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Environmental Factors in the Aetiology of Autism – Lessons from Animals Prenatally Exposed to Valproic Acid

Tomasz Schneider[1] and Ryszard Przewłocki[2,3]
[1]*University of Oxford,*
[2]*Institute of Pharmacology PAS*
[3]*Jagiellonian University,*
[1]*United Kingdom*
[2,3]*Poland*

1. Introduction

1.1 Diagnosis

Autism was first described by a child psychologist Leo Kanner as 'inability to relate themselves in the ordinary way to people and situations from the beginning of life' (Kanner, 1943). For many years autism was thought to be a consequence of bad parenting; fortunately, in the late 60-ties it was shown that there was no difference in parenting style between the parents of autistic and non-autistic children and a neurobiological basis of autism was suggested (Rutter et al., 1967; Rutter, 1968). Nowadays, autism is classified within the broad domain of pervasive developmental disorders (PDD) which also includes Rett syndrome, childhood disintegrative disorder, Asperger syndrome, and PDD not otherwise specified (American Psychiatric Association, 1994). There is a high phenotypic heterogeneity within this class of disorders and the debate regarding their clinical boundaries is ongoing. Instead of a classical categorical approach, a more useful description of this group of disorders as "autistic spectrum disorders" (ASD), not including Rett syndrome, has been proposed (reviewed in Willemsen-Swinkels & Buitelaar, 2002). ASD is characterized behaviourally by impairments in three core domains: social interaction, verbal and nonverbal communication, and restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities appearing before the age of three (American Psychiatric Association, 1994). Clinical pattern and severity of impairment vary along these dimensions from mild to severe including a complete absence of interest in interacting with others but also subtle dysfunctions in managing social interactions, a complete absence of spoken language but also mild impairment and idiosyncratic vocabulary or even hyper-linguism in some of the Asperger cases, simple motor stereotypies and a preference for sameness but also complex rituals accompanied by distress and aggression when they cannot be fulfilled. The core symptoms are frequently accompanied by a spectrum of neurobehavioral derangements, including: hyperactivity, aberrant sensitivity to sensory stimulation, reduced

joint attention, and anxiety (Ayres & Tickle, 1980; Bodfish et al., 2000; Dawson et al., 2004; Militerni et al., 2000; Muris et al., 1998; Pierce & Courchesne, 2001). Additional commonly associated characteristics include large head circumference, mental retardation, seizures, self injury, sleep disturbances, upset to change in routine, and lack of theory of mind (Baron-Cohen et al., 1985; Dawson et al., 2002; Richler et al., 2007; Volkmar & Nelson, 1990; Woodhouse et al., 1996). Similarly to core symptoms, intellectual capabilities also vary across the entire IQ spectrum with the majority of autistic individuals displaying low IQs (Charman et al., 2011) and the high functioning Asperger patients at the high end of the IQ spectrum (Pring, 2005). Prevalence estimates suggest a rate of 0.1-0.2% for autism and 0.6% for a broader autistic phenotype (Fombonne, 2009). Studies based on both clinical and epidemiological samples find a higher incidence of autism in boys than in girls, with reported ratios averaging around 4 to 1 (Newschaffer et al., 2007).

1.2 Intervention

The past 50 years have seen a myriad of interventions targeted at people with autism. Attempts to develop drugs that specifically improve social and communicative functioning have failed. However, medications such as atypical antipsychotics (e.g., risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole), psychostimulants (methylphenidate), presynaptic noradrenergic blocking agents (clonidine and guanfacine) and serotonin reuptake inhibitors (clomipramine, fluoxetine, sertraline) have been shown to reduce symptoms of affective instability, irritability, hyperactivity and inattentiveness, aggression, self-injury and stereotypies (reviewed by (Myers, 2007). Several reports have also suggested efficacy of early intensive behavioural therapy in attenuation or reversal of the core autistic symptoms (Lovaas, 1987; Ozonoff & Cathcart, 1998). The gains of the behavioural therapy appear to sustain over time (McEachin et al., 1993).

1.3 Pathology

Pathological studies have revealed an association between autistic symptoms and certain pathological changes in brain structure and cellularity (reviewed in (Bauman & Kemper, 2005). Postmortem autopsy of autistic brains revealed alterations in neuronal anatomy within frontal (Bailey et al., 1998), temporal (Bachevalier, 1994), parietal (Courchesne et al., 1993), limbic (Bauman, 1991), brainstem and cerebellar (Kemper & Bauman, 1998) regions. The few cross-sectional studies that examined age-related changes revealed a complex pattern of growth abnormalities in the cerebellum, cortex, amygdala, and hippocampus (Courchesne, 2004; Hashimoto et al., 1995; Schumann et al., 2004; Schumann et al., 2010). It has been suggested that early dysfunction of the amygdala and frontal cortex might be the substrate for the severe socio-emotional deficits seen in autism (Bachevalier, 1994; Baron-Cohen et al., 2000). However, the most consistent findings have been found in the cerebellum: marked reduction in Purkinje cell number in the cerebellar hemispheres, a reduction in granule cell numbers, and decreased size of the deep cerebellar nuclei. The globose and emboliform nuclei were most severely affected, while the dentate nucleus was spared. The abnormalities noted in the deep nuclei were age dependent: younger individuals had large cells in the deep nuclei relative to controls, but in older cases the cell were reduced in size (Courchesne, 2004; Fatemi et al., 2002). Loss of Purkinje cells may play an important role in the aetiopathogenesis of the disorder (Kern, 2003).

1.4 Neurotransmitter systems

Many neurotransmitters have been implicated in aberrations observed in autism including serotonin (5-HT), dopamine, norepinephrine, acetylcholine (Ach), glutamate, gamma-aminobutyric acid (GABA), endogenous opiods, oxytocin, and cortisol (reviewed in Lam et al., 2006). The most consistent finding was hyperserotoninemia. Serotonin blood levels are highly elevated in a significant number of autistic children (Betancur et al., 2002; Singh et al., 1997). Direct in vivo measurements using positron emission tomography demonstrated asymmetries of 5-HT synthesis in the frontal cortex, thalamus and cerebellum in autistic boys (Chugani et al., 1997). Also, while 5-HT synthesis is usually high in young children and then gradually declines, in autistic children 5-HT levels are persistently high (Chugani et al., 1999). Because metabolism, catabolism and transport mechanisms for 5-HT do not seem to be affected in autism (Cook & Leventhal, 1996; Persico et al., 2002), it has been suggested that the elevated 5-HT level is a consequence of excessive stimulation of synthesis and release. While it is tempting to view this elevated 5-HT level as a fundamental cause of ASDs, treatments that increase 5-HT levels seem to improve some symptoms of autism, such as perseverations and social relatedness (Fatemi et al., 1998), while depletion of tryptophan, a serotonin precursor, exacerbate autistic symptoms especially stereotypies, self-injury and anxiety (McDougle et al., 1996). The role of 5-HT in ASDs therefore remains unclear.

1.5 Genetic background

The aetiology of autism is not known but it has a strong genetic component revealed by up to 60% concordance between monozygotic twins and almost 90% heritability (Wassink et al., 2004). Sibling risk is around 2–7%, which is much higher than in the general population (0.01–0.08%) (Orsmond & Seltzer, 2007). This might suggest that autism may lay at the extreme of a continuum of some autistic traits. In line with such an assumption, relatives of individuals with autism show a plethora of mild autistic traits, including personality, social-behavioural and language aberrations (Bolton et al., 1998; Piven et al., 1997). Despite its high heritability, only approximately 10% of autism cases can be traced to a known genetic aberration (Barton & Volkmar, 1998). Several large linkage analyses have identified genome regions of significant linkage for autism harbouring multiple candidate genes, suggesting a complex multigenic cause of this disorder, which might involve anything from 2 to a dozen genes with complex gene–gene and/or gene–environment interactions (Persico & Bourgeron, 2006). Genetic studies have suggested several molecular pathways with the potential to disrupt neurodevelopmental trajectories *in utero* that might be involved in the pathogenesis of autism, including signalling molecules such as neurotrophin, Reelin, and hepatocyte growth factor, and synaptic proteins such as neurexin and neuroligin (reviewed in Pardo & Eberhart, 2007). Despite considerable effort, these underlying risk alleles have been remarkably elusive, with the exception of a few large effect genes and several single gene disorders associated with an increased risk for autism (Freitag, 2007). The obstacles encountered in mapping the risk alleles have led to new models of inheritance including contributions of *de novo* mutations and/or epigenetic mechanisms in the underlying genetic susceptibility to autism (Persico & Bourgeron, 2006).

