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Review

Current knowledge, challenges, new perspectives of the study, and treatments of Autism Spectrum Disorder

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ABSTRACT

Over the past 70 years, the understanding of Autism Spectrum Disorder (ASD) improved greatly and is characterized as a heterogeneous neuropsychiatric syndrome. ASD is characterized by difficulties in social communication, restricted and repetitive behavior, interests, or activities. And it is often described as a combination of genetic predisposition and environmental factors. There are many treatments and approaches to ASD, including pharmacological therapies with antipsychotics, antidepressants, mood regulators, stimulants, and behavioral ones. However, no treatment is capable of reverting ASD. This review provides an overview of animal models of autism. We summarized genetic and environmental models and then valproic acid treatment as a useful model for ASD. As well as the main therapies and approaches used in the treatment, relating them to the neurochemical pathways altered in ASD, emphasizing the pharmacological potential of peptides and bioinspired compounds found in animal venoms as a possible future treatment for ASD.

1. Introduction

The understanding of Autism Spectrum Disorder (ASD) improved greatly over the past 70 years, is now characterized as a heterogeneous neuropsychiatric syndrome, and defined as a neurodevelopmental disorder [1]. According to the Statistical Manual of Mental Disorders (DSM-V) DSM-5, ASD is characterized by difficulties in social communication and interaction, restricted and repetitive behavior, interests, or activities. ASD individuals may also present impairments in language development, self-injurious, hyperexcitability, and motor abnormalities [2]. Along with these symptoms, ASD individuals often exhibit a lack of concentration, hyperactivity, anxiety, sleep disturbances, and unusual reactivity to sensory stimuli. ASD is estimated to affect 1 in 150 children globally, the prevalence being 5 per 10.000 children to 1:59 children (one in 37 boys and one in 151 girls) [3]. Besides, the prevalence in men is nearly three times higher than in women [4] and is more common to affect white children when compared to African American or Hispanic children [2].

The etiology of ASD is often described as a combination of genetic predisposition and environmental factors. The contribution of genetic components in the ASD etiology includes genes that are involved in intellectual disability and neuropsychiatric disorder, as well as common pathway genes, ASD-risk genes, DNA mutations, environmental effects on gene expression, and protein function [5]. Some rare genetic risk factors are estimated to contribute up to 20 % to ASD. It is surmised that 400–1000 genes might lead to a susceptibility to autism, although the genetic etiology for ASD remains mostly unknown [5]. Studies have identified various risk factors for ASD. Perinatal and neonatal environmental risk variants have been associated with autism-related symptoms, such as exposure to chemicals in pregnancy (i.e., valproic acid, thalidomide, misoprostol, alcohol, cocaine, and toxic metals), infections (i.e., rubella), maternal and fetal inflammation, and diseases (i.e.

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diabetes mellitus) [6]. Vulnerable physiology, in the postnatal period, has been suggested to make individuals susceptible to environmental influences, such as organic pollutants, that may be associated with autism-related symptoms [7].

The ASD characteristics also have other causes, such as cerebral development started in prenatal phase and continued in postnatal phase, this fact explains the VPA exposition model, since it affects the white matter region, responsible for the neurodevelopmental disorder caused by the glial cells physiology. The number of glial cells increase in the postnatal phase, like astrocytes that have growth after birth. Oligodendrocytes appear at the end of pregnancy, and together with the astrocyte, are produced in the postnatal period in the subventricular zone. When migration occurs, the differentiation between gray and white matter happens (for review see Stouffer et al. [116]).

The prevalence rates of ASD have increased globally over time. In the United States alone, it is estimated that ASD affects more than 3 million individuals, having a prevalence of 1 in 54 children nowadays, much higher than it was decades ago, and being the fastest-growing developmental disability in the U.S. [39].

Along with the increasing incidence of ASD, the cost of care is expected to consistently grow over the next decade. Currently, autism costs the U.S. over $268 billion per year (CDC, 2020), it is estimated that the mean annual cost for an individual with ASD varies from $50520 to $107863, depending on age and whether the patient presents intellectual disability or not. Moreover, the cost of ASD to society is potentially likely to increase further over time [118].

Furthermore, despite the high costs of health care for the patients, a cure for ASD remains unknown, with treatments focusing mainly on the symptoms of the disorder. Therefore, it must be regarded as a priority that strategies be made to prevent ASD occurrence, as well as promoting a thorough investigation on it is pathogenic mechanisms.

This review aims to provide an overview of animal models of autism, especially the induction with valproic acid (VPA). We first summarize the types of animal models of ASD, like genetic and environmental models, and then VPA exposed rodents as a useful animal model for investigating mechanisms linked to ASD. There are many treatments and approaches to ASD, including pharmacological therapies with antipsychotics, antidepressants, mood regulators, stimulants, and behavioral ones, yet no treatment is capable of reverting ASD. Thus, it is necessary to develop new pharmacological treatments for these symptoms and for improving the quality of life of ASD individuals. Moreover, the main therapies and approaches used in the treatment of ASD, emphasizing the pharmacological potential of peptides and bioinspired compounds found in animal venoms as a possible future treatment for ASD.

Many laboratories have investigated the mechanisms involved in the development of ASD, as is important to understand the neurobiology of underlying ASD behavior. Also, researchers observed neurochemical alterations in autism etiology. In a recent review, Marotta et al. [3] highlighted the main research findings of the neurochemical alterations in autism etiology. Many neurotransmitters and neuropeptides play a role in autistic brain neurochemistry: gamma-aminobutyric acid (GABA), glutamate, serotonin, dopamine, endogenous opioids, and others [3].

2. Animal models of ASD

One of the main problems with animal models is how to validate them. Research using animal models is based on the principle that animals and humans share neurobiological mechanisms associated with complex behavior, however, biological substrates as well as metabolic pathways may be different in animals and humans. A gene that is structurally similar at the DNA levels, or at the RNA organizational level, or has similar functionality in two species, may result in two different phenotypes in these same species [8]. A pertinent limitation is the lack of specificity of the behaviors studied when it comes to a particular mental disorder, therefore, an elaborate model of ASD should induce social and communication impairments, as well as stereotyped behaviors that permeate the disorder [1].

It is worth noting that one of the main interests of animal models is not to validate a specific model for autism, but to study and obtain tools about the neurobiological mechanisms possibly involved in ASD through a multidimensional approach [9]. The association tested in an animal model between a behavioral trait and a biological mechanism is questionable because the same abnormal behavior, such as stereotyped behaviors in rodents, can be produced by different biological mechanisms [8]. Therefore, it is suggested that animal models for studying ASD use a multidimensional approach that accounts for the combination of behavioral, neuropathological, biochemical, and genetic mechanisms of the disorder. The more features that are contemplated in a model, the closer the model will be to reflecting ASD in humans [8,9]. Thus, animal models are of great value because they aid clarifying complex mechanisms (even if simplified) involved in neuropathological disorders. They also help to understand the relationship between biological and behavioral variables, and how both act upon environmental factors.

