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

Teresa Morales*

Departamento de Neurobiología Celular y Molecular, Instituto de Neurobiología, Universidad Nacional Autónoma de México, 76230, Querétaro, México.

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.

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-

*Address correspondence to this author at the Instituto de Neurobiología, UNAM, Boulevard Juriquilla 3001, 76230, Querétaro, Qro. México.; Tel: (5255) 5623-4071; Fax: (5255) 5623-4005;
E-mail: marter@servidor.unam.mx; marter@inb.unam.mx

1876-5289/10

icity [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 comparison to virgin rats in the diestrus phase of the estrous cycle [10]. The main structures of the dorsal hippocampus affected by kainate administration in the animals treated during diestrus 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 diestrus phase [10]. Moreover, the score of the behavioral manifestation of motor seizures showed that diestrus rats treated with KA reached the severity stage of 4-severe to 5-mild according to the Zhang scale [22], while lactating rats showed only early signs of behavioral seizure [10].

Pregnancy decreases the frequency of spontaneous recurrent seizures induced by KA injected into the dorsal hippocampus, and reduces the affinity of kainate receptors [13, 14]. This might explain the neuroprotective effects of lactation, but more studies on this aspect are necessary. Indeed, lactation exerts a protective instead of preventative action against KA, since neuroprotection has been documented for up to 72 h after intracerebral injection of KA [11]. How hormones of lactation participate in this downregulation of the glutamate receptor, and the glial remodeling of this area during reproduction, and induced by KA treatment remains to be determined. The influence of suckling and exteroceptive stimuli on these protective effects of lactation cannot be excluded since exposure to an enriched environment, as occurs in the maternity experience, can have protective effects against KA-induced seizures [23].

Role of Steroid Hormones (Corticosterone, Estrogen and Progesterone

Corticosterone. Studies on the vulnerability of the hippocampus 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 corticosterone can exacerbate glutamate-induced cell death in hippocampal neurons [25]. Lactation is considered a state of hypercorticalism [7], and considering that chronically high levels of corticosterone accelerate and exacerbate KA-induced neurotoxicity in the CA3 hippocampal area in male rats [25], this condition would appear to make the maternal brain more vulnerable to excitotoxic damage. Moreover, the level of corticosterone influences the expression of mRNAs for kainate receptor subunits in the rat hippocampus [26]. However, it has not yet been determined whether there are changes in the glutamatergic or kainate receptor subunits in the hippocampus of the dam.

One of the pioneer examples connecting the neuroendocrine and immune networks are the actions of corticosterone on the immune system. Apart from the well-known peripheral actions of glucocorticoids on the immune system [27], exposure to high glucocorticoid levels renders hippocampal neurons more susceptible to neurological insults, such as sodium nitroprussiate-induced excitotoxicity [28]. This effect could be explained by a direct interaction between glucocorticoids and their receptors within neurons, or by a lack of the neuroprotective properties of innate immune cells. Glucocorticoids can alter NF-kappaB signaling and activation of microglia, which are potent neuroprotective mechanisms against an excitotoxic agent [28].

Estrogen and progesterone. The neuroprotective effects of these ovarian hormones in the CNS are well-documented [29, 30]. Progesterone treatment reduces limbic seizures in a variety of experimental models, including the kainic acid model of epilepsy, where it has been shown that low but not high doses of progesterone reduce seizures, thereby reducing damage to the hippocampus [31]. The progesterone metabolites, dihydroprogesterone and allopregnanolone, significantly diminish cell loss in the hippocampus after KA treatment [30-33]. Allopregnanolone is a potent allosteric modulator of the GABA-A receptor, and several studies propose that the interaction between allopregnanolone and the GABA-A receptor is the mechanism whereby progesterone attenuates seizure activity [reviewed in 31]. These data suggest that progesterone and/or its metabolites might play an important role in the neuroprotective effects of lactation since this hormone is elevated for a significant period during this phase.

With regard to estrogen, a few studies suggest that despite the potential for increased seizures, estrogen may reduce 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 17-β 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 diestrus rats, suggesting a strong correlation between expression of ERs, especially ER-β, in lactating CA1 and CA3 hippocampal regions in response to kainate administration, and the neuroprotection 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 comparable 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 apoptosis [41], it suppresses programmed cell death, it forms ho-

modimers as well as heterodimers with a homologous protein Bax, a promoter of cell death, and it is required to maintain cellular viability in the CNS [42]. Increased Bcl-2 label in the CA1 hippocampal region of lactating animals correlates with less damage [10]. In addition, there are studies suggesting that antioxidant effects seen with high doses of estrogen protect neurons from cell death [43], which could be another protective action of ovarian steroids.

