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Early Life Experience, Maternal Separation, and Involvement of GABA and Glutamate Transporters

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Abstract

The physiological response initiates with activation of the hypothalamic-pituitary-adrenal axis, the autonomic nervous, and the immune systems. All actions promoted cellular adaptive changes in cells and tissues that protect the body and promote their survival. Diverse protocols of maternal separation (MS) in rodents presented alterations in central nervous system (CNS) such as learning disabilities, voluntary alcohol intake, and neurochemical changes. It is believed that the properties of these early life procedures are mediated by the high plasticity of the developing CNS. During critical development stage, brain regions, mainly those related to aggressive conditions, can have advancement abnormalities occasionally irreversible and thus adjust emotional processing when they grow to be adults. Early postnatal period and relationship between mother and infant are essential of normal stress response and emotional behavior. Probably, it involves the activation of intracellular signaling pathways, genome adaptations, adjusts in gene expression, and neural action. The objective of this article is to provide an overview of the current state of knowledge in the field focused on the maternal separation model, early life experience of postnatal stress, and the involvement of γ-aminobutyric acid (GABA) and glutamate transporters.

Keywords: development plasticity, early maternal separation, acute and chronic stress, transporters, GABA, glutamate

1. Introduction

Actually, it has been accepted that postnatal exposure to adverse events like stress can influence the offspring neurodevelopment, its neuroendocrine, and immune systems and induce behavioral changes thus disturbing neuroplasticity [1, 2].

The central nervous system (CNS) maintains a degree of adaptive plasticity, which allows adjusting to certain situations and adapting innate designs from neuronal connections. There is an abundant bibliography where it is shown that the unfavorable measures in the early life of an individual present profound and persistent effects on the cerebral functions, being able to represent a risky influence for the future development of the psychopathology [4, 5]. Epidemiological studies have shown that postnatal stress or emotional trauma, especially when suffering from early life, is usually associated with an increased possibility of depression [6]. During the critical period of certain brain regions, mainly those related to adverse situations, such as the frontal cortex (CF), hippocampus (Hic), and amygdala, hypothalamic-pituitary-adrenal (HPA) axis can develop almost irreversible abnormalities and alter the response to stress throughout the life of the animal [6, 7]. A recent study of the consequences of maltreatment and stress during childhood at early ages has shown the effects of this experience on brain structures. These structural changes were associated with changes in levels of stress hormones and neurotransmitters, resulted in maltreatment and stress in childhood at early ages, a variety of disorders including depression, anxiety, aggression, impulsivity, hyperactivity, criminal tendency, or abuse of toxic substances [8–11]. With all these evidences, we can deduce that an excess of stress at early ages of the developing life restricts with the paused, progressive, and normal development of the brain [5, 12, 13].

The brain is vulnerable to early-life programming, and this can be manifested in childhood or adulthood as stress hyper-reactivity by deregulation of the HPA axis and increased susceptibility to affective disorders like anxiety, depression, and schizophrenia [14, 15]. Exposure to early stressful adverse life events may increase vulnerability to psychopathology in adult life. There are important memory disturbances in stress-related psychiatric disorders [16].

The term neuroplasticity refers to the potential of the brain to reorganize by creating new neural pathways to adapt, as it needs [2]. This phenomenon requires the stable modulation of gene expression, which is mediated at least in part by epigenetic processes such as DNA methylation and histone modifications. Both the genome and the epigenome cooperate interactively in the mature phenotype and determine the sensitivity to environmental factors and the subsequent risk of disease [17–19]. There is increasing evidence that environmental factors, particularly stressful events experienced early in life, increase the risk of developing a psychiatric illness and/or a behavioral disorder [3, 18, 19]. The experiences of chronic stress are a factor that mainly influences numerous neuropsychiatric diseases, since it often leads to maladaptive responses [20].

While the childhood adversity as a negative childhood experience associated with increased lifetime risk of poorer health and social outcomes have been described postnatal experiences. Several studies in psychiatry have shown a long-term negative effect on health and society such as depression [21], alcohol abuse, use of consumer drugs, family abuse, and other social practices that interact with these processes [22].

The aim of this article is to overview on the current state of knowledge in the field focusing an animal model of maternal separation (MS), early life experience of postnatal stress, and the involvement of γ-aminobutyric acid (GABA) and glutamate transporters.

