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Neurobiology and consequences of social isolation stress in animal model—A comprehensive review

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ABSTRACT

The brain is a vital organ, susceptible to alterations under genetic influences and environmental experiences. Social isolation (SI) acts as a stressor which results in alterations in reactivity to stress, social behavior, function of neurochemical and neuroendocrine system, physiological, anatomical and behavioral changes in both animal and humans. During early stages of life, acute or chronic SIS has been proposed to show signs and symptoms of psychiatric and neurological disorders such as anxiety, depression, schizophrenia, epilepsy and memory loss. Exposure to social isolation stress induces a variety of endocrinological changes including the activation of hypothalamic–pituitary–adrenal (HPA) axis, culminating in the release of glucocorticoids (GCs), release of catecholamines, activation of the sympatho-adrenomedullary system, release of Oxytocin and vasopressin. In several regions of the central nervous system (CNS), SIS alters the level of neurotransmitter such as dopamine, serotonin, gamma aminobutyric acid (GABA), glutamate, nitrergic system and adrenaline as well as leads to alteration in receptor sensitivity of N-methyl-D-aspartate (NMDA) and opioid system. A change in the function of oxidative and nitrosative stress (O&NS) mediated mitochondrial dysfunction, inflammatory factors, neurotrophins and neurotrophicfactors (NTFs), early growth response transcription factor genes (Egr) and C-Fos expression are also involved as a pathophysiological consequences of SIS which induce neurological and psychiatric disorders.

1. Introduction

The brain is a vital organ, susceptible to alterations under genetic influences and environmental experiences [1–3]. Stress negatively affects the regions of brain which are mainly involved in regulation of emotion including the cortex and hippocampus [4–6]. A number of researchers has been reported that exposure to early life stress experiences (maternal deprivation, social isolation or social defeat in mammals can evidently and adversely affect the normal brain development and respective adult behavior [7–13]. Animal models of stress has been used as helpful tool to investigate the underlying mechanisms through which, stress exerts its detrimental effects on the functions of brain and animal behavior [14,15].

Stress can be physical or psychological, exposure to stress leads to neurochemicals, physiological and pathophysiological alterations, involved in neurophysiological response and pathophysiology of various neuronal and psychiatric disorders [16–18]. In the developmental stages of life, exposure to chronic stress caused remarkable neuroplastical alterations, changes in neuroplastical function cause alterations in structure and function of receptors that affect synaptic neurotransmission (excitatory and inhibitory) in several regions of the brain [19,20].

A challenge to the organism that can potentially disrupt homeostasis is defined as stressor, therefore, requires a physiological response. During development (childhood and adolescence) when plastic capacity is maximal, is critical period for the maturation of the neural circuits that control energy homeostasis and stress responses of an organism [21]. To promote a proper neuronal organization in adolescent or neonatal the duration and time of a stressful experience is necessary and these parameters can exacerbate the vulnerability to long term neurochemical and behavioral changes [22].Stressor can be exteroceptive or psychological depending on the organism's age and gender during s exposure to stress, nature and severity of stressor,

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chronicity of the stressor and subjectively recognized threat [23].

In animals, the model of social isolation (SI) rearing is commonly considered as an early life stressor [24]. Social isolation is considered as potent stressors in both humans and animals [25,26]. Social isolation stress (SIS) was evolved in 1960 s when researchers reported social isolation as hyper emotional and abnormally reactive to handling [27]. It can alter the behavioural responses to subsequent stress, early life isolation of laboratory rats from social interaction leads to stressful experience [28]. The concept of SIS in adolescencecan result in alterations in reactivity to stress, social behavior, neurochemical, physiological, anatomical and alteration in function of neuroendocrine system in both animal andhumans that may remain during adulthood [12,29,30]. Furthermore, the SIS is a miserable social condition which contributes to fatigue, modification in a variety of behaviours and the responsitivity to psychotropic drugs and predisposes individuals to various diseases [31,32].

The degree and intensity of SIS induced effects are variable among species depending upon social organization of respective species [33–35]. The maintenance of mental and physical health and human well-being depends on social interaction and lack of social contact is associated with higher risk of cognitive deterioration and neuronal disorders. The SIS induced studied on neuronal disorders generated new knowledge in various research fields including pharmacology, behavior and neurobiology [23,36,37].

The major long lasting symptoms caused by social isolation stress (SIS) in rodent studies have been observed in number of behavioral disorders especially in anxiety and depression [30,38,39]. In mice SIS is also able to induce learning deficits [40]. The SIS has marked effect on cell proliferation and neurogenesis as reprted by many researchers [35,41,42]. The release of neurotransmitter including dopamine, serotonin and glutamate is affected by SIS induced changes in brain activity [43].

In mice housed in isolation for one month, the disrupted brain connectivity from post-natal day 35 onwards, prominently affecting the dorsolateral orbitofrontal cortex by using, neuroimaging methods [44]. During the critical period the experience of social isolation streee may result in immature neural circuitry between pre frontal cortex and subcortical targets [45]. A previous study reported the reduced fractional anisotropy in the uncinate fasciculus [46].