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 estimulates 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 ovarectomized 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.

ACKNOWLEDGMENTS

The author acknowledge Dr. Dorothy Pless for grammatical review. Research support for studies described in this paper was obtained from PAPIIT-UNAM and CONACYT.

REFERENCES

[1] Russell JA, Douglas AJ, Ingram CD. Brain preparations for maternity-adaptive changes in behavioral and neuroendocrine systems during pregnancy and lactation. An overview. Prog Brain Res 2001; 133: 1-38.

[2] Woodside B. Morphological plasticity in the maternal brain: comment on Kinsley *et al*.; motherhood and the hormones of pregnancy modify concentrations of hippocampal neuronal dendritic spines. Horm Behav 2006; 49: 129-30.

[3] Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. Annu Rev Neurosci 2005; 28: 377-401.

[4] Oliet SH. Functional consequences of morphological neuroglial changes in the magnocellular nuclei of the hypothalamus. J Neuroendocrinol 2002; 14: 241-6.

[5] Armstrong WE, Hatton GI. The puzzle of pulsatile oxytocin secretion during lactation: some new pieces. Am J Physiol Regul Integr Comp Physiol 2006; 291: R26-8.

[6] Numan M. Motivational systems and the neural circuitry of maternal behavior in the rat. Dev Psychobiol 2007; 49:12-21.

[7] Lightman SL, Windle RJ, Wood SA, Kershaw YM, Shanks N, Ingram CD. Peripartum plasticity within the hypothalamo-pituitary-adrenal axis. Prog Brain Res 2001; 133: 111-29.

[8] Kinsley CH, Madonia L, Gifford GW, *et al*. Motherhood improves learning and memory. Nature 1999; 402: 137-38.

