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Mom doesn't care: When increased brain CRF system activity leads to maternal neglect in rodents

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ABSTRACT

Mothers are the primary caregivers in mammals, ensuring their offspring's survival. This strongly depends on the adequate expression of maternal behavior, which is the result of a concerted action of "pro-maternal" versus "anti-maternal" neuromodulators such as the oxytocin and corticotropin-releasing factor (CRF) systems, respectively. When essential peripartum adaptations fail, the CRF system has negative physiological, emotional and behavioral consequences for both mother and offspring often resulting in maternal neglect. Here, we provide an elaborate and unprecedented review on the implications of the CRF system in the maternal brain. Studies in rodents have advanced our understanding of the specific roles of brain regions such as the limbic bed nucleus of the stria terminalis, medial preoptic area and lateral septum even in a CRF receptor subtype-specific manner. Furthermore, we discuss potential interactions of the CRF system with other neurotransmitters like oxytocin and noradrenaline, and present valuable translational aspects of the recent research.

1. Introduction

Across all species, reproduction and hence, successful rearing of the young represents the major aim in life. Approximately 90% of all mammals have established a promiscuous, uniparental care system with the mother as primary caregiver due to her ability to lactate (Numan and Insel, 2003). Thus, maternal behavior has emerged as one of the most important pro-social female behaviors to secure the survival and development of the offspring. In mothers, this aim is achieved by a wide array of behavioral and physiological adaptations (Numan and Insel, 2003; Stolzenberg and Champagne, 2016; Stern and Lonstein, 2001). However, in up to 30% of mothers these adaptations are dysregulated and can lead to psychological disorders. Postpartum mood disorders such as postpartum depression or anxiety are detrimental and affect both mother and offspring, which often leads to infant neglect or even abuse. For developing such disorders, the main risk factor is stress (Dickens and Pawluski, 2018). Therefore, the key stress peptide corticotropin-releasing factor (CRF) has received increasing attention during the last years of (pre-)clinical research. This review will give an unprecedented, up-to-date overview of the vital implications of the CRF system in the occurrence of maternal behavior implementing data on several brain regions and providing an outlook about its potential role in the etiology of postpartum mood disorders.

2. The CRF system

The CRF system consists of four polypeptidergic ligands, i.e. CRF (protein: CRF; gene: *Crh*) (Vale et al., 1981); Urocortin (protein: UCN; gene: *Ucn*) 1 (Vaughan et al., 1995; Donaldson et al., 1996), UCN2 (Reyes et al., 2001) and UCN3 (Lewis et al., 2001), and the CRF receptors (protein: CRF-R; gene: *Crhr*) 1 and 2 (De Souza et al., 1985, 1984). While both CRF-R subtypes can be activated by UCN1 and CRF, the latter primarily binds to CRF-R1 with $\times 40$ higher affinity over CRF-R2. UCN2 and UCN3 are exclusive ligands for CRF-R2 (Reyes et al., 2001; Hsu and Hsueh, 2001). In addition, the CRF binding protein (protein: CRF-BP; gene: *Crhbp*) is a regulatory glycoprotein (Behan et al., 1995b, 1989; Potter et al., 1991); for review see (Ketchesin et al., 2017), which is released from astrocytes - and possibly from neurons - and binds free CRF and UCN1, thereby making these ligands unavailable for further receptor activation (Behan et al., 1995b), but also see (Westphal and Seasholtz, 2006). The CRF family members are expressed both peripherally and centrally as shown in rodents. In the periphery, CRF family members are found in blood vessels, skin, lung, testes, ovaries and placenta (Boorse and Denver, 2006). Centrally, CRF and CRF-R1 are widely distributed in cortical and subcortical areas while UCNs and CRF-R2 are mostly restricted to limbic brain regions. Among them are the bed nucleus of the stria terminalis (BNST), medial preoptic area (MPOA), lateral septum (LS), amygdala, and