1.5.1 Epigenetic factors in autism

Epigenetics refers to the reversible regulation of various genomic functions mediated through partially stable modifications of DNA and chromatin histones (Henikoff & Matzke,

1997). Epigenetic processes are essential for normal cellular development and differentiation, and allow the regulation of gene function through non-mutagenic mechanisms. Systems that initiate and sustain the epigenetic state of DNA, and hence an epigenotype, include histone modifications, RNA- associated silencing, and DNA methylation (Petronis, 2010). Involvement of epigenetic factors in autism spectrum disorders is demonstrated by the central role of epigenetic mechanisms in the pathogenesis of Rett syndrome and fragile X syndrome (FXS), single gene disorders commonly associated with autism (Hagerman, 2006; Samaco et al., 2005). Rett syndrome arises from mutation in the gene encoding the methyl-CpG-binding protein 2 (MeCP2), one of the key mediators of epigenetic regulation of gene expression (Amir et al., 1999). FXS arises through silencing of FMR1 (fragile X mental retardation 1) gene (Hagerman et al., 2005). Importantly, brain tissues from patients with autism have reduced expression of MeCP2 (Samaco et al., 2005) and about 5% of patients with autism have duplications of the imprinted region of chromosome 15q11-q13 (Cook, Jr. et al., 1997). Additionally, autism has been observed in conjunction with an incidence of prenatal exposure to the histone deacetylase inhibitor, valproic acid (Rasalam et al., 2005). Children with autism have also a lower level of methylation intermediates in their plasma, possibly causing an impaired methylation capacity (James et al., 2004). A possible role of epigenetic factors in autism might be one of the reasons for the problems encountered in mapping risk alleles for autism; disruption of gene expression via epigenetic mechanisms is not reflected in the primary nucleotide sequence and may evade detection by standard mapping strategies. The epigenome is most vulnerable to the effect of environmental factors during embryogenesis when the rate of DNA synthesis is high and the epigenetic marks needed for normal tissue differentiation and development are being established (Dolinoy, 2007). Therefore, epigenetic adaptations in response to *in utero* environmental exposure may play an important role in development and disease susceptibility after birth (Dolinoy et al., 2007; Persico & Bourgeron, 2006). Indeed, evidence has accumulated that exposure to toxic substances during early embryogenesis and/or very soon after birth can trigger the onset of autism (Arndt et al., 2005).

2. Environmental risk factors for autism

Converging lines of evidence suggest that autism spectrum disorders (ASDs) have their origins in early prenatal life (for in depth reviews see Arndt et al., 2005; Miller et al., 2005). This assumption is based on reports showing that (1) many of minor malformations that occur frequently in people with autism as well as anomalies reported from histological studies of the autistic brains are known to arise during embryogenesis; (2) congenital syndromes with high rates of autism include somatic aberrations originating in the first trimester; (3) the environmental factors known to increase the risk of autism have critical periods of action in the first 3 months of pregnancy. In this section we will present evidence showing that the first trimester is a critical time point for environmental/drug insults triggering autism.

2.1 Onset of symptoms vs. time of exposure to insults

Autism spectrum disorders are commonly diagnosed at the age of two or three when typically developing children become increasingly social and communicative; however, most, if not all, children who will be diagnosed with autism show symptoms long before that age. This was first noticed in the late 70ties by Ornitz and colleagues (1977). Using

parental questionnaires they showed that children who were later diagnosed with autism exhibited developmental delays even during the first year of life. This was confirmed by studies using home videos from the first two years of life of children later diagnosed with psychoses. Video recordings from children's natural environment showed fewer age appropriate behaviours in this group (Rosenthal et al., 1980) especially aberrant social attention (e.g., looking at people) and social behaviour (e.g., smiling at people and vocalizing to people), while most measures related to objects (e.g., looking at objects and smiling at objects) did not differ from control subjects in the first six months of life (Maestro et al., 2001). Better controlled studies of movies from the first birthday parties showed that most children later diagnosed with autism can be distinguished from controls at one year of age by such anomalies as failure to point to objects and failure to respond to their name (Osterling & Dawson, 1994). These results were confirmed by more recent studies (e.g., (Zwaigenbaum et al., 2005). Even at the biochemical level neonates who would later be diagnosed with either autism or mental retardation were distinguished by increased blood concentrations of neuron-related products: vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), brain-derived neurotrophic factor (BDNF) and neurotrophin 4/5 (NT4/5) (Nelson et al., 2001; Nelson et al., 2006). The two clinical groups did not differ from each other. These results clearly suggest that children with autism are already different from typically developing children at the time of birth.

2.2 Evidence for early injury in autism

2.2.1 Dysmorphic features

Dysmorphic facial features and increased occipitofrontal circumference reported in most cases of idiopathic autism (not co-morbid with the known genetic disorder) can not be induced postnatally, and most of the reported minor anomalies must have originated from the first eight weeks post-conception (e.g., (Miles & Hillman, 2000; Rodier et al., 1997a; Walker, 1977). For example, Rodier and colleagues (1997a) described minor physical malformations linked to autism in a population in Nova Scotia, Canada. Posterior rotation of the external ears was the most characteristic feature of children with autism compared to their unaffected siblings and non-autistic children with developmental delay. Importantly, these types of ear abnormalities have also been found in children with autism following exposure to thalidomide or valproic acid (Miller et al., 1998; Moore et al., 2000; Stromland et al., 1994). Dysmorphic features observed in idiopathic autism are strongly correlated with the extend of brain abnormalities revealed by imaging techniques and with increased male to female ratio (Miles et al., 2005; Miles & Hillman, 2000). Although, all of the physical anomalies reported in autism are also seen in children with other developmental disabilities, and in the population of typically-developing children, they might be useful in specifying critical periods for neurodevelopmental injuries in autism.

2.2.2 Neuroanatomical abnormalities

There are several neuroanatomical and histological arguments in favour of very early alterations of development as part of the aetiology of ASDs. For example, autopsies reported by Bailey and colleagues (1998) showed extra tracts running through the pontine tegmentum in one of the autistic brains studied and two brains with smaller and not fully separated pyramidal tracts. Because the basic tracts of the neuroaxis are established before

parturition, the described anomalies were clearly of prenatal origins. Further, histological studies of one of the most consistent findings in pathology of autism, a marked reduction in Purkinje cell number in the cerebellar hemispheres, showed that the lose of these cells must have taken place during first weeks of neurodevelopment: (1) Purkinje cells body are normally wrapped by neighbouring basket cells and the late loss of Purkinje cells is characterized by the presence of ''empty baskets'', which were not observed in autistic brains (Bailey et al., 1998); (2) if reduction in Purkinje cell numbers appears after the 30th week *in utero* this results in massive retrograde loss of neurons in the inferior olive (Sakai et al., 1994; Takashima, 1982); while abnormalities of the inferior olive have been reported in autistic brains (Bailey et al., 1998; Bauman & Kemper, 1985), the nucleus is not affected to the extend that would be expect if cells were degenerating in response to a late loss of Purkinje cells. Similarly, a brain from a patient with autism, studied by Rodier and colleagues (1996), had a massive reduction in the number of motor neurons in the facial nucleus (400 vs. 9000). In the normal brain used for comparison, this nucleus was outlined by a capsule created by passing fibres, but in the brain of autistic patient no capsule was present, which suggest that the neurons forming the facial nucleus were not in position when passing fibres made their tracts. If the facial neurons had been lost in late gestation or postnatal life, the capsule would still be there. Thus, again the obvious conclusion is that the nucleus failed to form early during neurodevelopment. Each of these findings supports the conclusion that the neuroanatomy of people with autism is altered in a very early gestation.