The main hypothesis in the etiology of ASD suggests the influence of environmental factors in neural tube closure (NTD). During embryonic development, two phenomena must occur without errors or flaws: (a) genetic instructions for morphogenesis and (b) the ability of tissues to complete the general metabolic process, which requires cells to survive and replicate [10]. The embryonic neural tube is particularly sensitive to teratogenic stimuli that result in the non-closure of this structure, causing functional deficits in the offspring. It has been reported that prenatal exposure to VPA causes disturbances in gene expression associated with ectopic cell migration in the offspring of epileptic mothers and, as it is a highly teratogenic substance, defects in NTD closure [10,117]. The central nervous system (CNS) is susceptible to be affected by failures in neural tube closure when compared to other systems, which can result in developmental abnormalities, including autism. The spatial and temporal separation of extracellular signals is finely regulated during embryonic development [11–13]. Therefore, delayed migration can be deleterious due to exposure to the wrong environment causing delays in maturation, maladaptive compensatory and hyperexcitability [116].

Different factors may be involved in the etiology of ASD, including oxidative stress, neuroinflammation, mitochondrial, and biochemical disorders. Factors leading to maternal immune activation (MIA) such as viral infections, cytomegalovirus, rubella, or bacterial infections may cross the placenta and interfere with fetal development, and evidence suggests that prenatal factors are a risk for autism [6,14]. Although animal models are essential for the development of new therapies, establishing models that (Table 1).

VPA is a teratogen, as are several of the antiepileptic drugs. It was already observed that prenatal exposure to VPA is related to higher rates of a range of major congenital malformations, such as neural tube, cardiac, craniofacial, and limb malformations in humans [39,40,41]. A recent review demonstrated that in comparison with other antiepileptic drugs used in the prenatal period, the prevalence of major congenital malformations is attributed to the use of VPA, ranging from 6.7 to 10.3% [42]. Moreover, neurodevelopmental problems were reported to be associated with *in utero* exposure to VPA, such as reduced cognitive function, learning difficulties, and attention deficit disorder [43].

An embryopathy denominated fetal valproate syndrome was first related by DiLiberti et al. [44], and consists of a specific craniofacial phenotype associated with prenatal exposure to VPA. Neural tube defects, including spina bifida aperta and anencephaly/exencephaly, were also observed [43]. It was related that children diagnosed with this syndrome presented typical social deficits consistent with ASD [45], a finding that was supported by larger studies [46,47].

In a population-based study that analyzed a total of 56 children exposed to VPA were observed an 8.9 % prevalence of ASD, demonstrating that VPA was the antiepileptic drug most associated with ASD [47]. Moreover, another study showed that *in utero* exposure to VPA

Table 1
A Summary of Behavioral Deficits, Cellular and Molecular Alterations in models of autism spectrum disorder.

Animal model	Model mechanism	Dose administration	Outcome	Reference
C. elegans	genetic mechanisms	ND	hyporeversal phenotype, a ↓in changing directions towards backward movement ↑ sensitivity to oxidative stress and some heavy metals, ↓ lifespan underlie mechanosensory hyperresponsivity impaired habituation learning changes in the defecation cycle, mechanosensory response, exploration capacity, rate of movement and response to an osmotic shock sensitivity to an acetylcholinesterase inhibitor, cholinergic agonist and a GABA antagonist	Schmeisser and Parker [15]
Zebrafish	Cas9- induced microdeletions	ND	↑ aggressive behavioral ↓ shoal formation, social interaction ↑ repetitive behaviors, stereotypic mouth opening and more specific locomotor changes and patterns ↓ social preference and olfactory, auditory and lateral line	Meshalkina and Kaluef [71]
Mouse	GSTMI Nrf2 knockout mouse VPA postnatal exposure; PND14	400 mg/kg VPA; single s.c. injection	↑ hippocampal and cerebellar apoptosis alterations in serotonin secretion deficits in social behavior ↑ apoptosis in granule cells of the hippocampus and deficits in learning and memory in the Morris water maze, ↓activity in the open field and less success on the rotarod	Ming et al. [16]; Williams et al. [17] Furnari et al. [18] Yochum et al. [19]
Mouse	*FMR1* knockout mouse *(*fragile X-syndrome)	ND	impairments in multiple socio-emotional responses, hyperactivity, obsessive-repetitive behaviors, susceptibility to seizures impaired novel object recognition and abnormal social behavior hypoactive in the open field, impaired in rotarod performance	Bhattacharya et al [20]
Mouse	*MECP2* knockout mouse *(*Rett syndrome)	ND	neurodevelopment similar to ASD individuals autism-like behavior	Samaco et al [21]
Mouse	C58/J or Grin1 knockout mouse (oxytocin deficiency)	ND	impaired maternal behavior and social memory ↑ locomotion ↑ aggression, ↓ cognitive flexibility ↓ sexual behavior, social interactions, ultrasonic vocalization towards females ↑ self-grooming and anxiety ↑ repetitive behaviors	Teng et al [22]; Teng et al [23]; Lee et al. [24]; Zhang et al [25]; Wagner and Harony-Nicolas [26]
Mouse	BTBR T + tf/J (BTBR) mouse	ND	impaired interaction and social communication dysfunction of the immune system stereotyped movements indifference to sweets several changes in genes related to brain functions, BDNF in the hippocampus and cerebral cortex, changes in several synaptic proteins changes in DNA methylation in the cerebellum	Meyza and Blanchard [27]
Mouse	VPA postnatal exposure; PND14	400 mg/kg VPA; s.c. injection	↓ social interactions (anogenital sniffs, allogrooming, crawl under/over behaviors) ↓ motor activity in a social context ↑ aggression, ↓ avoidance and impaired reversal learning, ↓ dendritic spine density, dendritic spine morphological and abnormalities in the medial prefrontal cortex no differences in motor activity in non-social settings	Yochum et al. [28]; Norton et al. [29]
Mouse	Activation of MIA in pregnant with increased levels (*in útero)* of IL-17A in offspring; E11-E14.5	ND	↑ cell death in the external granule cell layer of the cerebellum and in the dentate gyrus of the hippocampus ↑ behavioral abnormalities social interaction deficits in adult offspring ↑ repetitive and perseverative behaviors MIA induces abnormal USV in offspring spatially restricted deficit in Purkinje cells	Ornoy et al [6]; Choi et al [14]
Mouse	Influenza virus i.n. mice	ND	series of behavioral abnormalities deficits in social interaction alteration in transcription in the brains	Patterson [30]
Rats	Administration of immunogens during pregnancy - LPS or Poly IC leads to activate MIA; E11-12	2 i.p. 75 mg/kg LPS 20 mg/kg i.p. Poly IC	↓ level of serotonin in the cerebellum sociability deficits ↓ motor activity LPS and Poly-IC treated - repetitive behavior	Carpentier et al [31]; Ohkawara et al [32]; Xuan et al (2014)