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paraventricular nucleus (PVN), as well as some mid- and hindbrain regions, such as the locus coeruleus (LC), periaqueductal gray (PAG) and raphe nuclei (Vaughan et al., 1995; Reyes et al., 2001; Lewis et al., 2001; Hsu and Hsueh, 2001; Lovenberg et al., 1995; Potter et al., 1994; Chalmers et al., 1995; Van Pett et al., 2000; Swanson et al., 1983; Sawchenko and Swanson, 1985). The CRF system is involved in the regulation of a variety of peripheral and central responses to stress. Peripherally, CRF mainly initiates the hypothalamo-pituitary-adrenal (HPA) axis by stimulating the release of adrenocorticotropic hormone (ACTH) from the pituitary, which in turn activates the release of glucocorticoids from the adrenals (cortisol in humans, corticosterone (CORT) in rodents; for reviews see (Jankord and Herman, 2008; Aguilera and Rabadan-Diehl, 2000). Centrally, activation of CRF-R acts anxiogenic and pro-depressive, it can impair social behavior, and affect stress coping, arousal and food intake depending on the brain region (Klampfl et al., 2014; Reul and Holsboer, 2002; Bale and Vale, 2004; Nemeroff, 1996). Thus, the CRF system is involved in most stress-related behaviors, which are beneficial in a stress context. At the same time, this neuropeptide system is thought to play a central role when those behaviors are excessively displayed and become symptomatic for psychiatric diseases.

3. Involvement of the brain CRF system in mood disorders: link to the postpartum period

Mood disorders like anxiety and depression are among the most common neuropsychiatric disorders worldwide. In fact, depression affects approximately 20% of the population with the incidence being two times higher in women than in men (Gutierrez-Lobos et al., 2002; Kornstein et al., 2002). Accumulating evidence suggests that an increased central CRF drive is a key feature often seen in major depression and anxiety disorders (Reul and Holsboer, 2002; Nemeroff, 1996; Deussing and Wurst, 2005; Holsboer and Barden, 1996; Keck, 2006). For example, increased CRF concentrations in the cerebrospinal fluid have been repeatedly observed in major depression (Nemeroff et al., 1984; Banki et al., 1987; Hartline et al., 1996), posttraumatic stress disorder patients (Bremner et al., 1997), and suicide victims (Arato et al., 1989). Furthermore, *Crh* mRNA and peptide expression is increased in the hypothalamus, cortical areas, pontine nuclei and the LC postmortem in humans (Austin et al., 2003; Merali et al., 2006; Raadsheer et al., 1994; Bissette et al., 2003). This is paralleled by a down-regulation of CRF-R1, but not CRF-R2, in cortical areas of suicide victims, all pointing to a hyperactive CRF/CRF-R1 interaction in depression (Merali et al., 2004; Nemeroff et al., 1988). The relevance of overactive limbic CRF-R1 transmission in depression is underlined by the fact that selective CRF-R1 antagonists exert antidepressant effects at doses that do not influence baseline or stimulated HPA axis activation in humans (Kunzel et al., 2003; Zobel et al., 2000). Furthermore, the CRF-BP is down-regulated in the amygdala of patients with bipolar disorder (Herringa et al., 2006), and UCN1 expression is upregulated in the Edinger-Westphal nuclei of suicide victims (Kozicz et al., 2008). In addition, evidence has been accumulating that disturbances in the regulatory control of the HPA axis play a pivotal role in the etiology of mood disorders, particularly major depression (Holsboer, 2000; Steckler et al., 1999). The reported hyperactivity of the HPA axis is most likely caused by hyperactive CRF/CRF-R1 gating (Reul and Holsboer, 2002). Most interestingly, high blood CRF levels during pregnancy were recently shown to be predictive of developing postpartum depressive symptoms in women (Iliadis et al., 2016).

