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Hormonal and non-hormonal bases of maternal behavior: The role of experience and epigenetic mechanisms

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ABSTRACT

This article is part of a Special Issue "Parental Care".

Though hormonal changes occurring throughout pregnancy and at the time of parturition have been demonstrated to prime the maternal brain and trigger the onset of mother–infant interactions, extended experience with neonates can induce similar behavioral interactions. Sensitization, a phenomenon in which rodents engage in parental responses to young following constant cohabitation with donor pups, was elegantly demonstrated by Rosenblatt (1967) to occur in females and males, independent of hormonal status. Study of the non-hormonal basis of maternal behavior has contributed significantly to our understanding of hormonal influences on the maternal brain and the cellular and molecular mechanisms that mediate maternal behavior. Here, we highlight our current understanding regarding both hormone-induced and experience-induced maternal responsivity and the mechanisms that may serve as a common pathway through which increases in maternal behavior are achieved. In particular, we describe the epigenetic changes that contribute to chromatin remodeling and how these molecular mechanisms may influence the neural substrates of the maternal brain. We also consider how individual differences in these systems emerge during development in response to maternal care. This research has broad implications for our understanding of the parental brain and the role of experience in the induction of neurobiological and behavior changes.

Introduction

Hormonal changes occurring during gestation serve a critical role in altering maternal physiological and neuroendocrine systems to facilitate fetal development and prepare the mother for parturition and lactation. These hormones also induce both short- and long-term changes in the maternal brain that contribute to maternal behavior during the postnatal period. Estrogen and progesterone priming with downstream consequences for prolactin and oxytocin systems have been explored extensively in the context of maternal behavior, with converging evidence from both pharmacological and genetic studies illustrating the mediating role of these hormones. However, maternal behavior can occur in the absence of hormonal priming. In a seminal paper titled "Nonhormonal Basis of Maternal Behavior in the Rat" published in Science in 1967, Jay Rosenblatt established empirical evidence for the role of exposure to pups in eliciting maternal behavior among both male and female adult rats (Rosenblatt, 1967). These findings were striking and suggestive that though hormones may influence the onset of maternal responses during the postnatal development of offspring, experience with offspring could similarly trigger these behavioral responses. These initial findings have formed the basis of many ongoing research avenues within the study of the maternal brain. In particular, recent studies of experiential effects on maternal behavior have highlighted the critical role of epigenetic mechanisms in shaping maternal responses. Here, we will describe how the ongoing study of the non-hormonal basis of maternal behavior has contributed to these research themes and the implications of this research for our understanding of variation in the parental brain.

Non-hormonal basis of maternal behavior

Rosenblatt (1967), expanding on the work of Weisner and Sheard (1933), demonstrated that hormonal stimulation is not required to induce the onset of maternal behavior in rats. Using an experimental design in which rats were housed continuously across consecutive days with 5–10 day old pups, maternal responses (retrieving and licking of pups, crouching over pups, nest-building) were found to emerge in both male and female adult rats within the period of 10–15 days (Rosenblatt, 1967; Weisner and Sheard, 1933). The process by which continual exposure to pups induces maternal responses in rats has been termed sensitization. The discovery of the phenomenon of sensitization was groundbreaking and addressed several fundamental questions regarding the nature of maternal behavior. First, continual cohabitation with pups induced the onset of maternal behavior in

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nearly all the rats tested. This finding suggests that the neural substrate that supports caregiving behaviors must exist in rats of both sexes and activation of these systems can occur in the absence of hormone stimulation. Subsequent studies building on this finding have demonstrated that the hormonal events of pregnancy and birth function to reduce the amount of exposure to pups that is sufficient to induce caregiving behaviors (Siegel and Rosenblatt, 1975a,b). Second, the findings reported in Rosenblatt (1967) suggest that circulating ovarian and/or pituitary hormones are not involved in the pup-induced onset of maternal behavior. Removal of the ovaries or pituitary gland did not delay the onset of maternal behavior. Third, cohabitation with pups was not found to alter estrous cycling in gonad intact virgin females, suggesting that sensitization is not mediated by pup-induced changes in peripheral steroid hormone secretion. More recently, it has also been determined that pup-induced maternal behavior is not mediated by local steroid hormone production within the brain (neurosteroids). Transgenic mice lacking a functional copy of the aromatase gene, which is required for synthesis of estradiol in the brain and periphery, show sensitization that is not significantly different from virgin female mice (Stolzenberg and Rissman, 2011).

Though the induction of maternal behavior through repeated pup exposure is not likely to occur under natural conditions (pups would not survive without milk), study of the non-hormonal basis of maternal behavior in rats has facilitated the investigation of the neural substrate upon which hormonal fluctuations during pregnancy and birth act to induce maternal behavior (Mayer and Rosenblatt, 1979). Rosenblatt described the non-hormonal and hormonal bases of maternal behavior as distinct processes that are mediated, at least in part, by overlapping or common mechanisms (Rosenblatt et al., 1988). For example, the onset of maternal behavior (hormonal or non-hormonal) involves the modification of two classes of behavioral responses toward pups. For the neophobic female rat, fear responses must be inhibited toward novel pups. However, reducing fearfulness alone is not sufficient for a rapid onset of maternal behavior (Fleming, 1989; Fleming and Rosenblatt, 1974a,b). A rapid onset of maternal behavior (hormonal or non-hormonal) also requires an increase in approach responses toward pups, suggesting the role of neural systems involved in motivation. Understanding of the distinct vs. common pathways underlying hormonal and non-hormonal maternal responses in rats may also facilitate the investigation of the neural systems that sustain maternal care over the course of the extended postpartum period (Numan, 2006, 2015; Numan and Insel, 2003; Numan and Stolzenberg, 2009). Pregnancy hormones are involved in priming the brain to respond to infant stimuli. However, hormone levels reduce significantly within a few hours of birth, and the long-term maintenance of maternal behavior throughout the postpartum period is hormone-independent (Bridges, 1975; Numan, 2015; Numan and Insel, 2003; Rosenblatt, 1975a).

