

*Current Perspective***Preventive Effects of an Enriched Environment on Rodent Psychiatric Disorder Models**Kazuhiro Takuma¹, Yukio Ago¹, and Toshio Matsuda^{1,2,*}¹Laboratory of Medicinal Pharmacology, Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan²United Graduate School of Child Development, Osaka University, Kanazawa University and Hamamatsu University School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

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Abstract. Interplay between genetic and environmental factors plays a key role in psychiatric disorders, as well as other brain diseases, cancer, and metabolic syndrome. In accordance with epidemiological findings, animal studies have pointed out the importance of a variety of environmental factors, such as viral infection during pregnancy or infancy, early parental loss or separation, and physical or sexual abuse in early life, in the etiology of psychiatric disorders. Conversely, positive effects of environmental factors against the pathogenesis of psychiatric disorders are also demonstrated, in which most of the animals are exposed to an “enriched environment”. This review summarizes recent progress of research in this field focusing on the preventive effects of an “enriched environment” against the expression of behavioral abnormalities in rodent models of psychiatric disorders.

Keywords: psychiatric disorder, gene–environmental interaction, environmental enrichment

1. Introduction

Both nature and nurture likely play an important role in the etiology of CNS disorders including neurodegenerative diseases and psychiatric disorders. Most studies over the recent decades have focused on the identification of the genetic factors, but the roles of environmental factors remain poorly characterized. Several epidemiological investigations of neurological and psychiatric disorders have pointed out the importance of environmental factors. For example, a monozygotic twin with schizophrenia results in a risk of approximately 50% for developing the disorder. Several environmental factors, such as viral infection during pregnancy or infancy, early parental loss or separation, and physical or sexual abuse in childhood, may be involved in schizophrenia. In addition, a number of animal studies imply that environmental factors are involved in psychiatric disorders. Shi et al. (1)

reported that prenatal immune activation by exposure to human influenza virus and a synthetic viral mimetic induce psychosis-related behaviors in rodents after growth. Fone and Porkess (2) have shown that maternal separation or prolonged social isolation, under which communicative stimuli are lacking, can induce a variety of abnormal behaviors including increased aggressiveness and hyper locomotion, many of which are similar to the symptoms found in psychiatric disorders, in laboratory animals. Some of the behavioral impairments in animal models of psychiatric disorders are ameliorated by rearing the animals under the conditions of an “enriched environment” (3). These studies suggest that the interaction between genetic and environmental factors plays a key role in the developmental expression of some psychiatric disorders. This review summarizes recent studies on the preventive effects of an “enriched environment” against the expression of behavioral abnormalities in rodent models of psychiatric disorders.

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2. Environmental enrichment as an experimental concept

Generally, the standard housing condition for laboratory rodents constitutes single-sex housing in groups with bedding and free access to food and water. In contrast, environmental enrichment as an experimental concept was first proposed by Donald Hebb in 1947 (4). Although enriched rearing conditions often vary between laboratories, enriched environment cages most commonly consist of enlarged cages with tunnels, ladders, running wheels, differently colored and textured plastic toys, and nesting materials (Fig. 1). In addition, periodical changing of the objects and the position of the objects brings ‘complexity’ or ‘novelty’ to animals. Therefore, environmental enrichment is considered to enhance cognitive, motor and sensory functions relative to the standard (5), leading to various changes in the molecular,

anatomical, and behavioral levels in the brain. In fact, several studies demonstrated that environmental enrichment causes an increase in hippocampal neurogenesis (6, 7), enhanced learning and memory, and the induction of neural plasticity in wild-type laboratory animals (8). During the last decade, environmental enrichment has been revealed to compensate for impaired performance in transgenic mouse models of neurodegenerative disorders such as Huntington’s disease, Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, and ischemic brain injury (5). These studies also provide an experimental basis for the application of an enriched environment in both prophylaxis and therapy of neurodegenerative disorders. Furthermore, more recent studies demonstrated that environmental enrichment can prevent emotional disturbances in animal models of psychiatric disorders summarized in Table 1 and described below.

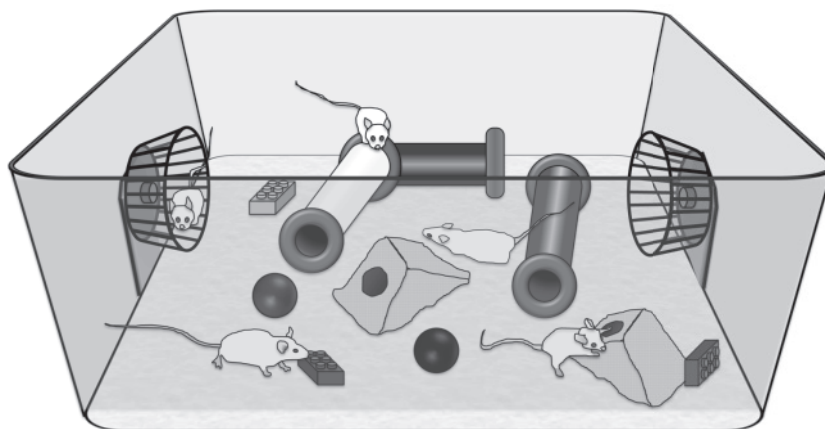


Fig. 1. Example of an enriched environment condition.