Women are twice as likely to be affected by mood disorders than men suggesting a sexual dimorphism in the underlying mechanisms (Rubinow and Schmidt, 2018; Kessler, 2003; Marcus, 2009). The time of the highest risk for women to develop anxiety and depressive disorders is throughout periods of prominent (steroid) hormone changes, i.e. premenstrual, perimenopausal, pregnancy and postpartum (Dickens and Pawluski, 2018; Brummelte and Galea, 2010). Especially the hormonal fluctuations during pregnancy and postpartum are thought to be a major factor in the development of depressive symptoms. Particularly women who have a (family) history of high anxiety, experienced abuse, had pregnancy complications, gave birth prematurely, delivered a low birthweight infant or are caring for an infant with a birth defect are prone to suffer from a (new) episode of high anxiety during this greatly vulnerable period of life. Mood disorders and depressive symptoms can already evolve during pregnancy, with up to 15% of women suffering from it (Dickens and Pawluski, 2018; Iliadis et al., 2016; Marcus, 2009; Lancaster et al., 2010), and a potential involvement of the HPA axis in perinatal depression is conceivable (for detailed reviews see (Dickens and Pawluski, 2018; Brummelte and Galea, 2010; Lancaster et al., 2010). There is either no link between depressive symptoms and perinatal cortisol levels or, in cases where a correlation between the HPA axis and depression in pregnancy is found, HPA axis profiles from mothers suffering from perinatal depression differ from those with postpartum depression (Dickens and Pawluski, 2018). The outcome of perinatal depression can be diverse between affected pregnant women and, thus, the detection and treatment cannot be easily standardized but are rather variable (Dickens and Pawluski, 2018). However, it is indisputable that perinatal depression likely continues into motherhood. Mothers with postpartum mood disorders exhibit bidirectional parenting styles; one group shows reduced coping and reactivity to the infant while the second group displays a highly protective mothering style, termed 'helicopter parenting'. Despite the dramatic hormonal changes peripartum likely underlying the high susceptibility to develop mood disorders, dysfunctions in neuropeptidergic systems regulating mood and anxiety peripartum are highly feasible as well. Unfortunately, peri- and postpartum anxiety disorders are still under-investigated because the chances to detect elevated anxiety in postpartum women is very low (Coates et al., 2004), and suitable animal models are rare. The need for a better understanding is even more pronounced by the fact that women at risk of developing emotional disorders are more likely to suffer from anxiety than depressive episodes, and that peripartum anxiety is a very strong predictor of later postpartum depression (Dickens and Pawluski, 2018; Bergant et al., 1999; Heron et al., 2004; Ross et al., 2004; Stuart et al., 1998). Thus, a better understanding of postpartum anxiety could help to prevent a trajectory toward postpartum depression for some women (Lonstein, 2007).

Similar to anxiety, depressive symptoms are also influenced by reproductive events in women. After parturition, women can suffer from three different forms of depressive disorders: postpartum blues, postpartum depression, and postpartum psychosis (Hillerer et al., 2014). Postpartum blues is a transient and mild condition characterized by mood disturbances beginning a few days after parturition and lasting less than two weeks. It is extremely common with prevalence estimates of up to 84% of parturient women (Henshaw et al., 2004), and often resolves spontaneously within two weeks without bearing negative consequences for mother and child (Seyfried and Marcus, 2003). In contrast, postpartum depression is more serious for both mother and infant (O'Connor et al., 2002; Deave et al., 2008) but is not as prevalent as postpartum blues with estimates of 15% (Goodman, 2007). However, the actual number is likely higher due to the reluctance of mothers to admit their depressive state during a time of expected happiness (Marcus, 2009). Postpartum depression represents an episode of major depression with a specific temporal manifestation, which is still under debate. A crucial feature of maternal depression that distinguishes it from other depressive episodes is the loss of interest in the infant (Atkinson et al., 2000; Lovejoy et al., 2000), which may lead to maternal neglect due to an aversive perception of the child (Adamakos et al., 1986; Bifulco et al., 2004). Finally, postpartum psychosis is probably the most serious postpartum disorder and has a prevalence of 0.1–0.5% in parturient women. It has been hypothesized to be a feature of bipolar or schizoaffective disorder and may even culminate in suicide and/or filicide (Appleby et al., 1998).

In order to gain important information on the neurobiological basis and mechanisms behind the dysregulations of the brain leading to postpartum mood disorders, animal models represent valuable tools. The following chapters summarize our current knowledge of how the CRF system contributes to such dysregulations, thereby mainly focusing on rodent studies where we present evidence from central and local (i.e., BNST, MPOA, LS) manipulations of the CRF system and its effects on maternal behavior.