2.2.3 Syndromes with high rates of autism

There are several congenital conditions originating from disruption of very early development with highly increased rate of autism including (1) Moebius sequence (Briegel et al., 2009); (2) the CHARGE association (Hartshorne et al., 2005); (3) Goldenhar syndrome (Johansson et al., 2007); (4) Duane syndrome (Miller et al., 2009); (5) Joubert syndrome (Ozonoff et al., 1999); (6) Cornelia de Lange syndrome (Moss et al., 2008); and (7) Smith–Limli–Opitz syndrome (Sikora et al., 2006). These syndromes are different in many ways, but they all involve abnormal development in the embryonic period. For example, (1) Möbius syndrome involve a variety of functional anomalies linked to congenital aberrations of the sixth and seventh cranial nerve, limb defects, and craniofacial anomalies involving the tongue and lip; (2) the CHARGE association is characterized by a co-occurrence of congenital malformations including colobomas, heart defects, choanal atresia, retarded growth or development, genital anomalies, and ear abnormalities and/or hearing loss; (3) Goldenhar syndrome is a combination of epibulbar dermoids, lipodermoids, and preauricular skin tags and fistula, upper lid coloboma, facial, and vertebral anomalies; (4) Duane syndrome is characterized by absent or hypoplastic abducens nucleus and nerve, and innervation of the lateral rectus eye muscle by a branch of the oculomotor nerve; (5) Joubert syndrome is an extremely rare recessively inherited disorder characterized by breathing difficulties, hypotonia, ataxia, eye movement anomalies, failure of development of the cerebellar vermis and the cranial nerve motor nuclei, and failure of the superior cerebellar peduncles to cross; (6) the phenotype of Cornelia de Lange syndrome includes epicanthal folds, ptosis, broad nasal bridge, short nose, long upper lip, micrognathia, anomalies of the limbs, heart, and gastrointestinal tract, and growth reduction; (7) Smith–Limli–Opitz syndrome (SLOS) is characterised by facial features including a broad, high forehead,

hypertelorism, ptosis, epicanthal folds, broad nasal bridge, short nose with reverted nares, and micrognathia, low set and small ears, sometimes cleft palate, syndactyly, and genital anomalies. The dysplasias of the brain stem nuclei and cerebellar vermis observed in these syndromes suggest that their neurodevelopment have been disturbed in the fourth or fifth week postconception, when those structures are forming. Autism has been reported in a very high rate in all these syndromes, 25-68% for full autism and 50-100% for autistic features (Johansson et al., 2010; Moss et al., 2008; Ozonoff et al., 1999; Sikora et al., 2006). Why autism exists in a significant number in these syndromes is still a mystery and we do not know how early-onset insult affecting multiple brainstem structures can lead to malfunction of the higher centres not yet formed at the time of initial injury and most commonly linked to autism.

2.2.4 Critical period of exposure to teratogens increasing the risk of autism

A number of teratogenic substances have been identified in epidemiological studies as the key triggers of autism including maternal rubella infection (Chess, 1971), ethanol (Nanson, 1992), misoprostol (Bandim et al., 2003), thalidomide (Stromland et al., 1994), and valproic acid (Moore et al., 2000; Rasalam et al., 2005). The critical period for exposure to these teratogens appears to be during the first trimester.

2.2.4.1 Thalidomide exposure

A study of patients in the Swedish thalidomide registry revealed that about 30% of children exposed to thalidomide on the 20–24th day of gestation became autistic, which was 250 times the rate in the general population at this time (Stromland et al., 1994). The original aim of this study was to describe the ocular motility dysfunctions (strabismus) and other eye anomalies or visual disturbances in thalidomide victims, but this was fortunately accompanied by psychiatric evaluation. The neurological abnormalities observed in the five thalidomide-autistic cases included the following: three had Duane syndrome (failure of the abducens cranial nerve to innervate the lateral rectus muscle by the eye with subsequent re-innervation of the muscle by the oculomotor cranial nerve); one patient had face paresis (oculomotor palsy); four had Möbius syndrome (failure of the facial cranial nerve to innervate the facial muscles); two had abnormal lacrimation (due to a failure of the neurons of the superior salivatory nucleus to innervate the lacrimal apparatus). All five patients had ear malformations and hearing deficits. Importantly, ear malformations (Walker, 1977), eye motility problems (Scharre & Creedon, 1992), and Möbius syndrome (Gillberg & Steffenburg, 1989) had previously been associated with autism. In fact, external ear malformations are the most common physical abnormality observed in autism and the ones which best distinguish between autism and mental retardation (Rodier et al., 1997a; Walker, 1977). What makes the thalidomide cases so informative is that the external signs of thalidomide teratogeny allow accurate dating of the stages of development when exposure to the teratogen took place (Miller, 1991). On the bases of that timetable of teratogenic effects of thalidomide it was concluded that the ophthalmologic and cranial nerve dysfunction involving ocular structures observed in thalidomide-autistic cases occurred from teratogen intake during the 4th week post-conception (Stromland et al., 1994); i.e., at the time of neural tube closure and development of the first neurons, which form the motor nuclei of the cranial nerves (Altman & Bayer, 1982). That was the first study related to autism in which we had a known cause, a set of physical, neurological, and psychiatric autistic symptoms, and identified stage of development when the triggering insult occurred.

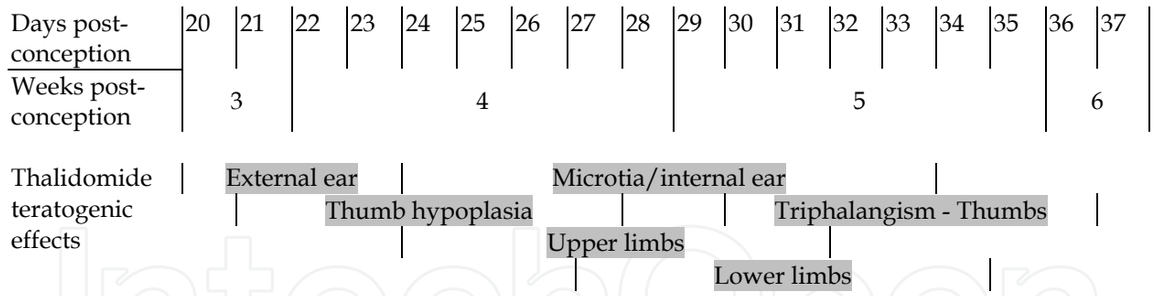

Fig. 1. Timing for teratogenic effects of thalidomide in humans (Lenz & Knapp, 1962; Miller, 1991).

2.2.4.2 Valproic acid

An antiepileptic drug increasing the risk for autism, valproic acid (Moore et al., 2000; Rasalam et al., 2005), is typically taken throughout the entire pregnancy, thus the timing for its teratogenic effect cannot be estimated directly. However, the timing of injury to the developing nervous system can be estimated from accompanying somatic features in exposed children. Children prenatally exposed to VPA exhibit similar patterns of physical malformations as those exposed to thalidomide, but with a decreased severity of symptoms (Ardinger et al., 1988; DiLiberti et al., 1984; Kozma, 2001). These include dysmorphic features indicative of injury around the time of neural tube closure, e.g., neural tube defects, congenital heart disease, craniofacial abnormalities, and abnormally shaped or posteriorly rotated ears, which are common in idiopathic autism (e.g., (Miles & Hillman, 2000; Rodier et al., 1997a) and were also reported in thalidomide-autism cases with the known exposure time to teratogen during the 4th week postconception. Based on this pattern of abnormalities we can estimate that VPA and thalidomide injured the developing nervous system at a similar time during embryogenesis.

2.2.4.3 Misoprostol

Misoprostol (Cytotec®), a prostaglandin type E analogue, was used as a self-administered abortion drug, especially in Brazil. Misoprostol is typically used in the first trimester of pregnancy. Self-induced, but failed abortions lead to several cases of infants born with malformations involving limbs and cranial nerves (Gonzalez et al., 1998; Shepard, 1995). In some of these cases, the children had Möbius syndrome (Shepard, 1995) and a rate of autism was highly increased in this population (Bandim et al., 2003).

2.2.4.4 Rubella

Epidemiological studies showed an increased risk for autism after rubella infection and noted that all the children in rubella-induced autism had multiple symptoms of rubella injury (Chess, 1977; Chess et al., 1978). Previous studies found that cases with multiple symptoms after rubella exposure came mainly from mothers exposed within the first eight weeks postconception, with mothers of children suffering from severe mental retardation showing an onset of rash even earlier at the 2nd to 5th week postconception (Ueda et al., 1979). This suggests that exposure to rubella virus in autistic cases took place during the first weeks of development.

The coincidence of critical periods for the described environmental risk factors for autism is a strong evidence that autism arises very early in development; however, the fact that each of these teratogens appears to act during the embryonic period (the first eight weeks of life)

does not obviously rule out the possibility that autism could be initiated at other stages of development. Again, we do not know how early-onset insults affecting multiple brainstem structures can lead to malfunction of the higher centres not yet formed at the time of initial injury and most commonly linked to autism. It might be that a group of unidentified progenitor cells for higher brain centres get injured during early insults or that failure of axonal guidance under conditions in which important landmarks are absent or misplaced in the lower brain structures disturb normal development of higher brain centres. These are hypothesis that might be studied in animal models.

