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Dynamics of mother-pup interactions: tradeoff between environment and physiology

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Abstract

The emergence and maintenance of maternal behavior are under the influence of environmental cues such as light and dark periods. This article discusses the characteristic neurobiology of the behavioral patterns of lactating rats. Specifically, the hormonal basis and neurocircuits that determine whether mother rats show typical sequential patterns of behavioral responses are discussed. During lactation, rats express a sequential pattern of behavioral parameters that may be determined by hormonal variations. Sensorial signals emitted by pups, as well as environmental cues, are suggested to serve as conditioned stimuli for these animals. Finally, the expression of maternal behavior is discussed under neuroeconomic and evolutionary perspectives.

Keywords: maternal behavior, hormones, light/dark cycle

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Introduction

The influence of circadian factors on the modulation of maternal behavior is poorly understood. Particularly interesting is how circadian factors such as daylight interact with hormonal changes during late pregnancy and early lactation. The activation of biochemical and neural pathways modulates systems that are influenced by environmental factors during this critical period in the female organism, generating important behavioral changes. The intensity by which some hormone levels are influenced by circadian, endogenous, and environmental cues varies according to the physiological state (Bridges et al., 1993). Hormonal changes occur during late pregnancy, determining the onset of maternal behavior (Bridges, 1984). Two heuristically significant paradigms are involved in this context: pregnancy-induced changes in grooming patterns (in which female rats increase the time spent licking their mammary glands; Serafim and Felicio, 2002) and the opioidergic-progesterone interplay by the end of pregnancy, generating tardive influences on nursing (Cruz et al., 2010, 2011; Sukikara et al., 2011). Among the hormones involved in these processes are estrogen, progesterone, prolactin, oxytocin, vasopressin, corticosterone, cholecystokinin (CCK), and β-endorphin (Felicio et al., 1991; Mann et al., 1995). Circadian variations in serum levels have been described for some of these hormones, whereas the expression of these rhythms is modulated by the reproductive physiological state (Bridges et al., 1993; Wharfe et al., 2011).

The complexity of the interplay between endocrinology and ethology affords a rich source of information about the role of behavior in modifying the internal environment. Some neuroethological approaches in which naturally occurring patterns of behavior generate functional changes in neural pathways allow the investigation of how they can influence endocrine function. Therefore, this review discusses the circadian influences on hormones and its correlation with maternal behavior. Possible neural sites and mechanisms that determine such influences are discussed. Finally, research perspectives in this area are discussed in an evolutionary–developmental (*evo-devo*) context.

Hormones: Role in Maternal Behavior and Their Rhythms

Hormonal changes that occur during late pregnancy and lactation, such as changes in the levels of estrogen, progesterone, prolactin, oxytocin, β-endorphin, vasopressin, and CCK, are needed for the establishment and expression of maternal behavior. These hormones interact with other hormones and neurotransmitters, influencing various aspects of reproductive physiology. Usually the final behavioral output observed is a consequence of the sequential or simultaneous actions of various hormones.

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Thus, some hormones may be mentioned in sections that discuss other hormones. This occurs when their interactions are functionally relevant.

Progesterone

Progesterone is important for the maintenance of pregnancy and also influences maternal behavior. Serum concentrations of this hormone remain elevated during most of the pregnancy, and the levels drop abruptly before parturition. These temporal changes in progesterone concentrations appear to play a role in the induction of the expression of maternal behavior. Recently, our group described an interesting relationship between progesterone and opioids in the control of maternal behavior in which we investigated the endocrine aspects of this animal model. Serum corticosterone, progesterone, estradiol, and prolactin concentrations were measured after each morphine injection from day 17 to day 21 of pregnancy. No significant differences were found in serum corticosterone, estradiol, or prolactin concentrations. However, progesterone concentrations significantly increased from day 18 to day 20 (Sukikara et al., 2011). Another experiment investigated the effects of daily progesterone injections during the same period on the sensitivity to the inhibitory effects of morphine on maternal behavior during lactation. Progesterone-pretreated dams were more sensitive to the opioidergic inhibition of maternal behavior (Cruz et al., 2011). This effect is similar to that observed in morphine-pretreated animals, suggesting that increased progesterone concentrations may account for the behavioral effects observed in lactating rats treated with morphine during pregnancy (Felicio and Canteras, 2008). Thus, the interaction between endogenous opioids and progesterone may play a role in programming the brain to optimize adaptation to the post-partum environment by the mother and offspring.