[9] Kinsley CH, Trainer R, Stafisso-Sandoz G *et al*. Motherhood and the hormones of pregnancy modify concentrations of hippocampal neuronal dendritic spines. Horm Behav 2006; 49: 131-42.
[10] Vanoye-Carlo A, Morales T, Aguilar E, Mendoza Rodríguez A, Cerbón MA. Neuroprotective effects of lactation against kainic acid treatment in the dorsal hippocampus of the rat. Horm Behav 2008; 53:112-3.
[11] Cabrera V, Cantú D, Ramos E, Vanoye-Carlo A, Cerbón M, Morales T. Lactation is a natural model of hippocampus neuroprotection against excitotoxicity. Neurosci Lett 2009; 461: 136-9.
[12] Abbud R, Hoffman GE, Smith MS. Cortical refractoriness to N-methyl-D,L-aspartic acid (NMA) stimulation in the lactating rat: recovery after pup removal and blockade of progesterone receptors. Brain Res 1993; 604: 16-23.
[13] Standley CA. N-methyl-D-aspartate receptor binding is altered and seizure potential reduced in pregnant rats. Brain Res 1999; 844: 10-9.
[14] Berzaghi Mda P, Amado D, Cavalheiro EA. Pregnancy decreases the frequency of spontaneous recurrent seizures in rats with kainic acid lesions of the hippocampus. Epilepsy Res 1987; 1: 142-4.
[15] Ben-Ari Y, Cossart R. Kainate, a double agent that generates seizures: two decades of progress. Trends Neurosci 2000; 23: 580-7.
[16] Djebaili M, Lerner-Natoli M, Montpied P, Baille V, Bockaert J, Rondouin G. Molecular events involved in neuronal death induced in the mouse hippocampus by in-vivo injection of kainic acid. Brain Res Mol Brain Res 2001; 93: 190-8.
[17] Ferrer I. Cell signaling in the epileptic hippocampus. Rev Neurol 2002; 34: 544-50.
[18] Choi DW. Excitotoxic cell death. J Neurobiol 1992; 23: 1261-76.
[19] Frerking M, Nicoll RA. Synaptic kainate receptors. Curr Opin Neurobiol 2000; 10: 342-51.
[20] Wisden W, Seeburg PH. A complex mosaic of high-affinity kainate receptors in rat brain. J Neurosci 1993; 13: 3582-98.
[21] Palomero-Gallagher N, Bidmon HJ, Zilles K. AMPA, kainate, and NMDA receptor densities in the hippocampus of untreated male rats and females in estrus and diestrus. J Comp Neurol 2003; 459: 468-74.
[22] Zhang X, Gelowitz D, Lai C, Boulton A, Yu P. Gradation of kainic acid-induced rat limbic seizures and expression of hippocampal heat shock protein-70. European J Neurosci 1997; 9: 760-9.
[23] Young D, Lawlor PA, Leone P, Dragunow M, During MJ. Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. Nat Med 1999; 5: 448-53.
[24] Sapolsky RM, Krey LC, McEwen BS. Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. J Neurosci 1985; 5: 1222-27.
[25] Dinkel K, MacPherson A, Sapolsky RM. Novel glucocorticoid effects on acute inflammation in the CNS. J Neurochem 2003; 84: 705-16.
[26] Joels M, Bosma A, Hendriksen H, Diegenbach P, Kamphuis W. Corticosteroid actions on the expression of kainate receptor subunit mRNAs in rat hippocampus. Brain Res Mol Brain Res 1996; 37: 15-20.
[27] Sorrells SF, Sapolsky RM. An inflammatory review of glucocorticoid actions in the CNS. Brain Behav Immun 2007; 21: 259-72.
[28] Simard AR, Rivest S. Neuroprotective effects of resident microglia following acute brain injury. J Comp Neurol 2007; 504: 716-29.
[29] Hoffman GE, Merchenthaler I, Zup SL. Neuroprotection by ovarian hormones in animal models of neurological disease. Endocrine 2006; 29: 217-31.
[30] Singh M. Mechanisms of progesterone-induced neuroprotection. Ann N Y Acad Sci 2005; 1052: 145-51.
[31] Hoffman GE, Moore N, Fiskum G, Murphy AZ. Ovarian steroid modulation of seizure severity and hippocampal cell death after kainic acid treatment. Exp Neurol 2003; 182: 124-34.
[32] Ciriza I, Azcoitia I, Garcia-Segura LM. Reduced progesterone metabolites protect rat hippocampal neurones from kainic acid excitotoxicity *in vivo*. J Neuroendocrinol 2004; 16: 58-63.
[33] Dubrovsky BO. Steroids, neuroactive steroids and neurosteroids in psychopathology. Prog Neuropsychopharmacol Biol Psychiatry 2005; 29: 169-92.
[34] Jover T, Tanaka H, Calderone A, *et al.* Estrogen protects against global ischemia-induced neuronal death and prevents activation of apoptotic signaling cascades in the hippocampal CA1. J Neurosci 2002; 22: 2115-24.
[35] Mellon SH, Griffin LD. Neurosteroids: biochemistry and clinical significance. Trends Endocrinol Metab 2002; 13: 35-43.
[36] Zhao L, Wu TW, Brinton RD. Estrogen receptor subtypes alpha and beta contribute to neuroprotection and increased Bcl-2 expression in primary hippocampal neurons. Brain Res 2004; 1010: 22-34.
[37] Azcoitia I, Fernandez-Galaz C, Sierra A, Garcia-Segura LM. Gonadal hormones affect neuronal vulnerability to excitotoxin-induced degeneration. J Neurocytol 1999; 28: 699-710.