2. Early environmental experiences

The brain in the early stages of development presents a high level of plasticity, facilitating both adaptive variations on behalf of opportunities, and malformations alterable vulnerability. At present, neuropsychiatric illnesses evident as complex combinations of cognitive, emotional, and behavioral discrepancies have their origins of development fixed primary in the initial placement of the functional impression of the brain [23]. Postnatal periods are critical for CNS development [24]. After birth, the brain continues to grow with its total volume doubling in the first year, measured by 15% rise in the second year [25]. In particular, this increase is explained by the development of neuronal connections in gray matter (synapses and dendrites), long-range axons, and myelination; all of these are necessary for the society of circulated functional systems; regressive development includes the pruning of the synapses and axons during the childhood period, permitting the restructuring of the primarily practical circuits [26].

Animal models are useful tools that help us to understand how genetic vulnerability factors can modulate responses to early environmental factors and provide insights into behavioral and physiological mechanisms involved in the pathways through which early stress might produce long-term effects. In this review, we will focus in the models of MS.

3. Maternal separation

Adverse childhood experience is considered one of the main risk factors for the development of psychopathology. Maternal separation in rodents (rats or mice) is a well-known animal model of early stress to explore the neuroendocrine and behavioral properties of early difficulty. This paradigm discusses to the daily separation of puppies (usually rodents) from their mothers for a short period of time (1 hour) or prolonged (3–6 hours) during the first 1–3 weeks after birth. The paradigmatic MS puppies remain together as a litter [27]. This process is performed between birth and weaning for diverse periods of time and permits a set of experimental designs, which vary in the frequency, the duration, and the age at which the MS occurred.

Studies in animal models show the influence of life conditions during the postnatal period in the establishment of neurological factors that control behavior and response to stress [28]. Acute and chronic MS has both short and long-term effects on behavior and neuroendocrinal responses [29].

Different experimental protocols of MS in rodents have shown changes in CNS functioning: learning impediments, voluntary alcohol consumption, and behavioral variations [30]. This handling in animals is used for diverse experiments, for example, Studies in life sciences sometimes require repeated manipulation in rodents during the course of the experiment (handling). The main function of the handling is to minimize the stress associated with behavioral, pharmacological and endocrine studies [31–33].

The early life of most mammals is expended in near contact with the mother and for the newborn. Early MS is a traumatic occurrence that, conditioning on the different situations, can form its behavioral and neurochemical phenotype in adulthood. Studies in rodents exhibited that a

very short separation cooled by a greater maternal care can completely affect the development of offspring. Nevertheless, prolonged MS origins stress. The significance of this stress and HPA axis hyper-reactivity is articulated in adulthood and continues throughout the life [34]. MS in rodents, particularly in rats, was used as a model for various psychotic conditions, especially depression and anxiety [30, 32]. The most popular MS technique of a daily separation of 3 hours from the second to the 12th postpartum day produces a model of high-construct depression and predictive validity. The results of studies of MS in rat lead to a discussion to its benefits for the neonates. This procedure might be contributed for the mental health of the offspring in adulthood [34].

4. Physiological mechanisms involved in early maternal separation: neurobiological responses to early life stress

4.1. HPA axis

The hypothalamo-pituitary-adrenal axis is a key component of the stress reaction. Many studies have shown the impact of stress exposure during development on the HPA axis activity and on psychoemotional disorders during adulthood [19, 35].

Lifelong variations in HPA axis perform examined as a result of developmental complexities (maternal separation) demonstrate connections with psychiatric disorders containing schizophrenia depression, which may be characterized by irregularities in the activity of HPA axis and reaction to stress [4, 36, 37].

4.2. Neurotrophins reaction

Neurotrophins, also called neurotrophic factors, are a family of proteins that favor the survival of neurons. Family members include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin 4/5 (NT4/5) [38–40]. During development, limiting amounts of neurotrophins function as survival factors to ensure a match between the number of surviving neurons and the requirement for appropriate target innervation. In addition, they arrange cell destiny decisions, axon growth, dendrite pruning, the pattern of innervation, and the expression of proteins critical for normal neuronal role, such as neurotransmitters and ion channels. In the adult CNS, they control synaptic activity and plasticity, while ongoing to modulate neuronal survival [41].

