increase the risk of autism have critical periods of action during embryogenesis. Congenital syndromes are found in high rates in patients with autism including somatic changes originated early in the first trimester [5].

The link between rubella and autism came from epidemic rubella in which the incidence of autism diagnosis in prenatally exposed offspring was more than 10-fold higher than normal. The study describes 243 children exposed to congenital rubella, where 25% presented mental retardation, 15% had reactive behavior and 7% was included in the autism spectrum [6].

Valproic acid (VPA) has traditionally been prescribed for epilepsy, but is increasingly used for psychiatric condition, such as bipolar disease by its modulation on GABA neurotransmission [7]. Furthermore, it has been also shown to be associated with an increased prevalence of autism. In fact, prospective and retrospective studies demonstrate that exposure to VPA during pregnancy is associated with approximately three-fold increase in the rate of major anomalies

and a possible set of dysmorphic features with decreased intrauterine growth [8, 9], characteristics of Fetal Valprotate Syndrome (FVS) described in item 3. Histone deacetylase (HDAC) inhibition by VPA and changes in gene expression may explain part of the teratogenicity of this drug. *In utero* exposure of rodents to VPA has been proposed to induce a phenotype with behavioral characteristics reminiscent of those observed in ASD and provides a robust animal model for social cognitive impairment understanding and a potential screen for the development of novel therapeutics for this condition [10]. Other possible explanations include either the effect of VPA through the increase of fetal oxidative stress, affecting mainly the brain in comparison to other fetal organs, or its inhibitory action on the folic acid mechanism [11]. In agreement, it is possible to duplicate a number of anatomic and behavioral features characteristic of human cases by exposing rat embryos to a teratogenic agents at the time of neural tube closure [12].

Thus, *in utero* exposure to VPA has been used as a reliable model to increase the understanding of behavioral effects evaluated by specific tests as sociability, social preference and stereotypic behavior, also observed in human patients [9, 13, 14]. The present chapter summarizes the current knowledge on the relationship between *in utero* exposure to VPA in humans and in autism-like animal model phenotypes, highlighting the importance of this model to the neurobiology of autism studies.

2. Valproic acid

The compound VPA (Figure 1A) is a fatty acid synthesized in 1882 [15] as an analogue of valeric acid, found naturally in valerian (*Valeriana officinalis*), used at that time as an organic solvent. The chemical names to VPA and derivatives are shown in Table 1. Antiepileptic properties of VPA, which is structurally unrelated to other antiepileptic drugs, were discovered by chance in 1962, when the French researcher Pierre Eymard in a serendipity discovery observed the anticonvulsant properties of VPA while using it as a vehicle for a number of other compounds that were being screened for anti-seizure activity [16]. He found that it prevented pentylenetetrazol-induced convulsions in rodents. Since then, it has also been used for migraine and bipolar disorder. The U.S. Food and Drug Administration (FDA) approved VPA in 1978 for the treatment of seizure disorder and in 1986 approved its enteric-coated counterpart valproate semisodium (Figure 1B) also named divalproex sodium (USA), for the same indication. Valproate semisodium is a stable co-ordination compound comprised of sodium valproate (Figure 1C) and valproic acid in a 1:1 molar relationship in an enteric coated form. An enteric coating is a barrier applied to oral medication that controls the location in the digestive system where it is absorbed. This compound dissociates to release valproate ions into the gastrointestinal tract. Once in the blood, sodium valproate can be converted also in the acid form or conjugated as valproate semisodium [17]. The acid form is currently used to quantify plasma levels of all three.

http://dx.doi.org/10.5772/54824

Valproic Acid	2-Propylvaleric acid, 2-Propylpentanoic acid or Di-n-dipropylacetic acid
Sodium Valproate	Sodium 2-propylvalerate
Valproate semisodium	Sodium hydrogen bis(2-propylvalerate)
Valproate Pivoxil	Hydroxymethyl 2-propylvalerate pivalate
Valpromide	2-Propylvaleramide

