Environmental Enrichment Intervention in Animal Models of Autism

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ABSTRACT

Autism spectrum disorder (ASD) is a complex neurodevelopment disorder caused by genetic and environmental factors. Animal models of autism could help to explore the cellular and molecular mechanisms underlying the pathogenesis and treatment approaches of this disease. Environmental enrichment has been demonstrated to exert beneficial effects in wild-type rodents as well as animal models of various neurological and psychiatric disorders. Here we review the findings about the effect of environmental enrichment on animal models of autism. Generally, environmental enrichment results in less anxiety-like behavior, reduces repetitive behavior and the deficits in social and cognitive behaviors. Environmental enrichment therefore appears to be an effective model for non-pharmacological intervention in autism therapy.

Key words: Autism; Animal model; Behavior; Environmental enrichment

1 INTRODUCTION OF AUTISM

Autism spectrum disorder (ASD) is a complex neurodevelopment disorder, characterized by core features of impairments in social interaction and communication, and repetitive and stereotyped behaviors[1], along with some co-occurring symptoms such as sleeping disorder, anxiety and aggression[2]. The exact etiology of autism remains unclear. Numerous studies on twins and siblings found a more than 90 % concordance rates in monozygotic twins[3,4], as compared with 0 - 10 % in dizygotic twins[3,4] and 3 - 14 % in siblings[5-7], which revealed the contribution of genetic factors to this disorder.
Using genetic techniques such as linkage studies, association studies and chromosomal studies, many genetic variations linked to autism have been identified, including several replicated susceptibility loci, maternal 15q11-13 duplications and mutations in the synaptic genes such as NRXN1, NLGN3, NLGN4 and SHANK3. Some human syndromes resulted from genetic alteration also display autistic symptoms, such as Rett syndrome (a mutation in MECP2) and Fragile X syndrome (CGG repeats). Besides genetic factors, several environmental factors might also contribute to the development of autism, including prenatal viral infection, zinc deficiency, prenatal and perinatal stress, prenatal exposure to toxins such as valproic acid (VPA) and thalidomide.

Currently there is no effective pharmacological therapy for the core symptoms of impairments in social interaction and communication in autism. Despite the many potential therapy targets suggested by basic neuroscience researches, there are only two FDA-approved medicine for autism, risperidone and aripiprazole. Both of them are aimed at treating irritability in autism, including tantrums, aggression and self-injury, but not the core features. On the other hand, early behavioral interventions are currently the only well-established and effective treatment for autistic children. Usually provided through special programs, these interventions use principles and procedures from Applied Behavior Analysis to provide intensive skill-oriented training sessions to help children to develop adaptive and functional skills.

Studies using structural and functional imaging techniques have revealed neurobiological abnormalities of the autistic brains. Magnetic resonance imaging (MRI) scans found an abnormal overgrowth of the autistic brain during infancy and early childhood. Magnetic resonance spectroscopic imaging revealed brain chemical abnormalities in autistic children aged at 3-4, showing a reduced concentrations of neuron-related molecules such as N-acetylaspartate, creatine, and myoinositol. Post mortem studies found decrease in Purkinje neurons and cerebral cortex dysgenesis in autistic brains. However, although these noninvasive imaging techniques and post mortem studies could reveal some structural and functional abnormalities of autistic brains, it is difficult to use these techniques to investigate the detailed molecular pathogenesis of this disease. On the other hand, experimental animal models, which allow invasive studies, provide opportunities to explore the detailed cellular and molecular mechanisms underlying the pathogenesis and treatment approaches of this disease.

Several genetic and non-genetic rodent models have been developed to mimic human autistic symptoms. According to Nestler, et al, an effective animal model of neuropsychiatric disorder should meet three criteria of validity: face validity (which refers that the model resembles important features of the human disease), construct or etiologic validity (which refers that the model is constructed in a way that causes the disease in humans), and predictive validity (which refers that effective treatment in humans should also be effective on the animal models). Animal models of autism are commonly generated based on the etiology of autism, either by genetic manipulation to induce genetic variations that are observed in human autism patients, or by exposing the pregnant animals to certain chemicals that are known to induce autism in human. Some inbred mouse strains expressing phenotypes relevant to autism are also used as autism models.

Although it is helpful to employ animal models of autism to study the detailed mechanism underlying behavioral intervention therapy, it is difficult to model the behavioral therapies in animals. Environmental enrichment is a common non-pharmacological treatment used in animal models of developmental and degenerative disorders, and was approximately used as a model of human early behavioral intervention. The following part of this review summarized the findings about the effect of environmental enrichment on some commonly used experimental autism models. We reviewed the approach of carrying out enriched environmental stimulation in autism models, the beneficial outcome and the neurobiological changes after intervention. Behavioral intervention is currently the only effective treatment of autism, and these studies in animal models may help better understanding the mechanism underlying the therapeutic processes.