3. Animal models of autism

Because the primary diagnostic criteria of autism are abnormal behaviours, rather than biochemical or neuroanatomical factors, the use of animal models in the study of autism is unavoidable, as this is the only way to study behavioural defects in context of a whole organism. Rodent models in particular allow an extensive multi-omics approach to autism with a spectrum of non-invasive and invasive approaches at the genetic, molecular, cellular, synaptic, and behavioural levels. Currently used animal models of autism can be classified into three categories: (1) models created by neonatal lesions of brain areas shown to be abnormal in autism, e.g., cerebellum, the amygdala, hippocampus, or the medial prefrontal cortex; (2) genetically modified animals, e.g., targeted mutations in genes associated with autism or localized in chromosomal regions identified by linkage analyses; and (3) models mimicking environmental factors that increase the risk for autism in humans, e.g., prenatal exposure to valproic acid (VPA, 2-propyl-pentanoic acid) or pre- and neonatal immunological challenges. The first two approaches were extensively reviewed elsewhere (Ey et al., 2011; Moy & Nadler, 2008; Tordjman et al., 2007). In the present chapter we will focus on two animal models of autism induced by environmental factors: neonatal exposure to Borna disease virus and prenatal exposure to valproic acid. We will use these model to show and explain how human data can inform creation of animal models of autism and how animal model can be used to extend our understanding of autism and potentially lead to new therapeutic interventions for this still incurable disorder; but first a short introduction to *in vivo* modelling.

3.1 Concepts for *in vivo* modelling

There is an ongoing discussion about the criteria to be used in the evaluation of animal models. It has been suggested that the only meaningful initial evaluating criterion for an animal model is its ability to lead to accurate predictions about the disorder in question (predictive validity). Other authors stressed that the demonstration of construct validity (similarity to the underlying causes of the disease) represents the most important and necessary component in validation of an animal model. Others claim that the modelling of symptoms (face validity) must remain the primary goal of animal models of psychiatric disorders (for review see Fernando & Robbins, 2011). The resolution of this puzzling controversy depends on the desired purpose of the model that one wishes to validate. Although, regarding complex psychiatric disorders such as autism, a multidimensional approach should be used as an optimal strategy.

3.2 Challenges for animal models of autism

In recent years, several rodent models of autism have been developed that reflect some behavioural, genetic, and neuroanatomical alterations associated with this disorder. One of

the main problems for the development of a relevant model is to define markers of autism, addressing its complexity and diversity. An ideal rodent model of autism should display symptoms of aberrant social interaction and communication, as well as repetitive behaviours. Tasks that could examine these behavioural symptoms in rodents have been already developed (for reviews see Crawley, 2004; Crawley, 2007) and are summarized in Table 1. However, an animal model of autism based solely on behavioural assays would be incomplete. Animal model should also address a combination of the neuropathological, biochemical and genetic factors implicated in autism. Another challenge lies in the fact that many clinical hallmarks of autism are difficult or almost impossible to replicate in rodents, e.g., theory of mind (ability to intuit the feelings and intentions of others) or speech deficits. It is also important to realize that assumed ''core'' psychopathological phenomena observed in autism are present as common clinical features in schizophrenia, depression, obsessive-compulsive disorder and other medical and psychiatric illnesses. What is specific for autism is a pattern of socio-behavioural aberrations and their appearance before the age of three, and animal models should try to address this fact.

3.3 Behavioural tests for autistic-like aberrations in rodents

Impairment in social interaction is a critical component for animal models of autism. Rodents are highly social animals displaying a plethora of different social behaviours. The propensity of animals to spend time with conspecific rather than non-social novel objects can be used as one of the measures. This can be best done in an automated three-chambered apparatus in which social interactions, social recognition, and social memory can also be scored (Moy et al., 2004; Nadler et al., 2004). Measures of the level of social approach can be accompanied by more specific analyses of reciprocal social interactions, including, nose-to-nose contacts, anogenital inspections, aggression, escape behaviour, nesting patterns, juvenile rough and tumble play, etc. (Moy et al., 2008; Moy et al., 2009). Impairments in social communication may be measured in rodents using olfactory and auditory communication tasks. Different kinds of ultrasonic vocalizations can be elicited in rodents, starting from separation calls in pups isolated from their mothers, to frequency modulated vocalizations in social situations in adult animals, treated, at least in rats, as indicators of positive and negative affective states (Portfors, 2007; Scattoni et al., 2009). Both frequency and time structures of ultrasonic vocalizations can be analyzed. Olfactory social signals, including deposition of pheromones, are another form of rodent communication (Arakawa et al., 2008). Rodents' chemical signals play a particularly important role in determining social dominance and intersexual relationships. Finally, repetitive behaviour encompasses both motor stereotypy and self-injury, can be scored using standardized scales, and behaviours reflecting general cognitive rigidity, such as ability to change, resistance to change, and responses to the change in routine can be investigated by exploratory choices and reversal tasks using spatially contingent reinforcers, e.g., reversal learning in T-maze or water maze (Crawley, 2004; Silverman et al., 2010). Because autism is accompanied by a plethora of neurobehavioral aberrations, it is important to include a range of additional behavioural tasks assessing, e.g., anxiety, seizure susceptibility, sleep patterns, sensitivity to sensory stimuli, learning and memory, and maturation and development. Finally, both pathological features of autism (e.g., decreased number of Purkinje neurons) and biological findings (e.g., increased serotonin levels) should be addressed.

Tests analogous to core autistic symptoms	**Tests analogues to associated symptoms**
1. *Impairment in social interactions* • reciprocal social interactions (partner grooming, nose-to-nose contacts, anogenital inspections, aggression, escape behaviour, juvenile rough and tumble play etc.) • propensity to spend time with conspecific vs. novel objects • conditioned place preference to conspecifics • preference for social novelty • aggression (resident-intruder test) • social recognition • nesting patterns in the home cage 2. *Impairments in social communication* • behavioural responses to social olfactory cues from conspecifics • deposition of social olfactory pheromones • vocalizations emitted during social interactions • responses to vocalizations from conspecifics • parental retrieval of separated pups • ultrasonic vocalizations by separated pups 3. *Repetitive, stereotyped patterns of behavior, interests, and activities* • motor stereotypies • extinction of a learned response in an operant chamber • reversal of a position habit in an appetitive T-maze task, aversive Y-maze task or the Morris water maze • spontaneous responses to errors during reversal tasks	1. *Anxiety* elevated plus maze; light-dark box exploration; Vogel conflict licking test; marble burying; 2. *Theory of Mind deficits* location of buried food following observation of conspecifics; social transmission of food preference; avoidance of aggressive encounters; 3. *Mental retardation* acquisition of Morris water maze task; acquisition of T-maze tasks; contextual and cued fear conditioning; operant learning tasks; attentional measures in the five choice serial reaction time task; 4. *Seizure susceptibility* spontaneous seizure activity; sensitivity to audiogenic seizures; sensitivity to drug-induced seizures; 5. *Motor clumsiness* balance beam foot slips; rotarod motor coordination and balance; gait analysis; 6. *Sleep disturbances* circadian running wheels; videotaped observations of home cage sleep and activity patterns; 7. *Idiosyncratic responses to sensory stimuli* acoustic startle; tactile startle; hot plate; Von Frey filaments; unresponsiveness to sensory attentional cues (failure to disengage attention); discriminative eyeblink conditioning and reversal; 8. *Developmental milestones and progression* brain weight and volume; size of structures and pathways; repeated testing of all relevant behaviours at juvenile and adult ages;