4. Implication of the brain CRF system in the peripartum period

4.1. The stress reactivity is attenuated in lactation

In order to prepare a female for the changing demands of maternity and at the same time protect her from the detrimental consequences of postpartum mood disorders, the maternal brain undergoes tremendous modifications. Besides peripartum adaptations on the behavioral level, e.g. appearance of maternal behavior and reduced anxiety, and on the neuroendocrine level, e.g. up-regulated expression and release of pro-maternal neuropeptides such as oxytocin (OT), vasopressin (AVP) and prolactin, pregnant and lactating females show remarkable changes in their stress reactivity, which is evidently associated with the CRF system. During pregnancy, the basal and stress-induced HPA axis activity is significantly reduced in rats, mice (Johnstone et al., 2000; Douglas et al., 2003) and humans (Schulte et al., 1990; Hartikainen-Sorri et al., 1991). This adaptation occurs despite or even because of the drastic hormonal changes during that sensitive time of pregnancy (reviewed elsewhere (Dickens and Pawluski, 2018; Brummelte and Galea, 2010; Slattery and Neumann, 2008; Brunton and Russell, 2008; Brunton and Russell, 2011). In rats, this hypo-responsiveness is evident as of day 15 of gestation and persists through pregnancy (Neumann et al., 1998), parturition (Wigger et al., 1999) and lactation until weaning (Windle et al., 1997b). It is reflected by reduced ACTH and CORT secretion into the blood following acute stressor exposure. This involves adaptations not only at the level of the anterior pituitary and the hypothalamus, but also at higher brain areas (da Costa et al., 1996). In the pituitary of pregnant and lactating rats, corticotropes are less reactive to administered CRF (Neumann et al., 1998; Toufexis et al., 1999) or AVP (Ma et al., 2005) compared to virgins. At the level of the hypothalamus, CRF and AVP neurons in the parvocellular PVN of pregnant/lactating rats are less stimulated by stress compared to virgins, which is reflected by reduced CRF and AVP synthesis (Brunton et al., 2006; da Costa et al., 2001). In addition, CRF's ability to activate neurons within the PVN is reduced from early lactation onward (da Costa et al., 2001, 1997). Interestingly, the excitatory drive to PVN neurons from the limbic forebrain (da Costa et al., 1996) and the brainstem nuclei (Brunton et al., 2005) in response to emotional and physical stressors, respectively, is impaired. At the level of higher brain regions, expression of *Crh* mRNA is reduced in the central amygdala (Walker et al., 2001) and the parvocellular PVN (Johnstone et al., 2000; Walker et al., 2001; Lightman et al., 2001; Klampfl et al., 2013), whereas it is increased in the dorsolateral (Walker et al., 2001), anterodorsal and anteroventral (by trend) portion of the BNST (Klampfl et al., 2016b) and the MPOA during lactation (Walker et al., 2001). Furthermore, immediate early gene expression in the BNST, arcuate nucleus, LS, and medial amygdala is elevated in response to centrally administered CRF (da Costa et al., 1996, 1997). In general, the central nervous system of lactating rats seems to be less responsive to CRF compared to virgin females (da Costa et al., 1996, 1997). Thus, decreased synthesis of CRF, reduced stimulation of CRF release, and/or decreased responsiveness of the brain to CRF could contribute to the beneficial adaptation of reduced anxiety and stress reactivity during lactation. Even though this assumption seems highly intuitive, it cannot be generally applied; *Crh* mRNA levels can even be increased in maternally relevant brain regions, e.g. BNST and MPOA (da Costa, 2001; Walker et al., 2001; Klampfl et al., 2016b); and *Crhr* mRNA expression patterns are unchanged in these regions compared to virgin rats (Klampfl et al., 2014, 2016b, 2018). Here, we need to consider that changes in mRNA levels might not necessarily reflect altered expression levels of functional proteins; or they do reflect functional protein levels, but the down-regulation is brought about by a different mechanism or via specific interactions with different neurotransmitter systems (see Section 5). Interestingly, increasing levels of CRF, which strongly cross-talk with the peripheral OT system, are also observed peripherally just before parturition (for review see (Hillhouse and Grammatopoulos, 2002; Grammatopoulos and Hillhouse, 1999). Here, placental CRF seems to protect the myometrium of preterm contractions until its expression reaches a certain threshold; this in turn induces delivery, also known as the "placental clock" (Smith and Nicholson, 2007; Mastorakos and Ilias, 2000).

In addition to CRF's prominent role in regulating the mother's stress reactivity and the induction of parturition, the CRF system appears to be also involved in the behavioral adaptations associated with the peripartum period. Although only few research groups have investigated potential effects of CRF and its related peptides on maternal behavior, essential progress has been made during the last years using rodent animal models.

4.2. Overview of maternal behavior in rodents

Before going further into detail of the negative effects of an activated CRF system on the maternal brain in rodents, we first define and dissect this highly specific social behavior. Maternal behavior is defined as "any behavior of a member of a species toward a reproductively immature conspecific that increases the probability that the recipient will survive to maturity" (Numan and Insel, 2003). Thus, maternal behavior has emerged as the most important pro-social female behavior, which guarantees the survival and development of the offspring. Typically, it is divided into three main categories: maternal care, maternal motivation, and maternal aggression, all of which are accompanied by adaptations in maternal anxiety.