Prolactin

Prolactin is a phylogenetically ancient hormone. The diversity of action of prolactin involves osmoregulation, amphibian metamorphosis, control of immune responses and inflammation, luteotrophic and luteolitic actions, and some centrally mediated phenomena such as stimulation of the production and secretion by the pigeon "crop sac" and the regulation of sexual behavior and parental behavior (Nasello and Felicio, 1991; Carvalho-Freitas et al., 2011). By acting centrally, prolactin facilitates maternal behavior by acting on prolactin receptors in the medial preoptic area (MPOA). More than one kinetic mechanism may allow prolactin to reach this locus (Felicio and Bridges, 1992). Central prolactin originates from the pituitary and reaches central loci that are sensitive to maternal behavior by spreading from the hypophyseal portal tuberal system and may be actively transported through the choroid plexus, reaching the ventricular system and then spreading throughout the central nervous system. Prolactin may also be synthesized in the central nervous system and might be involved in neurogenesis and maternal memory. Although the functional meaning of such findings with regard to maternal behavior remains to be investigated, the physiological conditions and time periods when prolactin interferes with brain function and behavior are the major factors that determine prolactin–behavioral interactions.

Cholecystokinin

Neuronal CCK is, in its majority, the sulfated terminal octapeptide CCK8. A small fraction the four amino acid final sequence CCK4, which is identical to gastrin terminal, is present in the central nervous system as well. The function of CCK varies according to specific CCK pathways and specific brain regions. It has also met several criteria to be designated a neurotransmitter. The distribution of CCK8 within the hypothalamus and limbic system overlaps with steroid-concentrating regions. The central concentrations of CCK8 appear to depend on gonadal hormones because gonadectomy induced a clear decrease in CCK. In the amygdala and ventromedial hypothalamic nucleus, CCK concentrations vary according to the phase of the estrous cycle. Postprandial CCK release increases during pregnancy (Uvnas-Moberg, 1989). In addition to central CCK transmission, peripheral signals of this hormone can trigger subdiaphragmatic terminals of the vagus nerve. Suckling-induced CCK release appears to be vagal nerve-mediated. Abdominal vagotomy blocked the suckling-induced release of CCK. Cholecystokinin also blocked the opioid-induced inhibition of maternal behavior, especially when it was administered directly in the preoptic area (POA) and lateral periaqueductal gray (lPAG; Felicio et al., 1991; Mann et al., 1995; Miranda-Paiva et al., 2007). Both CCK1 and CCK2 (previously referred to as CCKA and CCKB) receptor antagonists potentiate the inhibitory effects of morphine on ongoing maternal behavior. This is consistent with previous results that demonstrated antagonistic effects of CCK and β-endorphin on this behavior. These results suggest that both CCK receptor subtypes might be involved in this multiple peptidergic control of maternal behavior in lactating rats. We also found that pretreatment with the CCK1 receptor antagonist lorglumide during late pregnancy disrupted maternal behavior in rats (Miranda-Paiva et al., 2002).

Curiously, neuronal CCK and dopamine are negatively correlated with circadian rhythms. Circadian variations in cholecystokinin and dopamine in the limbic system present distinct harmonic circadian rhythms (12 h, 6 h). Cholecystokinin decreases during the light phase and reaches a peak during the dark phase, and the opposite was found for dopamine. Thus, CCK/dopamine rhythms are negatively correlated, and the differences were significant at 11:00 AM, 1:00 PM, 9:00 PM, and 3:00 AM. These results indicate that circadian processes are involved in the neuronal transmission of CCK and dopamine (Schade et al., 1993). The same authors suggested the existence of a close interaction between CCK and dopamine in various areas of the rat brain, independent of colocalization (Schade et al., 1995).

Opioids

Morphine, the typical opioid agonist, inhibits maternal behavior in lactating rats (Bridges and Grimm, 1982). The modulatory effects of opioids on maternal behavior are plastic and adaptive. Both tolerance (for its sedative effects) and reverse tolerance and sensitization (for its excitatory and addictive effects) have been well described (Miranda-Paiva et al., 2001; Cruz et al., 2010). The plasticity of opioid transmission is important for the versatility and adaptation necessary for a lactating mother. Opioid stimulation that has inhibitory effects on maternal behavior may stimulate foraging in adult mothers (Sukikara et al., 2006, 2007). Because the expression of these behaviors can be influenced by circadian rhythms, investigations of how decision-making is influenced by opioidergic stimulation in lactating rats are worthwhile.