Table 1. Rodent Behavioural Tasks Relevant to Autism

3.4. Models created by environmental and immune factors

3.4.1 Neonatal Borna Disease Virus (BDV) infection in rat

Disturbed functioning of the immune system, especially pre- and/or neonatal immunological challenge has been long implicated in the pathogenesis of autism (Chess, 1977; Singh et al., 1991; Warren et al., 1986; Warren et al., 1990; Warren et al., 1996). The best characterized model of autism utilizing this approach is induced by neonatal Borna disease virus (BDV) infection in rat (Pletnikov et al., 2002a). Borna disease virus, an atypical, neurotropic, noncytolytic, negative strand RNA virus, shows affinity for limbic and cerebellar circuitry (de la Torre et al., 1990; de la Torre, 2002). Infection causes a spectrum of behavioural deficits depending on the age, immune status, central nervous system maturity, and genetics of the host (de la Torre, 2002; Pletnikov et al., 2001). Intracranial injection of the BDV in a newborn rat pup within the first 24–48 h after birth is the most common way of inducing neonatal BDV infection in rats (Pletnikov et al., 2002a). Neonatally infected Lewis rats have only transient inflammation (Hornig et al., 1999) but nonetheless have abnormalities of hippocampal and cerebellar development (Hornig et al., 1999; Pletnikov et al., 2003), growth (Bautista et al., 1994), spatial and aversive learning (Rubin et al., 1999), locomotor activity (Hornig et al., 1999), emotional reactivity (Hornig et al., 1999; Pletnikov et al., 1999a), and play behaviour (Pletnikov et al., 1999b), although duration of non-play social investigation (e.g. sniffing, approach, and follow) was higher in BDV-infected rats (Pletnikov et al., 1999b). These abnormalities mimic the impaired social interaction and atypical responses to sensory and emotional stimuli characteristic in autism. Injury to the cerebellum is one of the most salient morphological features of neonatal infection. BDV infection induces a prominent loss of Purkinje cells during the first seven months of life (up tp 75%). A loss of Purkinje cells and their dendrites in the molecular layer might be responsible for markedly reduced cerebellum size in this model (Pletnikov et al., 2003). In addition to injury of the cerebellum, neonatal BDV infection affects the postnatal maturation of the hippocampus and leads to continuing loss and eventual complete disappearance of dentate gyrus neurons by 45–55 postnatal days and their replacement by reactive glial cells (Gonzalez-Dunia et al., 2000; Pletnikov et al., 2002b). Neonatal BDV infection also induces cortical shrinkage. It has been shown that up to 30% of cortical neurons are lost in BDV infected rats by postnatal day 45 (Pletnikov et al., 2002b). At the cellular level diminished immunoreactivity for GAP-43 and synaptophysin is observed both in the neocortex and the hippocampus of neonatally BDV-infected rats (Gonzalez-Dunia et al., 2000). This model bears obvious similarities to behavioural and anatomical aberrations observed in autism; however, there is little serological evidence that suggests BDV infects humans (Chalmers et al., 2005), and its role in psychiatric disorders remains controversial. The disadvantage of infection models is that they lead to a persistent infection of the brain precluding more precise characterization of the time course and structural specificity of the created neuronal aberrations.

3.4.2 Animal model of autism induced by prenatal exposure to valproic acid

3.4.2.1 VPA exposure in humans

Clinically, VPA was first introduced in the 60-ties as an anticonvulsant and mood-stabilizing drug. Currently VPA (Depakene, Valproate, Valrelease) is used for treatment of epilepsy, bipolar disorder, and migraine prophylaxis (Rosenberg, 2007). Although there is clear evidence for teratogenic effects of VPA (Jentink et al., 2010), it is still used during pregnancy

when the benefits to the mother outweigh the risks to the embryo or foetus (category ''D'' classification by the FDA). These include situations where the mother's health would be at risk without taking the drug and for which safer drugs are not available.

3.4.2.2 Studies implicating VPA in autism

Many children exposed in utero to VPA exhibit fetal valproate syndrome (FVS), a syndrome characterized by a constellation of malformations, developmental delays and behavioural aberrations (Ardinger et al., 1988; DiLiberti et al., 1984; Kozma, 2001). Common facial features of FVS include epicanthal folds, broad nasal bridge, short nose with inverted nostrils, long upper lip, and low set, posteriorly rotated ears. The link between prenatal VPA exposure and autism was based on seven case studies of children with FVS diagnosed with autism (Christianson et al., 1994; Williams et al., 2001; Williams & Hersh, 1997). The first population study on 57 children with fetal anticonvulsant syndromes (a syndrome caused by a variety of anticonvulsant drugs) conducted by Moore and colleagues (2000) showed highly increased prevalence of autistic symptoms in this group of children. The children were exposed to either VPA alone (60%), VPA in combination with another anticonvulsant drug (21%), or to non-VPA anticonvulsant drugs (19%). Moore reported 46 (81%) kids with speech delays and 34 (60%) kids with two or more autistic features, of which 6 (11%) had a diagnosis of ASD. Furthermore, 46 (81%) had behavioural problems, 22 (39%) displayed hyper-activity and poor concentration, of which 4 (7%) had a diagnosis of attention deficit/hyper-activity disorder. Forty-four (77%) kids had learning difficulties, 34 (60%) had gross motor delay, and 24 (42%) had minor motor delay. A more recent long-term study of the effects of prenatal exposure to antiepileptic drugs in 260 children (122 males, 138 females) showed a very similar pattern of behavioural aberration: 26 (16 males) children were reported by parents to have social or behavioural difficulties, 11 children (6 males, 5 females) fulfilled the DSM-IV criteria for autistic disorder and one (female) fulfilled the DSM-IV criteria for ASDs (Rasalam et al., 2005). These children comprised 4.6% of the exposed group studied, and 1.9% of all exposed children born during the study period. Other children from this group (26 in total) had difficulties in areas of speech and language development and social communication but did not meet the criteria for autism spectrum disorders. Sodium valproate was the drug most commonly associated with ASDs, five of 56 (8.9%) children exposed to sodium valproate alone had either autistic disorder or ASDs. Thus, the rate of autism in humans prenatally exposed to VPA is much higher than in the general population (approximately 0.1-0.16%, (Fombonne, 2005).

3.4.2.3 Valproic acid mechanisms of action

The mechanism of action of valproic acid is not fully understood. Effects of the drug may be related, at least in part, to increased brain concentrations of the inhibitory neurotransmitter GABA. Animal studies have shown that valproic acid inhibits GABA transferase and succinic aldehyde dehydrogenase, enzymes which are important for GABA catabolism (Johannessen, 2000); however, current hypotheses for the mechanism for VPA action are mostly focused on its epigenetic properties. VPA is an inhibitor of histone deacetylases (HDACs) (Gottlicher, 2004; Phiel et al., 2001) and its teratogenic effects are mediated specifically by inhibition of HDACs (Gurvivh et al., 2005). HDACs regulate chromatin structure by removing acetyl groups from lysines in the amino-terminal tails of core histones in the nucleosome regulating chromatin structure and gene expression (Dokmanovic & Marks, 2005). This process leads to expression of a small number of normally silent genes.

3.4.2.4 VPA-exposure as an animal model of autism

A study of patients in the Swedish thalidomide registry revealed that about 30% of children exposed to thalidomide on the 20–24th day of gestation became autistic, which was 250 times the rate in the general population at this time (Stromland et al., 1994). The 20–24th day of gestation is the time of neural tube closure and development of the first neurons, which form the motor nuclei of the cranial nerves. Since thalidomide does not have the same teratogenic effect in rodents as in primates (Schumacher et al., 1972), valproic acid was used to injure rats' brainstems in utero (Rodier et al., 1996). VPA exposure induces similar patterns of abnormal development across species with skeletal and cranial nerves abnormalities reported in mice (Nau et al., 1991), rats (Vorhees, 1987), and monkeys (Mast et al., 1986). Most importantly, prenatal VPA exposure leads to several-fold increase in the rate of autism (Bromley et al., 2008; Moore et al., 2000; Rasalam et al., 2005).

3.4.2.4.1 Neuroanatomical similarities to autism

In rats, the neural tube closes on day 11; by the 12th day of gestation production of the motor nuclei of trigeminal, abducens, and hypoglossal nerves is completed (Altman & Bayer, 1980). Malfunctions of the targets of these neurons were reported in autism (reviewed in Arndt et al., 2005; Miller et al., 2005). Offspring of female rats injected with VPA during neural tube closure show several brain abnormalities, resembling those found at autopsy and in brain-imaging studies of autistic patients: abnormalities of the cranial nerve motor nuclei, hypoplasia of brainstem structures, reduced volume of posterior parts of cerebellar vermis and hemispheres, a loss of Purkinje cells, and injury to deep nuclei of the cerebellum (Ingram et al., 2000; Rodier et al., 1996; Rodier et al., 1997b). Changes in the timing of exposure to VPA were used to produce different injuries. In brief, a single intraperitoneal NaVPA injection on PND 11.5 at a dose of 350 mg/kg VPA resulted in a significant reduction in the trigeminal and hypoglossal nuclei. Exposure on day E12 resulted in abnormalities of the abducens, trigeminal, and hypoglossal nuclei, and exposure on day E12.5 resulted in reductions of neurons in the oculomotor, abducens, trigeminal, and hypoglossal nuclei. Insults affecting these neurons are associated with abnormalities in facial features that are common in idiopathic autism and were observed in all of the five autistic thalidomide cases (Rodier et al., 1997a; Stromland et al., 1994). Cerebellar abnormalities consistent with human cases of autism were found following exposure of 600 mg/kg sodium valproate on day E12.5. Purkinje cell numbers in posterior lobules (VI–VIII and X) of the vermis were reduced, but were normal in the anterior lobes (IV–V) (Ingram et al., 2000), which resembles human MRI studies that have shown decreased size of the posterior cerebellar vermis in autism (Courchesne et al., 1994a; Courchesne et al., 1994b; Hashimoto et al., 1995).Further, the interpositus nucleus, corresponding to the globose and emboliform nuclei in humans, but not dentate nucleus was significantly reduced in VPA rats (Rodier et al., 1997b). In human cases, the globose and emboliform nuclei are much more severely affected than the dentate nucleus (reviewed in Kemper & Bauman, 1998). The overall brain volume in the treated animals was reduced by 18% (using brain weight).

