Hippocampus Neuroprotection During Lactation: a Model to Study Neuroendocrine-Immune Interactions

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INTRODUCTION

A unique feature of mammals is their mammary glands and the capacity to feed their newborn litters. Adequate lactation together with the maternal care (provided by the mother) are essential for reproduction and survival of mammals as individuals and as species. In accordance with fulfilling the nutritional demand of the pups, care of the offspring involves a wide set of behaviors, for which, the mother must adapt her physiology to satisfy the demands of the litter as well as her own needs [1]. Thus, the maternal brain goes through a series of adjustments that synchronize neuroendocrine, autonomic and behavioral responses, and can be considered a natural model for neuroplasticity [2]. Plasticity can be defined as an intrinsic property of the nervous system retained throughout the lifespan, that involves dynamic, functional or morphological changes in the brain that occur in response to modifications in the afferent input or the efferent demand [3]. The establishment of new connections through dendritic growth and arborization may follow such rapid ongoing changes, and this is the mechanism for development, growth, and learning [3].

In this sense, lactation represents a state in which internal signals trigger a system reorganization that is maintained by the afferent stimuli, including suckling, and results in adaptive efferent responses. Such reorganization might be demonstrable at the level of behavior, anatomy, and physiology. Work on plasticity in the maternal brain has focused on hypothalamic and limbic structures associated with the physiology of lactation [4, 5], expression of maternal behavior [6], and the stress response [7]. Morphological alterations induced by lactation include remodeling of cell structure in nuclei of the hypothalamus and other brain areas, especially of the limbic system, where functional changes include a variety of alterations related to neurotransmission, the stress response, anxiety, cognitive performance, learning and memory, and particularly those related to maternal behavior [8, 9]. Recent studies have examined dynamic changes occurring in the maternal brain, especially in the hippocampus, and the consequences of such changes.

NEUROPROTECTION IN THE HIPPOCAMPUS DURING LACTATION

Among the various morphological and functional adaptations that reproduction imposes on brain of the female, recent reports from our group have demonstrated that the dorsal hippocampus of the maternal brain is protected against excitotoxicity induced by kainic acid (KA) injection [10, 11]. Lactation in the rat is accompanied by a dramatic increase in the resistance to N-methyl-D-aspartate (NMDA)-induced neuronal activity. This refractoriness to NMDA-mediated activity is evident through a lack of behavioral responses, such as hyperexcitability and seizures, and a lack of c-fos expression in specific regions of the brain [12]. Also, pregnancy decreases the frequency of spontaneous recurrent seizures in rats with KA lesions of the hippocampus [13, 14], and it reduces binding to glutamate and kainate receptors [13].

KA is a cyclic agonist of glutamate that can depolarize both pre- and postsynaptic neurons through its interaction with the kainate and AMPA ionotropic glutamatergic receptors [15]. The administration of KA to rodents is widely used to induce excitotoxic cell damage in the hippocampus. KA increases the production of reactive oxygen species, disrupts mitochondrial function, and induces cell death by both necrotic and apoptotic pathways [15, 16]. It is known that the CA1 and CA3 regions and the hilus of the dentate gyrus of the hippocampus are particularly sensitive to KA excitotox-

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Abstract: During motherhood the maternal brain undergoes a collection of adaptive changes including behavioral, neuroendocrine, and autonomic responses related to maternal behavior and milk production. Steroid (estradiol, progesterone, and corticosterone) and peptide hormone (oxytocin and prolactin) levels fluctuate having an impact in areas of the maternal brain inducing structural and functional changes. Recent reports from our laboratory documented neuroprotection in the hippocampus of lactating rats against excitotoxic damage induced by kainic acid. This review focuses on recent studies about neural plasticity induced by reproduction in the maternal brain, with special focus on lactation as a model for neuroprotection, and on the possible involvement of the immune system in this phenomenon.

Keywords: Lactation, kainic acid, hippocampus, corticosterone, estrogen, progesterone, prolactin, neuroprotection.
icit [15-19], mainly because of the distribution of kainate
and AMPA receptors located in those areas [20, 21].

We took advantage of the kainate model of epilepsy to
investigate the neuroprotective actions of lactation in the
maternal hippocampus, and we found that CA1, CA3, and
CA4 areas are protected against KA-excitotoxicity [10, 11].
We reported that lactation protects the dorsal hippocampal
regions CA1, CA3, and the hilus of the dentate gyrus against
damage caused by systemic KA administration, in compari-
sion to virgin rats in the diestrous phase of the estrous cycle
[10]. The main structures of the dorsal hippocampus affected
by kainate administration in the animals treated during di-
estrus were the CA1 and CA4, and to a lesser degree CA3,
whereas lactating rats only showed minor alterations in the
CA3 region and only with the higher dose. These results
clearly showed that the susceptibility to cellular degeneration
by kainate excitotoxicity was higher in animals in the di-
estrus phase [10]. Moreover, the score of the behavioral
manifestation of motor seizures showed that diestrous rats
lactation protect the dorsal hippocampal
during chronic stress have shown that cumulative
prolactinate involves the regulation of apop-
tosis [41], it suppresses programmed cell death, it forms ho-

Role of Steroid Hormones (Corticosterone, Estrogen and
Progesterone)

Corticosterone. Studies on the vulnerability of the hippo-
campus during chronic stress have shown that cumulative
exposure to corticosterone over the lifespan may contribute
to age-related loss of neurons in the hippocampus, and that
prolonged stress or exposure to corticosterone accelerates
this process [24]. In the experimental model of neurotoxicity
induced by KA, stress or glucocorticoids such as corticoste-
one can exacerbate glutamate-induced cell death in hippo-
campal neurons [25]. Lactation is considered a state of hy-

With regard to estrogen, a few studies suggest that de-
spite the potential for increased seizures, estrogen may re-
duce neuronal death from seizures [34-38]. Physiological or
supraphysiological levels of estrogen reduce neuronal cell
death from seizures, but have little effect on seizure severity
[31]. In addition, estradiol and progesterone can reduce the
neurotoxic effects of glutamate on the hippocampal region of
the brain, and several studies have shown that 17β estradiol
can downregulate caspase-3 expression and upregulate the
expression of antiapoptotic proteins of the Bcl-2 family [34, 36].
Moreover, the hippocampus is able to synthesize estradiol
after KA administration [37, 39].