(*continued on next page*)

Table 1 (*continued*)

Animal model	Model mechanism	Dose administration	Outcome	Reference
Rats	Infection with Borna disease virus	newborn rats inoculated with 20 μL of infected brain homogenate (BDV) i.c.	↑ stereotyped repetitive behavior and anxiety ↓ playful activities and exploratory activity ↑ stereotyped behavior ↓ time in active social interaction and ↑ time in following their partners ↓ aggression towards the intruders	Lancaster et al [33]
		200 mg/kg VPA; single s.c injection	changes in emotional and cognitive domains deficits in attention, cognitive and motor geotaxis and water maze performance regression of acquired skills (mid-air righting) self-injurious behavior developmental retardation ↓ social interaction	
Rats	VPA prenatal exposure; E12-17	600 mg/kg VPA, single i.p. injection	↓ sensitivity to pain involving both spinal (tail flick) and supraspinal (paw withdrawal) levels ↑sensitivity to nonpainful stimuli diminished acoustic prepulse inhibition locomotor and repetitive, stereotypic-like hyperactivity combined with lower exploratory activity ↓number of social behaviors and ↑ latency to social behaviors.	Wagner et al. [115]; Schneider and Przewlocki [34]; Schneider et al. [35]; Markram et al. [36]
Rat and mouse	Activation of MIA in pregnant rodents	ND	changes in cytokine expression in the fetal brain morphological changes were described, mostly in the hippocampus and cerebral cortex. behavioral and neuroanatomical deficits	Boksa [114]
	VPA prenatal exposure; E12-17	400 mg/kg VPA, single i.p. injection	↑repetitive behaviors and anxiety social behavior deficits, deficits in communication	Rodier et al. [37]; Roullet et al. [38]

VPA = valproic acid; E = embryonic day, PND = postnatal day, i.p. = intraperitoneal; s.c. = subcutaneous; i.c. = intracranially; i.n. = intranasal, USV = ultrasonic vocalization, BDV = Borna Virus Disease, Cas9 = protein that cleave DNA target, chd8 = zebrafish ortholog gene to *CDH8* (human gene associated with ASD, Chromodomain helicase DNA-binding protein 8), ND = not dosed. (↑) = increase situations; (↓) = decrease situations.

monotherapy resulted in a seven times higher incidence of ASD or ASD-like features, when comparing children exposed to VPA and the control group [46]. In a review, Ecker et al. [48] related the insights into macroscopic and microscopic neuroanatomy and structural connectivity in ASD brain using neuroimaging and neuropathological studies. Neuroimaging studies suggest that ASD patients present atypical brain

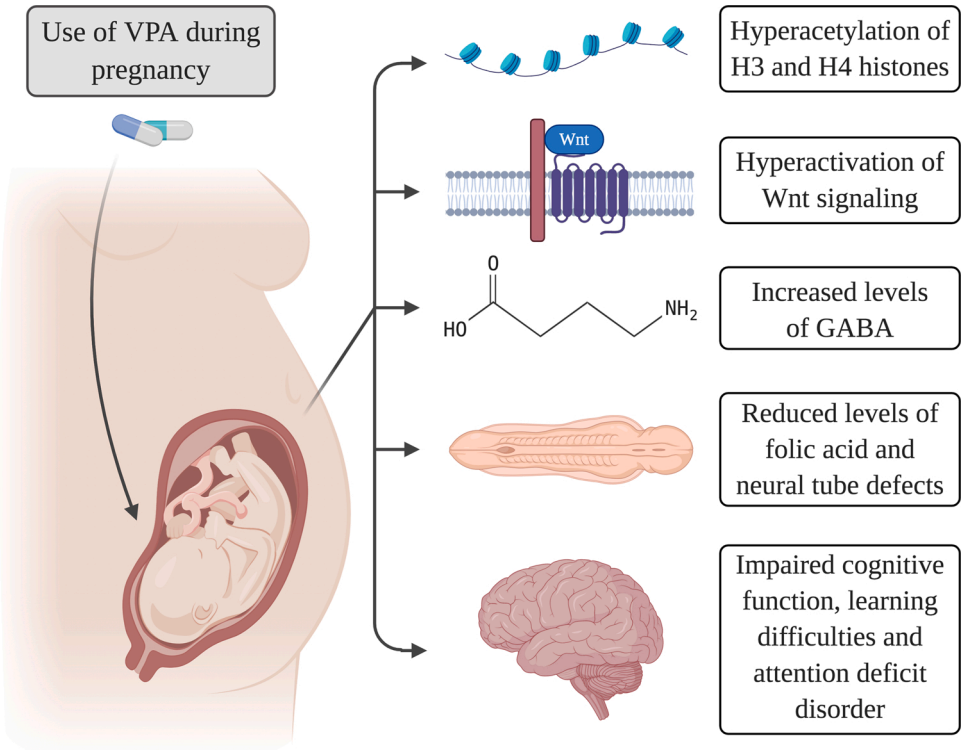

Fig. 1. Possible teratogenicity mechanisms of valproic acid during gestation. The use of antiepileptic drug VPA during pregnancy can cause deficits consistent with Autism Spectrum Disorder. Abbreviations used in the figures: VPA, valproic acid. The figure was created using BioRender (www.biorender.com).

anatomy development and connectivity. On the other side, little is known about cellular and molecular mechanisms that mediate the brain development in ASD. Besides that, it has been suggested that impaired neuronal migration, synaptogenesis and pruning and myelination are also involved with ASD in humans (for review, see [48]).

Although it is known that prenatal exposure to VPA can cause autism-like behaviors, the mechanisms by which this happens are not entirely elucidated (See Fig. 1). However, this effect could be associated with elevated levels of acetylated H3 and H4 histones, hyperactivation of the Wnt signal pathway, increased concentrations of GABA, neural tube defects, and reduced levels of folic acid [49–51]. In light of that, the use of VPA for autism induction in animal models shows relevance for research in this disorder, given that it helps understand its pathophysiological mechanisms and it also provides a basis for the development of possible treatments.

Many studies have proposed the VPA model as a useful animal model (See Fig. 2). The exposure during the prenatal period in rodents results in behavioral and neuroanatomical deficits that include decreased social interaction, increased repetitive behaviors, and increased anxiety, similar to those observed in humans with ASD [34–38,115]. In a recent review, Nicolini and Fahnestock [50] describe the valproic acid prenatal exposure as a robust model of autism, highlighting the behavior effects in rodents, cellular and molecular abnormalities associated with autism-like behavior, and sex differences. They provide information about different conditions of VPA administration, timing, species, and strain, along with other review paper on the valproate model (for review see Roulet et al. [38]). Beyond the impairment in social skills development, deficits in attention, cognition, and motor skills were observed in rodents exposed to VPA during the embryonic period. Rodents postnatally exposed to VPA also showed behavioral deficits like those observed in human ASD [115].