In another study, in male rats reared in isolation for 15 weeks after weaning an increased size of the lateral but not third ventricles together with a decrease in brain size and body weight was observed [47]. Controlled studies on the effect of severe social isolation in humans are rare due to the ethical implications. The result of a follow-up study of children reared in orphanages showed smaller cortical white matter volumes in institutionalized children [48].

This review will examine the impact of social isolation stress on brain development and discuss its potential correlations with symptoms of neuropsychological disorders in particular to anxiety, depression, schizophrenia, Obesity and epilepsy. This review will also focus on the effects of social isolation stress on endocrine functions in animal models of rat or mice, with particular attention being given to the role of the neurotransmitters in brain dysfunction associated with early social isolation and provide insight into the etiology and the major signaling mechanisms underlying some symptoms of major depressive disorder (Fig. 1).

2. Prognosis of SIS as underlying cause in etiology of various nervous disorders

During early stages of life, acute or chronic stress can promote the onset of emotional and affective disorders, such as depression and anxiety [49]. The plasticity-driven organization of neural circuits in the hippocampus, prefrontal cortex and amygdala is associated with adolescence [50]. The susceptibility to stress is maximum in adolescence and the emergence of neurobiological disorders such as schizophrenia, depression and anxiety is at its higher level in this periods [51,52].

In adolescence the SI uniquely affects the response to the psychotomimetic drug amphetamine and is detrimental for normal development and may be particularly relevant to the investigation of developmental psychopathology [53]. During adolescence the SIS in non-human primates also impaired hippocampal neurogenesis in time-dependent manner [54]. Another study showed that during adulthood the SIS has been shown to delay the proneurogenic effects of exercise in rats [55]. A recent study has been conducted to investigate the influence of isolation stress during adolescence on exercise-induced increases in neurogenesis in sedentary and running conditions. Results of study showed that during adolescence SIS, did not affect hippocampal neurogenesis, it prevented an exercise-induced increase in neurogenesis in the ventral hippocampus [56].

Although the underlying mechanisms are still poorly understood, SIS in rats has been proposed to show similar signs and symptoms characteristic of human psychiatric disorders such as anxiety, depression and schizophrenia [57,58].In isolation-reared rats some of behavioural and neurochemical alterations has seen which leads to development of schizophrenia, which has led to SIS being proposed as an animal model of this disorder. There is a consensus view that adult disorders like schizophrenia is developed by number of early environmental factors (physiological, psychological, pharmacological) and among psychological factors SIS is one of leading cause to develop schizophrenia [59,60].

A large number of researchers reported social isolation stress in animal models induced behaviors relevant to depression and anxiety or SIS can produce depression and anxiety co-occurrence [30,61,62]. A number of researchers have reported the SIS as animal model in rodents can induce variety of anxiety like behaviours in a variety of behavioral tests [63]. Isolation reared rats have been believed to show sings characteristic of human anxiogenic profile such as neophobia [58]. Isolation reared rats in the early stages of life have reported Behavioural disturbances including an anxiogenic profile in the elevated plus maze [64,65].

Another study demonstrated that in isolation-reared rats on the elevated plus mazemodest increases in anxiety related behaviours were observed [66]. Moreover, a number of studies revealed thatunder SIS the anxiety-like behaviors increased [67–69]. Furthermore, theisolation reared rats were less sensitive to the anxiolytic effects of diazepam and showed more aggressive behavior in comparison with socially reared rats [70].

Ethnopharmacological relevance Xiaochaihutang (XCHT) exert an antidepressant effect on social isolation (SI)-reared mice demonstrated that it improved depressive/anxiety-like behaviors of SI reared mice by regulating the monoaminergic system, neurogenesis and neurotrophin expression [71].

Studies had reported that the anxiety and depression like behaviours in mice along with a reduction in levels of neuroplasticity genes are maximum under SIS [72,73]. The exposure to social isolation in rodents, recognized to depressive-like behaviours and induce anxiety as reported by many researchers [73,74]. Anxiety-induced anorexia and *reductions* in body mass was observed in housing hamsters in social isolation selectively in females. The results of study showed that Syrian hamsters tolerate both stable social housing and social isolation in the laboratory [75].

Depression, associated with altered mood and aversion, is among highly prevailing and serious brain disorders that results in decreased concentration during activities, constant sadness, irritability, fatigue, pain, anxiousness and insomnia [76]. Stressful life events, Social isolation, behavioural withdrawal and loss of social contact are considered as major predisposing factors associated with the aetiology of depression [77]. Many important symptoms of depression e.g., feeling of worthlessness, suicidal thinking cannot be modeled in animals whereas, symptoms of Depression resembling core clinical symptoms i.e. depressed mood and anhedonia, are studied in rodent models by using