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Review

Maternally responsive neurons in the bed nucleus of the stria terminalis and medial preoptic area: Putative circuits for regulating anxiety and reward

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ABSTRACT

Postpartum neuropsychiatric disorders are a major source of morbidity and mortality and affect at least 10% of childbearing women. Affective dysregulation within this context has been identified in association with changes in reproductive steroids. Steroids promote maternal actions and modulate affect, but can also destabilize mood in some but not all women. Potential brain regions that mediate these effects include the medial preoptic area (mPOA) and ventral bed nucleus of the stria terminalis (vBNST). Herein, we review the regulation of neural activity in the mPOA/vBNST by environmental and hormonal concomitants in puerperal females. Such activity may influence maternal anxiety and motivation and have significant implications for postpartum affective disorders. Future directions for research are also explored, including physiological circuit-level approaches to gain insight into the functional connectivity of hormone-responsive maternal circuits that modulate affect.

1. Introduction

Changes in reproductive steroids, such as those that occur during the puerperium, are associated with increased vulnerability for affective dysregulation (Soares and Zitek, 2008). In fact, an estimated 10–20% of perinatal women are afflicted by a mood disorder, such as anxiety or depression (Gaynes et al., 2005). Further, perinatal depression is the leading cause of maternal mortality, resulting from suicide (Osborne and Monk, 2013). The sequelae of these disorders entails not only elevated anxiety and disrupted mood for the mother, but also aversive outcomes for the developing infant (Hendrick et al., 2000; Grace et al., 2003). The symptomatology of postpartum affective disorders, such as anhedonia, anxiousness, and agitation (DelRosario et al., 2013), implies a dysregulation of neural circuitry that regulates emotion and motivation. However, the neurobiological etiology of postpartum affective disorders remains unclear, perhaps due to the complexity of hormonal and environmental contributors that influence maternal affect and the lack of previous tools to disentangle the functional elements of these neural circuits.

Throughout pregnancy, the brain organizes adaptations that prepare the mother for a timely parturition and the rapid onset of maternal care following parturition. Pregnancy hormones drive these adaptations before parturition, but afterward maternal actions are maintained by external infant stimuli (Brunton and Russell, 2008). Ordinarily, maternal brain adaptations reduce anxiety and promote maternal actions that facilitate infant-associated motivation and reward (Numan, 2007; Lonstein, 2007; Slattery and Neumann, 2008). However, neural maladaptation and hormone withdrawal during the puerperium may precipitate anxiety and depressive behavior. While environmental and hormonal correlates of maternal anxiety and mood (Brunton and Russell, 2008; Lonstein, 2007; Slattery and Neumann, 2008; Neumann, 2009), as well as relationships between the brain, endocrine systems, and maternal care (Numan, 2006, 2007; Bridges, 2014; Dulac et al., 2014; Rilling, 2013; Nephew and Murgatroyd, 2013) have been reviewed elsewhere, no review to date has focused on the precise hormone-responsive brain regions central to both maternal behavior and affective regulation. The most prominent candidates include the medial preoptic area (mPOA) and ventral bed nucleus of the stria terminalis (vBNST), two sexually dimorphic

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steroid-sensitive nuclei (Semaan and Kauffman, 2010; Xu et al., 2012) essential for maternal behavior (Tobiansky et al., 2013; Numan and Stolzenberg, 2009). In addition, the BNST regulates anxiety (Adhikari, 2014; Hammack et al., 2007; Davis et al., 2010) and motivated behavior (Adhikari, 2014; Davis et al., 2010; Stamatakis et al., 2014). Further, we have recently demonstrated that vBNST sub-circuits have opposing roles in divergent anxiety and reward states in male mice (Jennings et al., 2013). It is unclear whether similar circuit processing occurs in females or is influenced by reproductive steroids, parturition, or infant stimuli.

In this review, we examine the regulation of neural activity in the mPOA and vBNST by environmental and hormonal concomitants in the puerperal female. Since the vBNST and mPOA control similar maternal functions but lack clear anatomical demarcations and most tools used to date have been limited in their capacity to delineate between their functions, we will refer to them as an adjoining region (mPOA/vBNST). Herein, we discuss mPOA/vBNST inputs engaged by hormonal or infant stimuli and their potential outputs that orchestrate maternal actions, anxiety, and motivated behavior. We also identify candidate steroid and peptide hormones that could prepare the phenotype of mPOA/vBNST neurons late in pregnancy, allowing for altered reactivity to infant, emotional, or rewarding stimuli. Lastly, we identify gaps within the current literature that require further investigation, especially pertaining to the functional connectivity of circuits that influence anxiety and reward processing in response to hormones and maternal experience.

