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MINI-REVIEW

A MINI-REVIEW ON THE LATEST DEVELOPMENTS OF THE AUTISTIC PATHOLOGY AND A DESCRIPTION OF SOME RELEVANT ANIMAL MODELS

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Abstract. *Autism spectrum disorders along with other neurodevelopmental disorders, constitutes psychiatric conditions considered public health issues with a strong socioeconomic impact. The onset of autism is before the age of 3 and characterised by aberrant social interactions, communication problems with language deficits and restrictive and repetitive behaviors. The etiology of autism is not well understand, but both environmental and genetic factors may be involved probably in a interactional model type. The key symptoms of autism spectrum disorders have been intensively studied using genetic animal models and also the valproic acid (VPA)-induced model. The existence of such animal models of autism could allow for a rigorous evaluation of the effects produced by environmental factors on the behavioral expression of neuropathological deficits in VPA-treated animals.*

Key words: autism, neurodevelopmental disorders, genetic factors, animal models (VPA)

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AUTISM- GENERALITIES AND CLINICAL ASPECTS

Autism spectrum disorders (ASD) were first diagnosed in the 1930s by Kanner and Asperger. However, the diagnostic criteria were not codified until the release of the Diagnostic and Statistical Manual of Mental Disorders in 1994 [1]. The prevalence rate of autistic syndromes varies from 1 in 500 individuals to 1 in 2500 individuals [2]. Autism is a common neurodevelopmental disorder characterized as a neuropsychiatric condition diagnosed based on three behavioral criteria: aberrant

social interactions, communication problems with language deficits, and restrictive and repetitive behaviors (stereotyped behavior) [3].

This rise in the number of ASD cases is the result of both improved diagnostic tools over the past years and the increased awareness of the challenges faced by affected individuals in society [4]. Generally, diagnostic of autism is established by correlating informations obtained through a detailed clinical examination of the child with the data provided by the caregiver focused on the child behavior and development, but also with the results from specific psychometric scales for autism.

The onset of the disease is before the age of 3, although an early diagnosis is rather challenging [5]. Early symptoms of autism include non-verbal language impairment, restricted facial expressions of emotions, inability to interpret emotions described by others' facial expressions, limited social orientation, attention problems and hypersensitivity to sensory stimuli [6]. Despite these general signs defining the autistic syndrome, clinical presentations and the severity of these key symptoms vary widely among affected individuals [7].

Other neuropsychological deficiencies have also been observed in autism with a greater frequency compared to neurotypical children including epilepsy, intellectual disability, enlarged cranial circumference, minimal visual contact, resistance to change, sleep problems, depression, anxiety or epilepsy [8, 9, 10, 11]. Several theories attribute these so-called emotional alterations to abnormalities in neural networks mediating social-cognitive processes, such as processing or empathy [12, 13]. However, the mechanism underlying these emotional process alterations remains largely unknown [7]. Developmental and intellectual functioning levels also largely vary within individuals with autism. In this way, there are cases ranging from high IQs to severe intellectual disabilities [14, 15].

Regarding treatment of autism there are important limitations and currently the aim of it is to control some of the symptoms. The most effective intervention has proven to be intensive behavioral therapy, such as the Early Start Denver Mode that focus on improvment of social behaviour and language skills. However, there are also pharmacological therapies, clinically used to control some behavioural manifestations with the only ones approved by the American Medical Association being risperidone and aripiprazole [16].

Data regarding autism is obtain also through genetic studies and research based on animal models. In order to induce the autism syndrome and obtain a conventional animal model for this disease, the model classically used in research is based on Schneider and Przewlocki method (2005), as it is more detailed described below. While it is not possible to replicate all autistic symptoms in animals (language deficiencies, intuitive abilities, etc.), most animal models of autism that have been developed so far present the ability to model a range of specific symptoms of autism that may be demonstrated through specific laboratory testing, assessing sociability, routine change, anxious behavior, vocalization, etc. [17].

Nonetheless, it is important to uderstand that autism is a complex syndrome with multiple and variable symptoms. Some of these symptoms, such as language deficits and an inability to intuit the emotions and intentions of others, are difficult or even impossible to induce in mouse models of autism [18]. However, the key characteristics of this syndrome are considered to have conceptual analogs in the behavioral repertoire of this rodent species, making animal models an acceptable tool in studying autism [6]. Therefore, animal models used in behavioral and genetic tests relevant to specific autism symptoms are important translational tools in research, aiming to identify the biological mechanisms underlying key features of ASD [6].

THEORIES ON THE ETIOPATHOGENESIS OF AUTISM

ASD are characterized by a complex etiology and pathophisiological process with an early clinical manifestation. Regarding etiology of the ASD, numerous studies have shown a pronounced genetic component of this condition [19, 20, 21] but a clear cause has not been established to date [22] challenge lies in understanding the consequences of these environmental perturbing factors and genetic factors, as well as the interactions between these two groups [23]. Considering that there are different forms of autism with a large spectrum of clinical presentation the broad heterogeneity of autism is likely caused by multiple factors [7].