2 EFFECT OF ENVIRONMENT IN AUTISM MODELS

Environmental enrichment refers to the addition of objects to the animals’ environment which increases levels of novelty and complexity and enhances sensory stimulation, cognitive activity and physical exercise. Various approaches are used to provide environmental enrichment to animals. One approach is to use physical enrichment by rearing animals in enriched cages, including lager space, equipments to climb and explore, toys of different color, shape and texture, and novelty (materials presented in cages are changed on schedule). Another approach is to use social enrichment, in which multiple animals
are induced to facilitate social interaction.

In wild type rodents, environmental enrichment enhances learning and memory, reduces aging related memory decline, possibly through its effects on synaptic plasticity and hippocampal neurogenesis [26]. Environmental enrichment has also been demonstrated to exert beneficial effects in animal models of various neurological and psychiatric disorders, including Huntington’s disease, Alzheimer’s disease, Parkinson’s disease, stroke, depression, etc. [26,27]. Here we summarized the current studies about the effect of environmental enrichment on animal models of autism.

2.1 Effect of environmental enrichment on autism models generated by genetic manipulation

2.1.1 Fragile X syndrome models

Fragile X syndrome is a common genetic disorder which causes mental retardation. It is caused by a CGG trinucleotide expansion (greater than 200 CGG repeats) in the fragile X mental retardation 1 (Fmr1) gene on the X chromosome which encodes the FMR protein. This genetic alteration results in the absence of the FMR protein, which controls synaptic plasticity and maturation [28]. Fragile X syndrome shares some common symptoms as autism, including pragmatic deficits, language delays, reduced eye contact, difficulty with regulation of attention, self-injury and aggression [29]. Fmrl knockout mice are the predominantly used animal model for Fragile X syndrome. These mice also display several autistic-like features, including hyperactivity in the open field, perseveration and repetitive behaviors such as hand flapping and high level of self-grooming, and reduced affiliative behaviors toward a female [30]. Restivo, et al. found that Fmr1 knockout mice showed impaired habituation, which was observed in autism [31,32], and rearing in enriched cages could restore the habituation to objects in this mice model [33]. In this study enriched cages failed to reverse the hyperactivity in the open field [33], while another study found that hyperactivity of this model was eliminated when animals were raised in social enriched environment [23]. Early social enrichment also rescued the reduced investigative / affiliative behaviors in male Fmrl knockout mice [23]. Postmortem studies discovered an reduction in the dendritic branching in the hippocampus of autistic children [34]. Fmrl knockout mice also showed a decrease of basal dendrite branching and this alternation was reversed by rearing in enriched cages [33].

2.1.2 Rett syndrome models

Rett syndrome is an X-linked progressive disorder that affects girls during early childhood. It is usually caused by mutations in MeCP2, a gene coding for methyl-CpG binding protein that regulates RNA splicing and chromatin remodeling [35]. Children with Rett syndrome exhibit autistic features in the early period of the disease. The autistic features include “lack of following and expressionless face”, “lack of eye-to-eye contact”, “hypersensitivity to sound”, etc. [36]. MeCP2308/Y (generated by truncation at amino acid 308) and MeCP2Tg (overexpression of MeCP2) mice display increased anxiety-like behavior and stereotypies [37]. MECP-/y (MECP2 null mutants) mice showed increased anxiety-like behavior in the open field and early environmental enrichment could rescue this behavior [38]. Enriched housing environment also rescued the increased anxiety-like behavior in novelty suppressed feeding in the female heterozygous MeCP+/y mice [39]. BDNF is one of the transcriptional targets of MeCP2 and related with autism [40]. Serum BDNF levels were found to be significantly lower in females with typical autism, compared with controls [41]. In female MeCP+/y mice, the protein levels of BDNF in hippocampus were significantly lower than that of wildtype mice while environmental enrichment normalized the hippocampal BDNF protein levels [39]. Similarly, environmental enrichment could augment cortical BDNF levels, which was decreased in MECP-/y mice [38].