2. Maternal vBNST/MPOA circuitry

In mammalian females, external infant cues stimulate multiple sensory modalities to trigger maternal responses. In rodents, low frequency ultrasonic vocalization pup calls promote licking and nursing behavior by the mother (Ehret and Bernecker, 1986) and high frequency distress calls induce search and retrieval behavior by the mother when pups are separated from the nest (Hahn and Lavooy, 2005). Multisensory infant cues are processed by mPOA/vBNST circuits that receive hormonal and infant input and orchestrate complex maternal actions essential for offspring survival (Numan, 2006, 2007; Petrulis, 2013). The mPOA/vBNST receives widely distributed inputs from forebrain, hypothalamic, and brainstem regions and has reciprocal interactions with many of these structures, allowing for bidirectional control (illustrated in Fig. 1). Preoptic inputs that regulate maternal responsiveness have been reviewed in greater detail elsewhere (Numan, 2006; Dobolyi et al., 2014). The mPOA/vBNST are functional nodes within these circuits, as mPOA/vBNST lesions impair maternal behavior (Numan et al., 1988; Miceli et al., 1983; Numan, 1990; Terkel et al., 1979) and pup-associated motivation (Lee et al., 1999; Oxley and Fleming, 2000; Hansen et al., 1991a) in female rodents.

In rodents, chemosensory input originates from olfactory and vomeronasal systems and is relayed to the mPOA/vBNST through the medial amygdala (MeA) (Simerly and Swanson, 1986; Scalia and Winans, 1975; Krettek and Price, 1978). The vomeronasal organ and main olfactory epithelium are both important for retrieval of pups that stray from the nest (Fraser and Shah, 2014). Olfactory bulbectomy eliminates neuronal Fos activity in the MeA following mother–pup interactions and slightly decreases but does not eliminate Fos expression in the mPOA/vBNST (Numan and Numan, 1995; Walsh et al., 1996). However, these females still display relatively normal maternal behavior. Thus, other sensory stimuli are likely critical for the expression of maternal care (Fraser and Shah, 2014). Somatosensory infant input is provided during nursing, although nipple removal does not affect maternal behavior (except crouched nursing), maternal anxiety (Lonstein, 2005), or pup-induced Fos expression in the mPOA/vBNST (Numan and Numan, 1995; Stern and Johnson, 1990). However, when olfactory bulbectomy is coupled with nipple removal a significant reduction in Fos expression in the mPOA/vBNST is observed, although maternal care is still present (Numan and Numan, 1995). Therefore, infant generated neural

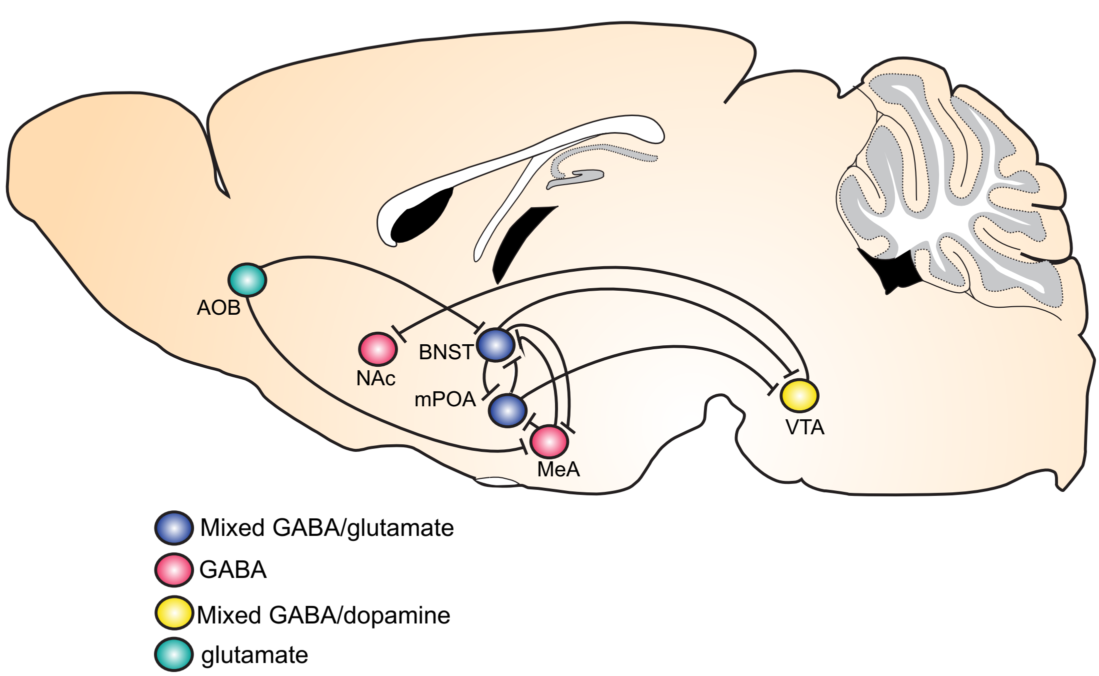

Fig. 1. Schematic detailing medial preoptic (mPOA) and bed nucleus of the stria terminalis (BNST) afferent and efferent connectivity implicated in maternal functions. The BNST receives inputs from the accessory olfactory bulb (AOB), medial amygdala (MeA), medial preoptic area (mPOA) and ventral tegmental area (VTA, projection not shown). The BNST sends projections to the VTA, MeA, and mPOA. The mPOA receives inputs from the AOB, MeA and BNST and sends outputs to the VTA. The VTA has reciprocal connections with the nucleus accumbens (NAc). Cellular phenotypes are indicated by color; mixed GABAergic/glutamatergic populations shown in purple, GABAergic shown in pink, mixed GABAergic/dopaminergic shown in blue, and glutamatergic shown in green.