Available online at www.sciencedirect.com
ScienceDirect
Behavioural Brain Research 176 (2007) 66–74
BEHAVIOURAL BRAIN RESEARCH
www.elsevier.com/locate/bbr

Research report

Animal models of restricted repetitive behavior in autism

Mark H. Lewis [a,b,c,*], Yoko Tanimura [a,b], Linda W. Lee [a,c], James W. Bodfish [d]

[a] *McKnight Brain Institute and Department of Psychiatry, University of Florida, Gainesville, FL, USA*
[b] *Behavioral Neuroscience Program, Department of Psychology, University of Florida, Gainesville, FL, USA*
[c] *Department of Neuroscience, University of Florida, Gainesville, FL, USA*
[d] *Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Received 1 March 2006; received in revised form 10 August 2006; accepted 17 August 2006
Available online 25 September 2006

Abstract

Restricted, repetitive behavior, along with deficits in social reciprocity and communication, is diagnostic of autism. Animal models relevant to this domain generally fall into three classes: repetitive behavior associated with targeted insults to the CNS; repetitive behavior induced by pharmacological agents; and repetitive behavior associated with restricted environments and experience. The extant literature provides potential models of the repetitive behavioral phenotype in autism rather than attempts to model the etiology or pathophysiology of restricted, repetitive behavior, as these are poorly understood. This review focuses on our work with deer mice which exhibit repetitive behaviors associated with environmental restriction. Repetitive behaviors are the most common category of abnormal behavior observed in confined animals and larger, more complex environments substantially reduce the development and expression of such behavior. Studies with this model, including environmental enrichment effects, suggest alterations in cortical-basal ganglia circuitry in the development and expression of repetitive behavior. Considerably more work needs to be done in this area, particularly in modeling the development of aberrant repetitive behavior. As mutant mouse models continue to proliferate, there should be a number of promising genetic models to pursue.

Keywords: Stereotypy; Deer mice; Environmental enrichment; Basal ganglia; Repetitive behavior

1. Introduction

1.1. Restricted, repetitive behavior in autism

Restricted, repetitive behavior is one of three behavioral domains, which concurrent with deficits in social interaction and communication, is required for the diagnosis of autism (ICD-10, World Health Organization, 1990; DSM-IV, American Psychiatric Association, 1994). Despite the clinical significance of this class of behavior, the literature devoted to the study of this repetitive behavior in autism is relatively small in comparison with the extensive literature on social and communication deficits [40].

Repetitive behavior refers to the broad class of behaviors linked by repetition, rigidity, and invariance. In autism these include stereotyped motor movements, repetitive manipulation of objects, repetitive self-injurious behavior, specific object attachments, compulsions, rituals and routines, an "anxiously obsessive desire for sameness" [32], repetitive use of language, and narrow and circumscribed interests. This broad range of behavior has been conceptualized as two clusters: "lower-order" motor actions (stereotyped movements, repetitive manipulation of objects and repetitive forms of self-injurious behavior) that are characterized by repetition of movement, and more complex or "higher-order" behaviors (compulsions, rituals, insistence on sameness, and circumscribed interests) that have a distinct cognitive component. The latter behaviors are characterized by an adherence to some rule or mental set (e.g., needing to have things "just so") [40,64,80]. Indeed, factor analyses of items from the Autism Diagnostic Interview-Revised (ADI-R) [10,73] have yielded two factors (repetitive sensory motor behavior and resistance to change) supporting this categorization. As autism is characterized by the co-occurrence of "lower-order" and "higher-order" repetitive behaviors [4], it is important that

* Corresponding author at: 100 S. Newell Dr., P.O. Box 100256, Gainesville, FL 32610, USA. Tel.: +1 352 294 0415; fax: +1 352 294 0425.
E-mail address: mlewis@psychiatry.ufl.edu (M.H. Lewis).

0166-4328/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbr.2006.08.023

relevant animal models include attempts to model both motor and cognitive features of repetitive behaviors.

1.2. Modeling restricted, repetitive behavior in animals

Animal models relevant to restricted, repetitive behavior in autism generally fall into three classes: repetitive behavior associated with targeted insults to the CNS; repetitive behavior induced by pharmacological agents; and repetitive behavior associated with restricted environments and experience. These models have generally focused on stereotyped motor behaviors which, in animals, are easier to model than, for example, rituals or insistence on sameness. Nevertheless, some animal work, which we will review, has addressed the domain of cognitive rigidity or resistance to change characteristic of "sameness" behaviors.