For instance, the discovery of a high heritability rate in monozygotic twins and a male-to-female ratio of approximately 4:1 in the prevalence of this syndrome led to a significant interest in research concerning identification of genes involved in autism [6]. It is known that there isn't just a single gene involved in ASD and also environmental factors have most likely a causative role in this syndrome. Various genetic studies on autistic patients had led to hundreds of genes being involved with this condition. Largely, the proteins associated with these genese have two main functions including synapse formation and transcriptional regulation and chromatin-remodeling [24]. In fact, the initial pathological changes in this syndrome seem to involve abnormal expression of various growth factors during embryogenesis which persist into adulthood [4]. In this way, the most studied proteins in relation to autism are brain-derived neurotrophic factor and Interleukin 1 beta that are known to be also related to apoptotic processes [23, 25]. Moreover, studies in recent years confirm the involvement of apoptotic processes in the pathology of this syndrome [26, 27]. The activation of pathological apoptotic processes negatively influences the normal maturation of the brain and mediates the phenotypical presentation of autism. Recent studies have provided new and promising results in the research for discovering the causes underlying the appearance of the autistic syndrome. Results from various animal studies confirm the involvement of apoptotic and neurodegenerative processes in autistic pathology [27, 28, 26] studies of pro and anti-apoptotic proteins could provide new information for the development of prevention and treatment methods for autism and other neurodevelopmental syndromes [29].

Regarding the brain regions considered responsible for autism, studies suggest potential foci located in the cortex - frontal lobe (prefrontal area), temporal lobe (superior temporal gyrus), brainstem (dorsal raphe nucleus, superior and inferior olivary nuclei, facial nerve nucleus), or the limbic system (cingulate gyrus, septal area, amygdala, hippocampus) [9]. Among these, the amygdala and areas associated with the limbic system (septal area, anterior cingulate cortex, nucleus accumbens) seem to be the main cause of communication and relational deficits [30]. Although the mechanisms of autism remain incompletely elucidated, some mentioned causes include variations in the levels of certain neurotransmitters in blood and cerebrospinal fluid, as well as genetic synaptic dysfunctions [31].

Studies generally indicate anomalies in the serotonergic system as the main mechanism in the pathogenesis of the autism spectrum [12]. These cause difficulties in adapting to new environment, socialization problems, and cognitive function impairment, as well as disturbances in the sleep-wake cycle, a symptom of early-stage autism. Thus, individuals with autism exhibit high blood serotonin concentrations, leading to low intracerebral concentration due to a negative feedback loop of serotonergic neurons [32]. Moreover, disruptions in serotonin synthesis in certain brain areas have been identified, along with a significant difference compared to the healthy brain. Most regions considered responsible for autism are densely innervated by projections of serotonergic neurons, and abnormalities in serotonin neurotransmission are implicated in autistic pathogenesis [33]. There are also studies suggesting abnormalities in the medial prefrontal cortex related to the functioning of the dopaminergic system [9] with high levels of catecholamines identified in the blood, urine, and cerebrospinal fluid in some autistic patients [31]. Because dopamine is involved in the prefrontal area in functions such as selective attention (anterior cingulate gyrus) and sustained attention (dorsal prefrontal area), abnormalities in the dopaminergic system are considered causes of hyperactive attention deficits observed in some autistic patients [34].

There are hypotheses even regarding exposure to toxic and immunological agents that resulted from studies using organism modeling of autism of species such as mice, rats and monkeys [30]. Although the etiological mechanisms still remain incompletely elucidated, clinical cases of idiopathic autism suggest the involvement of teratogenic environmental agents in ASD development [35].

ANIMAL MODELS OF AUTISM – VALPROIC ACID - INDUCED ANIMAL MODEL OF AUTISM

The recent increase in cases of idiopathic autism suggests that teratogenic environmental agents could represent an important factor in the development of autism spectrum disorders [36, 35]. Therefore, inducing autism in animal models by exposure to different environmental agents is an important avenue towards discovering the neurobiological basis of autism [7]. It has been found that all

teratogenic agents that can lead to this condition act mostly in the first eight weeks after conception, providing evidence that autism occurs very early in individual development [37]. This is a crucial aspect in generating potential animal models of autism. One such example is the animal model of autism induced by valproic acid (VPA) exposure [37, 38].

This model is based on the discovery of adverse effects of administering the anticonvulsant drug VPA to pregnant women; VPA administration during the first trimester of pregnancy increases the chances of offspring presenting autism spectrum disorders and intellectual disabilities [36, 35]. In order to create this animal model, pregnant females are given a single dose of VPA at approximately the 12.5th day of embryonic development during gestation; the embryonic period is chosen for VPA administration as it marks a significant event in brain development: the closure of the neural tube. This model was adapted in studies and conventionally a 600 mg/kg VPA dose is being used and injected in pregnant female rats, considering that to be the optimal dose for inducing the autistic model [39].