Every mother must engage in survival issues where she must weigh the trade-offs between subsistence and reproduction. Recent data have begun to uncover the adaptive mechanisms that increase the chances of survival of lactating animals in various environments. Endogenous opioids may stimulate hunting by superseding maternal behavior during lactation, and mechanisms that involve opioidergic transmission during pregnancy and lactation might be reproductively meaningful. Thus, opioidergic transmission may play a role in the regulation of behavioral selection during lactation (Sukikara et al., 2007; Cruz et al, 2010). The onset of maternal behavior is closely related to the action of opioids in the MPOA during lactation. Immunohistochemical and pharmacological studies suggested the importance of the lPAG in the opioidergic inhibition of maternal behavior. The activation of other regions of the PAG is important for the postural kyphosis reflex that optimizes breastfeeding. Therefore, some questions emerge. Does the PAG play a role in breastfeeding cycles in the absence of predators or prey? Would such mechanisms play a role in the basic physiology of mother–infant interactions? Knowledge of the emergence and maintenance of maternal behavior and how it is controlled by interactions among environmental, biochemical, hormonal, and neural factors is highly relevant.

Functional Neuroanatomy of Maternal Behavior

Inhibitory pathways

The activity of inhibitory pathways prevents the expression of maternal behavior in virgin mammals. In virgin females, the major sensorial input that triggers such inhibition is the odor stimuli from a newborn. The olfactory input goes from the olfactory bulb to the medial amygdala. From the medial amygdala, some neurons project to the anterior hypothalamic area (AHA) and ventromedial hypothalamic nucleus (VMN). Other amygdala neurons project to the MPOA and bed nucleus of the stria terminalis (BNST). Therefore, the lack of maternal behavior observed in virgin rats may be attributable to exposure to pup-related odors that directly inhibits the MPOA/BNST. Alternatively, pup odors might activate brain regions that play an essential positive role in maternal behavior. The lack of expression of maternal behavior in virgin rats may be attributable to the inhibitory tone of projections from the medial amygdala to AHA/ventral medial nucleus. Medial amygdala projections to the MPOA/BNST appear to be functionally relevant for the expression of maternal behavior in lactating females (Sheehan et al., 2001). The AHN and VMN project to the PAG. Because the PAG is involved in the regulation of anxiety-like, fear, and escape behavior, activation of this structure may lead to avoidance/escape responses and other processes that prevent a maternal response. Thus, the PAG plays a dual role in which the dorsal PAG (dPAG), apart from organizing defensive responses, also appears to account for the behavioral inhibition of nondefensive responses such as maternal behavior (Sukikara et al., 2010).

Activation pathways

Medial preoptic area and ventral BNST (vBNST) neurons promote maternal behavior. Efferents from these regions project to the lateral septum (LS), shell region of the nucleus accumbens, AHN, VMN, ventral tegmental area (VTA), PAG, and retrorubral field (for review, see Numan, 2006).

Data from the literature support the hypothesis that the acute behavioral effects of dopamine receptor antagonists on maternal behavior are attributable to dopamine receptor blockade in the nucleus accumbens. Thus, limbic dopaminergic pathways play a role in ongoing maternal behavior (Silva et al., 2001, 2003). Projections from MPOA/vBNST neurons to the lateral septum (LS) appear to have functional implications in terms of promoting maternal behavior (Numan, 2006). Fos-expressing MPOA and vBNST neurons are activated during maternal behavior. Such MPOA neurons project to the VTA and LS and the medial hypothalamic region (Numan, 2006).

Maternal behavior that is indirect or not directed to the pup

The female brain undergoes significant reorganization toward motherhood. Neonates benefit from the mother's behavioral changes. Some of these changes, such as modifications of grooming patterns and nest building, begin to occur during pregnancy. Indirect maternal behaviors also include maternal aggression. Grooming behavior varies according to the female endocrine milieu. During pregnancy, female rats change their grooming patterns, tending to lick their mammary glands more than prior to pregnancy (Roth and Rosenblatt, 1966; Serafim and Felicio, 2002). This in turn has been shown to be important for mammary gland development and lactation. Thus, self-licking of the mammary glands is important for good lactation. Because mammary gland grooming is necessary for good lactation, its modulation might be part of a physiological process that leads to the optimization of the entire reproductive phenomenon. To be reproductively successful, mammals present different behavioral strategies.

Behaviors displayed during the first days immediately before and after parturition that are preparatory to the arrival of the young, such as nest building and threatening conspecifics in the case of maternal aggression, are considered to involve mechanisms that affect other behavioral systems that impact the mother's responses to their young including affect, attention, perception, behavioral flexibility, and learning.