The animal studies that we will review largely reflect studies modeling the repetitive behavioral phenotype in autism and are not models of etiology or pathophysiology. This is consistent with our limited understanding of the etiology and pathophysiology of these behaviors in autism. In addition, little work has used relevant models to identify novel biological treatments, although our work and the work of others point to the potential importance of early experiential interventions. In addition to highlighting the role of early experience, we will also review work relevant to resistance to change in animals and highlight animal studies relevant to the critical issue of the development of repetitive behavior.

1.2.1. CNS insult and repetitive behavior in animals

The advent of gene targeting technologies has given rise to the generation of mutant mouse models of various neurodevelopmental disorders. In select cases, the behavioral aberrations characteristic of these genetic models also include specific forms of repetitive behavior. For example, mutations in the methyl-CpG binding protein 2 (*MECP2*) gene are responsible for the majority of cases of Rett syndrome, one of the pervasive developmental disorders. Mice expressing truncated MeCP2 protein exhibit repetitive forelimb movements resembling the distinctive hand stereotypies (e.g., hand-wringing, waving, and clapping) observed in Rett syndrome patients [48,70].

The *gabrb3* homozygous knockout mouse also shows stereotyped behavior such as intense circling or "tail-chasing" which may continue for hours [11,25]. The GABRB3 gene, which codes for the β3 subunit of the $GABA_A$ receptor, lies within the q11-13 region of chromosome 15. In addition to being implicated in autism, deletions or mutations of this region are associated with two human genetic disorders, Prader-Willi syndrome and Angelman syndrome depending on parental contribution. Compulsive behaviors are a particularly salient feature of the behavioral phenotype of Prader-Willi syndrome [12]. Ts65Dn mice are segmentally trisomic for the distal portion of mouse chromosome 16, the region containing murine orthologs to human chromosome 21, and provide a model for Down syndrome. The behavioral repertoire of Ts65Dn mice includes repetitive jumping and cage-top twirling. Repetitive motor behaviors, in addition to being diagnostic for autism, are also frequently observed in individuals with Down syndrome [78].

Compulsive grooming leading to hair removal and self-inflicted wounds has been identified as a major behavioral phenotype of the *Hoxb8* homozygous mutant mouse [21]. These mice spent almost twice the time self-grooming as wild-type mice and excessively groomed or barbered control cagemates. Interestingly, high levels of expression of *Hoxb8* were observed in brain regions known to comprise circuitry mediating obsessive compulsive disorder (OCD) symptoms in patients. This model is particularly relevant to OC spectrum problems such as trichotillomania as well as self-injurious behaviors observed in individuals with autism.

Rather than targeting the major candidate genes or loci thought to be associated with autism, other animal models have examined the role of prenatal risk factors in the etiology of autism. Some models have been generated based on the observation that prenatal exposure to teratogenic agents increases the risk of autism. For example, exposure to valproic acid (VPA), an antiepileptic drug, on embryonic day 12.5 in rats not only produces neuroanatomical abnormalities similar to those reported in autistic individuals but also long-term disturbances in postnatal behavior including increased time spent engaged in stereotypic activity [27,63,67]. The stereotypies expressed by the VPA-treated rats are sensitive to environmental perturbations such that housing in an enriched environment results in their attenuation [68]. The VPA induced repetitive behaviors reported in this study represent small movements in the same location in an automated activity monitor. Although such methods allow for high throughput testing, detailed information on the form and temporal structure of the repetitive behavior is often lacking.

The pathogenesis of autism has also been linked to viral infection and lesion-induced damage during early development. In support of this putative association, intracerebral inoculation of newborn rats with Borna disease virus (BDV) induces neuroanatomical and neurochemical deficits similar to those seen in autism. The resulting phenotype of the BDV rat recapitulates many of the behavioral impairments, including stereotypies, commonly observed in autism spectrum disorders [26]. In non-human primates, early damage to amygdala, hippocampal formation and adjacent temporal cortex resulted in a number of behavioral abnormalities including stereotypies [1]. Again, the stereotypies associated with these models are not well described in terms of topography, intensity, or temporal structure.

1.2.2. Drug-induced repetitive behavior

Much of what has been learned about the neurobiological basis of repetitive motor behaviors comes from studies of drug-induced stereotyped behavior. For example, early experiments established the importance of the basal ganglia in the mediation of repetitive behaviors by showing that dopamine or a dopamine agonist (e.g., apomorphine) injected into the corpus striatum induced stereotyped behavior in rats (e.g. [13]). Intrastriatal administration of the glutamate receptor ligand, NMDA, also induces stereotyped behavior that is often indistinguishable from dopamine agonist-induced stereotypy. Such stereotypy can be attenuated by intrastriatal administration of the NMDA recep-