The born pups exhibit anatomical defects and manifest behavioral abnormalities similar to those present in humans affected by autism [40, 41, 17]. Exposure to VPA is a risk factor for the development of this disorder [42]. In humans, VPA causes somatic dysfunctions as well as central nervous system dysfunctions, described as "fetal valproate syndrome," which has recently been linked to autism [43, 36, 44].

Exposure to VPA during this exact stage is critical for inducing the animal model of autism, since VPA is a well known teratogenic agent. VPA is derivated of valeric acid and has effects on GABA, glutamate and dopamine, transmission. It has mainly anticonvulsant properties but is clinically used in a variety of neuro-psychiatric conditions including in the treatment of epilepsy, bipolar disorders, schizophrenia, personality disorders, alcoholism etc. [45].

The key symptoms of autism spectrum disorders have been intensively studied using these animal models in which autism was induced using VPA [46]. The mechanism by which VPA induces teratogenic effects is not completely understood at present [7]. Various biochemical studies indicate that VPA can suppress neuronal activity by blocking sodium and calcium channels and stimulate the inhibitory neurotransmitter GABA's function in the brain [47]. Moreover, studies have demonstrated VPA's ability to alter gene expression in vitro and in vivo [48, 49] and these effects have been attributed to the inhibitory process determined by VPA on the histone deacetylase (HDAC) enzyme [50]. HDAC plays an important role in controlling the transcription process during fetal development [18]. Consequently, HDAC inhibition can induce abnormal gene expressions during embryogenesis, causing delayed behavioral defects that manifest in later stages of development [51]. A recent study on rodents found that in utero HDAC inhibition is sufficient to determine phenotypes similar to autism spectrum disorders, including social deficits in offspring exposed to VPA during uterine development [52].

Similarities between human patients and rodent species (mice and rats) treated with VPA, regarding autism-specific behavior and pathology, suggest the utility of a VPA-treated animal model of autism in defining common pathways of disruption in normal behavioral patterns and evaluating vulnerable periods and triggering sources of this currently considered incurable syndrome [18]. The existence of such an animal model of autism could also allow for a rigorous evaluation of the effects produced by environmental factors on the behavioral expression of neuropathological deficits in VPA-treated animals. The animal model of autism exhibits prominent similarities in terms of anatomy, pathology, and etiology with data collected from human patients [17].

On the other hand, there is important data coming from genetic studies on animal models of autism. Since, autism spectrum disorders present a high degree of heritability [19, 53], but for most autism cases, the status of genes playing a crucial role in the development of this syndrome and how they interact with environmental factors to induce it remains unclear [7]. Most existing animal models for autism have been created using the knockout technique by inhibiting the expression of a single gene [54]. One approach is through gene mutations of genes responsible for neurotransmission or developmental genes regulating social behaviors. For instance, mutations induced in the oxytocin gene have resulted in animal models with deficits in social interaction and recognition [55, 56], and mouse models with mutations in the vasopressin gene cannot habituate to a stranger [57].

The discovery of the importance of genetic factors in autism has led to the development of mouse models of autism, aiming to deepen our understanding of the biological mechanisms underlying autistic behaviors. Rodent models of human neuropsychiatric diseases aim to optimize: 1) resemblance to symptoms manifested by humans; 2) similarity regarding the causes underlying this syndrome; and 3) predicted responses to treatments proven effective in human disease [6].

Rodent animal models of human neuropsychiatric diseases have a long history. It is crucial to understand that an animal model of a rodent cannot exactly replicate a human disease or syndrome, but key symptoms can be "approximated" to test theories regarding the biochemical mechanisms and genetic causes of the human condition [18]. Since rodents exhibit certain similarities with humans in terms of biochemistry, physiology, anatomy, and genetics, species like mice (Mus musculus) have been involved in biomedical research as translational tools [52]. However, differences between species exist in drug metabolism, alternative metabolic pathways, genetic variants, and toxicology. Therefore, 100% predictive validity cannot be expected regarding the effectiveness and practicality of these animal models concerning human medicine [58]. Taking these discrepancies into account, research groups have applied evaluation methods to proposed therapies for autism spectrum disorders, assessing their ability to prevent the development of a pathological phenotype in animal models [3].

CONCLUSIONS

Considering the significant increase in the number of autism cases discovered in the last decade, the development of treatments strategies and therapies to combat this syndrome has become crucial. Although there are data showing the involvment of both environmental and genetic factors in autism, probably in a interactional model type, there isn't a complete understanding on all the factors involved, or the relation between them. Autism, along with other neurodevelopmental disorders, constitutes psychiatric conditions considered public health issues with a strong socioeconomic impact. The use of animal model in autism research opens the way to new hypotheses and research ideas for the future, for the purpose of brodening the knowleddge regarding ASD with focus on therapeutically relevant results for human pathology.

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