3.4.2.4.2 Behavioural similarities to autism

There is a vast body of evidence that administration of VPA on day 12 of gestation has long-term effects on postnatal behaviours in male but not female rats, which include (1) lower sensitivity to pain and higher sensitivity to nonpainful stimuli, (2) diminished acoustic prepulse inhibition, (3) locomotor and repetitive/stereotypic-like hyperactivity combined

with lower exploratory activity, (4) decreased number of social behaviours and increased latency to social behaviours, (5) decreased seizure threshold; (6) and higher anxiety (Markram et al., 2008a; Narita et al., 2010; Schneider et al., 2001; Schneider et al., 2007; Schneider et al., 2008; Schneider & Przewlocki, 2005; Schneider & Przewlocki, 2007). In addition, VPA rats showed delayed maturation, lower body weight, delayed motor development, and attenuated integration of a coordinated series of reflexes, and delayed nest-seeking response mediated by olfactory system (Schneider & Przewlocki, 2005). Interestingly, all behavioural aberrations described in those animals appear in adolescent animals, which could distinguish the VPA rat model of autism from other animal models of neurodevelopmental disorders, especially rodent models of schizophrenia. Similar behavioural abnormalities and developmental delays have been observed in autism. Indeed, autistic patients express: social interaction deficits (Kaufmann et al., 2004); hyperactivity with decreased exploratory activity (Pierce & Courchesne, 2001); motor repetitive/stereotypic behaviours (Militerni et al., 2002); lowered sensitivity to pain (Militerni et al., 2000); deficits of information processing and attention with impaired sensorimotor gating (Allen & Courchesne, 2001; McAlonan et al., 2002), higher anxiety and phobias (Evans et al., 2005; Gillott et al., 2001); a greater risk for developing seizure disorder (Volkmar & Nelson, 1990); and delayed sensorimotor development (Losche, 1990). VPA-treated offspring also exhibited greatly amplified conditioned cued and contextual fear responses when tested up to 3 months after conditioning. Fear memories were not only amplified, but also more generalized to other stimuli configurations and more resistant to extinction than in control animals (Markram et al., 2008a). Again, autistic children are known to have impairments in extinction learning and to display strong perseverations (Coldren & Halloran, 2003; Mullins & Rincover, 1985). Those results confirm existence of similarities between the observed pattern of aberrations in VPA rats and features of disturbed behaviour in autistic patients. Noteworthy, VPA rats express a very specific pattern of aberration in eye-blink conditioning test (Murawski et al., 2009; Stanton et al., 2007), which is similar to that reported by Sears and colleagues (1994) in autistic patients, i.e., normal basic sensory and motor function, but exaggerated amplitude of conditioned blinks, and altered timing of conditioned blinks. One difference between children with autism and the VPA-exposed rats was that the animals did not display a higher rate of acquisition of conditioned responses. Almost all studies using eye-blink conditioning in human disorders (e.g., schizophrenia, (Bolbecker et al., 2009); mental retardation, (Hogg et al., 1979); Huntington disease, (Woodruff-Pak & Papka, 1996); Fragile X Syndrome, (Tobia & Woodruff-Pak, 2009) show impairment in conditioning ability compared to control subjects. It is therefore surprising that children with autism and rats exposed to VPA *in utero* display an enhancement of eye-blink conditioning, which might actually lead to the first 'autism-specific' test for between species comparisons.

3.4.2.4.3 Biochemical similarities to autism

Prenatal exposure to VPA in Sprague–Dawley rats on embryonic day 9 (neural plate stage) leads to increased serotonin levels in the hippocampus, increased dopamine in the frontal cortex, and hyperserotonemia (Miyazaki et al., 2005; Narita et al., 2002; Tsujino et al., 2007). VPA administration also alters serotonergic neuronal differentiation and migration in the dorsal raphé nucleus (Miyazaki et al., 2005; Tsujino et al., 2007). These results are strikingly similar to the data obtained on the serotonergic system in human autism (Anderson et al.,

1990; Lam et al., 2006). Serotonin is not only a neurotransmitter, but also a regulator of development of several brain areas, such as the neocortex, hippocampus, and cerebellum. It has been previously shown in other models that depletion of serotonin results in a significant delay in maturation of cortical structures (Bennett-Clarke et al., 1995; Vitalis et al., 2007) and excessive serotonin during early development results in hyper-innervation and expansion of cortical architecture (Vitalis et al., 1998). Thus, increased serotonin level in VPA rats may be one of the factors triggering altered developmental patterns observed in this model. Indeed, a more complex dendritic arborization in apical dendrites of pyramidal cells in motor cortex had been shown in VPA-exposed animals (Snow et al., 2008), suggesting disturbed pruning process, which is consistent with theories related to abnormal human brain development in autism. VPA rats also express altered functioning of opioidergic (Schneider et al., 2007) and glutamatergic (Rinaldi et al., 2007) systems. Recently, the same model has been replicated in mice. VPA-mice share behavioural phenotype described previously in rats but also had decreased NLGN3 mRNA expression in hippocampus and somatosensory cortex (Kolozsi et al., 2009; Roullet et al., 2010), which again resembles human literature showing that mutations in neuroligin3 gene may predispose to autism (Bourgeron, 2009; Jamain et al., 2003).

3.4.2.4.4 Immunological similarities to autism

Prenatal VPA exposure in rats led also to immunological aberrations resembling decreased cellular immunity observed in autism (reviewed in Cohly & Panja, 2005). Decreased weight of the thymus, decreased splenocytes proliferative response to concanavaline A, lower IFN-γ/IL-10 ratio, and increased production of NO by peritoneal macrophages were described in male VPA rats, whereas females exhibited only decreased IFN-γ/IL-10 ratio (Schneider et al., 2008). Some of these might have been mediated by increased basal level of corticosterone (Schneider et al., 2008). The neuroimmune network is involved in the adaptation to stressful stimuli and an inadequate response to environmental stressors has been linked to its dysfunction (reviewed in (Merlot et al., 2008; Petrovsky, 2001). Previous studies have shown that prenatal exposure to VPA on day 8 of gestation leads to lesions in thymus (Gossrau & Graf, 1989), even though colonization of the thymus by pluripotent stem cells occurs in rat around day 13 of gestation (Dietert et al., 2000), which is a typical exposure time in VPA models. Described changes were transient, but in VPA rats thymus atrophy was persistent even in adult rats, which might suggest a potential role of increased susceptibility to stress and of increased level of corticosterone observed in VPA male rats, as corticosteroids are known to cause thymic atrophy (Gorski et al., 1988). There is also mounting evidence that stress may induce a shift in the type 1/type 2 cytokine balance toward a type 2 cytokine response (Agarwal & Marshall, Jr., 1998; Elenkov & Chrousos, 1999), which is consistent with decreased IFN-γ/IL-10 ratio observed in VPA rats. The ratio of IFN-γ to IL-10 in culture supernatants is of critical importance in determining their pro- or anti-inflammatory capacity, i.e., either activation (IFN-γ) or inhibition (IL-10) of monocytic and lymphocytic function (Katsikis et al., 1995). Similar imbalance in Th1/Th2 response has been reported in autism (e.g., Gupta et al., 1998). Thus, the mechanism of the immunomodulatory effect of prenatal VPA exposure may be related to its indirect impact exerted through activation of autonomic nervous system and/or the hypothalamic–pituitary–adrenal axis.