Perspectives

Neuroeconomics in an evo-devo context

Evo-devo is a branch of biology that investigates the links between evolution and the development of different organisms. Analyzing maternal behavior in such a context is worthwhile and appears to have heuristic value. Exposure to peripuberal unbalanced diets can modify the formation of neuroendocrine systems, leading to dysfunction in adulthood, and predispose the body to serious diseases such as diabetes, obesity, and affective disorders (Sisk and Zehr, 2005). Studies in mice with induced obesity suggested that the developmental period between 3 and 5 weeks of age is critical to the propensity to diet-induced obesity (Ikenasio-Thorpe et al., 2007). An evo-devo overview is particularly helpful for coalescing a variety of multifactorial aspects including relevant development and phylogenetic aspects of the placenta and the immune and nervous systems. Evo-devo is also important with regard to the applicability of certain animal models to particular aspects of placental anatomy and physiology.

Achieving the best balance between subsistence and reproduction is one of the most important challenges for female mammals. Environmental perils and food availability must be considered and perhaps anticipated correctly. Thus, strong evolutionary pressure is placed on females to select those that are best able to exercise this balance. During pregnancy and after delivery, the central nervous system undergoes significant adjustments, with sensory and cognitive changes that result from changes in the intensity of the activation of circuits and formation of new connections. In addition to expressing maternal behavior toward their offspring, lactating females must also assess the risks and seek food in general, thus enabling their own subsistence. Understanding of the neural basis of these adjustments has been increased by the work of Kinsley and colleagues whose studies have described the positive effects of maternity on learning and memory (Kinsley et al., 1999; Kinsley and Amory-Meyer, 2011; Zimberknopf et al., 2011). Maternal care is a specific behavior for each species. Mental processes that involve the brain cortex are markedly different among lower species. Studies in lower animals related to cognitive function are not as likely to be helpful as those related to emotional disorders such as anxiety problems or depression or memory disorders related to the hippocampus. Cognition is associated with the human cortex that developed during a recent brief period of evolution, whereas emotion and memory are associated with brain structures that have not substantially changed over long evolutionary periods between lower and higher species. The emergence and maintenance of maternal behavior are controlled by interactions between environmental, biochemical, hormonal, and neural factors (Numan and Woodside, 2010).

Role of reproductive immunology

Mammalian reproduction may be considered an immunological paradox. A pregnant female must adapt her immunological system to hold a developing fetus. The uterus is the very first environment to which one must adapt. Reproductive experience has been shown to generate functional changes in the immune system. Multiparous female rats generally show greater resilience to stress, decreased anxiety, and better memory ability than female rats that have never experienced motherhood (Kinsley et al., 1999). Moreover, neural changes remain long after the last pregnancy. Among the modifications related to reproductive experience are behavioral, neural, and neuroendocrine changes in rodents. The time of day induces changes in dopamine-related behavioral, neurochemical, and endocrine responses. Yawning and stereotypy induced by the dopamine receptor agonist apomorphine change according to the time of day and previous reproductive experience (Byrnes et al., 2001; Hucke et al., 1998, Zimberknopf et al., 2011; Nasello et al., 1995). Studies of striatal and hypothalamic neurotransmitter concentrations during daylight hours have shown that reproductive experience increases striatal and hypothalamic dopamine levels in pregnant rats (Felicio et al., 1996; Sider et al., 2003). Prolactin has also been identified as a possible immunoregulatory factor in rodents. Lactation was recently shown to strongly affect the immune system in laboratory rats, but the impact on blood and mesenteric lymph nodes varies (Jaedicke et al., 2009). The activity of peritoneal macrophages in lactating rats may be modulated by prolactin and caused by dopamine receptor blockade. The intensity and direction of this change depends on the time of incubation and previous reproductive experience in females. These data suggest that reproductive experience is associated with a reduction of serum prolactin levels. Cells in experienced female organisms, including macrophages, also become more sensitive to the effects of prolactin. The possibility that reproductive experience-induced changes in the neuroendocrine and immune systems in female rats play a role during lactation appears likely. Future studies are necessary to investigate the direct and indirect impacts of immunological processes on the expression of maternal behavior.

In summary, environmental factors such as the light/dark cycle and food availability interact with endogenous cues such as hormonal variations, immunological function, and neuronal activation to influence postpartum behaviors. The way in which these interactions occur is a major field of basic and translational investigation. This research approach may place maternal behavior in a more appropriate neuroethological context.

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