Even though the mechanisms of these pathways are not entirely elucidated, there are many studies that may explain them. This effect could be associated with different pathways based on existing evidence, namely by an Excitatory-Inhibitory (E/I) imbalance, hyperserotonemia, and Histone deacetylase (HDAC) inhibition [52]. The E/I imbalance is caused by an increase in glutamatergic receptors density and a reduction in GABA receptors [53,54]. A study showed that VPA-treated rats have more than two times higher serotonin levels in the plasma, and also increased serotonin in the hippocampus, than the control group. The abnormal development of serotonergic neurons in the dorsal raphe nucleus of the fetus of VPA-treated pregnant animals, keeping these cells immature, could be one of the explanations for the increase in serotonergic concentrations in the plasma [55,56]. Studies have also shown that VPA-treated embryonic mice had an increase in acetylated histones level, causing apoptotic cell death in the neocortex. HDAC is a negative regulator of gene expression which, in vitro, has been shown to be inhibited by VPA, causing hyperacetylation of HDACs targets ([57]; Kataoka et al., 2011).

Wagner et al. [115] evaluated a new strategy to model autism in BALB/c mice exposed to VPA during the pre- and postnatal period. Their experiments demonstrated that uterus exposure to VPA resulted in developmental retardation, with a delayed appearance in the maturation of surface and mid-air righting, negative geotaxis, grip strength, motor activity, and low water maze performance in BALB/c mice. The VPA exposure during the postnatal period caused similar retardation in the maturation of negative geotaxis, water maze performance, and regression of acquired skills (mid-air righting). This evidence provides that VPA exposure in the embryonic and weaning period may be used in the context of a new strategy to models of developmental disorders, as well as autism. Additional behavioral data support the evidence of impairments in social interactions in postnatal VPA exposure. Yochum et al. [28] observed that mice injected on a postnatal day 14 of life with 400 mg/kg VPA showed fewer social interactions (including anogenital sniffs, allogrooming, and crawl under/over behaviors) and reduced motor activity in a social context., although, no differences in motor activity in non-social settings were observed between VPA and control mice. At the histopathological analysis, the VPA-exposed mouse presented enhanced cell death in the external granule cell layer of the cerebellum and the dentate gyrus of the hippocampus. This evidence supports the correlation between social deficits and histopathology after postnatal VPA exposure.

While some authors investigated the effects of postnatal VPA exposure in the juvenile period, Norton et al. [29] evaluated the behavioral and neurochemical profile in adulthood. Using the same protocol of treatment, the VPA was administered to mice during the early postnatal period. Male VPA treated presented increased aggression, decreased avoidance, and impaired reversal learning, although females did not

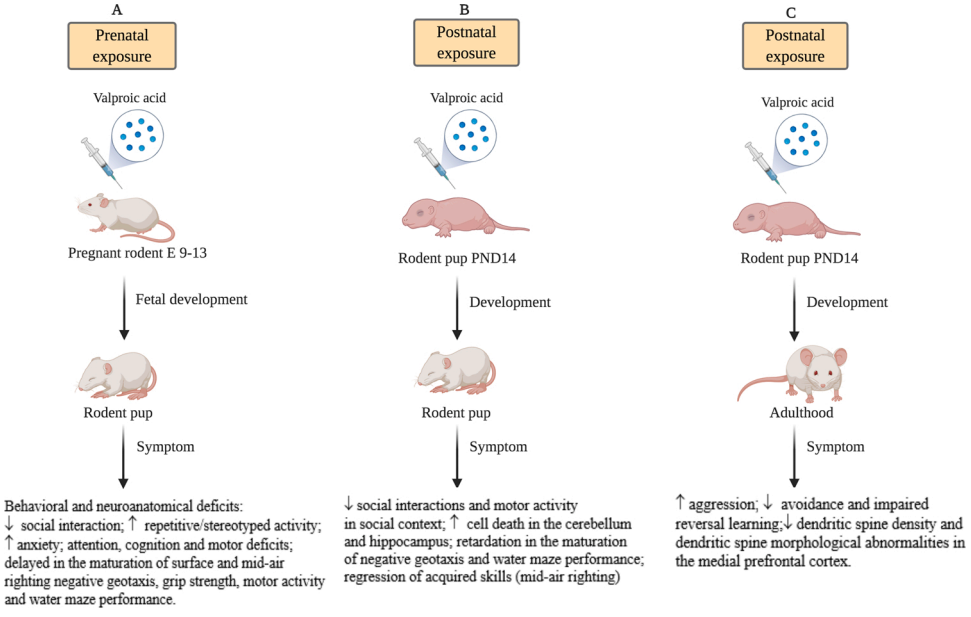

Fig. 2. Representation of valproic acid animal models of autism spectrum disorder. (a) VPA prenatal exposure model and evaluation of symptoms in pup rodent, (b) VPA postnatal exposure model and symptoms evaluation in pup rodent, and (c) VPA postnatal exposure model and evaluation of symptoms in rodent adult life. Abbreviations used in the figures: VPA, valproic acid, E, embryonic day, PND, postnatal day. The figure was created using BioRender (www.biorender.com).

exhibit these behaviors. The authors reported decreased dendritic spine density, dendritic spine morphological abnormalities in the medial prefrontal cortex and findings consistent with the behavioral changes. The author concludes these types of long-lasting deficits are common to other developmental disorders, as well as ASD, attention deficit hyperactivity disorder (ADHD), and conduct disorder.

As the etiology of autism remains unknown, imbalances in the oxidative stress system have been linked to genetic alterations in autism [16,17]. Yochum et al. [19] have shown that genetically altered mice may be particularly sensitive to VPA exposure on postnatal day 14, suggesting that autism is the result of genetic alterations interacting with exposure to environmental toxicants. Their experiments used genetically altered mice with a deletion of glutathione-S-transferase Mu 1 (gene name GSTM1), an enzyme involved in the management of toxicant-induced oxidative stress and associated with increased risk of autism [16,17]. In another study, Furnari et al. [18], using Nrf2 knockout mice exposure to valproic acid, observed behavioral deficits. Nrf2 (nuclear factor-erythroid 2 related factor 2) is a transcription factor that protects against oxidative stress. In the experiments, they observed that Nrf2 knockout mice exposure to VPA presented behavioral impairments, such as deficits in learning and memory in the Morris water maze, reduction of activity in the open field, and less success on the rotarod. These data suggest that Nrf2 mice are more sensitive to damage caused by valproic acid.