2.1.3 μ-opioid receptor gene knockout mice

Genetic variation in the μ-opioid receptor gene (Oprm1) is reported to associate with social behaviors. Children carrying the Oprm1 A118G polymorphism display improved parent-child relations, and G allele carriers displayed significantly higher sensitivity to social rejection than A allele homozygotes [41]. μ-opioid receptor knockout mice display social deficits, including deficits in maternal separation induced ultrasonic vocalization and reduced maternal attachment in pups, and altered social reward in juvenile mice, and thus are proposed as a monogenic model of autism [41-43]. Early social enrichment (double mothering) was reported to rescue the abnormal response to maternal separation in Oprm1 knockout pups, and restore the preference for a social stimulus versus an object as wildtype mice [44].

2.1.4 Potter-Lupski syndrome model
Potocki-Lupski syndrome is caused by a duplication of chromosome 17p11.2. Patients with this syndrome display abnormal behaviors such as anxiety, inattention, cognitive deficit and autistic symptom. Mice models for Potocki-Lupski syndrome have been generated by chromosome engineering and these mice display all core autistic behaviors typically utilized to diagnose autism, including abnormal social interactions, impaired communication and the presence of restrictive or repetitive behavior, while rearing in enriched environment mitigated some of the abnormalities, resulted in less aggression and anxiety-like behavior. Elevated serotonin was observed in about a third of patients with autism. In this animal model, elevated serotonin was also observed, and enrichment was found to rescue the altered serotonin levels in the primary somatosensory cortex and decrease the levels of 5-HIAA in the hippocampus.

2.2 Effect of environmental enrichment on inbred mouse models of autism

Some inbred mouse strains expressing phenotypes relevant to autism are also used as autism models. Studies revealed that C58/J mice displayed increased activity and repetitive behaviors, as well as less social approach in the three-chamber test. Environmental enrichment (rearing in enriched cages) was reported to reduce repetitive behaviors and improve reversal learning in this strain.

BTBR T+tf/J is another inbred strain that serve as model of autism, which display avoidance of a nose-to-nose contact with conspecifics, reduced ultrasonic vocalization in social situations and high levels of repetitive self-grooming. Social enrichment (peer-rearing with B6 mice) was reported to rescue sociability deficits, but not high level of repetitive self-grooming, while rearing in enriched cages could reduce the time spent in repetitive grooming.

2.3 Effect of environmental enrichment on chemical induced autism models

Prenatal exposure to VPA is commonly used to generate autism model in rodents. VPA is a frequently used antiepileptic drug. However, more studies indicated a linkage between prenatal VPA exposure and an increase risk of autism. To mimic human intra uterine exposure, animals were usually exposed during organogenesis, commonly between day 9 to 13. Offsprings are reported to display autistic behaviors, including hyperactivity, repetitive and stereotypic behaviors, increased anxiety and decreased social behaviors. In Wistar rats that were prenatally exposed to VPA, environmental enrichment (rearing in enriched cages) was reported to result in lower locomotor activity, less repetitive/stereotypic-like behavior, decreased anxiety-like behavior, increased number of social exploration and total social behaviors. In ICR mice subjected to prenatal VPA exposure, environmental enrichment improved anxiety-like behavior, social deficits and cognitive impairment. Prenatal VPA exposure also resulted in decreased dendritic spine density in the hippocampal CA1 region and this change could also be reversed by enriched housing.

3 CLINICAL APPLICATION OF ENVIRONMENTAL ENRICHMENT IN AUTISM

Although environmental enrichment was used to model behavioral intervention in rodent models of autism, it is quite different from the early behavioral interventions that are used in autistic children. In clinical, environmental enrichment is rather a form of Sensory Enrichment Therapy. Abnormal sensory-based behaviors are commonly observed in autism, displaying hyper or hypo-sensitivities in processing of auditory, visual or tactile sensory. Thus it was suggested that this therapy might help to decrease abnormal sensory responses and ultimately result in reduction of other symptoms of autism. Two randomized clinical trials were carried out by Woo, et al. to examine the effect of environmental enrichment in autistic children. Compared with usual care, environmental enrichment resulted in significant decrease in autism symptoms, improved cognitive skills and receptive language skills, but did not affect expressing language skills. However, given the small sample sizes and short study durations, these results were considered to be of low strength of evidence for the effect of environmental enrichment in autism. Thus further long-term follow-up and studies with larger sample sizes are still warranted.

4 CONCLUSION
In sum, although the effect of environmental enrichment on autism remains uncertain in clinical, it has been demonstrated to exert beneficial effects in several animal models of autism, resulting in less anxiety-like behavior, decreasing repetitive behavior and the reversing the deficits in social and cognitive behaviors. Environmental enrichment therefore provides an effective model for investigating the neurobiological changes after non-pharmacological intervention in autism therapy.

CONFLICTS OF INTEREST

The author declares that there is no conflict of interest regarding the publication of this paper.

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