Neurobiology of Learning and Memory 124 (2015) 71–87

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Review

Autism Spectrum Disorders: Translating human deficits into mouse behavior

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ARTICLE INFO

Article history:
Received 14 April 2015
Revised 4 July 2015
Accepted 20 July 2015
Available online 26 July 2015

Keywords:
Autism Spectrum Disorders
Human behavior
Mouse behavior
Social interaction
Repetitive behaviors
Hyperactivity
Cognitive impairment

ABSTRACT

Autism Spectrum Disorders are a heterogeneous group of neurodevelopmental disorders, with rising incidence but little effective therapeutic intervention available. Currently two main clinical features are described to diagnose ASDs: impaired social interaction and communication, and repetitive behaviors. Much work has focused on understanding underlying causes of ASD by generating animal models of the disease, in the hope of discovering signaling pathways and cellular targets for drug intervention. Here we review how ASD behavioral phenotypes can be modeled in the mouse, the most common animal model currently in use in this field, and discuss examples of genetic mouse models of ASD with behavioral features that recapitulate various symptoms of ASD.

1. Introduction

The word autism derives from the Greek word αὐτός (autós) meaning "self" and was first used by the psychiatrist Eugen Bleuler in the 1910s to describe a group of patients presenting schizophrenic symptoms and withdrawn behavior. In 1943, the child psychiatrist Leo Kanner at Johns Hopkins University used the term "early inborn autism" to describe 11 children with social and emotional problems and a profound preference of aloneness (Kanner & Eisenberg, 1957). In the same period, the German scientist Hans Asperger described a mild form of autism now named after him, Asperger's syndrome (AS). However, not until the 1970s did the different neural etiology of schizophrenia and autism became clear (Kolvin, 1972; Rimland, 1968; Rutter, 1972; Volkmar & McPartland, 2014).

Given the phenotypic heterogeneity and the variations in severity of autism, understanding the genetic versus environmental influences on pathology is of fundamental importance (Anderson, 2015). In 1977 a twin study highlighted the importance of genetic background in autism for the first time (Folstein & Rutter, 1977; Volkmar & McPartland, 2014), refuting the "refrigerator mother" theory, a genuine lack of maternal care, as the cause of autism (Kanner & Eisenberg, 1957).

In the 1980s, objective criteria for diagnosing autism were introduced and autism was included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) under the term "infantile autism", later changed to "autism disorder" (Volkmar & McPartland, 2014). The latest DMS-5 has introduced the spectrum disorder model for autism (APA, 2013). Autism Spectrum Disorders (ASDs) are defined as a range of heterogeneous neurodevelopmental disorders with an underlying unity. Two core affected domains have been identified: impaired social interaction and communication, and restricted, repetitive and stereotyped behaviors. However, individuals with ASDs also present relatively high risk for developing co-occurring emotional and behavioral disorders (EBDs). Associated symptoms may appear in subsets of individuals with autism and include seizures, anxiety, intellectual impairment, hyperactivity, hyper-responsiveness and hypo-responsiveness to sensory stimuli, sleep disruption, and gastrointestinal distress (Abrahams & Geschwind, 2008; Banerjee, Riordan, & Bhat, 2014; Leyfer et al., 2006; Matson, Dempsey, Lovullo, & Wilkins, 2008; Matson & Nebel-Schwalm, 2007; Volkmar & McPartland, 2014;

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http://dx.doi.org/10.1016/j.nlm.2015.07.013
1074-7427/

Volkmar, Reichow, & McPartland, 2012; Zoghbi & Bear, 2012). The relationship between autism and these associated symptoms is still under debate (Anderson, 2015).

The prevalence of ASDs is estimated to rise every year, currently affecting 1–1.2% of the adult population (Kogan et al., 2009; McPartland & Volkmar, 2012). The onset of autistic symptoms is usually observed in early childhood, by the age of 3. Some milder forms of autism, such as AS, can be diagnosed in school-aged children and adolescents. Last year the Center for Disease Control (CDC) identified around 1 in 68 American children to be on the autism spectrum. Furthermore, ASDs affect males more than females at a ratio of 4:1. In AS the ratio of affected males to females is as high as 14:1 (Fombonne, 2005; McPartland & Volkmar, 2012).

Because the etiologies and the clinical features of ASDs are complex and highly heterogeneous, the uncovering of their biological basis remains a challenge. Many different potential risk factors such as genetic causes and environmental influences have been described to contribute to ASD (Anderson, 2015). Large genome wide association analyses (GWAs) have revealed copy number variants (CNVs), point mutations, chromosomal duplications and deletions that participate in the development of different types of ASDs. Many of the genes implicated encode proteins relevant for synaptic formation, transcriptional regulation and chromatin-remodeling pathways (Banerjee et al., 2014; Baudouin et al., 2012; Clarke et al., 2015; De Rubeis et al., 2014; Malhotra & Sebat, 2012; Marshall & Scherer, 2012; Valnegri, Sala, & Passafaro, 2012). Besides genetic causes, environmental factors such as heavy metals, pesticides, food dietary, exposure to toxic contaminants and maternal stress during pregnancy might predispose and cooperate in the development of ASDs (Banerjee et al., 2014; Durkin et al., 2008; Kinney, Munir, Crowley, & Miller, 2008; Pessah et al., 2008).