Table 1. Environmental enrichment conditions in studies on rodent models of psychiatric disorders

Disorder	Model animals	Gender	Age / Duration of enriched environment	Refs
Schizophrenia	PACAP-knockout CD1 mice	Males	4-week-old / 4 weeks	12
	PLC- β 1-knockout SV129-C57BL/6 mice	Not shown	4-week-old / 4 weeks	13
Attention deficit/hyperactivity disorders (ADHD)	Spontaneously hypertensive (SHR) rats	Males	3-week-old / 3 months	14
Pervasive developmental disorders	MeCP2 null B6.129-C57BL/6 mice	Both	10-day-old / 50 days	18
	FMR1-knockout C57BL/6 mice	Males	3-week-old / Until 60 days of age	19
	FMR1-knockout C57BL/6 mice	Both	3 – 4-week-old / At least 4 weeks	20
	Wister rats exposed to valproic acid on embryonic day 12.5	Both	Exp. 1: 7 – 10-day-old / At least 20 days Exp. 2: 22 – 35-day-old / At least 55 days	21
Post-traumatic stress disorder (PTSD)	Sprague Dawley rats exposed to the inescapable foots shocks	Males	9 – 13-week-old / At least 2 weeks	22
Drug addiction	See Review by Solinas et al. (2010)			23

3. Preventive effects of environmental enrichment on abnormal behaviors in animal models of psychiatric disorders

3.1. Schizophrenia

Molecular genetics studies over the last few years offer great promise towards the discovery of candidate susceptibility genes for schizophrenia. Accordingly, accumulating evidence implies that genetically modified mouse models with disease susceptibility exhibit endophenotypes relevant to schizophrenia (9). Hashimoto et al. (10) have revealed that genetic variants of the genes encoding pituitary adenylate cyclase-activating polypeptide (PACAP) and its selective receptor, PAC1, are associated with schizophrenia. Mice lacking the *Adcyap1* gene encoding the PACAP display remarkable psychosis-related abnormal behaviors, such as hyperactive and explosive jumping behaviors in an open field, increased exploratory behavior, less anxiety in the elevated plus maze, depressive-like behavior in the forced swim test and prepulse inhibition deficits (11, 12). In addition, we have recently demonstrated that environmental enrichment for 4 weeks during the early developmental period (from 4-week-old) improves the psychomotor abnormalities in genetically engineered PACAP knockout mice (12). Similar effects of environmental enrichment are observed in mice with a null mutation in phospholipase C- β 1 (PLC- β 1), a gene implicated in postnatal-cortical development and neuronal plasticity (13). The PLC- β 1 null mice display locomotor hyperactivity, sensorimotor gating deficits, and cognitive impairment, which are regarded as endophenotypes homologous to schizophrenia-like symptoms in rodents. The abnormal phenotype in PLC- β 1 null mice is subject to beneficial modulation by environmental enrichment. It should be noted that the protection against abnormal behavior in PACAP-KO mice by environmental enrichment is age-dependent: rearing of 8-week-old PACAP-KO mice under the enriched conditions for 4 weeks did not improve the abnormal behaviors (12).

3.2. Attention deficit/hyperactivity disorder (ADHD)

ADHD, one of the most prevalent childhood psychiatric diseases, is also considered to arise from the interaction between genes and environment factors. To date, there is no report showing that the effects of environmental enrichment in mouse models with ADHD susceptibility gene. Pamplona et al. (14) recently demonstrated that environmental enrichment from the post-natal day 21 until 3 months of age improved ADHD-like abnormal behaviors in open field habituation, water maze spatial reference, social, and object recognition tasks of the inbred spontaneously hypertensive rat (SHR) strain, which has often been considered as an animal model of

ADHD.

