Neuroscience and Biobehavioral Reviews 43 (2014) 199–212

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Ultrasonic vocalizations in *Shank* mouse models for autism spectrum disorders: Detailed spectrographic analyses and developmental profiles

Markus Wöhr*

Behavioral Neuroscience, Experimental and Biological Psychology, Philipps-University of Marburg, Gutenbergstr. 18, D-35032 Marburg, Germany

ARTICLE INFO

Article history:
Received 27 November 2013
Received in revised form 25 February 2014
Accepted 31 March 2014

Keywords:
Animal model
Neurodevelopmental disorders
Postsynaptic density
Ultrasonic communication
Social behavior

ABSTRACT

Autism spectrum disorders (ASD) are a class of neurodevelopmental disorders characterized by persistent deficits in social behavior and communication across multiple contexts, together with repetitive patterns of behavior, interests, or activities. The high concordance rate between monozygotic twins supports a strong genetic component. Among the most promising candidate genes for ASD is the *SHANK* gene family, including *SHANK1*, *SHANK2* (*ProSAP1*), and *SHANK3* (*ProSAP2*). *SHANK* genes are therefore important candidates for modeling ASD in mice and various genetic models were generated within the last few years. As the diagnostic criteria for ASD are purely behaviorally defined, the validity of mouse models for ASD strongly depends on their behavioral phenotype. Behavioral phenotyping is therefore a key component of the current translational approach and requires sensitive behavioral test paradigms with high relevance to each diagnostic symptom category. While behavioral phenotyping assays for social deficits and repetitive patterns of behavior, interests, or activities are well-established, the development of sensitive behavioral test paradigms to assess communication deficits in mice is a daunting challenge. Measuring ultrasonic vocalizations (USV) appears to be a promising strategy. In the first part of the review, an overview on the different types of mouse USV and their communicative functions will be provided. The second part is devoted to studies on the emission of USV in *Shank* mouse models for ASD. Evidence for communication deficits was obtained in *Shank1*, *Shank2*, and *Shank3* genetic mouse models for ASD, often paralleled by behavioral phenotypes relevant to social deficits seen in ASD.

Contents

* Correspondence to: Behavioral Neuroscience, Experimental and Biological Psychology, Philipps-University of Marburg, Gutenbergstr. 18, 35032 Marburg, Germany. Tel.: +49 6421 28 23612; fax: +49 6421 28 23610.
E-mail address: markus.woehr@staff.uni-marburg.de

http://dx.doi.org/10.1016/j.neubiorev.2014.03.021
0149-7634/

1. Introduction

Autism spectrum disorders (ASD) are a class of neurodevelopmental disorders characterized by persistent deficits in social behavior and communication across multiple contexts, together with repetitive patterns of behavior, interests, or activities (American Psychiatric Association, 2013). Impairments in reciprocal social communication and social interaction are pervasive and sustained, with varying manifestations in verbal and nonverbal deficits. Symptom severity depends on several factors, including the individual's age, intellectual level, and language ability. Language deficits may range from a complete lack of intelligible speech and severe delays in language acquisition to reduced conversational skills due to echolalia, pronoun errors, and overly literal use of language, with stereotyped and idiosyncratic words and phrases. Even when formal aspects of language, syntax and semantics, are intact, normal back-and-forth conversation is typically impaired, particularly because of deficits in the domain of pragmatics, namely the ability to use language for communicative purposes, e.g. by taking the context of utterance into account when interpreting the meaning. As a result, comprehension of speech is often poor. Existing language thus commonly lacks social reciprocity and is used to request or label rather than to comment and converse or to share feelings and interests. The spontaneous flow of an everyday conversation with one information leading to another is missing. Deficits in verbal communication are typically paralleled by nonverbal abnormalities, such as absent, reduced, or atypical use of eye contact and body language, including total lack of facial expressions and gestures, e.g. pointing to objects to establish joint attention in order to share interest. Speech intonation often appears inappropriate. As for verbal communication, comprehension is often impaired, including deficits in understanding facial expressions and gestures. If present, verbal and nonverbal communication are typically not well integrated (American Psychiatric Association, 2013; Frith, 2003).