Data from our group show that during lactation there is a
significant change in the expression of estrogen receptor
(ERs) in the hippocampus as compared to diestrous rats, sug-
estrating a strong correlation between expression of ERs, es-
specially ER-β, in lactating CA1 and CA3 hippocampal
regions in response to kainate administration, and the neuro-
protection observed during this reproductive period [40].
The neuroprotective actions of ER-α and ER-β in experimental
neuroprotective models include enhanced Bcl-2 expression
in hippocampal neurons that is enhanced to an extent compa-
rable to their neuroprotective capacity. Activation of either
ER-α or ER-β can promote neuroprotection in hippocampal
neurons, suggesting that both receptor subtypes could be
involved in estrogen neuroprotection [40].

The neuroprotective effects provided by lactation could
result from changes in Bcl-2 protein expression. The Bcl-2
protein family has been implicated in the regulation of apop-
tosis [41], it suppresses programmed cell death, it forms ho-
Role of Peptide Hormones (Oxytocin and Prolactin)

Two main peptide hormones involved in lactation are prolactin and oxytocin. Release of both hormones is affected by KA administration [44, 45], and the sensitivity of oxytocin magnocellular neurons to KA is altered during lactation [46]. Oxytocin triggers uterine contraction and milk ejection. Besides their projection to the posterior pituitary lobe, oxytocinergic neurons project centrally and their fibers reach the hippocampus [47]. Oxytocin has effects on the hippocampus that improve memory and learning by promoting the establishment of long-lasting connections between neurons in the hippocampus [48], and it reduces the restraint stress-induced c-fos expression within the dorsal hippocampus (CA1-CA4 and dentate gyrus) [49]. Concerning glutamate activation oxytocin can show both inhibitory and excitatory actions, depending on the state of the animal and the dose employed [5].

Prolactin stimulates milk secretion in the mammary gland, and its central actions include a variety of behavioral and neuronal actions, including promotion of maternal behavior and grooming [50], anxiolytic and neuroprotective actions [51]. Prolactin is released in the CNS in response to suckling and restraint stress, and its hypothalamic expression is enhanced in pregnant and lactating animals [52]. These authors have shown that chronic intra-cerebral administration of prolactin blocks restraint stress-induced neuronal activation within the CA3 layer and the dentate gyrus of the dorsal hippocampus.

Prolactin has also been reported to be neuroprotective in the hippocampus by counteracting the reduction in cell survival induced by chronic stress [51]. Furthermore, reduced c-fos expression in the ventral hippocampus under basal conditions suggests that prolactin modulates inputs to the hippocampus [53] where the prolactin receptor is expressed [54]. Hypoxia/ischemia induces a robust activation of prolactin in regions of the cerebral cortex, and prolactin is involved in the gliogenic response during recovery from cerebral injury [55], prolactin also regulates oligodendrocyte precursor proliferation and mimics the regenerative effects of pregnancy observed in multiple sclerosis [56]. Chronical treatment of PRL has been correlated with a decrease in audiogenic-epileptic seizures [57] and unpublished data from our laboratory indicate that prolactin treatment exerts a protective effect in the hippocampal areas of intact and ovariectomized female rats against KA injection, and diminishes the progression and intensity of KA-induced seizures.

CONCLUSION

Lactation is associated with increased levels of oxytocin, prolactin, progesterone, and glucocorticoids that are maintained by suckling stimulation and reinforced by external signals from the litter. During pregnancy and lactation, the fluctuation of the ovarian hormonal levels is modified, and the circadian secretion of corticoids is lost. Neuroprotection in the hippocampus observed during lactation might involve actions of anyone or a combination of these hormones on the maternal brain.

Changes in the hippocampus as a result of motherhood include dendritic architecture, synaptic plasticity, and decreased cell proliferation in the hippocampus during the lactation period [reviewed in 58]. Those changes, including the protective effect of lactation on the neurons of the hippocampus [10], could serve the purpose of maintaining neurons that have undergone pregnancy-induced changes necessary for the expression of behavioral and endocrine changes that occur during this phase. Lactation is the feature by which the mammals are distinguished and represents a natural model for plasticity because of the new requirements for maternal behavior and nursing.

Apart from the adaptations in the maternal behavior and physiology that involve a set of behaviors for care of the newborn, production of milk, and metabolic changes, lactation is a natural model to study neuroprotection. Systemic injection of KA induces progressive limbic seizures in rats [15], leading to neuronal cell death by induction of reactive oxygen species production and mitochondrial dysfunction in many regions of the brain, particularly in hippocampal CA1 and CA3, and the hilus of dentate gyrus [15-18]. Moreover, delayed induction of proinflammatory gene expression, such as TNF-α, IL-1β, IL-6, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), are regarded to induce prolonged neurodegeneration [59, 60]. Thus, one unexplored but important aspect of neuroendocrine-immune interactions is the correlation between hormones of lactation and the local immune response induced by a damaging agent, like KA, in the hippocampus of the mother.

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