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Animal Models of Autism Spectrum Disorder

Abstract

Animal models are developed to test hypotheses about causes of disease, and potential treatments. With genetic, molecular, imaging and electrophysiological studies being supported by animal models, autism research has been flourishing in recent years. On different aspects of autism research, a significant number of reviews have been published. Several of them treated animal models to help current knowledge around its etiology while some others had standpoint of species or neuroanatomical findings. In this article, we present an overview of the animal models.

Keywords: Autism spectrum disorder; Animal models

Review Article

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Introduction

Experimental models are indispensable for dissecting the pathogenic mechanisms of brain disorders. Several numbers of reviews have been published to demonstrate available animal models of Autism Spectrum Disorder (ASD). However, they do not reflect the entire disease state. Animal models, mostly rodents are extensively used to study cortical circuit development, genetic analysis and molecular mechanisms of ASD. Rat has become the most widely used animal in neuroscience [1]. Mouse models have also been used often by the neuroscience community. As compared to mice, rats promise more advantages; with richer social behavioural repertoire, they show various types of social behaviours and use a rich communication system [2]. Surgical experiments, histopathological evaluation, electrophysiological recordings are easier in rats by reason of their larger size. Furthermore, they have the capability of being the major objects of pharmaceutical industry in testing drug efficacy, dosage and toxicology. However animal models on genetic alterations were defined in mice so far.

Recently different animals like the zebrafish (*Danio Rerio*) has also become a popular model organism in neuroscience to study ASD. It seems to be a strong model organism due to representation of highly social animals and looks promising for complementing traditional rodent models [3]. Because of the capacity of vocal learning, songbird animal model was supposed to contribute important insights to our understanding of the communication deficits in ASD [4]. Besides social features, they display characteristically human traits like monogamy and cultural inheritance. Due to its high degree of correspondence to human behavior and their striking homology in the anatomy of neural circuits that mediate social behavior, non-human primate (NHP) model is largely believed to help bridge the gap between humans and lower vertebrate systems [5]. Use of NHP model has the advantages of contributing to some more behavioral aspects of ASD research. However, ethical implications of NHP research and the absence of genetic knockouts in NHP models tend to pose limitations [6]. Surprisingly, a fruit fly, Drosophila and a sea hare, Aplysia and a nematode, C. elegans provide the potential of carrying out large scale screens using the sophisticated genetic tools available despite being millions of years apart on the evolutionary scale. They are likely to facilitate the dissection of the genetic basis of ASD [6].

According to a common hypothesis, ASD results from the interaction of a genetic predisposition and an early environmental insult [7]. We have chosen to focus on methodology in conducting the animal models for ASD. Therefore, we thought that it would be efficacious to reveal keypoints by following the mechanisms set up in animal models.

Genetically Manipulated Animal Models

Numerous candidate genes, most of which are thought to encode proteins involved in neural development and function, have been identified in a general chromosomal locus [8]. To provide insight into the pathophysiology of ASD, copy number variations (CNV) and point mutations should be detected while rare variants in synaptic cell adhesion proteins and pathways are identified [9]. Fortunately, the genetic pathways implicated in ADS and the identification of rare variants are accessible to modeling in experimental systems. However, complex genetic architecture of ASD involves genomic abnormalities, de novo gene mutations, and common genetic variants. It has been challenging to translate genetic risk into a biological mechanism on this account.

Several different strains of mouse, expressing ASD-like behaviors was used to show the identifying factors that may be responsible for ASD and mouse soon became the model of choice.

However, generation of the rat knockout models in 2010 was probably the most important development for animal models of ASD. Fmr1, Nlgn3, Nrxn1, mGluR5 and Mecp2 knockout rats were included in first released autism models [10]. Many ASD-associated genes seem to be involved in regulation of synaptic adhesion and lead to an imbalance between excitatory and inhibitory control in brain circuits [11]. Synapses comprise of pre- and post-synaptic elements with regard to synaptic connectivity (neuroligins and neurexins, contactins), formation of the postsynaptic protein signaling complex (shank) and neuropeptide regulation, that work together to provide synaptic integrity and functionality [12].

Synaptic cell adhesion molecules, namely, neuroligins, neurexins and contactins play critical role in the formation and function of synapses. Neuroligin (Nlgn) is adhesion transmembrane protein that localize to the post-synaptic membrane of glutamatergic or GABAergic synapses [13]. NLGN gene family comprises five genes in humans. NLGN3 and NLGN4X are implicated in the etiology of ASD due to mutations [14]. Mutant forms of NLGN 3 and NLGN 4X are presented with mutant proteins in endoplasmic reticulum resulting in reduced cell surface binding to Neurexin (NRXN) [15]. These alterations were used to generate animal models in mice and other species. NLGN3 (R451C) mice presented challenged social interactions, enhanced inhibitory synaptic transmission, and altered spatial learning abilities [16]. *NLGN3* knockout mice demonstrated reduced ultrasound vocalization and a lack of social novelty preference [17]. *NlgN4* knockout mice displayed reduced reciprocal social interactions and vocalizations consistent with observations in human ASD patients [18].