Table 1. Chemical names of VPA and derivatives

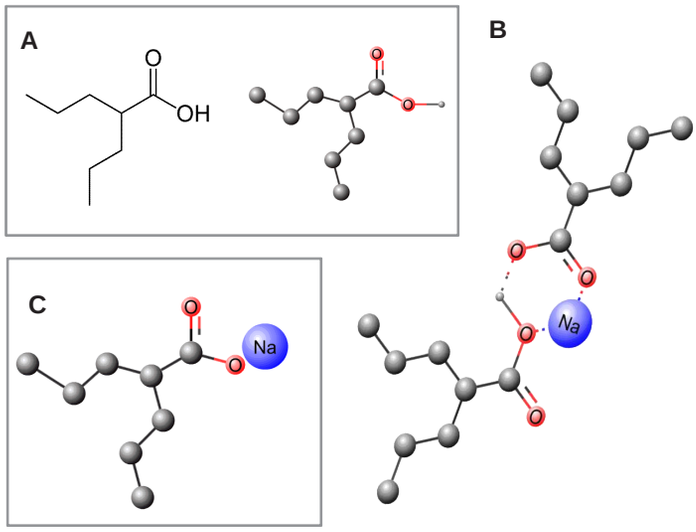

Figure 1. The molecular structure of VPA and derivatives showed in ball and stick view. A. Valproic acid. B. Valproate semisodium, C. Sodium valproate. In A is possible to compare both chemical and ball and stick structures (used also to illustrate derivatives).

The therapeutic concentration of sodium valproate (the sodium salt of VPA) during chronic oral treatment ranges from 40-100 mg/mL (280–700 mmol/L) in plasma and from 6–27 mg/g (42–190 mmol/g) in brain [18]. From this point, to simplify the reading throughout the text, the VPA abbreviation will be used when referring to valproic acid and derivatives.

The VPA is marketed under brand names including: Convulex (Pfizer-UK and Byk Madaus-South Africa), Depakene (Abbott Laboratories-USA, Brazil and Canada), Depakine (Sanofi Aventis-France and Sanofi Synthelabo-Romania), Deprakine (Sanofi Aventis-Finland), Encorate (Sun Pharmaceuticals-India), Epilim (Sanofi Synthelabo-Australia), Valcote (Abbot Laboratories-Argentina).

The VPA effects of clinical importance include GABAergic activity increase, excitatory neurotransmission decrease, and modification of monoamines [19]. The biochemical and biological effects of VPA are summarized in Table 2.

Target of action	Biological effects	Reference
HDAC (inhibition)	Open DNA transcription	[20]
Mitochondria	Energy metabolism impairment	[21]
Lymphocytes	Modification of the epigenotype	[22]
Neurons from *substantia nigra*	Reduction in firing rate	[23]
c-Jun N-terminal kinase (JNK)	Defective neurite formation	[24]
GSK3β inhibitor	Promotion of hair re-growth	[25]
Beta-catenin-Ras-ERK-p21Cip/WAF1 pathway	Differentiation and inhibition of proliferation in neural progenitor cells	[26]
Constitutive androstane receptor (CAR) and pregnane X receptor (PXR)	Up-regulation of *CYP3A4* and *MDR1* gene expression	[27]
Matrix metalloprotease-9 inhibitor	Attenuation of blood-spinal cord barrier (BSCB) after spinal cord injury (SCI)	[28]
PI3K/Akt/mTOR pathway	Skeletal muscle hypertrophy	[29]

Table 2. Biochemical and biological effects of VPA

3. Valproic acid as an environmental risk factor in the development of autism

After the VPA license for use in 1978, the first adverse report of a fetus exposed to the drug was published in 1980 [30]. Since then. particular attention has been directed to the occurrence of neural tube defects in infants exposed to VPA *in utero* [31, 32]. The critical period for exposure to teratogens shown to increase the risk of autism is early in the first trimester [33]. Some of the critical teratogens related to autism risk are maternal rubella infection [6], ethanol [34], thalidomide [35] and VPA [8, 9]. Approximately one in 250 pregnancies is known to be exposed to antiepileptic drugs [36] and a significant proportion of these are exposed to VPA, either as monotherapy or as part of a polytherapy drug regimen.

The timing for the teratogenic effect of VPA that increases the risk for autism cannot be estimated directly, as the drug is typically taken throughout the entire pregnancy [33]. Many children exposed *in utero* to VPA exhibit FVS, first described in 1984 [37] and characterized by a major and minor malformations and developmental and behavioral delays [8, 12, 38-40]. Specific impairments observed in FVS includes neural tube defects, trigonocephaly, radial ray defects, pulmonary abnormalities, coloboma of iris/optic disc, low verbal IQ and features of ASD [41] and has been reported in a number of sibling pairs [12, 21, 37, 42-44] with different degree of severity among affected siblings. Common facial features of FVS include epicanthal folds, broad nasal bridge, short nose with antiverted nares, long upper lip, and low set, posteriorly rotated ears [41].