Although screening and diagnostic approaches have been improved in the last two decades, behavioral and language therapies remain the primary treatments of children with autism. Therefore, using different animal models such as primates, rodents, fruit flies, song birds and worms, scientists try to model and recapitulate the basic features of ASDs in order to (a) understand the responsible and/or involved neuronal circuits; (b) identify the cellular and molecular mechanisms underlying the described brain dysfunctions; (c) reveal the genetic interactions that underlie such a wide spectrum of disabilities; (d) find diagnostic markers; and (e) identify molecules/drugs that could be beneficial for new interventions together with the behavioral and language therapies.

Here we review the behavioral approaches currently used to detect ASD-like symptoms in mouse models taking into account the clinical observations in humans (Table 1). For more in depth descriptions of the specific behavioral tests and lists of genetic mouse models exhibiting ASD-like behaviors in genetic mouse models, readers are referred to several comprehensive reviews (Crawley, 2012; Kas et al., 2014; Silverman, Yang, Lord, & Crawley, 2010a). The use of these tests in examples of genetic mouse models of ASDs that aim to understand the biological mechanisms underlying ASDs is also discussed (Table 2). Finally, future trends for behavioral assessment of ASD-like phenotypes will be discussed.

2. Social interactions and communication deficits

Deficits in social interaction and communication are one of the core symptoms of autism (Abrahams & Geschwind, 2008; Volkmar & McPartland, 2014). Social anxiety, inability to empathize, poor eye contact, reluctance to share objects and hypersensitivity to stimuli are all recurrent features of individuals affected by ASDs. Withdrawn behavior in autistic children is often associated with impaired verbal communication and delayed speech development (Ellis Weismer & Kover, 2015). The age of a child's first spoken words and sentences and a delayed ability to use language at the age of five are related to adult outcome (de Vries & Geurts, 2015). The inability to infer other's emotions is also crucial for social interactions and might be one of the reasons why individuals with ASD present deficits in responding to other's feelings and in interactions with peers (Frith, 2001; van Roekel, Scholte, & Didden, 2010). Challenging behaviors such as aggression, stereotypic behaviors and self-stimulations have also been reported in ASDs (Fodstad, Rojahn, & Matson, 2012; Walton & Ingersoll, 2013) but they are more often observed in individuals diagnosed with both ASDs and intellectual disability (Chiang, 2008). On the other hand, challenging behaviors are less frequently reported in individuals with ASDs that are classified as high functioning. The inability of individuals affected by ASDs to engage in positive social interactions interferes with cognitive and emotional development and is often accompanied by peer rejection, social anxiety and isolation and lower academic performance (Lowe, Werling, Constantino, Cantor, & Geschwind, 2015; Rudie et al., 2012), further contributing to social segregation. Concerning social interaction, it is interesting to note that children with autism perceive loneliness differently from typically developing children (Whitehouse, Durkin, Jaquet, & Ziatas, 2009). Recently, reduced activation of the brain area relevant for social recognition has been observed in children with ASDs, suggesting impairment in the capacity for visual analysis of human faces (Kim et al., 2015). At a therapeutic level, several strategies to improve social skills have been used, including video modeling, self-management, social stories and pivotal response training with highly satisfactory improvements (Camargo et al., 2014).

2.1. Social interactions in mouse models of ASD

Rodents are highly social species and can be easily tested for social exploration, social interactions and social preference skills, nesting, territorial and sexual behavior. The study of socialization and communication in mice has immensely contributed to the understanding of the molecular pathways involved in such processes. Most rodent ASD models have been extensively tested in such paradigms and many show deficits compared to wild-type animals. The impairments observed during social interaction and communication may be analogous to the inappropriate communication and interaction often observed in autistic patients (Table 1).

2.1.1. Reciprocal social interactions

To test reciprocal social interactions, two unfamiliar mice are placed in a standard cage or specific environments and relevant interactions such as approaching, sniffing, climbing, following and allogrooming are scored using a video-tracking system (Fig. 1). Several ASD mouse models present deficits in this task. Specifically, reduced reciprocal interaction and a delay to engage the first contact were reported (Clipperton-Allen & Page, 2014; Jamain et al., 2008; Santini et al., 2013; Schmeisser et al., 2012; Tabuchi et al., 2007; Zhou et al., 2009). Examples are *Eif4ebp2*$^{-/-}$ and *Shank3*$^{-/-}$ mice, which both spend less time in social interactions (Gkogkas et al., 2013; Peca et al., 2011) compared to wild-type pairs. Additionally, when testing direct interaction between male *Shank3B*$^{-/-}$ mice and wild-type females, *Shank3*$^{+/-}$mice show reduced interest (Bozdagi et al., 2010). *Tsc1*$^{+/-}$ females also show reduced reciprocal social interactions (Goorden, van Woerden, van der Weerd, Cheadle, & Elgersma, 2007), while *Tsc2*$^{+/-}$ males do not show impairments in sociability (Ehninger et al., 2008). Increased sociability has been reported in *Fmr1*$^{-/-}$ mice (McNaughton et al., 2008), a model for Fragile X