Neurexins are predominantly presynaptic adhesion transmembrane proteins which are associated with three genes, NRXN1, NRXN2 and NRXN3 encoding α- and β-isoforms for each [19]. They form trans-synaptic cell-adhesion complexes with their postsynaptic counterpart neuroligins [20]. Variations in the NRXN1 gene have been found associated with ASD [21]. NRX1 *α* knockout mice showed electrophysiological changes, impaired spatial memory and increased repetitive behaviors [22]. Impairments in synaptic adhesion, due to interactions between NLGN and NRXN induce deficits in functioning of synapses, resulting in ASD-like phenotypes.

The Contactins (CNTNs) are defined as glycosyl phosphatidyl-inositol (GPI) anchored immunoglobulin (Ig) superfamily proteins functioning in myelination [23], synapse formation and plasticity [24]. Contactin 4 (CNTN4), also known as BIG 2 (brain-derived immunoglobulin superfamily molecule 2), is mainly expressed in the brain (cerebellum, thalamus, amygdala, and cerebral cortex) where it is thought to play an essential role in the formation of axonal connections during development [25]. Disruption of CNTN4 and small deletions near CNTN3 are associated with ASD [26]. Scaffolding proteins are also fundamental for synaptic function. Among the various genetic models generated within the last few years, Shank genes (Shank 1-3) were supposed to be important candidates for modeling ASD in mice. Shank proteins contribute to synapse formation and spine maturation by taking part in connecting neurotransmitter receptors and other membrane proteins to actin cytoskeleton and signaling effectors in dendritic spines [27]. Correlation between single mutations in Shank3 and ASD was reported in several studies [28]. Shank3B mutant mice display repetitive grooming, reduced social behaviours, striatal hypertrophy and reduced cortico-striatal glutamatergic transmission while Shank3A mice show a milder phenotype, characterized by normal social behaviours and reduced recognition of social novelties [29].

Fragile X syndrome, the disorder sharing a number of symptoms in common with autism is caused by mutations in the FMR1 gene on the X chromosome. FMR1 mice display core behavioural features of ASD including impaired social interaction and repetitive behaviour [30]. FMR1 KO mice display abnormally long and thin dendritic spines of layer V pyramidal neurons in the cerebral cortex [30,31]. These findings are relevant with ASD. Discovery of Rett syndrome related gene, MeCp2 resulted in a conditional KO model of mouse. In the female model of MeCP2 disruption, mice show normal development for about the first month of life, followed by behavioural deficits including hypoactivity, seizure-like responses, stereotyped forelimb movements, body trembling and aberrant social interactions [32]. It was suggested that the GABA neurons are important for behavioral abnormalities because MeCp2 KO mice specifically within GABAergic neurons exhibit ASD-like behaviour [33].

Tuberous sclerosis (TSC) may present with autism-like symptoms when mutations in a TSC gene cause benign tumors in the brain [34]. There are abnormalities of cerebellum in many children with tuberous sclerosis [35]. For, there is a positive correlation between cerebellar pathology and ASD either [36]. Mamalian target of rapamycin (mTOR) is inhibited by hamartin and tuberin, which are the protein products of TSC1 and TSC2 [34]. It is reported that mice expressing mutant TSC1 specifically in cerebellar Purkinhe cells, displayed autism-like behaviours [37]. Contactin associated protein like 2 (CNTNAP2) is a well-validated ASD susceptibility gene, which is a member of the neural neurexin superfamily [38]. CNTNAP2 localizes at high levels in circuits of the human cortex that are important for language development [39]. CNTNAP2 is supposed to play a role in the developing brain regions which are usually affected in ASD. CNTNAP2 mutant mice showed three core symptoms of ASD including hyperactivity and epileptic seizures [40]. Neuronal migration abnormalities, a significant reduction in the number of interneurons and abnormal neuronal activity were also reported [40].

Inbred strains of mice with phenotypes relevant to the symptoms of ASD enables to increase our knowledge of this complicated disease. BTBR T+tf/J (BTBR), is an inbred strain which exhibits decreased play behavior and lacks sociability [41], emits fewer ultrasonic vocalizations in various social settings [42] and shows high levels of repetitive behaviour throughout their lifespan [41,43]. These behaviors are similar with the three core symptoms of ASD domains of autism. Several alterations in the hippocampus with reduced hippocampal commissure are presented in BTBR mice [44] and they have reduced density of serotonin transporter in PFC, hippocampus, and nucleus raphe with increased 5-HT1A capacity in CA1 hippocampal region [45]. Additionally, reduced or underdeveloped corpus callosum has been observed in BTBR mice [44].