4.2.1. Maternal care

During motherhood, a rodent dam cares for her young by displaying a variety of pup-directed behaviors. The mother shows licking and grooming (LG; Fig. 1A) of the pups to help them urinate and defecate, yet it also has a high impact on the offspring's social and emotional development (Caldji et al., 1998; Champagne, 2008). Additionally, the dam employs various nursing positions including blanket posture, hovering over the pups, and arched back nursing (ABN; Fig. 1B) to provide the young with sufficient nourishment. Among those nursing positions, ABN is the most characteristic one in rats and mice. It is classified as the only active nursing position with the dam being fully engaged in a quiescent kyphotic posture (Stern and Johnson, 1990). The quiescence of the dam is important not only to enable the pups to become and remain attached to the teats, but also for the occurrence of milk ejection in response to the suckling stimuli. Sufficient offspring suckling is required to induce a behavioral quiescence, which is accompanied by slow-wave sleep and immobility (Lincoln et al., 1980; Voloschin and Tramezzani, 1979).

Two of the brain regions that are highly implicated in the regulation of maternal care are the limbic BNST and MPOA (Numan and Insel, 2003; Bosch, 2011). Especially the ventral BNST and the dorsal MPOA act in concert to form a maternal "super-region" (Numan and Insel, 2003). This neural complex receives input from the medial amygdala, which is the crucial relay site to forward olfactory stimulation from the pups either to a pup fear/avoidance circuit in virgins or to a pup attraction/approach circuit in lactating rats (Numan and Insel, 2003; Rosenblatt and Mayer, 1995; Numan and Woodside, 2010).

4.2.2. Maternal motivation

The mother's brain needs to undergo further adaptations to be responsive to her young and to seek and maintain contact with them. She

Fig. 1. Maternal behavior in lactating rats. (A) Licking and grooming by the mother stimulates the pups to urinate and defecate, and it has a significant impact on their social and emotional development. (B) Arched back nursing is characterized by a quiescent kyphotic posture, which enables the pups an unhindered access to the teats in a protective environment. (C) Pup retrieval reflects the mother's motivation to approach pups and to either transport them back to the nest or to move them to a new nesting site. (D) Maternal aggression displayed by the mother toward a virgin rat to defend the pups.

shows high motivation to do so when she carries them singly in her mouth to either transport displaced pups back to the nest or to move them to a new nesting site (Fig. 1C). This pup retrieval is referred to as maternal motivation and is described as an appetitive response that is voluntary, proactive, and goal-directed (Numan and Woodside, 2010; Numan and Stolzenberg, 2009; Pereira and Morrell, 2011). Appetitive maternal motivation is mainly regulated by the MPOA. Its interactions with the telencephalon via the mesolimbic dopamine system appear to be the route through which MPOA neurons mediate such a goal-directed behavior (Numan and Woodside, 2010).

4.2.3. Maternal aggression

Along with the establishment of maternal care and maternal motivation, lactating females exhibit a dramatic increase in pup protection, i.e. maternal aggression (Fig. 1D). The term "maternal aggression" was introduced in 1968 (Moyer, 1968) to describe an agonistic behavior displayed by females defending their young, and is clearly distinguished from irritable, territorial, sex-related, fear-induced, predatory, and intermale aggression. Thus, maternal aggression is not directed against the young, but is aimed to protect the offspring from potential external threats, e.g. infanticidal conspecifics, and is measured in the maternal defense test (Neumann et al., 2001; Bosch, 2013). This intruder-targeted maternal aggression is an adaptive and highly conserved behavior that likely increases the fitness of the offspring (Wolff, 1985). Besides extrinsic factors such as the presence of the pups, a variety of intrinsic factors modulates the onset and maintenance of maternal aggression (Bosch, 2013). Increasing levels of estrogen (but not dropping progesterone) at the end of pregnancy prime for and stimulate a first onset of maternal aggression (Lonstein and Gammie, 2002). After birth, adaptations of neuropeptidergic systems and the mother's decreased innate anxiety are crucially involved in the appearance of maternal aggression. Among others, the OT and AVP systems facilitate pup defense in a brain region-specific manner, e.g. in the MPOA and BNST, as has been reviewed in detail elsewhere (Bosch, 2013; Bayerl and Bosch, 2019). Particularly the BNST and the LS have emerged as key regions in the limbic system modulating maternal aggression.