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The classical autism was first reported to be one of the behavioral outcomes of VPA exposure [41] through several case reports [12, 39, 45]. The first epidemiological study with drugs as environmental risk factors of autism was described in 2000, with 57 offspring of women taking anticonvulsants (see ref [46], summarized in Tables 3 and 4).

Features	% of children
Poor social interaction	53
Poor communication skills	49
Short attention span	46
Insistence on routines	44
Hand flapping	25

Table 3. Autism features in children exposed *in utero* to anticonvulsants.

	No of children	VPA exposure in mg (weeks of gestation)
Neural tube defect	1	1000 (0-5), 800 (5-40)
	1	1200 (1-17), 1500 (17-26), 2000 (26-40)
Genitourinary	1	1000 (0-40)
	1	1000 (0-5), 800 (5-40)
	5	1500 (0-40)
Extremities	2	1000 (0-40)
	1	1500 (0-40)
Eyes	1	700 (0-40)
	1	800 (0-40)
Teeth	2	1000 (0-40)
	1	1700 (0-40)
Diastasis recti	1	1200 (0-40)

Table 4. Congenital malformations in children exposed *in utero* to VPA

Fifty two children were ascertained through the Fetal Anticonvulsant Syndrome Association (FACS) and five were referred to the Aberdeen Medical Genetics Service (AMGS). The number of patients exposed *in utero* to each anticonvulsant alone was 34 (60%) to VPA, 4 (7%) to carbamazepine, 4 (7%) to phenytoin, and 15 (26%) to more than one anticonvulsant. The number of patients with behavioral problems was 46 (81%), with hyperactivity or poor concentration was 22 (39%) and with attention deficit and hyperactivity disorder 4 (7%). Autistic features were present in 34 patients (60%).

4. Animal model of autism induced by prenatal exposure to VPA

Considering human evidences of autism followed by early *in utero* exposure to teratogens, such as thalidomide and VPA, the next step was to develop a model of autism induced by prenatal exposure of animals to the same drugs, particularly VPA [47]. The *in utero* exposure to VPA induced patterns of abnormal development across species as demonstrated in Table 5.

Patterns of abnormal development	Specie	References
Skeletal abnormalities	Mice	[48, 49]
	Rabbits	[50]
	Rhesus monkey	[51]
Cardiac abnormalities	Mice	[52]
Neural tube defects (including spina bifida)	Mice	[53]
Cranial neural tube defects	Rats	[54]
Behavioral abnormalities	Rats	[55]

Table 5. Patterns of abnormal development across species after *in utero* exposure to VPA.

The use of animal models allows a wide range of research possibilities including the search for etiologic clues, molecular targets, and biomarkers. The main aspects to take into account in developing animal models, is (i) to reproduce a circumstance that would lead to a certain condition, for example, inducing a genetic disease by manipulating a specific gene; (ii) to induce similar patterns found in the studied condition, for example, observing the same behavioral alterations found in a particular impairment; (iii) to observe if the model has similarities to a human features when exposed to certain treatment [56]. The time of induction, dosage of VPA and the way of administration in rodents are variable in the literature, as demonstrated in Table 6. It is important to observe that in rats, 600 mg/Kg VPA at 12.5 days of pregnancy is the most investigated due to similarities in the features of autism. Besides the higher number of studies describing prenatal exposure to VPA, there are some protocols reporting also postnatal exposure and behavioral features of autism [57, 58].

The diagnoses of autism take into account behavioral alterations in three main areas: sociability, communication and behavioral stereotypies and narrow range of interests. Therefore, a consistent animal model must show similar behavioral abnormalities, which might indicate common neural alterations.

Our group has administrated a single intraperitoneal injection of 600 mg/kg VPA in pregnant rats at the embryonic day 12.5, observing variations in social memory, and flexibility to change strategy [84]. Females were kept separate and with free access to their own litters. Somatic aspects observed during the pups' development, included body weight, ear unfolding and eye opening which were unchanged between groups. In three-chambered-apparatus test, used to

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Embryonic Day(s)	Procedure (mg/Kg VPA)	References
Mice		
9	IP (200, 400, 800)	[59]
9	SC (400)	[60]
9, 12.5, 14.5	IP (500)	[61]
11	OA (800)	[62, 63]
12, 13, 14	IP (100)	[64]
12.5	IP (500)	[65]
13	SC (600)	[66, 67]
Rats		
7, 9.5, 12, 15	IP (400)	[68]
8, 9, 10, 11	OA (800)	[69]
9	IP (600)	[70]
9	OA (800)	[71-74]
9, 11	AO (800)	[75, 76]
11, 12, 13	IP (200)	[77]
1.5	IP (500)	[78]
1.5, 12, 12.5	IP (350)	[9]
12	IP (400)	[79]
12	IP (600)	[80-83]
12.5	IP (600)	[10, 14, 84-93]
12.5	SC (350)	[94]
12.5	IP (350)	[95]
12.5	IP (400, 500, 600)	[77]
12.5	IP (500)	[96]