4.3. Neurochemical response

Adverse early life practices can provoke neurochemical alterations that may underlie modifications in HPA axis reaction, emotionality, and cognition [42]. The impact of stress on brain function is known. Different substances are released in response to stress and can influence various neural circuits. The individual effects of functional neuronal mediators of stress (neurotransmitters, neuropeptides, and steroids) and plasticity are integrated. This causes the stress instruments to produce an orchestrated "symphony" that allows for adjusted responses to the various challenges [42]. Different neurotransmitters, such as NA, 5-HT, Glutamate, and

GABA, and neuromodulators, such as neuropeptide Y, oxytocin, a gaseous molecule, and nitric oxide, have been implicated in the pathogenesis of stress-dependent disorders in early stages of life [43].

We will focus on the GABA and Glutamate neurotransmission, especially in their transporters.

5. γ-Aminobutyric acid (GABA)

γ-aminobutyric acid (GABA) is the chief inhibitory neurotransmitter of the adult mammalian CNS. During the early post-natal development, GABA acts as an excitatory neurotransmitter, serving as a neuronal and neurotrophic migration factor, separately from taking part in synaptogenesis. The GABAergic system has a large, complete molecular machine, by which it performs its actions, including enzymes for its synthesis and metabolism, membrane receptors, and transport proteins. Recent literature demonstrates that GABA transporters, as well as the GABAA receptor, are proteins of importance for the normal functioning and development of the central nervous system. All these molecules allow GABA to perform an essential function, both in the developing brain as in the adult brain. For this reason, the expression profile of the different subtypes of the molecules previously mentioned will be described in this article, in order to obtain a thorough knowledge of the molecular behavior of the GABAergic system from conception to adulthood [44, 45].

During the early postnatal development, GABA acts as an excitatory neurotransmitter, serving as a neuronal and neurotrophic migration factor, apart from taking part in synaptogenesis. The GABAergic system has a large, complete molecular machine, by which it performs its actions, including enzymes for its synthesis and metabolism, membrane receptors, and transport proteins. There is abundant literature showing that GABA transporters, as well as the GABA A receptor, are proteins of particular importance for the normal functioning and development of the central nervous system [46–49]. GABA-mediated inhibition exerts a powerful control over cortical neuronal activity, and GABA transporters (GATs) contribute to modulate the action of GABA [45]. Altered GATs activity and/or expression are likely to affect markedly cortical function, with their possible involvement in the pathophysiology of selected human disease.

5.1. Transporters of GABA (GATs)

The regulation of extracellular levels of GABA is essential for normal CNS development and functioning. The principal mechanism by which the levels of the neurotransmitter are regulated is through Na^+-dependent high-affinity uptake carried out by synaptic and glial located transporter proteins called GABA transporters [50]. The others GAT-1, GAT-2, and GAT-3 have been identified from the GATs identified and cloned, although there is also a fourth isoform, BGT-1 (Betaine Carrier/GABA). Although all these transporter molecules have high affinity and selectivity for GABA, they present differential characteristics in pharmacology, localization, and functionality [13, 50, 51]. In fact, the levels of expression during postnatal CNS development vary markedly between the two transporters [13, 52]. There is another GAT, located intracellularly, which is the vesicular GABA transporter (VGAT), which plays a primordial role in the normal development of the immature brain [52].

- **GAT-1**: This transporter is one of the most important isoforms of GATs. They are brain-specific proteins [53–56]. This transporter has the particularity of being found in both neurons and glial cells and is the main isoform of GATs in the mature brain [52].

- **GAT-2**: It is the least abundant isoform. Although low levels of GAT-2 have been detected in GABAergic neurons, this transporter is considered as extraparenchymal and its localization is limited to leptomeningeal and ependymal cells [52, 57]. In all postnatal stages, GAT-2 is detected in the arachnoid layer and in the arachnoid trabecula of the subarachnoid space. In some cases, expression of GAT-2 is observed across the entire diameter of the blood vessels supplying the cortex. The latter characteristic occurs mainly between postnatal day 0 and 5, and this transporter may be considered as the main source of peripheral GABA [52].

- **GAT-3**: This isoform of the GABA transporter is among the most abundant along with GAT-1. GAT-3 is the predominant isoform during the early postnatal stages regulating neuronal excitability at these times [52, 58] and has its unique location in astrocytes [52].