Animal Models Obtained by Destruction of Certain CNS Areas

Like autistic humans do, animals with alterations in the particular regions show behavioural abnormalities. Ablation studies have improved our knowledge of the relations between anatomical structures and clinical experience in ASD. Unilateral or bilateral lesions of amygdala were performed in animal models. Non-human primates with lesions in amygdala, have failed to initiate social interactions or respond to social gestures [46,47]. On macaques, bilateral lesions of the amygdala resulted in less social contacts and showed more social withdrawal than control subjects [46]. While ablation of superior temporal sulcus region reveal difficulties in responding to social cues like eye gaze [48], Olexová et al. [49] have stated that more extensive lesions of the medial temporal lobe, including the amygdala, hippocampus and ventromedial temporal cortex initiated an even more profound effect on the social interactions of macaques, including a 'lack of social skills' and flat affect [49].

ACC damage in macaque and rat models have also diminished interest in other individuals and showed decrease in the time spent on social interaction. Furthermore, relative reduction in memory for social stimuli was observed in these studies [50,51]. Mentioned findings corresponds well to the behavioural changes seen in the autistic population. Although attempts to model such impairments in animals have focused on the OFC, its lesions did not compromise aspects of social interaction and appraisal sufficiently as ACC lesion did [51].

Animal Models Obtained by using Maternal Factors

It is already known that early exposure to some agents during critical periods of pregnancy results in autism. Increased incidence of ASD associated with prenatal exposure to ethanol, thalidomide and misoprostol was reported [52]. These drugs show their effects by modulating the expression of the genes involved in processes such as proliferation, apoptosis, neuronal differentiation and migration, synaptogenesis and synaptic activity. Valproic acid (VPA), an anti-epileptic increases the risk in the development of ASD when used in the first trimester of the pregnancy [53]. Three core symptoms of ASD including deficits in social and communication skills and restricted /repetitive behaviours were demonstrated in animals after in utero VPA exposure [54]. Affected offspring exhibit certain typical brain abnormalities including abnormalities in the amygdala [54-56]. The inhibition of depolarizing rectification in amygdalar neurons [56], the hyper reactivity of the amygdala to electrical stimulation with boosted synaptic plasticity as well as a deficit in inhibition were reported [55]. Additionally, VPA rats also represent a good model with cerebellar abnormalities characterized by a smaller cerebellum, reduction in the number of purkinje cells in both hemispheres and vermis, and a reduced cerebellar nucleus interpositus [57]. In a recent study, it was also reported that exposure to VPA alters anatomical parameters of cortical limbic regions as prefrontal cortex, hippocampus, and basolateral amygdala with implication in the ASD [58]. The VPA animal model is frequently used to study alterations at the level of morphology, gene expression and neuronal functioning and it is supposed to be one of the best validated models for ASD.

In a large epidemiological study, examination of 10,000 autism cases revealed a significant association with maternal viral infection in the first trimester [59]. When rodents were exposed to maternal immune activation with polyinosine:cytosine (poly I:C) at embryonic day 9.5, the offspring displayed abnormalities that resembled autism [60]. It is suggested that viral infections in the mother induce immune system alterations in both mother and fetus leading to longterm epigenetic changes in the offspring [61].

It has been proposed that one cause of the disease is exposure of the fetal brain to maternal autoantibodies during pregnancy [62]. To provide evidence for this hypothesis, four rhesus monkeys were exposed prenatally to human IgG collected from mothers of multiple children diagnosed with ASD. Four control rhesus monkeys were exposed to human IgG collected from mothers of multiple typically developing children. Five additional monkeys were untreated controls. Monkeys were observed in a variety of behavioral paradigms involving unique social situations. Behaviors were scored by trained observers and overall activity was monitored with actimeters. Rhesus monkeys gestationally exposed to IgG class antibodies from mothers of children with ASD consistently demonstrated increased whole-body stereotypes across multiple testing paradigms. These monkeys were also hyperactive compared to controls. Treatment with IgG purified from mothers of typically developing children did not induce stereotypical or hyperactive behaviors. These findings support the potential for an autoimmune etiology in a subgroup of patients with neurodevelopmental disorders. This research raises the prospect of prenatal evaluation for neuro developmental risk factors and the potential for preventative therapeutics [63].