[38] Veliskova J, Velisek L, Galanopoulou AS, Sperber EF. Neuroprotective effects of estrogens on hippocampal cells in adult female rats after status epilepticus. Epilepsia 2000; 41 Suppl. 6: S30-5.
[39] Garcia-Ovejero D, Azcoitia I, Doncarlos LL, Melcangi RC, Garcia-Segura LM. Glia-neuron crosstalk in the neuroprotective mechanisms of sex steroid hormones. Brain Res Brain Res Rev 2005; 48:273-86.
[40] Vanoye-Carlo A, Mendoza-Rodriguez A, Morales T, Langley E, Cerbón M. Estrogen receptors increased expression during hippocampal neuroprotection in lactating rats. J Steroid Biochem Mol Biol 2009; 116:1-7.
[41] Shacka JJ, Roth KA. Regulation of neuronal cell death and neurodegeneration by members of the Bcl-2 family: therapeutic implications. Curr Drug Targets CNS Neurol Disord 2005; 4: 25-39.
[42] Strauss KI, Narayan RK, Raghupathi R. Common patterns of bcl-2 family gene expression in two traumatic brain injury models. Neurotox Res 2004; 6: 333-42.
[43] Ozacmak VH, Sayan H. The effects of 17beta estradiol, 17alpha estradiol and progesterone on oxidative stress biomarkers in ovariectomized female rat brain subjected to global cerebral ischemia. Physiol Res 2009; 58: 909-12.
[44] Pinilla L, Tena-Sempere M, Aguilar R, Aguilar E. Effects of N-methyl-D-aspartic acid and kainic acid on prolactin secretion in hyper- and hypoprolactinaemic conditions. Eur J Endocrinol 1998; 138: 460-66.
[45] Zelena D, Makara GB, Nagy GM. Effect of glutamate receptor antagonists on suckling-induced prolactin release in rats. Endocrine 2003; 21: 147-52.
[46] Israel JM, Poulain DA. 17-Oestradiol modulates *in vitro* electrical properties and responses to kainate of oxytocin neurones in lactating rats. J Physiol 2000; 524: 457-70.
[47] Buijs RM. Intra- and extrahypothalamic vasopressin and oxytocin pathways in the rat. Pathways to the limbic system, medulla oblongata and spinal cord. Cell Tissue Res 1978; 192: 423-35.
[48] Tomizawa K, Iga N, Lu YF *et al*. Oxytocin improves long-lasting spatial memory during motherhood through MAP kinase cascade. Nat Neurosci 2003; 6: 384-90.
[49] Windle RJ, Kershaw YM, Shanks N, Wood SA, Lightman SL, Ingram CD. Oxytocin attenuates stress-induced c-fos mRNA expression in specific forebrain regions associated with modulation of hypothalamo-pituitary-adrenal activity. J Neurosci 2004; 24: 2974-82.
[50] Bridges RS, Ronsheim PM. Prolactin (PRL) regulation of maternal behavior in rats: bromocriptine treatment delays and PRL promotes the rapid onset of behavior. Endocrinology 1990; 126: 837-48.
[51] Torner L, Karg S, Blume A, Kandasamy M, Kuhn HG, Winkler J, Aigner L, Neumann ID. Prolactin prevents chronic stress-induced decrease of adult hippocampal neurogenesis and promotes neuronal fate. J Neurosci 2009; 29: 1826-33.
[52] Torner L, Neumann ID. The brain prolactin system: involvement in stress response adaptations in lactation. Stress 2002; 5: 249-57.
[53] Donner N, Bredewold R, Maloumby R, Neumann ID. Chronic intracerebral prolactin attenuates neuronal stress circuitries in virgin rats. Eur J Neurosci 2007; 25: 1804-14.
[54] Nogami H, Hoshino R, Ogasawara K, Miyamoto S, Hisano S. Region-specific expression and hormonal regulation of the first exon variants of rat prolactin receptor mRNA in rat brain and anterior pituitary gland. J Neuroendocrinol 2007; 19: 583-93.
[55] Moderscheim TA, Gorba T, Pathipati P, Kokay IC, Grattan DR, Williams CE, Scheepens A. Prolactin is involved in glial responses following a focal injury to the juvenile rat brain. Neuroscience 2007; 145: 963-73.

[56] Gregg C, Shikar V, Larsen P, Mak G, Chojnacki A, Yong VW, Weiss S. White matter plasticity and enhanced remyelination in the maternal CNS. J Neurosci 2007; 27: 1812-23.
[57] Doretto MC, Oliveira-e-Silva M, Ferreira-Alves DL, Pires SG, Garcia-Cairasco N, Reis AM. Effect of lactation on the expression of audiogenic seizures: association with plasma prolactin profiles. Epilepsy Res 2003; 54: 109-121.
[58] Kinsley CH, Lambert KG. Reproduction-induced neuroplasticity: natural behavioural and neuronal alterations associated with the production and care of offspring. J Neuroendocrinol 2008; 20: 515-25.
[59] Ananth C, Gopalakrishnakone P, Kaur C. Protective role of melatonin in domoic acid-induced neuronal damage in the hippocampus of adult rats. Hippocampus 2003; 13: 375-87.
[60] Lee JK, Won JS, Singh AK, Singh I. Statin inhibits kainic acid-induced seizure and associated inflammation and hippocampal cell death. Neurosci Lett 2008; 440: 260-4.

Received: July 14, 2009 Revised: November 08, 2009 Accepted: January 20, 2010