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Social Isolation Rearing Induces Neuropsychiatric Diseases: Updated Overview

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Abstract
Neuropsychiatric and neurologic diseases cause a great burden for individuals, families, and societies. Social isolation rearing can trigger a variety of psychiatric diseases. New advances suggest that epigenetic factors along with other neurochemical changes can be an important topic in neuropsychiatric diseases. It is thought that the prevention of social isolation rearing that occurs around birth can reduce the occurrence of neuropsychiatric diseases. It has been suggested that the environment can induce epigenetic alternation. So, for the diagnosis of a proportion of neuropsychiatric diseases, assessing epigenetic factors may be helpful. Also, apart from epigenetic factors, new advances have been made about new mechanisms of and treatments for such a disorder.

Introduction

Neuropsychiatric diseases encompass a wide variety of symptoms that are the cause of great morbidity and disability. Overall, the prevalence of psychiatric disorders is estimated to be 6.7% [1]. Psychiatric disorders, especially in childhood and adolescence, encompass anxiety (3.2%), depression (6.2%), eating disorders (4.4%), autism spectrum disorders (16.1%), attention-deficit/hyperactivity disorder (5.5%), and conduct disorder (5%) [1]. Many studies have been performed to elucidate the basic molecular mechanism that is responsible for the occurrence of such diseases.

Recent studies have shown that early-life experiences can influence adulthood behavior [2]. This is important because in this way we can show that genetics is not the only factor that influences the behavior of the organism in adulthood [3]. Also, it implies that nurturance is an important factor that influences adulthood behavior [4]. Although many studies support the theory that genetics is an important factor that influences behavior in adulthood, environmental factors can also be important as independent factors that influence behavior in adulthood [5]. Important findings of recent studies about the etiology of neuropsychiatric diseases suggest that the neurobiological mechanisms underlying these abnormalities have been discovered.

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Behavioral Changes

In later stages of life, a wide variety of behavioral abnormities develop after social isolation rearing. Here, we mention neuropsychiatric abnormalities that can develop after social isolation rearing.

Anxiety

Recent studies suggest that anxiety will be increased by social isolation rearing. The increase in anxiety is caused by the alternation of neuroplasticity [6].

Depression

Depression is another disorder that occurs in social isolation reared male Sprague-Dawley rats. This behavior was assessed after 107 days of social isolation. This disorder originates in the serotonergic system and adrenergic system [7].

Impulsivity

Impulsivity, a symptom that occurs in some childhood psychiatric disorders, develops in social isolation reared male Lister Hooded rats. The duration of social isolation was 23 days [8].

Schizophrenia

This type of neuropsychiatric disorder also increases in social isolation rearing. Since schizophrenia manifests as a constellation of symptoms such as polydipsia, reversal learning, impaired prepulse inhibition, and many others, animal studies have focused on these symptoms. Investigating the occurrence of this disorder, polydipsia in male Sprague-Dawley rats after 62 days of social isolation [9], reversal learning in male Sprague-Dawley rats after 52 days of social isolation [10], and prepulse inhibition in male Wistar rats after 21 days of social isolation [11] were assessed. It was seen that schizophrenia-related symptoms occurred in social isolation reared rats. Also, oxidative stress disturbance, as a result of 8 weeks of social isolation rearing, increases the incidence of schizophrenia in male Sprague-Dawley rats [12].

Pain

Pain is also another behavior that is influenced by social isolation rearing. In one study, it has been shown that allodynia was reduced in a mice model of chronic inflammatory pain [13].

Cognitive Function

Another brain function that is influenced by social isolation rearing is memory. Different kinds of memory, assessed by the Morris water maze in male mice after 4 weeks of social isolation [14] and by the novel object recognition test in female Lister Hooded rats after 28 days of social isolation, were impaired [15]. Also, attention that is needed for proper cognitive performance was disturbed in socially isolated male Sprague-Dawley rats [16].

Addictive Behaviors

Addiction is a complex disorder with many adverse effects for the addicts and also for the society [17]. For the development of addiction, circuits that control pleasure are disturbed [18]. Normally, reward and anti-reward are in balance with each other [19]. The important point is the evaluation tool that assesses the brain circuits that involve these behaviors. Sucrose consumption is one of them that, in social isolation reared rats, has been shown to be altered [20]. The adrenergic and dopaminergic system has been shown to be increased in the nucleus accumbens area in male Long-Evans rats that were socially isolated for 6 weeks [21].

Other Behaviors

Other behavior can also be negatively affected by social isolation rearing. In fish, social isolation rearing induces continued fights [22]. In another experiment in rodents, social isolation rearing disturbed male-male social interaction [23].

The Mechanisms behind Social Isolation Rearing-Induced Neuropsychiatric Disorders

Epigenetic Changes versus Polymorphism

Assessing the Role of the Environment

Previously, the biopsychosocial model, both in philosophy and clinical practice, illustrated well how suffering, disease, and illness are affected by multiple levels of organization, from societal to molecular organization [24]. This model confirmed that the environment can change the behavior of an organism especially in early life [25]. However, at that time, because of a lack of knowledge, some important concepts were missing. For delineating the impact of environment, we discuss two important concepts in genetics: polymorphism and epigenetic changes. Susceptibility for the emergence of neuropsychiatric disorders is determined by the complex interaction of environment and genetic susceptibility.