- **VGAT**: The vesicular GABA transporter is essential for GABAergic neurotransmission to occur, as it introduces GABA into the presynaptic vesicles using a proton gradient. In this way, the GABA is stored to be released after the arrival of an action potential to the presynaptic terminal [59].

Odeon et al. [60] evaluated the effects of acute MS (AMS) and CMS (Chronic MS) + cold stress on the expression levels of GAT-1 in FC and Hic, whose appearance correlates with the concentration of corticosterone at different postnatal day from birth to young adulthood. In response to AMS + cold stress in FC, they demonstrated a decrease expression of GAT-1 at PD13. But in CMS, the levels of GAT-1 increased both at PD57 and PD63. At AMS in HIc, they observed an enhance in GAT-1 expression of either PD7 or PD13. Conversely, CMS decreased either PD57 or PD67 and increased at PD71 hippocampal levels expression of GAT-1. With respect to the levels of corticosterone, they observed an increase in all age groups studied in AMS. On the contrary, they showed a decrease in corticosterone levels in CMS. These authors concluded that a low responsiveness of the early postnatal period to stress, involvement of GABAergic system, suggesting that GATs may contribute to the deregulation of neuronal excitability that accompanies at neurobiological consequences of early stress. These dates obtained in this experimental condition serve as a starting point, elucidating the molecular mechanism of GAT regulation in GABA system throughout postnatal development.

In homogenates of FC and Hic acquired from either acute or chronic MS + cold stress, we found variations on the expression of GAT-1. GABA system plays a role in the pathophysiology of anxiety and mood disorders. The extracellular levels of GABA are regulated by specific high-affinity transporters, one of which, the plasma membrane GAT1, is considered the predominant neuronal transporter in the rodent brain [56, 61].

Although AMS might mimic a "dramatic" experience occurring at a precise developmental stage, the less dramatic repeated maternal separation can reproduce a more physiological situation [6].

The central nervous system maintains a degree of adaptive plasticity, which allows it to adjust to certain conditions and modify the innate patterns of neuronal connections [62]. These mediators exert a paradoxical damage-protection action. These variations can alter the functioning of the CNS, and consequently, the body's response to stress throughout life, as this treatment is done during the postnatal period, with the CNS in full development. A further support to this possibility came from the demonstration that prepulse inhibition disruption in maternally deprived rats occurs only after puberty [63, 64], with a temporal profile similar to the onset of schizophrenic symptomatology in patients, and was reversed by treatment with typical and atypical antipsychotic drugs [34], suggesting that the defects resulting from MS might be the consequence of an hyperactivity of the dopaminergic system [65].

The identification of neurobiological substrates that are affected by early life adverse experience may have important diagnostic implications and could contribute to identify novel molecular targets for the development of more effective treatments of psychiatric disorders. Further studies are now warranted to elucidate the type or the timing of early life events that are associated with enhanced risk for depression or anxiety may be different from those relevant to schizophrenia [66].

6. Glutamate

We will briefly describe glutamate as the main excitatory neurotransmitter in the brain. There are three families of ionotropic receptors with channels permeable to intrinsic cations: N-methyl-D-aspartate (NMDA), α- amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA), and Kainate. There are three groups of metabotropics, protein G-coupled glutamate receptors (mGluR) that modify neuronal and glial excitability through G-protein subunits acting on membrane ion channels and second messengers such as diacylglycerol and cAMP. Endogenous glutamate, by activating NMDA, AMPA or mGluR1 receptors, may contribute to acute brain damage following epilepsy, cerebral ischemia, or traumatic brain injury. It may also contribute to chronic neurodegeneration in disorders such as amyotrophic lateral sclerosis and Huntington's chorea. In animal models of cerebral ischemia and traumatic brain injury, NMDA and AMPA receptor antagonists protect against acute brain damage and delayed behavioral deficits. Other clinical conditions including epilepsy, amnesia, anxiety, and psychosis may respond to drugs that act on glutamatergic transmission [67, 68].

6.1. Transporters of glutamate (GluTs)

A family of transporter proteins, excitatory amino acid transporters (EAAT), regulates extracellular concentration of Glu. Several lines of evidence suggest that increases of Glu in extracellular levels are involved in the stress response [68]. Astrocytes are the main protectors of neurons from excitotoxicity in the normal CNS, and this protection is conferred by clearance of extracellular [69].