3.3. Pervasive developmental disorders

Pervasive developmental disorders, also called autism spectrum disorders (ASD), are a group of neurological disorders that are characterized by marked impairments in reciprocal social interaction, language, and communication and by stereotyped and repetitive behavior patterns. Pervasive developmental disorders include autism (autistic disorder), Asperger's disorder, Rett syndrome, pervasive developmental disorders-not otherwise specified, and childhood disintegrative disorder (also called disintegrative psychosis). Pervasive developmental disorders most often can be identified during infancy, toddlerhood, or early childhood, and they last throughout life. Genetics is believed to play a prominent role in the cause of pervasive developmental disorders, so that molecular studies over the last few decades have focused on the discovery of disease-causing gene mutations and found a variety of candidate susceptibility genes such as *Ube3a*, *Mecp2*, *Fmr1*, *Nlgn1-4*, *Tsc1/Tsc2*, and *Pten* (15). In addition, as shown in a recent review (16), the last decade of twin studies suggest the importance of environmental factors in the etiology of pervasive developmental disorders. Then, the recent research paradigm on pervasive developmental disorders shifts from purely genetic studies to the interaction between genes and environmental factors including toxins, biological agents, and vaccines. Mice with susceptibility gene mutations of pervasive developmental disorders are challenged with environmental stimuli to understand how genes and environmental factors interact during development. Recent studies demonstrated that environmental enrichment can prevent behavioral abnormalities in two genetically modified animal models of pervasive developmental disorders, Rett syndrome and Fragile X syndrome. Rett syndrome is a progressive neurodevelopmental disorder occurring primarily in girls, but can be rarely seen in boys. Patients with Rett syndrome exhibit reduced muscle tone, autistic-like behavior, purposeless hand movements, diminished ability to express feelings, and cerebral palsy. Rett syndrome is caused by mutations in the X-linked gene *Mecp2*, which encodes methyl-CpG-binding protein-2, an epigenetic transcription factor binding methylated DNA. In agreement with the clinical and genetic observations, mouse genetics studies demonstrated that dysfunction of brain MeCP2 leads to Rett syndrome-like symptoms including cognitive and social abnormalities (17). Several recent studies have indicated that environmental enrichment ameliorates behavioral abnormalities in male mice null for *Mecp2* and female heterozygous MeCP2-knockout mice (18). Fragile X syndrome, the most common known single gene cause of

inherited mental retardation and autism, is due to a silencing of the fragile X mental retardation 1 (FMR1) gene on the X chromosome. Similar to Fragile X syndrome patients, FMR1-knockout mice show both cognitive alterations and an immature neuronal morphology including a reduction in basal dendrite length and branching, and immature spines in layer V of the visual cortex (19). In addition, Meredith et al. (20) demonstrated that environmental enrichment restored unreliable calcium signaling in FMR1-knockout mice to wild-type levels. As of 2010, there is no study showing ameliorative effects due to environmental enrichment on autistic-like behaviors in mice with other genetically modified susceptibility genes of pervasive developmental disorders such as *Ube3a*, *Nlgn1* – 4, *Tsc1/Tsc2*, and *Pten*. It is noteworthy that environment–environment interactions are also presumably involved in the pathogenesis of pervasive developmental disorders. Maternal use of anti-convulsants and mood-stabilizing drugs, such as valproic acid and calbamazepine, during pregnancy has been implicated in the etiology of autism in children, and rodents exposed to valproic acid *in utero* display autism-related behavioral aberrations after growth. Schneider et al. (21) demonstrated that environmental enrichment reversed behavioral alterations observed in rats prenatally exposed to valproic acid.

3.4. Post-traumatic stress disorder (PTSD)

PTSD is a severe anxiety disorder that can develop after experiencing or witnessing a traumatic event, such as victims of accidents, criminal assaults, natural disasters, and terror. Recent clinical evidence, particularly with brain imaging analysis, suggests that hippocampal neurodegenerative pathology is involved in the illness. Hendriksen et al. (22) recently showed that environmental enrichment improved long-lasting PTSD-like anxiogenic behavior induced by inescapable foot shocks and enhanced hippocampal cell proliferation in an antidepressant-resistant rat model of PTSD.

3.5. Drug addiction

Drug addiction is a complex brain disorder that is characterized by intense and, at times, uncontrollable drug craving, along with compulsive drug seeking and use, despite the harm it causes. It is likely that drug addiction is strongly influenced by a combination of factors that include genetics, social environment, and stage of development. The beneficial effects of an enriched environment are also observed in rodent models of drug addiction and are summarized in a recent excellent review (23).