Animal Models of Virus-Induced and Neurotoxic Sequelae

Borna Disease Virus (BDV) is a neurotropic virus. It causes persistent but non-lethal infection of neural cells. Neuroanatomical defects in the cerebellum and limbic system, behavioral abnormalities and neurochemical defects occur after the neonatal infection of BDV. Research on neonatally BDV-infected rats resulted in first virus-induced animal model of ASD [64]. Infected animals shows longer durations of social exploration and deficits play behaviour due to increased extracellular levels of glutamate and decreased neuronal numbers and volume in the striatum [64,65]. It was not different when the procedure was reversed. Extracellular level of glutamate was increased in rats with BDV infection with abnormalities in social exploration and social play behaviour [64].

It was also stated that co-localization of activated microglia and Purkinje cell dropout in BDV-infected rats showed similarities with pathological features which are associated with abnormal social behaviours [65]. Exposure to methylmercury, an ubiquitous neurotoxicant, during childhood is associated with abnormalities in language, attention and memory [66]. It is reported that acute methylmercury exposure in early life leads to hippocampal cell death, reductions in neurogenesis and severe learning deficits [67]. In 7-day-old rats, a single injection of methymercury resulted

in hippocampal size, and cell number two weeks later, especially in the granula cell layer and hilus of the dentate gyrus [66].

Discussion

Wide variety of animal models in ASD results from diverse range of possible causes of ASD. Admittedly, alternative experimental models should be developed to understand the evolutionary conserved nature of social behavior and its molecular pathways. Beyond the experimental studies, the rapid accumulation of data extracted from published, peer-reviewed scientific literature poses a major challenge for systematic analysis. Autism Database (AutDB) which was created by Basu et al. [68] is of great importance in this regard. A module within AutDB for ongoing collection and comprehensive cataloguing of ASD-related animal models was introduced by Kumar et al. [69]. This study also should not escape the investigators' notice.

Since human genetic studies revealed marked heritability in ASD, numerous investigators prefer to use genetic model animals to examine features of ASD rather than to reconstitute the clinical disorder. Large amounts of data continue to reveal mutations of certain genes from ASD patients. Widely diverse suspected brain regions ranging from the prefrontal cortex to cerebellum, are under investigation [37]. Moreover, 'synaptic theory' of autism has been explicitly stated by many investigators due to strong evidence seems to be converging on certain molecular pathways at the synapse [14,28]. A greater understanding of the glutamatergic synapse in rodent models are supposed to be strategic for the development of effective therapies. Based on available evidence there does not appear to be a single causal deficit but rather various alterations in pre- and postsynaptic function, including changes in synaptic plasticity. Yoo et al. [70] have suggested that underlying cause may be an ongoing synaptopathy rather than an irreversible developmental abnormality. The possibility of reversing behavioural and phsiological deficits with pharmacological treatments could be the most exciting result of their study [70]. Animal models show varying amounts of resemblance to autism ranging from genetic models with specific mutations to broad interventions such as perinatal valproic acid treatment. Borna disease virus infection, VPA rats and BTBR T/+ mouse were suggested as the models which show differences in most brain structures that are similar to those seen in autistic individuals as well as showing behavioural patterns similar to social deficit [49].

There are several factors to consider when choosing and testing an animal model of human symptoms. In the area of social abnormalities, such as ASD, there are ways to measure social approach and reciprocal social interactions in juvenile and adult mice. Impairments in communication in mice may be investigated by tests analyzing responses to social cues, or ultrasonic vocalizations made by mice in the presence of socially-relevant stimuli. Using this model, researchers may study communication skills of mice with genetic or behavioral phenotypes similar to ASD to better understand how changes in genes may mediate change in behaviors of humans.

Until now, each animal model have focused only on one genetic, neuronal, behavioural or other pattern rather than complex screening. We have reached a point where the combinations and further explorations of animal models are needed. Only a complex model would make it possible to better understand the interactions between physiological and behavioural characteristics of autism. The majority of animal models used in autism research are rodents are considered as the most convenient species to work with in autism research. Behavioural results in mice can be conflicting considered in relation to human symptoms. To some extent, these discrepancies are due to the laboratory environment and the genetic background of the transgenic mice. The best target to address specific pathophysiological hypotheses is afforded by mammalian species, and in particular nonhuman primates, in view of their relatively high degree of anatomical and phylogenetic continuity with humans. Ethical considerations, however, dictate that experimentation on monkeys should be strictly limited to exceptional circumstances, where no viable alternatives are available, such as the research on simian immunodeficiency virus, as a neuro AIDS model. When we conduct our experimental models on animals we should study all these modalities separately to understand the effect of each mechanism. Then we must develop more complex models that hold all these properties in itself.

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