Table 6. Prenatal exposure of VPA in rodents: Time of induction and dosage

observe social memory, preferences and interests, the VPA group spent less time in the presence of a stranger rat and more time in the presence of an object, indicating a reduced place preference conditioned by conspecific and an increased preference for the object, revealing sociability impairments. As adults, they showed inappropriate social approach to a stranger rat, decreased preference for social novelty, apparently normal social recognition, no spatial learning deficits and normal resistance to change on Morris water maze.

5. Brain alterations induced by prenatal exposure to VPA

Once prenatal exposure to VPA became a reliable tool to model autism, more brain alterations were investigated in rodents exposed to this teratogen, as summarized in Table 7.

Rodent	VPA (mg/kg)	Findings	References
Rat	500	Altered distribution of 5-HT neurons in the dorsal raphe nucleus.	[71]
	350	Reduction in the number of motor neurons from hypoglossal and oculomotor nuclei.	[9]
	500	Reduction in the number of putative synaptic contacts in connection between layer 5 pyramidal neurons.	[97]
	400	Prolonged neuronal progenitor cells proliferation in embrionary period.	[79]
	600	Decreased number of purkinje cells, neuronal degeneration and chromatolysis.	[98]
Mice	500	Reduction in the number of Parvalbumin -positive inhibitory neurons in the neocortex.	[99]
	500	Nissl-positive cell loss in the middle and lower layers of the prefrontal cortex and in the lower layers of the somatosensory cortex.	[65]

Table 7. Brain alterations induced by *in utero* exposure to VPA

Behavioral outcomes started to be studied, demonstrating a number of anatomic and behavioral features characteristic of human cases by exposing rodents' embryos to VPA at the time of neural tube closure. One of the affected structures in the brains is the cerebellum. Magnetic resonance imaging showed that patients with autism have reduced size of the cerebellum when compared to controls, displaying smaller vermal lobules VI and VII. This abnormality is probably an outcome of developmental hypoplasia and not likely shrinkage or deterioration after full development had been achieved [100]. Similar alterations were found in brains from rat model of autism induced by prenatal exposure to VPA [9]. Exposed rats showed a reduction in the number of motor neurons of the earliest-forming motor nuclei (V, XII), and had the VI th and III rd cranial nerve nuclei affected. In the same way, another work found diminished number of cells in the posterior lobe of the cerebellum [86]. In this context, cerebellar anatomy alterations in humans might be due to loss of neurons in the cranial nerve motor nuclei, as demonstrated in rats.

The amygdala is likely to be also linked to autism, due to its involvement in social-emotional behavior. Rats exposed to VPA *in utero* had longer lasting and harder to extinguish fear memories, which could be explained by the hyperreactivity and hyperplasticity found in the lateral amygdala [96, 101]. Another work found enhanced long-term potentiation (LTP) in the

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medial prefrontal cortex of rats exposed to VPA, with enhanced synaptic plasticity and short- and long-term fear memories [82].

Synaptic impairments were already described in autism, which may be related to neuroligins alterations. Neuroligins are a family of proteins which play a central role in synaptic maturation and were affected in rats after *in utero* exposure to VPA. Neuroligin 3 mRNA expression was decreased in the hippocampus, especially in *cornu ammonis* (CA1) and dentate gyrus [62].

Synaptic plasticity is influenced by brain-derived neurotrophic factor (BDNF), a factor that modulates several neurochemical parameters. High levels of BDNF have been reported in the blood of patients with autism [102]. BDNF acts through TrkB-mediated activation of various signal transduction pathways, including pathways that involve PI3K, mitogen-activated kinase (MAPK), and phospholipase C-γ [103]. Infusion of BDNF in the nucleus *accumbens* of aged rats restored synaptic plasticity and improved cognition [104] and some environmental factors, such social isolation, results in low levels of BDNF in the hippocampus of rats [105]. Animals exposed to VPA *in utero* display decreased cortical BDNF mRNA expression. It is important to notice that altered levels of the transcript will not necessarily mean an altered protein expression [63]. Diminished BDNF may lead to altered synaptic development; once it is known that this neurotrophic factor is involved in development and function of serotonergic neurons [106].