4. Molecular and cellular mechanism for the effects of environmental enrichment

In 1997, Kempermann et al. (8) first demonstrated that environmental enrichment promotes neurogenesis in adult mouse dentate gyrus. In 1999, Young et al. (24) showed that increased levels of glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) result in neuroprotection. Since these observations, the roles of neurotrophic factors have been extensively studied to understand molecular and cellular mechanisms underlying the effects of an enriched environment. Landi et al. (25) demonstrated that early (postnatal days 1–7) administration of insulin-like growth factor-1 (IGF-1) mimics the effect of environmental enrichment on visual system development and suggested that early levels of IGF-1 play a key role in mediating the effects of an enriched environment on retinal development, which requires BDNF. In addition, Angelucci et al. (26) found that rats exposed to enriched conditions for 21 weeks from 21 days of age displayed a significant increase in cerebellar NGF and BDNF production, as compared to rats reared under standard conditions. They also revealed that the enriched environment caused a concomitant increase in NGF levels in the striatum while in the same brain region, BDNF levels were reduced. Goshen et al. (27) demonstrated that environmental enrichment corrects impairments of hippocampal memory and long-term potentiation observed in mice with a deletion of the IL-1 receptor and mice with CNS-specific transgenic over-expression of the IL-1 receptor antagonist, and these observations suggested that exposure to an enriched environment may be beneficial for individuals with impaired learning and memory related to genetic impairments of cytokine interleukin-1 (IL-1) signaling. Sztainberg et al. (28) have shown that the anxiolytic effect of environmental enrichment may be associated with very low levels of corticotropin-releasing factor (CRF) receptor type 1 expression in the basolateral amygdala. Taken together, a variety of molecules may be involved in the beneficial effects of environmental enrichment, but it still remains to be determined when and how these molecules bring specific and desirable changes, leading to antipsychotic action, in the brain during environmental enrichment.

5. Future perspectives

There is accumulating evidence from animal studies suggesting that environmental enrichment prevents the expression of psychiatric disorders, as well as neurodegenerative diseases. Here, we summarize recent representative findings of the antipsychotic effects of an en-

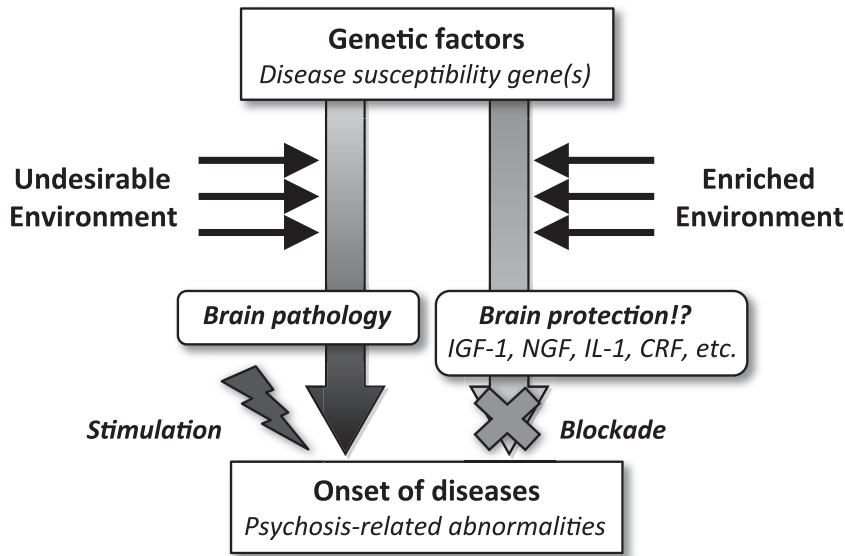


Fig. 2. Possible genetic–environmental interactions leading to psychiatric disorders from rodent studies. Undesirable environments such as social isolation and maternal separation stimulates the expression of psychosis-related phenotypes in rodents with susceptibility gene(s) of psychiatric disorders. In contrast, an enriched environment inhibits the pathogenesis in the disease model animals. Recent studies suggest the involvement of IGF-1 (25), NGF (26), IL-1 (27), and CRF (28) in such preventive effects of environmental enrichment.

riched environment in rodent models of psychiatric disorders and introduce the candidate molecules including neurotrophic factors, which are involved in such anti-psychotic effects (Fig. 2). It is likely that the identification of the molecular and cellular mechanisms operative in environmental enrichment may contribute to better understanding of the roles of the interactions between genes and environmental factors in the pathogenesis of the disorders. Recent studies have pointed out the importance of epigenetic regulation as a biological mechanism underlying environmental factors–mediated pathology of mental diseases (29). The idea that epigenetic dysregulation caused by environmental factors may be involved in the etiology of acquired neurodevelopmental disorders further gives us a new strategy to approach the molecular and cellular mechanisms for the effects of environmental enrichment. In other words, environmental enrichment may improve psychiatric disorders by epigenetic-based correct gene expression. On the other hand, there are still unsettled problems about studies on the effects of environmental enrichment (30). That is, the design and composition of the protocol for environmental enrichment vary widely between laboratories, which may lead to some of the inconsistencies among findings from different laboratories. A more detailed crosstalk analysis, possibly pursued by the same research group, between behavioral and molecular changes will contribute to a better understanding of the precise mechanisms underlying the preventive effects of environmental enrichment on the pathogenesis of psychiatric disorders.

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