ASD have first been described by Kanner and Asperger about 70 years ago (Asperger, 1944; Kanner, 1943; but see also Ssucharewa, 1926) and since then tremendous progress has been made in diagnosing this class of neurodevelopmental disorders, e.g. by means of the autism diagnostic observation schedule (ADOS-2; Jones and Lord, 2013; Lord et al., 2012a, 2012b). Yet, the causes of ASD are still largely unknown. The high concordance rate between monozygotic twins (Folstein and Rutter, 1977; Posthuma and Polderman, 2013) supports a strong genetic component, but the specific genetic alterations underlying ASD remain elusive in the majority of cases (Abrahams and Geschwind, 2008; State, 2010). Among the most promising candidate genes for ASD is the *SHANK* gene family, including *SHANK1*, *SHANK2* (*ProSAP1*; proline-rich synapse-associated protein-1), and *SHANK3* (*ProSAP2*; proline-rich synapse-associated protein-2) (Grabrucker et al., 2011; Guilmatre et al., 2014; Jiang and Ehlers, 2013; Ting et al., 2012). Durand et al. (2007) first described mutations in *SHANK3* in patients with ASD. Since then, genetic alterations, including point mutations and microdeletions of *SHANK3*, have been repeatedly reported in cases of ASD and schizophrenia patients with ASD traits (Boccuto et al., 2013; Dhar et al., 2010; Gauthier et al., 2009, 2010; Gong et al., 2012; Marshall et al., 2008; Moessner et al., 2007; Schaaf et al., 2011; Waga et al., 2011). Furthermore, *SHANK3* maps to the region of the 22q13.3 Phelan-McDermid deletion syndrome (Wilson et al., 2003), a neurodevelopmental disorder characterized by language impairment and ASD features (Phelan, 2008), thus further strengthening the association between *SHANK3* and social and communication behaviors. More recently, mutations in *SHANK1* and *SHANK2* were also found to be associated with ASD (Berkel et al., 2010; Leblond et al., 2012; Pinto et al., 2010; Sato et al., 2012).

SHANK genes encode for a family of multidomain scaffolding proteins located in the postsynaptic density of nearly all excitatory glutamatergic synapses in the mammalian brain (Grabrucker et al., 2011; Kim and Sheng, 2004; Kreienkamp, 2008; Sheng and Kim, 2000). Shank "master scaffolding proteins" (Kreienkamp, 2008; Sheng and Kim, 2000) are part of a multi-protein complex and interconnect the actin cytoskeleton of the dendritic spine with proteins of the postsynaptic membrane, including members of the NMDA and metabotropic glutamate receptor complexes (Grabrucker et al., 2011; Kim and Sheng, 2004; Kreienkamp, 2008; Sheng and Kim, 2000).

SHANK genes are therefore important candidates for modeling ASD in mice and various genetic models were generated within the last few years, with the main aims of understanding the roles of the *SHANK* gene family members in the etiology of ASD, discovering the neurobiological mechanisms underlying behavioral phenotypes with relevance to ASD observed in these genetic models, and, based on this, evaluating novel potential treatments for ASD. *Shank1*$^{-/-}$ null mutant mice were first generated and characterized by Hung et al. (2008). In addition, two *Shank2*$^{-/-}$ null mutant mice were established very recently (Schmeisser et al., 2012; Won et al., 2012). Finally, six *Shank3*$^{-/-}$ null mutant (Bangash et al., 2011; Bozdagi et al., 2010; Peça et al., 2011; Schmeisser et al., 2012; Wang et al., 2011) and a *Shank3 overexpressing* mouse line (Han et al., 2013) are available as well. A detailed overview on the various models generated was recently provided by Jiang and Ehlers (2013). Their overview includes a summary of the molecular, biochemical, synaptic, and behavioral phenotypes observed in *Shank1*$^{-/-}$, *Shank2*$^{-/-}$, and *Shank3*$^{-/-}$ null mutant mice.

As the diagnostic criteria for ASD are purely behaviorally defined (American Psychiatric Association, 2013), the validity of mouse models for ASD strongly depends on their behavioral phenotype. Behavioral phenotyping is therefore a key component of the current translational approach and requires sensitive behavioral test paradigms with high relevance to each diagnostic symptom category (Silverman et al., 2010). Over the last few years, a comprehensive set of mouse behavioral phenotyping assays for deficits in social behavior and communication across multiple contexts was generated, together with behavioral test paradigms to assess repetitive and stereotyped patterns of behavior (Bishop and Lahvis, 2011; Silverman et al., 2010; Wöhr and Scattoni, 2013). While behavioral phenotyping assays for social deficits and repetitive patterns of behavior, interests, or activities are well-established, the development of sensitive behavioral test paradigms to assess communication deficits in mice is a daunting challenge. Measuring ultrasonic vocalizations (USV) appears to be a promising strategy. In the first part of the review, an overview on the different types of mouse USV and their communicative functions will be provided. The second part is devoted to studies on the emission of USV in *Shank* mouse models for ASD. USV in other mouse models for neurodevelopmental disorders, including ASD, were recently summarized by Scattoni et al. (2009) and Michetti et al. (2012).

2. Ultrasonic vocalizations in mice: types and functions

Mice perceive and emit calls in the ultrasonic range, often referred to as USV. Typically, three distinct USV types are differentiated, mainly on the basis of the developmental stage of the mouse and social context: (I) isolation-induced USV in pups, (II) interaction-induced USV in juveniles, and (III) interaction-induced USV in adults, with emission rates and acoustic call features being strongly sex-dependent in adulthood. In adulthood, interaction-induced USV mainly occur during male–female and female–female social interactions, but less during male–male social interactions. USV were also observed in other contexts, e.g. in dams interacting