Several hypotheses have arisen to explain the social deficits in autism. One of these proposals points an alteration in opioidergic mechanisms as a likely causative of behavioral impairments in this disorder [107]. Opioid peptides are involved in stress responses and affective states, and blockage of their receptors causes dysphoria in humans. Enkephalins are part of the opioid family and are distributed in brain areas, like the striatum and the nucleus accumbens, involved in processing emotional information, anxiety and fear. Exposure to VPA reduced proenkephalin mRNA expression in both the core and shell of the nucleus *accumbens* and dorsal *striatum* of rats concomitantly to anxious-like behavior [91].

The monoamine system is also altered in patients with autism and their relatives. It was demonstrated that children with autism have increased 5-HT (serotonin) synthesis capacity when compared to children with typical development [108]. Besides, it is widely known that sleep disorders are common in autistic children [109]. Interestingly, increased levels of serotonin was found in pre-frontal cortex of rats prenatally exposed to VPA in association with disrupted sleep/awake rhythm. The elevated levels of 5-HT were found during light phase of animals' circadian rhythm [74]. It was proved that serotonergic neurons have a silent firing rate during REM sleep [110], indicating that the sleep disturbance found in the animals may be related to increased levels of 5-HT found in their prefrontal cortex. In addition, higher levels of 5-HT were also reported in the left side of hippocampus and in blood from rats [111]. However, using the whole hippocampus, it was demonstrated 46% decrease in 5-HT levels from rats exposed to VPA *in utero* [70].

Recently, we observed hippocampal reactive astrogliosis in the group of rats exposed *in utero* to VPA (see ref [84]). After 15 postnatal days, hippocampal astrocytes were intensely immunoreactive to the astroglial marker Glial Fibrillary Acidic Protein (GFAP) (Figure 2).

Astrocytes are the major cell type in the central nerve system (CNS) and provide a variety of critical supportive functions that maintain neuronal homeostasis, participating of the synapse and the glutamatergic metabolism [112]. These cells become reactive in VPA group, characterized by up-regulation of GFAP and apparently show higher number of processes than the control cells as demonstrated by the squares in A and B.

Seven Fresh-frozen *post mortem* tissues from individuals with autism and CSF from six living autistic patients were investigated for cytokine protein profiling [113]. This study shows an active neuroinflammatory process in the cerebral cortex, white matter, and notably in the cerebellum. Immunocytochemical studies showed marked activation of microglia and astroglia. The cytokine profiling indicated that the macrophage chemoattractant protein (MCP)-1 and tumor growth factor-beta1, both derived from neuroglia were the most prevalent cytokines in brain tissues. We presumed that microglia/macrophage-derived pro-inflammatory cytokines regulate the transition of astrocytes into reactive astrogliosis. Nevertheless, the mechanisms which regulate the level of astroglial cell activity in the hippocampus from VPA autism model need to be investigated.