Besides the animal model of valproic acid-induced autism-like behavior, several animal models have been used to better understand the pathophysiology of ASD and to develop better therapies. These models range from the use of *Caenorhabditis elegans* to non-human primates, past zebrafish, and rodents [58].

There are several strains of genetic models of autism. In the first model, animals have been genetically manipulated to silence a gene that will induce the expression of a well-defined human disease that, in animals, will present behaviors similar to autism. For example, KO-*FMR1* mice mimic human fragile X syndrome. These animals show neurodevelopment similar to that of individuals with ASD [20]. The other form uses genetically modified mice that present mutations in the gene encoding for *MECP2* and develop typical Rett syndrome and autism-like behavior [21].

BTBR T + *tf/J* (BTBR) mice are an inbred strain used as a model of ASD. The BTBR mice present impaired interaction and social communication, dysfunction of the immune system, and stereotyped movements, all characteristics similar to ASD [27]. Additionally, epigenetic changes (methylation of regions of DNA) were observed in the cerebellum and genes related to various brain functions, such as brain-derived neurotrophic factor (BDNF) in the hippocampus, cerebral cortex, and synaptic proteins [27]. This experimental model has been widely used for research related to the treatment of ASD [59–61]. *C58/J* or KO-*Grin1* mice exhibit behavior similar to that observed in ASD patients. This model is based on studies that show that oxytocin deficiency may cause behavioral impairment [24–26]. Chronic use of oxytocin showed a significant improvement in social and repetitive behavior [22,23].

Schmeisser and Parker [15] used the nematode *C. elegans* as a model for the study of ASD, this model has great potential in understanding the genetic and neuroanatomical approach to autism, despite being an overly simplistic model Schmeisser and Parker [15]. In humans, mutations in genes such as *neuroligin* (*NLGN1*) and *neurexin* (*NRXN1*) have already been demonstrated to be associated with ASD, since they disturb development and function of synapses, thus altering cognition [62–65]. *C. elegans* has orthologous genes of *NLGN1* and *NRXN1*, which are *nlg-1* and *nrx-1*, respectively [66]. These nematodes, with mutations in *nlg-1* and *nrx-1*, presents several phenotypes related to ASD, like absence of thermal responses, deficits in touch response, osmotic avoidance and possible impairment of dopaminergic and serotonergic pathways [66–69]. Mutations in other *C. elegans* genes, such as *shn-1*, *sel-2*, *sax-7/lad-1* and *lad-2*, also enable the study of ASD in this model (for review, see Schmeisser and Parker, 2017).

In a recent study, Rawsthorne et al. [70] investigated genes related to ASD by using *C. elegans* as a model organism, aiming to identify the effect of several mutations on behaviour and social biology. To identify those orthologous genes, the researchers used SAFRI Gene database and selected genes associated with synapses, neurons, cell signaling, epigenetic modification and metabolism of phospholipids. Subjects with mutated synaptic genes such as *nlg-1(ok259)*, *nrx-1(ds1)*, *glr-1(n2461)* and *nmr-2(ok3324)*, for instance, displayed deficits in social behavior and habituation phenotypes [70]. This type of study is relevant to elucidate the genetic basis and architecture of ASD, providing essential and valuable information related to the etiological mechanisms involved with ASD in humans.

Another promising model for the study of ASD is the use of zebrafish as experimental animals, this type of model has been widely used due to its versatility in the studies of molecular and genetic pathways, as well as the investigation of toxicological interventions [71]. Morphants of the genes *syngap1b* and *shank3a*, for instance, may reduce GABAergic neurons in the midbrain and the hindbrain, a relevant phenotype to ASD-like symptoms [72]. Mutations in other zebrafish genes, such as *kctd13*, *mapk3*, *cntnap2*, *auts2* and *nbea*, are also relevant for the study of ASD in this genetic model (for review, see [71]).

Genetic-based models are widely used and advantageous because they allow the performance of molecular and neuropathological studies on brain changes caused by ASD. These established models have clinical manifestations like autism-like behaviors and have been used with great potential for the study of the etiology, pathophysiology, prevention, and therapies for ASD [43].

In addition to genetic models, there are studies using animal models of inflammation and immune systems, associated with ASD. Epidemiological studies indicate that pregnant women exposed to infections or inflammation, in periods with high activation on the immune system, were associated with high rates of ASD in children [5]. Therefore, a relationship was established between maternal immune activation (MIA) and ASD neuropsychopathology [6,43]. Among inflammatory murine models, there are two main methodologies followed: (a) the use of pro-inflammatory cytokines, such as Interleukin 17A (IL-17A), that activate MIA [6,14]; (b) administration of immunogens during pregnancy such as lipopolysaccharide-induced inflammation (LPS) [31] and polyinosinic-polycyclidyl acid (Poly IC) - a double-stranded RNA that mimics viral infection [31].

Also, researchers are compared across the broad spectrum of the disorder. A study published in The American Journal of Psychiatry [73], analyzed the DNA of 547 individuals, all children approximately 12 years old, within the spectrum. It concluded that there is a common variant of clinical symptoms even though there is a great deal of variability. This research gathered people with genetic alterations and analyzed their phenotypes and genotypes and these analyzed characteristics were Full scale intelligence quotient, verbal intelligence quotient, performance inteligennce quotient. In the social domain we observed social interaction, peer relationships, shared enjoyment, socioemotional and reciprocity, when related to the communication domain we observed gestures and imagination associated with imitation, the parameter defined as restricted, repetitive and stereotyped behavious was subdivided into unsual interests, routines and rituals, motor mannerisms and sensorimotor interests, showing the predominance in each genetic variation and showing the wide phenotype observed.

In a review of behavioral phenotypes relevant to autism symptoms in rats, some symptoms were compiled in comparison to the DSM-5 as reduced reciprocal social interactions, low sociability, lack of preference for social novelty, reduced ultrasonic vocalizations, increased repetitive self-grooming, impaired nest-building behavior, reduced social interaction in an arena and social recognition [74]. Comparing the study done in children and the animal trials, we have the expressions of the disease in a very similar way.

Several studies correlated MIA with autism-like behaviors in the

offspring [6,14]. The principle of this correlation is based on the association of maternal immune system activation and later neurogenesis. This model is one of the most advanced ever, using non-human primates to investigate experimental parallels of organization, brain behavior, and potential treatments for the disorder [75].

The use of interleukin 17A (IL-17A), a proinflammatory cytokine, during the gestation period in mice is associated with activation of the maternal immune system [14]. The activation of auxiliary T helper 17 lymphocytes (T17) and cytokines IL-17A is related to the activation maternal immune system, leading to the development of behaviors similar to ASD [14]. This T17/IL-17A complex plays a role in cortical development, inflammation, and activates MIA, boosting cognitive deficits, and autism-like behavior [6].