The same condition does not trigger the development of neuropsychiatric diseases in all individuals, many studies have been conducted to find out the reason. It is believed that the environmental conditions prone an individual to show neuropsychiatric symptoms in a genetically susceptible organism. The susceptibility can happen through polymorphism and epigenetic modifications. Polymorphism makes some individuals susceptible to develop neuropsychiatric diseases with less influence of the environment (genetically determined polymorphism) [26], but it is believed that the environment triggers an individual to develop neuropsychiatric diseases through epigenetic modifications [27]. Genetic diversity or polymorphism is defined as the occurrence of neuropsychiatric disorders in the context of genetic diversity among individuals. Genetic diversity expresses itself as the occurrence of neuropsychiatric diseases not in all high-risk people. Epigenetic diversity has been well established in previous studies [28, 29]. Set apart from this are epigenetic factors that are defined as the cause of psychiatric disorders after the occurrence of some genetic modifications in the genetic material. A recent study attributed this to environmental modalities [30].

The behavioral changes that occur as the consequences of social isolation rearing can emphasize the role of environment on behavior. However, an important issue in this regard is epigenetics. Epigenetics, however, has recently been attributed great importance for abnormalities that occur around birth [31, 32]. Alternations of DNA function, as a consequence of epigenetics, do not affect the DNA sequence but instead they encompass chemical changes in the DNA composition that result in changes in transcription and modification of proteins [33]. Epigenetic changes do not involve DNA mutation. This is important because epigenetic changes occur with every change in the environment, and maybe they are reversible, but they may also cause permanent changes in bodily functions [34].

Epigenetics involves DNA methylation, histone modification, and non-coding RNAs [35]. There is some evidence that shows that epigenetic modifications can influence the development of the brain [36]. Many studies support the concept of microRNAs as a biomarker of psychiatric diseases [37, 38]. However, in order to determine if social isolation rearing can produce a biomarker that can predict the occurrence of psychiatric diseases in adulthood, more studies should be done. However, because of a lack of proper in vitro models, the detailed mechanism for such modifications is not well understood [36]. Recent studies support the evidence that with the application of stem cell treatment new advances in the understanding of epigenetics about brain development can be achieved [39]. The problems in this regard are the modeling of the proper microenvironment that can be the same as the microenvironment of the developing brain. The most challenging issue in these studies is glial cells [40].

Neurobiological Mechanism and Brain Areas

Behavioral and neurobiological changes that occur as the result of social isolation rearing occur in different brain regions. In several studies, the prefrontal cortex received great attention. Prefrontal cortex malfunctions have been demonstrated to be induced by a variety of mechanisms. Affected are NMDA receptors in mice after 3 months of social isolation [41], interneurons in mice [42], and central cannabinoid, serotonergic, and cholinergic systems in rats [43]. Aggressive behavior is influenced by social isolation rearing through prefrontal cortex activation [44]. The hippocampus is another brain region that is influenced by social isolation rearing. The hippocampus has been shown to be important for tolerating social isolation stress in rats that were isolated for 6 weeks [45]. Also, the serotonergic system in the hippocampus is affected by social isolation stress, since the maturation of these systems occurs 30 to 50 days postnatally [46]. After 6 weeks of social isolation rearing, the GABAergic neurons in the hippocampus have been shown to be affected in mice [47]. Eight weeks of social isolation rearing influences fear-learning, a behavior that is regulated by the hippocampus in male wild-type C57BL/6J mice [48]. Responses of the prefrontal cortex to another brain region are affected by social isolation rearing [49].

The amygdala is another brain region that is important for assessing the outcome of social isolation rearing. Inhibitory neurons of the amygdala in a rat model of schizophrenia [50], pyramidal neurons of the amygdala in male Long-Evans rats after 24 days of social isolation [51], and brain-derived neurotrophic factor (BDNF) signaling in the amygdala in rats after 4 weeks of social isolation [52] were all affected by social isolation rearing. Limbic system remodeling with selective prefrontal cortex volume loss has been shown to be involved in producing schizophrenic-like symptoms in socially isolated rats [53]. Eight weeks of social isolation rearing affects the striatum as part of the basal ganglia which is important for the movement control in rats [54]. Experiments have shown that the dopaminergic system in the striatum responds to 50 days of social isolation rearing in rats [55].

The dorsal raphe is another brain region that is affected by one month of social isolation rearing in male mice [56]. The dopaminergic neurons in the dorsal raphe have been shown to be involved after social isolation rearing in mice [57]. It should be noted that different types of rats (Wistar and Lister Hooded rats) respond differently to 6–8 weeks of social isolation rearing with regard to neurotransmitter release in different brain regions [58]. So, it can be concluded that a complex pathophysiology underlies the occurrence of such diseases.

Therapeutic Strategies

Since social isolation rearing causes a constellation of neurologic and psychiatric disorders, it is necessary to look for effective treatments for curing the core symptoms. Based on recent advances, treatments can be divided into two groups: medication therapy and environmental modalities. Treatment with medication is directed at antioxidant therapy, antipsychotic therapy, and antidepressants. Environmental modalities can combat against social isolation rearing [59]. Enriching the environment has a positive effect on the negative impact of social isolation rearing [60, 61]. Drug therapy is directed at the application of antidepressants like fluoxetine [62, 63], antipsychotics like clozapine [64, 65], and antioxidant therapeutics like N-acetyl cysteine [66]. The antagonist of cannabinoids has been shown to be effective for the long-lasting treatment of psychotic symptoms [67]. Disturbance of the immune system after social isolation rearing points toward therapy that is directed at immune system abnormalities [68, 69].

Conclusion

This overview suggests that social isolation rearing causes different symptoms of psychiatric diseases. New studies support the involvement of epigenetic factors in such disorders, but this important issue has not yet been the topic of recent studies. However, many advances have been achieved in knowing the pathophysiology and treatment of social isolation rearing disorders.

Disclosure Statement

The authors have no conflicts of interest to declare.

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