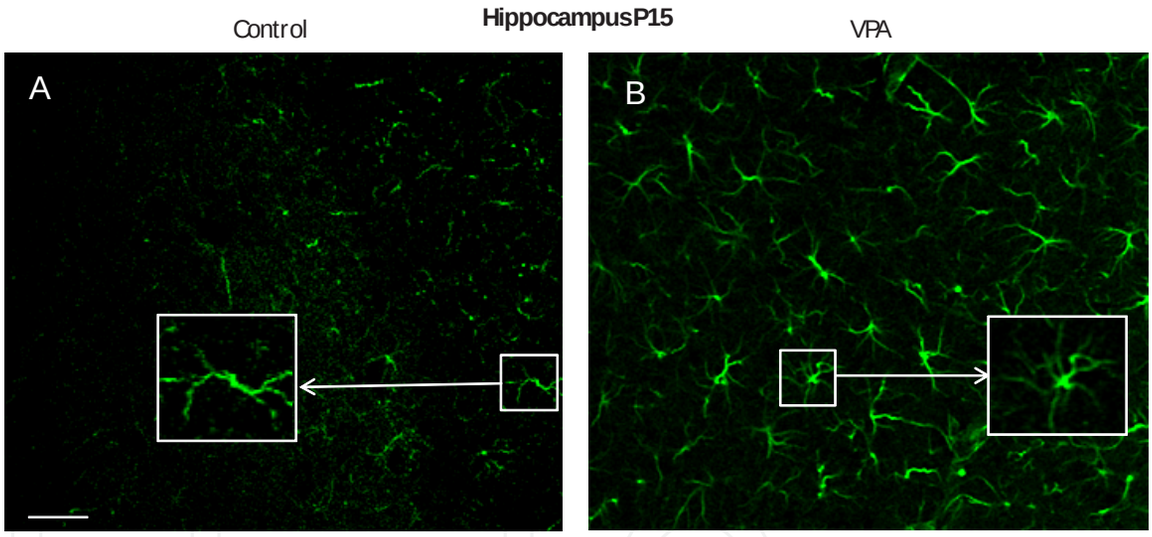

Figure 2. Astrocyte immunoreactive to GFAP in hippocampus from rats. A. Representative image from control group, B. Representative image from VPA group. Scale bar = 50 µm

Glutamatergic excitatory synapses are the major type of synapses in the brain and it was found that glutamate metabolism is altered in autistic CNS, particularly the glutamate receptors AMPA, NMDA and mGluR5 [114]. In agreement, rats exposed *in utero* to VPA show impairments in excitatory/inhibitory brain balance [78]. In this context, impairment in excitatory and inhibitory signaling during certain periods of development is proposed to be involved in the autism pathophysiology [115].

Although social impairments are one of the most important features observed in autism, patients present several other symptoms, including motor disturbances. Motor stereotypies are part of the so called autism triad of impairments, but hypotonia, motor apraxia,

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toe-walking, have already been reported [116]. Evaluation of motor cortex neurons of rats exposed to VPA *in utero* showed no changes in length or volume of either basilar or apical dendrites, but presented greater dendritic arborization in comparison with controls. This data indicates that pruning of neurons is abnormal in animals prenatally exposed to VPA [95]. Evidence suggests that the same may happen in patients with autism, since there are reports of increased brain weight in autopsy cases of autism [117]. However, the involvement of the abnormal pruning in motor cortex neurons with motor disturbances in autism deserves further investigation. Individuals with autism are more likely to present hearing deficits. In a study with a group of 199 children and adolescents, 3.5% had profound bilateral hearing loss or deafness [118].

The superior olivary complex (SOC) plays different roles in hearing. It is located within the lower brainstem and it is involved in encoding temporal features of sound and descending modulation of the cochlear nucleus and cochlea for listening in background noise. Rats exposed to VPA *in utero* showed reduced number of neurons and disrupted neuronal morphology in the SOC. Neuronal cell bodies were smaller and more round, indicating that these anatomical feature might have a role in the hearing difficulties that are a common in patients with autism [87]. In a study with brains of patients with autism similar morphological alterations were found, including soma size, shape and number of neurons in the SOC [119].

The cerebellum have been the focus of studies involving active and chronic neuroinflammatory process in autistic patients, demonstrating the presence of proinflammatory chemokines such as MCP-1 as well as antiinflammatory cytokines such as TGF-β1 in this brain structure. These findings support the idea that a chronic state of specific cytokine activation occurs in autism [113]. Because neuroimmune responses are influenced by the genetic background of the host, the role of neuroinflammation in the context of the genetic and other factors that determine the autism phenotype remains an important issue to be investigated.

6. Concluding remarks and scientific challenges

The spectrum of autism comprises a multifactorial group of disorders, with phenotypic diversity related to the symptoms and increasing prevalence. One of the major challenges of cognitive neuroscience is to understand how changes in the structural properties of the brain affect the plasticity exhibited whenever a person develops, ages, learns a new skill, make social interaction or adapts to a disease. In ASD, it is necessary studies in this field attempting to explain and understand the trigger of autism. In this context, it is not easy to find a single animal model able to captures the entire molecular and cellular alterations observed in patients with ASD.

Studies of *in utero* interventions in the search for animal models of autism, together with the study of potential clinical markers to ASD are innovative and may generate strategies aiming (a) the prevention of autism; (b) the construction of laboratory kits as new tools to improve and anticipate diagnosis; (c) the study of neuroglial plasticity; (d) the search for new clues to unravel the etiology of ASD. Challenged by these complexities, it is necessary to evaluate the

most representative animal model to which a research group may address its questions. Considering that neuroimmune responses are influenced by the host, the role of possible neuroinflammation triggered by environmental factors in utero followed by neuroglial alterations in the litters remain an important issue to be investigated.

The present chapter summarizes findings obtained in rodents exposed *in utero* to VPA which present important similarities to autism features, supporting it as a valuable experimental model to study neurodevelopmental alterations induced by VPA as an environmental risk factor.

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