3.4.2.4.5 Cellular level similarities to autism

On the cellular level VPA induced overexpression of NR2A and NR2B subunits of NMDA receptors and kinase calcium/calmodulin-dependent protein kinase I (CAMKI1), which is a

key signalling enzyme associated with NMDA receptor-mediated synaptic plasticity (Rinaldi et al., 2007). In contrast, AMPA receptor subunits GluR1, GluR2, and GluR3 and the obligatory subunit of the NMDA receptor, NR1, extracellular signal-regulated kinase (ERK) and cAMP response element binding protein (CREB), some phosphorylated forms of signaling proteins (pCREB-S133, pCaMKII-T286/287, GluR1-S831, pGluR1-S845, pNR1-S896, pNR1-S897, pNR2B-S1303), as well as the main metabotropic glutamate receptor subunits (mGluR1, mGluR5, mGluR4, mGluR6/7) and the kainite receptor subunits (GluR6/7), were not affected in the VPA-treated neocortex. This indicated a highly selective abnormality within the glutamatergic system in VPA-induced model of autism (Rinaldi et al., 2007).

Reactivity of microcircuits in VPA rats' somatosensory cortex, prefrontal cortex, and amygdala measured by a multi-electrode array (MEA) stimulator showed dramatic increase (x2) in reactivity to electrical stimulation and boosted synaptic plasticity as well as a deficit in inhibition in amygdala (Markram et al., 2008b; Rinaldi et al., 2007; Rinaldi et al., 2008a; Rinaldi et al., 2008b; Silva et al., 2009). Taking into account that paired recordings of excitatory AMPA-mediated synaptic responses were weaker in the VPA rats and the numbers of synapses per synaptic connection smaller, it was suggested that an excessive recurrent circuitry may play a crucial role in the observed hyperreactivity to electrical stimulation in brain microcircuits. Further, synaptic plasticity experiments between pairs of pyramidal neurons revealed increased postsynaptic long-term potentiation in the VPA treated slices (Rinaldi et al., 2007), which suggested hyperplasticity of glutamatergic synapses. At the same time, the pyramidal neurons required much more current to drive their voltage to spiking threshold and the number of spikes generated for a series of current stimuli was much lower than in control slices. There were no differences in the passive conductance. This hypo-excitability of pyramidal neurons may be an attempt to counter the hyper-reactivity as a compensatory mechanism (Rinaldi et al., 2007; Rinaldi et al., 2008b). Morphological examination of 3D reconstructions of pyramidal neurons did not show any significant differences between VPA-treated tissue and control. Hyper-reactivity of the neocortical microcircuitry is therefore not caused by larger or more elaborate neurons, more excitable neurons, an increase in neuron numbers, stronger synaptic connections, or by a loss of inhibition. Indeed, changes in these parameters seem to act in the opposite direction, perhaps part of a compensatory strategy (Rinaldi et al., 2007; Rinaldi et al., 2008a; Rinaldi et al., 2008b). The described hyper-connectivity was found only in neurons forming the typical dimensions of a neocortical minicolumn (~50μm somatic distance), but not for pairs of pyramidal neurons (100–200μm apart). The minicolumn is thought to be the smallest computational circuit in the brain (Lucke & Malsburg C., 2004). It consists of a core line of vertically ascending pyramidal and inhibitory neurons, their connections and input/output axons. Hyper-connectivity in microcircuits can lead to exaggerated recruitment of neurons when presented with a stimulus and could account for the hyper-reactivity found in these local circuits after VPA treatment. An important aspect of hyper-connectivity induced by VPA exposure is that pyramidal neurons target more neurons even at the expense of using less synapses per connection. Thus, the form of hyper-connectivity observed in this model can be seen as a hypertrophy of connectivity between neurons. Local hyperconnectivity may render cortical modules more sensitive to stimulation and once activated, more autonomous and more difficult to command (Rinaldi et al., 2007; Rinaldi et al., 2008b). Studies on minicolumnar arrangements in the frontal and temporal lobes showed altered neuronal anatomy and circuitry in autism with minicolumns abnormally narrow, both in the column

core and the neurophil containing inhibitory interneurons (Casanova et al., 2002). This suggests that the autistic brain may exhibits an increased number of minicolumns, i.e., more processing units, and more excitable/less inhibit microcircuitry.

3.4.2.4.6 Gender dimorphism in VPA model

Most of behavioural and immunological aberrations induced by prenatal exposure to VPA were observed in male but not female rats (Schneider et al., 2008). It is unclear how gender *in utero* can affect VPA-induced behavioural, endocrine, and immunological effects. Observed gender differences in functional outcome of prenatal exposure to VPA cannot be explained by differences in direct VPA effect on foetuses as morphological studies in VPA rats have not reported any differences between males and females in a kind of or extension of brain injuries induced by VPA (Ingram et al., 2000; Rodier et al., 1996; Rodier et al., 1997b). Gender differences in the model cannot be either explained by VPA influence on estrogenic receptors, which has recently been shown in vitro (Fortunati et al., 2008; Reid et al., 2005), as estrogen receptor system of the rat brain is not detected before day 16 of gestation (Miranda et al., 1994; Miranda & Toran-Allerand, 1992). Thus, attenuation of behavioural and immunological alterations observed in female VPA rats is probably not related to differences in direct teratogenic action of VPA. We would rather suggest that protective effects of estrogen and progesterone and sex-related differences in neurotransmitters systems development and/or functioning during consecutive developmental stages may play the crucial role in the observed attenuation of the VPA-induced aberrations in female rats. Estrogen and progesterone might reduce the consequences of brain injuries by enhancing anti-oxidant mechanisms, decreasing excitotoxicity (altering glutamate receptor activity, reducing immune inflammation, providing neurotrophic support, stimulating axonal remyelinization), and enhancing synaptogenesis and dendritic arborization (Roof & Hall, 2000a; Roof & Hall, 2000b; Stein, 2001). Importantly, it has been recently suggested that sex hormone action may be mediated via gene-specific epigenetic modifications of DNA and histones (Kaminsky et al., 2006). Hormone-induced DNA methylation and histone modifications at specific gene regulatory regions may modify the risk of a disease and lead to disproportion in male to female ratio in autism as well as to sex-specific phenotypes in VPA rats.

3.4.2.4.7 Beneficial effects of environmental enrichment in VPA rats

The availability of a valid animal model of autism opened the door to rigorous evaluation of the effects of environmental manipulations on the behavioural expression of neuropathological deficits in VPA exposed animals. Our own experiments have shown that environmental enrichment reverses almost all autistic-like behavioural aberrations observed in VPA rats (Schneider et al., 2006). VPA rats subjected to environmental enrichment compared to a VPA non-enriched group exhibited higher sensitivity to pain and lower sensitivity to nonpainful stimuli; stronger acoustic prepulse inhibition; lower locomotor, repetitive/stereotypic-like activity, and enhanced exploratory activity; decreased anxiety; increased number of social behaviours, and shorter latency to social explorations, and when compared to control non-enriched animals, increased number of pinnings in adolescence and social explorations in adulthood, and more numerous entries to open arms and longer time spent in the open arms of the elevated plus-maze, which suggest decreased anxiety. Mechanisms of this remarkable behavioural improvement are unknown. However, converging lines of evidence suggest that environmental enrichment in rodents leads to better performance in various learning tasks (Bruel-Jungerman et al., 2005; Rampon et al.,

2000), enhanced social play behaviour (Morley-Fletcher et al., 2003; Schneider et al., 2006), and lower anxiety (Gortz et al., 2008; Sztainberg et al., 2010). Improvements in behavioural performances were accompanied by changes in various neurochemical and anatomical features in rodent brains, e.g., increased dendritic spine density and branching in the cerebral cortex (Diamond et al., 1972; Greer et al., 1981), hippocampus (Bruel-Jungerman et al., 2005; Rampon et al., 2000), striatum (Turner et al., 2003), and cerebellum (Angelucci et al., 2009); reduced apoptosis (Young et al., 1999), and enhanced neurogenesis (Levi & Michaelson, 2007). Enrichment also causes a significant change in the expression of genes whose products are involved in neuronal structure, plasticity, and neurotransmission (Rampon et al., 2000). Finally, environmental enrichment reverses behavioural, cognitive and molecular aberrations resulting from prenatal or early postnatal factors such as maternal separation (Bredy et al., 2003) or developmental Pb^{2+} exposure (Guilarte et al., 2003), and has been shown to attenuate behavioural and morphological phenotype in mouse genetic models of Rett Syndrome (Lonetti et al., 2010) and the fragile X syndrome (Restivo et al., 2005), both commonly associated with autism.