The GluTs family is mediated by Na + dependent high affinity, this represents a critical factor in the Glu uptake and the regulation of homeostasis in the synaptic cleft [70]. Five

high-affinity GluTs were cloned into human and animal tissues and identified as a glutamate aspartate transporter (GLAST), excitatory amino acid carrier-1 (EAAT)-1, glial glutamate transporter-1 (GLT-1, EAAT-2); excitatory amino acid-carrier-1 (EAAC-1, EAAT-3), EAAT-4, and EAAT-5. Unlike other neurotransmitters, the action of Glu released into the synaptic cleft is terminated by uptake into neurons and surrounding glial cells via specific transporters. Within the nerve terminal, the glutamine released by glial cells and taken up by neurons is converted back to Glu [71]. Rapid removal of Glu from the extracellular space is required for the survival and normal function of neurons. Although GluTs are expressed by all CNS cell types, astrocytes are the cell type primarily responsible for Glu uptake [72]. Astrocytes express both GLT-1 and GLAST, while axon terminals in the neocortex only express GLT-1.

Previous studies have indicated that exposure to variable types of stressors during development produces persistent behavioral defects that are associated with hormonal, neurotransmitters, transporters, and functional changes, and resemble an array of psychopathological conditions.

Altered glutamate receptor (GluR) expression has been implicated in the pathogenesis of stress-induced disorders. Adrover et al. [73] have shown that glutamate neurotransmission might be impaired in the brain of prenatally stressed rats. They observed an increased uptake capacity for glutamate in the PFC of prenatal stress males, while no such changes were observed in the Hic. They concluded that prenatal stress produced long-term changes in the glutamatergic system, modulating the expression of glutamate transporters and altering synaptic transmission in the adult brain.

Odeon et al. [74] found that both ethanol intake and activity and protein expression of GluTs in certain areas of the rat brain are affected by repeated maternal separation (RMS). Also, they demonstrated that RMS increases glutamate uptake in frontal cortex and hippocampus, and RMS reduced both GLT-1 and EAAT-3 protein expression and increased GLAST protein levels.

Social loneliness has been used intensively as an animal model to study the consequences of social isolation during childhood on the brain and behavior. There is a crucial stage during which social isolation has very profound and sometimes irreversible effects.

Recent studies indicate that there are many aspects of alcohol and drug dependence that involve changes in glutamate transmission. Different investigations have reported that drugs of abuse, including alcohol and cocaine, modify GluTs [75, 76]. The effects of ethanol on glutamate transport may be mediated in part by the level of Ca^{2+}/calmodulin kinase activity [77]. Similarly, Othman et al. [78] indicated that in rat cortical astrocytes *in vitro* ethanol affects [^{3}H]-Glutamate uptake by affecting protein kinase C (PKC) modulation of transporter activity.

Odeon et al. [74] observed changes following RMS in the glutamatergic system which could be an effect of glucocorticoid. It is known that this hormone may regulate GluT expression [79] and ethanol intake [80]. A significant increase in glutamate uptake is observed. However, protein levels of the major glial (GLT-1) and neuronal (EAAT-3) transporters declined. It should be noted that a third glutamate transporter, GLAST, was found in glia of the frontal cortex, and hippocampus was studied. This transporter exhibits increased levels of protein expression after treatment. This could be due to the decreased expression of the major glutamate uptake proteins and the probable excitotoxic consequence, which triggered a compensatory mechanism through the increase of GLAST.

GluTs are neuronal and non-neuronal factors necessary for expression, maintenance, and transcriptional regulators of these proteins. The finding that RMS altered Glu regulation in the frontal cortex and hippocampus indicates a possible role for distorted glutamate regulation in the causal relationship between early life stress. Finally, I have some specific questions about this work: (1) Can early exposures with limited time produce lasting physiological changes? (2) Can these physiological changes lead to illness? (3) What factors could induce susceptibility to the adversity of normal development? Responses to these questions should influence the awareness of all social areas for the child's well-being and health throughout life.

7. Conclusions

The findings reviewed here explore some biological mechanisms that could explain the linkages between childhood negative experiences, possible diseases, and function of glutamate and GABA transporters. These results demonstrate efforts to improve quality of life throughout life. With the emergence of new tools, such as the biomarkers of early adversity, this will enable a new path of research with the close collaboration of physicians, health professionals, families, and communities on the basis of a deep understanding of the long term from early adversity.

Acknowledgements

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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