The administration of exogenous immunogen during gestation has been used to induce autism-like behaviors [31,32]. Xuan and Hampson [76] demonstrated that dams injected with LPS (simulate bacterial infection) or Poly IC (simulate viral infection), led the offspring to behaviors consistent with ASD in adulthood [76]. Furthermore, the results of this study exposed the differences between genders: the male is more affected, showing more stereotyped behaviors and sociability deficits than females [76].

Another inflammatory model with autism-like behavior is based on infection with Influenza virus and Borna disease virus. The influenza virus caused changes in social skills and inhibition of the pre-pulse when administered during the gestational period [30]. The neonatal rats infected with Borna disease showed a decrease in playful activities and exploratory activity. Besides that, animals showed stereotyped behavior befitting with ASD [33].

3. Current treatments

Pharmacological treatments for ASD are limited due to the heterogeneity of the disorder and the lack of real understanding of its pathology. Medical treatments are mainly used to control the secondary symptoms associated with ASD. A search made in clinicaltrials.gov for "ASD" came up with 510 trials that were completed, 202 being pharmacological interventions composed of 182 completed trials, 87 of which have public results, 17 were terminated and 3 were suspended. However, Risperidone and Aripiprazole are the only two pharmacological treatments approved by the FDA for the treatment of symptoms associated with ASD. Both antipsychotic drugs are used for treating irritability and aggressiveness. Moreover, other drugs are commonly prescribed for treating secondary symptoms, although without reliable studies to guide their usage. These treatments include antidepressants, antipsychotics, mood regulators, and stimulants [77,78].

4. Problems with drug development for ASD

Reliable studies for the development and identification of new pharmaceutical options for ASD are hard to be done. Some of the problems include the heterogeneity of the disorder, placebos presenting good responses, different ideas of what is considered typical behavior changes among cultures, and small sample sizes [78]. Moreover, effective treatments for the core symptoms including impairments in social behavior and communication are a major challenge. Siafis et al. [79] showed that 20 % of the placebo group participants presented a significant improvement in their core symptoms, such as social-communication, repetitive-restricted behavior, and sensory abnormalities in pharmacological and dietary supplements clinical trials.

These problems arise from the difficulty to measure what improvement represents, especially in the core symptoms trials. Standard models for reliably analyzing changes in social symptoms are lacking and there is a great diversity of measures in use. Most being diagnostic and screening tools, making it hard to compare results as each one has its method of analysis [79]. Trials using caregivers' evaluation have been used for measuring the improvement of ASD children. Possibly, this can modify patient behavior through placebo-by-proxy, resulting from changes in the perception of the symptoms by the caregivers. Besides, changes in the caregivers' behavior will consequently change the behavior of the children. Another problem is that most clinical trials are made focusing on treating the secondary symptoms, not the core symptoms of ASD, which are often only analyzed as secondary outcomes, thus, a standardized model for clinical trials in drug research in ASD is needed [79].

5. Antipsychotic drugs

Two antipsychotic drugs were approved by the FDA, the trials were designed to test ASD children that presented irritability problems, a secondary symptom. These drugs showed improvement in the core symptoms; however, it presented improvement only in ASD children with this secondary symptom. The modest improvements shown by these treatments may become overridden by their adverse effects [77].

Risperidone was the first drug approved by the FDA for ASD treatment, it acts blocking dopamine and serotonin receptors in the brain. Studies with ASD children showed great improvement in irritability, aggression, and hyperactivity [80], but it lacks data regarding adolescent and adult use. Though considered safe, risperidone causes various side effects including increased appetite, weight gain, nasal congestion, fatigue, dizziness, constipation, and diarrhea [81].

Aripiprazole, also an atypical antipsychotic, was the second drug approved for irritability treatment in ASD. Aripiprazole functions as a partial agonist and antagonist at dopamine (D2 receptor) and serotonin receptor (5-HT1A receptor), and as an antagonist at serotonin receptor (5-HT2A) [82]. This drug presents some improvement in irritability, hyperactivity, and mild improvements in core symptoms of ASD, such as inappropriate speech and social withdrawal. Similar to risperidone, aripiprazole has been shown to be safe. Some of the observed adverse effects were sedation, fatigue, somnolence, increased appetite, vomiting, and diarrhea [83]. Chronic treatment with Risperidone and Aripiprazole has also been shown to be effective in prenatal VPA-model animals for some core symptoms and secondary symptoms of ASD, improving social interaction deficits, recognition memory, and the reduction in prefrontal cortex dendritic spine density, corroborating with the clinical proof that these drugs are effective for the treatment of ASD in humans [84,85]. Moreover, it also suggests that the prefrontal dopaminergic system is a potential drug target for new drugs in the prenatal VPA-model of ASD [84].

Even though the treatments with dopamine antagonists are effective, other drugs have been studied. Drugs like methylphenidate and atomoxetine used for ADHD improved ASD behaviors [86]. These ADHD drugs have been proposed as a possible treatment for ASD behaviors. In a study, Hara et al. [86] used methylphenidate and atomoxetine, which increased dopamine release in the prefrontal cortex, led to changes in behavior and dendritic spine morphology in prenatal VPA model. Chronic treatment with attention deficit/hyperactivity disorder drugs improved behaviors and decreased the reduction in spine density [86].

A potential treatment for the main symptoms of the disorder is the use of Agmatine. E-I imbalance results from abnormal glutamatergic and GABAergic neurotransmission, it is a dysfunction characterized by overexcitability in ASD patients and causes various symptoms, like cognitive and social deficits, as well as seizures [87]. Agmatine is an NMDA receptor antagonist that can be used to normalize the E-I imbalance. A study with animals exposed to VPA prenatally showed that a single treatment of agmatine (50 mg/kg) and an agmatinase inhibitor (50 mg/kg), administered before animal behaviors tests, reverted the social, hyperactive, and repetitive behaviors. It also regulated the overactivation of the prefrontal cortex and the hippocampus, controlling its seizures [88].

Hyperserotonemia is the most common serotonin-related disorder found in ASD, found in about 25 % of affected children [89]. Studies with a knockout mice model for hyperserotonemia showed social

deficits and an increase in general anxiety. These effects improved with a diet of tryptophan restriction, a precursor of serotonin [90]. Therefore, modulation of serotonin levels and transporter function may potentially improve ASD symptoms in humans [91].

Alterations in the endocannabinoid system have been a possible factor in ASD pathogenesis. Recently, the endocannabinoid system has been of great interest as monotherapy or add-on treatment for the core symptoms of ASD. Studies using the prenatal VPA model have shown that it is possible to attenuate social behavior with the increase of anandamide, by inhibiting its reuptake [92]. Also, it has been shown that activation of CB1, an endocannabinoid receptor, is necessary for regulating social rewards through modulating oxytocin signaling. By inhibition of Fatty acid amide hydrolase (FAAH), an enzyme that degrades anandamide, it was possible to completely reverse the social impairment in the BTBR and the fragile X syndrome models [93]. Additionally, cannabidivarin, a phytocannabinoid, and a homolog of cannabidiol showed good results in improving the core symptoms in the prenatal VPA model. The treatment with 20 mg/kg/day i.p, during postnatal days 34–58 (symptomatic treatment) and 19–32 (preemptive treatment), in symptomatic rats, could revert and prevent most of the social symptoms in preemptive treatment, while being devoid of any adverse effects when administered in the control group [94] (See Fig. 3).