4. Conclusions

The advantage of animal models of autism is to study developmental and behavioural deficits in context of a whole organism. We can use such models to clarify complex relationships between genetic, behavioural and environmental variables to better understand and potentially cure autism. Rodent models described in this chapter allow an extensive multi-omics approach to autism with a spectrum of non-invasive and invasive approaches at the genetic, molecular, cellular, synaptic, and behavioural levels, which has greatly extended our knowledge about autism and mechanism underlying both autistic-like and normal behaviours in animals and humans. What we need now is to combine these different approaches into multidisciplinary studies determining the consequences of environmental factors (e.g., stress, teratogenic substances, enriched environment) on the development of autistic-like behavioural changes in genetically modified animals, and vice versa, to determine the genetic basis of negative and positive effects of environmental factors in animal models. Among currently used animal models of autism described in this chapter, the one induced by prenatal exposure to valproic acid seems to fulfil criteria for construct, face and predictive validity and may be used to further elucidate the neurobiological mechanisms underlying the functional effects of genetic and environmental factors relevant to autism. This model could become a common experimental platform to validate new pharmacological and behavioural interventions with potential relevance to autism.

4.1 Hypothesis based on VPA model and their implications for autism

4.1.1 Environmental enrichment

Of the vast number of animal studies that yield results of interest to human research, studies on the impact of an enriched environment on brain development and behaviour can be of enormous interest. What we need now is the development of a sound theory of the effects of specific environmental experiences on neurobehavioural development and a rationale for the external and internal mechanisms that mediate these effects. Studies on the influence of an enriched environment are one of the major attempts to understand the interaction between the environment and the genome in the regulation of the phenotype. At the very least, study of the beneficial effects of environmental enrichment in the VPA model indicates

that there are many opportunities for enhancing brain activity and behaviour, and that they can have pronounced therapeutic effects on behavioural alteration in the animal model of autism induced by prenatal exposure to VPA (Schneider et al., 2006). This leads us to a consideration of the relevance of this model to brain damage rehabilitation and behavioural-cognitive therapy attenuation of autistic features in humans. Having such a model we can start asking questions about genetic/epigenetic, molecular, biochemical and structural changes in the brain induced by environmental enrichment and how these changes can be related and used to improve therapeutic interventions in autism. For example, we can assume that the combination of enriched experience with pharmacological treatments may further strengthen these beneficial effects and improve their therapeutic effectiveness, and this can be tested first in VPA model. Thus, what we need now is both to identify the key external factors and understand the internal mechanisms that mediate the beneficial effects of environmental enrichment on neurobehavioural development of VPA rodents and to use this knowledge to help people suffering from autism.

4.1.2 Gender dimorphism

Gender dimorphism is another interesting phenomenon observed both in the VPA model and autism. Studies based on both clinical and epidemiological samples find a higher incidence of autism in boys than in girls, with reported ratios averaging around 4 to 1 (Fombonne, 2003; Newschaffer et al., 2007; Volkmar et al., 1993). The reason for this gender discrepancy is unknown. Accordingly, most of behavioural and immunological aberrations induced by prenatal exposure to VPA were observed in males but not females (Schneider et al., 2008). Gender differences in functional outcome of prenatal exposure to VPA cannot be explained by differences in direct VPA effect on foetuses as morphological studies in VPA rats have not reported any differences between males and females in the extend of brain injuries induced by VPA (Ingram et al., 2000; Rodier et al., 1996; Rodier et al., 1997b). Similarly, there are no structural or functional imaging data suggesting gender differences among autistic patients. We would rather suggest that protective effects of estrogen and progesterone and sex-related differences in neurotransmitters systems development and/or functioning during consecutive developmental stages may play the crucial role in the observed attenuation of the VPA-induced aberrations in female rats and skewed sex ratio in autism. As mentioned above, estrogen and progesterone might reduce the consequences of brain injuries by enhancing anti-oxidant mechanisms, decreasing excitotoxicity (altering glutamate receptor activity, reducing immune inflammation, providing neurotrophic support, stimulating axonal remyelinization), and enhancing synaptogenesis and dendritic arborization (Roof & Hall, 2000a; Roof & Hall, 2000b; Stein, 2001). Some of these effects might be mediated by epigenetic mechanisms (Kaminsky et al., 2006) suspected to play an important role in autism. This might be a very fruitful direction for future studies in neurotherapeutics for autism.

4.1.3 Intense World Syndrome as a unifying theory of autism

Based on results obtained in the VPA-induced animal model of autism a new unifying theory has been recently proposed describing autism as an 'intense world syndrome' (Markram et al., 2007; Markram & Markram, 2010), in which hyper-reactivity and hyper-plasticity of the brains' microcircuits causes excessive neuronal information processing and storage in the brain. Such excessive information overload is proposed to produce hyper-

perception, hyper-attention, and hyper-memory, which may lead to exaggerated perception/hyper-focusing of fragments of a sensory world instead of creating holistic, multimodal representations, and can diminish an ability to shift one's attention to new stimuli due to the difficulty for top-down mechanisms to coordinate the overly autonomous microcircuits. Inability to disengage attentional capacities has been frequently reported in autism (e.g., Landry & Bryson, 2004). Hyper-plasticity may also lead to exaggerated memorization of non-related stimuli and thus to over-generalization, which has been observed in fear conditioning test in VPA rats and might be related to decreased inhibition and hyper-reactivity in VPA treated amygdala. Therefore an autistic person may perceive the world not only as overwhelmingly intense due to hyper-reactivity of primary sensory areas, but also as aversive and highly stressful due to a hyper-reactive amygdala, which due to overgeneralization can make fear associations with usually neutral stimuli. The autistic person may well try to cope with the intense and aversive world by withdrawal. Thus, impaired social interactions in autism might be the result of an intense, overwhelming, and fragmented perception, which escapes any holistic interpretation. This theory is consistent with high anxiety levels as well as the hypertrophy of the amygdala in autism (Gillott et al., 2001; Sparks et al., 2002). Increased anxiety and phobias are common in autistic patients (Evans et al., 2005; Gillott et al., 2001) and their relatives (Micali et al., 2004), and frequency of autistic-like symptoms is highly increased in children with mood and anxiety disorders (Towbin et al., 2005). In line with this hypothesis, decreased amygdala activation has been linked to genetic hyper-sociability in Williams syndrome (Martens et al., 2009; Meyer-Lindenberg et al., 2005), whereas increased activation is observed in social phobia (Stein et al., 2002; Stein et al., 2007). Moreover, autistic children exhibit increased autonomic responses, indicative of enhanced amygdala activity (Corbett et al., 2006; Hirstein et al., 2001; Tordjman et al., 1997), and increased corticosterone blood level was observed in VPA rats (Schneider et al., 2008). Although this is still a preliminary proposal and needs further clarification it is well based on both human and animal data described in this chapter and may be used as an alternative unifying theory for previous theoretical proposals such as the 'weak central coherence theory of autism' (Happe & Frith, 2006), the 'executive function theory of autism' (Hughes et al., 1994; Russell & Hill, 2001) or the "theory of mind" conception of autism (Baron-Cohen, 1991; Frith & Happe, 1994). In fact, if this is hyper-reactivity that makes autistic individuals withdrawn from the world, a completely new approach to pharmacological intervention in autism should be considered. For example, while most of the commonly prescribed medications try to increase neuronal and cognitive functioning in autism, the autistic brain might rather need to be 'calmed down' and cognitive functions diminished in order to re-instate balance and functionality.

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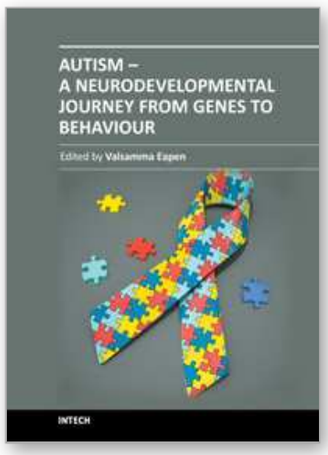

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The book covers some of the key research developments in autism and brings together the current state of evidence on the neurobiologic understanding of this intriguing disorder. The pathogenetic mechanisms are explored by contributors from diverse perspectives including genetics, neuroimaging, neuroanatomy, neurophysiology, neurochemistry, neuroimmunology, neuroendocrinology, functional organization of the brain and clinical applications from the role of diet to vaccines. It is hoped that understanding these interconnected neurobiological systems, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems, would no doubt assist in developing interventions that accommodate the way the brains of individuals with autism function. In keeping with the multimodal and diverse origins of the disorder, a wide range of topics is covered and these include genetic underpinnings and environmental modulation leading to epigenetic changes in the aetiology; neural substrates, potential biomarkers and endophenotypes that underlie clinical characteristics; as well as neurochemical pathways and pathophysiological mechanisms that pave the way for therapeutic interventions.

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