Hormonal basis of maternal behavior

Our understanding of the molecular and neural pathways through which pup exposure comes to alter maternal behavior requires consideration of the pathways through which hormones influence maternal behavior. The pattern of pregnancy hormone stimulation that primes the rodent maternal brain begins at mating when cervical stimulation initiates a twice-daily pattern of prolactin release from the anterior pituitary (for approximately 9–10 days after mating) that functions to prevent degradation of the corpora lutea (Terkel and Sawyer, 1978). Consequently, there is a steady increase in progesterone (P) during the first part of pregnancy, which prepares the uterine endometrium for implantation and maintains a uterine environment that promotes growth of the embryo (Csapo and Resch, 1979a,b; Zakar and Hertelendy, 2007). At mid-pregnancy, placental lactogens support the luteal secretion of P that is necessary for the continuation of pregnancy. Whereas rising levels of P promote the maintenance of pregnancy, the decline of P beginning in mid-pregnancy initiates a shift in hormonal events that eventually regulate the timing of parturition. Increasing levels of estradiol (E) secreted from the ovary prepare the uterine endometrium for labor by promoting rhythmic contractility of the uterus, and the sharp decline in P just before birth removes the inhibitory tone on the uterine muscles and allows them to respond to the surge in oxytocin (OT) from the posterior pituitary that induces uterine contraction and labor (Hertelendy and Zakar, 2004; Zhang et al., 1992).

Though the pregnant rat is exposed to circulating levels of pregnancy hormones, responsiveness toward pup stimuli is delayed until the final hours prior to parturition (Mayer and Rosenblatt, 1984). Rosenblatt hypothesized that the hormonal fluctuations present at this time may also prime the brain to respond to infant stimuli. Testing this hypothesis, it was determined that factors circulating in the blood at the time of birth and just after birth were responsible for initiating maternal responsiveness (Terkel and Rosenblatt, 1968, 1972) and could induce shortened (but not immediate) sensitization latencies in the virgin rat. Artificial termination of pregnancy by hysterectomy (removal of uterus and fetuses) during the latter half of pregnancy, which results in a decline in P and rise in E secretion produces an immediate onset of maternal behavior when pups are presented 48 h after surgery (Rosenblatt and Siegel, 1975). It is evident that the combined decline in P and elevation in E are necessary for the rapid induction of maternal behavior (Siegel and Rosenblatt, 1978). Thus, hormonal changes throughout pregnancy play a role in gradually shifting the behavioral responses of females and to trigger responding to pups at parturition. These hormonal changes influence several neural systems, and in particular modify hormone receptor levels and neural activity within the medial preoptic area of the hypothalamus (MPOA) (Numan, 2015; Numan and Insel, 2003). Estradiol benzoate (EB) implants in the MPOA of 16-day pregnant hysterectomized-ovariectomized females induces a rapid onset of maternal behavior (Numan et al., 1977). Moreover, pregnancy hormones have been found to increase estrogen receptor distribution and binding in the MPOA (Giordano et al., 1989, 1991), which contributes to the cellular and molecular changes that shape the maternal brain.

Interplay between hormones and epigenetics in organizing maternal responsivity

Estrogen acts through multiple cellular/molecular pathways to alter neural function and behavior (Numan, 2015; Stolzenberg and Numan, 2011; Vasudevan and Pfaff, 2008). However, the best characterized route of action involves estradiol-induced changes in gene transcription. Estradiol alters the transcription of estrogen responsive genes by binding estrogen receptors (ERα and ERβ), which are ligand-activated transcription factors. The ERα and ERβ receptor subtypes share almost 100% amino acid homology, but are encoded by different genes and have distinct transcriptional consequences (Delaunay et al., 2000; Katzenellenbogen and Katzenellenbogen, 2000). At these sites, ERs assemble multi-protein complexes, which function to remodel chromatin, recruit transcriptional machinery, and induce gene transcription (Green and Carroll, 2007; Mann et al., 2011; Nilsson et al., 2001). Estrogen receptors also recruit repressive protein complexes involved in silencing gene expression.

Within the nucleus, transcription factor action at DNA sequences is ultimately regulated by chromatin structure. Chromatin refers to DNA and the histone protein octamers that the DNA is wound around. The packaging of chromatin within the nucleus has dramatic effects on gene regulation. Tight chromatin configurations block access of transcriptional machinery to transcription start sites, resulting in gene silencing (Razin, 1998). Following ligand binding, the transactivation domain of ER interacts with proteins in the p160 coactivator family to recruit additional proteins, which modify the structure of chromatin in order to induce gene transcription (Nilsson et al., 2001). In this context, chromatin remodeling is mediated by post-translational modifications