6. Peptides as novel therapeutic strategies for ASD

Peptides are short polymers that consist of amino acids linked by peptide bonds, differing from proteins in terms of length and structural conformation. These molecules can present many advantages for therapeutic uses, being more tissue penetrating and less potentially immunogenic than proteins, besides having better activity by unit mass [95]. Moreover, peptides demonstrate to be more potent, selective, and specific than other small molecules, thus being less toxic and causing fewer drug interactions [95].

Nevertheless, the use of peptides as therapeutic agents also has some disadvantages, such as proteolytic degradation, rapid clearance from blood circulation, poor metabolic stability, and low bioavailability [95]. However, many approaches aim to ameliorate the pharmacokinetics of these molecules, like amino acid substitution or replacement, alteration of peptide amino or carboxy terminus, insertion of disulfide bridges, conjugation with polymers, and utilization of nanoparticles [95].

Considering that, animal venoms are resourceful tools in the search for novel therapeutic compounds. Through millions of years, animals have gone through evolutionary pressure and their venoms have become quite advantageous for their survival since they can paralyze prey or protect themselves from predators [96]. Thus, these venoms developed into an ample arsenal of biologically active compounds, including alkaloids, biogenic amines, glycoproteins, proteins, and peptides [97].

The molecules mentioned present various effects in the CNS of mammals, given that they have high affinity and selectivity to receptors and ionic channels of neurons that constitute both excitatory and inhibitory circuits [98]. For this reason, animal venoms are useful pharmacological tools and consist of a rich source of neuroactive molecules – especially peptides – which activity may be investigated for its utilization in the treatment of many neurologic disorders [98–102]. In this review, peptides from wasp venom will be emphasized.

Demonstrating the neuropharmacological potential of these peptides, Biolchi et al. [103] analyzed the venom of the wasp *Parachartegus fraternus* and identified a novel peptide called Fraternine. This peptide improved motor coordination in a murine model of parkinsonism induced by 6-hydroxydopamine at the doses of 0.01, 0.1, 1.0, and 10 μg/animal, also demonstrating potential neuroprotective activity [103].

Besides having therapeutic potential naturally, peptides from wasp venom can also serve as starting points to the rational design of synthetic peptides, aiming to upgrade pharmacokinetics and pharmacodynamics of the compound. Neuropolybin, for instance, is a synthetic peptide bioinspired by Ppnp7, a natural peptide isolated from the venom of *Polybia paulista* [104]. The bioinspired peptide showed antiseizure

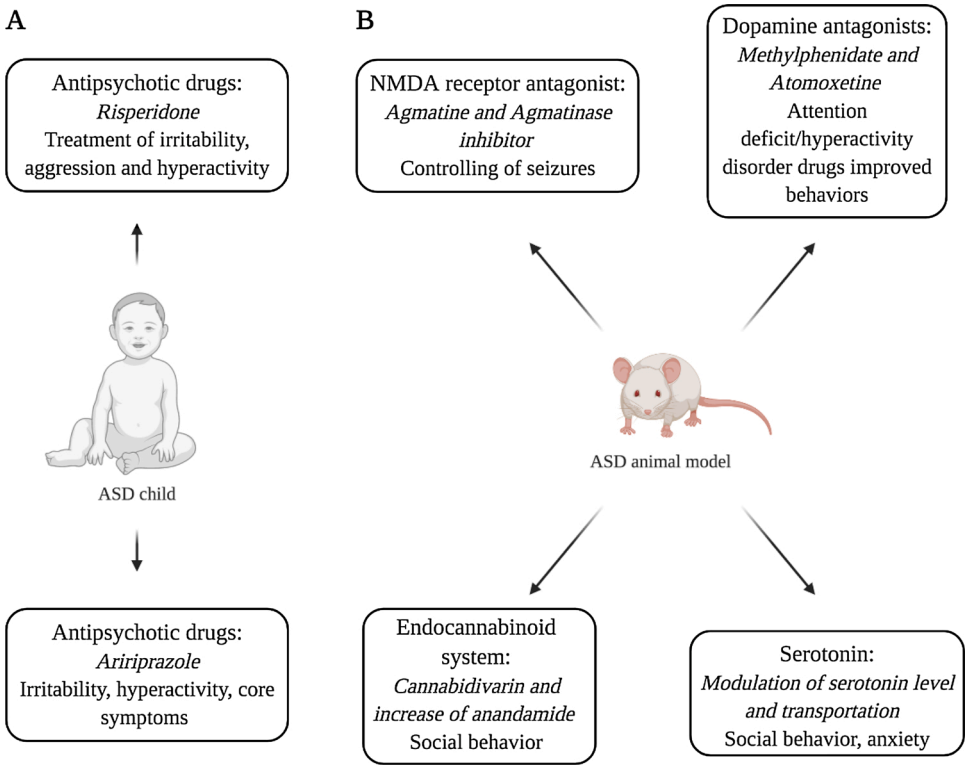

Fig. 3. (a) Drugs approved by the FDA for treatment of symptoms associated with ASD in humans, and (b) types of approaches that showed efficacy in treating core and associated symptoms in animal models of ASD. The figure was created using BioRender (www.biorender.com).

activity against PTZ-induced seizures in mice, at 1.2 and 2.5 nmol/animal, becoming a future possibility for treatment of epilepsy, with further studies [104].

Therefore, peptides derived from wasp venom have quite a lot of potential for the treatment of many illnesses – such as Parkinson's disease and epilepsy. Given that, perhaps these molecules could also be useful in the search for therapeutic options for ASD or, at least, for the symptoms of this disorder. Anxiolytic peptides or peptides that modulate GABA neurotransmission may be promising pathways to be followed in the pursuit of ASD treatments.

Anxiety is a common symptom in individuals with ASD, and wasp venom peptides with anxiolytic activity have already been reported. Polisteskinin R is one of them, being a natural peptide also isolated from the venom of *Polybia paulista* [105]. In rats submitted to the elevated plus maze test, this peptide demonstrated to attenuate anxious behaviors (1.5, 3, and 6 nmol/animal), given that the animals explored the open arms of the maze the most [105]. Moreover, another peptide – isolated from *Synoeca surinama* – also showed an anxiolytic activity at the elevated plus maze test (0.2, 2, and 6 nmol/animal), with effects comparable to Diazepam, a gold-standard drug for the treatment of pathological anxiety [106].

Another possible target is the signaling of GABA since there is a significant reduction of GABA neurotransmission in ASD. Thus, wasp venom peptides that increase GABA levels could also be investigated as therapeutic options for ASD. Pizzo et al. [107] evaluated the effects of *Agelaia vicina* crude and boiled venom on this neurotransmitter uptake. They added the radioligand [U-^{14}C]-GABA and the crude venom to a suspension of synaptosomal pellets and observed inhibition of GABA uptake in the presence of the venom Pizzo et al. [107]. The results showed a decrease of K_m and V_{max}, which indicates that there are compounds in the *Agelaia vicina* venom that inhibit GABA uptake in an uncompetitive way – thus, binding themselves reversibly to the transporter-substrate complex Pizzo et al. [107].

Given these results, the venom of *Agelaia vicina* was purified and this led to the identification of agelaiatoxin-8 (AvTx8) – a neurotoxin whose activity on nigrotectal GABA neurotransmission was investigated. For that purpose, de Oliveira et al. [108] performed microinjections of AvTx8 into the substantia nigra pars reticulata of rats, at the concentrations of 5 ng/0.2 μL, 10 ng/0.2 μL, 20 ng/0.2 μL, and 40 ng/0.2 μL. The results demonstrated that AvTx8 induced antipanic responses, by diminishing panic attack-like behaviors caused by bicuculline, a GABA antagonist which was administered in the deep layers of the superior colliculus [108].

Thereby, a more recent study aimed to elucidate the chemical structure and the mechanism of action of AvTx8, analyzing its activity on GABA uptake, release, and binding. It was found that AvTx8 is a potent inhibitor of GABA uptake, by acting in GABA transporters 1 and 3 [109]. This is the first natural peptide that demonstrated such a mechanism of action [109] and perhaps it could be investigated as a possibility for the treatment of ASD since enhancers of GABA signaling are promising pathways.

Besides wasp venom peptides, another promising therapeutic strategy consists of neuropeptides such as oxytocin – a compound that contributes to the regulation of social behaviors and is very investigated as a treatment for ASD (See Fig. 4). Dai et al. [110] found a deficiency of this peptide in VPA rats, compared to a control group. They observed that acute oxytocin intranasal treatment (1 μg/μL) improved the results in behavioral tests of VPA rats, partially reversing impaired sociability [110]. Furthermore, continuous oxytocin subcutaneous administration in neonate rats demonstrated long-term effects, treating the social impairments and repetitive behaviors evaluated in adolescence [110].

Another study found that oxytocin intranasal administration at a 200 μg/kg dose relieves autism-like behaviors in VPA mice, improving anxiety, depression, and cognition in these animals [111]. Besides, it was observed that this neuropeptide also attenuated oxidative stress and inflammation in the hippocampus and amygdala. In addition to these findings, Tanaka et al. [112] evaluated the effectiveness of oxytocin intranasal administration in rats, demonstrating that this route is quite promising for this peptide delivery to the brain in ASD treatment.

Furthermore, oxytocin intranasal treatment was also evaluated in humans, as well as the neural changes associated. Bernaerts et al. [113] observed that multiple-dose oxytocin treatment (participants self-administered a daily dose of 24 IU over 4 consecutive weeks) attenuates the activity of the bilateral amygdala, which is associated with better behavioral improvements. This finding demonstrates the anxiolytic effects of oxytocin, since the treatment elicited downregulation of negative affect and social distress, besides improving ASD symptoms such as social responsiveness and repetitive behaviors [113]. Considering all these results, oxytocin displays great potential as a therapeutic tool for the main social symptoms of ASD, given that it modulates human cognition and social behavior.

Therefore, the results of the studies presented demonstrate the great therapeutic potential of peptides – especially those derived from wasp venom. Moreover, another promising approach that already

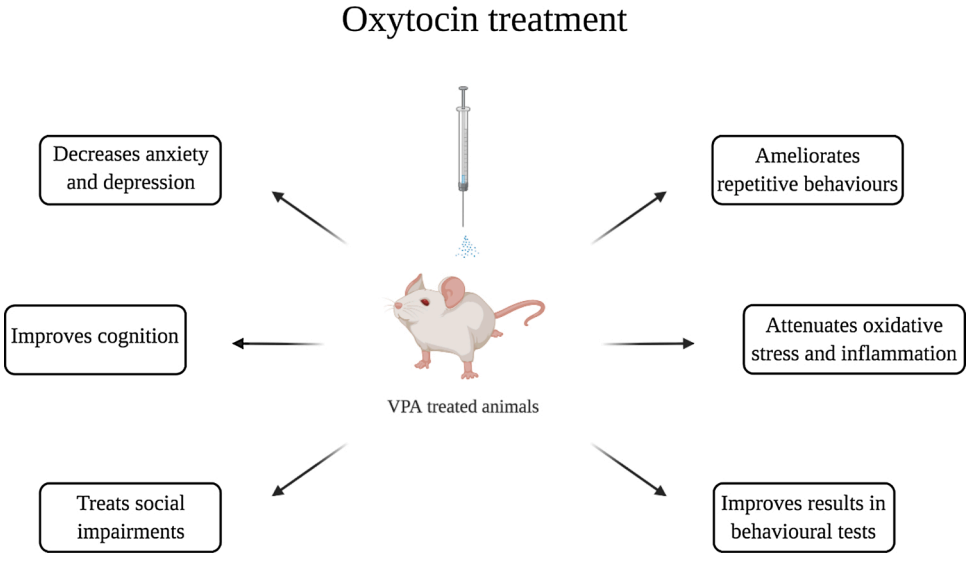

Fig. 4. Effects of oxytocin treatment for ASD in VPA-treated animals. Abbreviations used in the figures: ASD, Autism Spectrum Disorder, VPA, valproic acid. The figure was created using BioRender (www.biorender.com).

demonstrated relevant results is the utilization of oxytocin. Considering that, the evaluation of these compounds as strategies for the treatment of ASD seems quite promising and it is a pathway that perhaps could bring interesting results. Nevertheless, ASD is a very heterogeneous disorder, which is the reason why its pharmacological treatment is such a great struggle. This difficulty is reflected by the current therapies, which only alleviate the main symptoms and do not target the still unclarified physiopathological core of the ASD.

7. Conclusion

The etiology of ASD has been extensively studied and described as a combination of genetic and environmental factors. Alterations in several brain areas are associated with autism-behavior. Thus, the identification of changes in certain neurotransmitter systems is an important tool for the development of pharmacological treatment. Studies describe the VPA pre- or postnatal exposure model as a tool to investigate the neurobehavioral abnormalities in ASD. Additionally, the use of animal models makes it possible to explore potential interventions and therapeutics for ASD. Through this review, we can conclude that peptides are promising in the treatment of ASD core symptoms, due to their specificity.

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