Maternal care, maternal motivation, and maternal aggression are facilitated by the neuropeptide systems of OT and AVP (among others). Importantly, also the CRF system has emerged to play a central role in the regulation of those behaviors, though in a rather oppressing manner.

4.3. Activation of the CRF system under non-stress conditions impairs maternal care

4.3.1. Central CRF-R manipulations

In the past decades, studies on the regulation of maternal care have almost exclusively focused on neurotransmitter systems that promote this behavior, whereas those negatively affecting maternal care, such as the CRF system, were rather neglected. Pioneer work was done in the early 1990s when Pedersen et al. (1991) showed that acute intracerebroventricular (ICV) CRF infusion inhibits maternal-like care in nulliparous, ovariectomized, steroid-primed virgin rats following three days of pup exposure, termed "sensitization". Without this sensitization period, primed rats kill the pups. This study gave a first idea of the general actions of brain CRF-R activation, which cause detrimental effects on maternal behavior. In later studies, the role of the CRF system in maternal care was assessed using lactating mothers as more natural animal models of maternal behavior. In confirmation of the previous findings in primed virgin rats, also in lactating rats (Klampfl et al., 2013, 2014) and marmoset monkey mothers (Saltzman et al., 2011) central CRF infusion decreases the display of maternal care. The effects in lactating rats were investigated in greater detail by further distinguishing between the CRF-R subtypes as well as non-stress (basal) and stress conditions (immediately after exposure to an acute stressor such as the maternal defense test; see Section 4.4) (Klampfl et al., 2013, 2014, 2016a, 2016b, 2018).

Following acute central activation of CRF-R1/2 by UCN1 or of CRF-R1 only by CRF, rat mothers show less ABN and nursing, which supports the initial finding in ovariectomized, steroid-primed virgin rats (Pedersen et al., 1991). Interestingly, the previously observed pup-killing of primed virgin rats without versus with pup contact is not present in lactating rats. In turn, these results indicate that central activation of CRF-R enhances the aversive responses elicited by pup

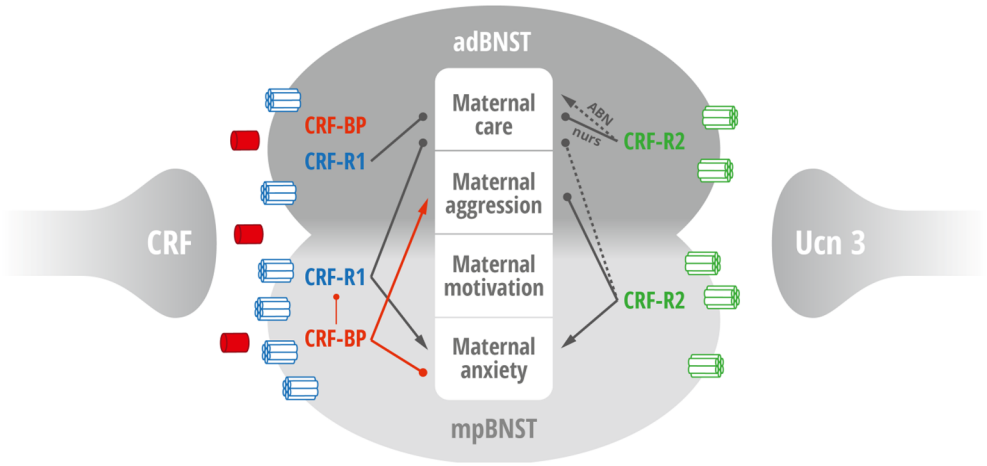

Fig. 2. Schematic representation of the effects of the CRF system within the BNST on maternal behavior. The BNST is divided into the adBNST (top) and mpBNST (bottom) of which each subdivision expresses CRF-R1 (left), CRF-R2 (right) and the CRF-BP (barrel). CRF-R1 is hypothesized to be stimulated by CRF while CRF-R2 is mainly activated by UCN3. CRF-BP only acts in the mpBNST. Arrows indicate stimulating effects while blunted ends represent inhibiting effects. Straight lines show immediate effects whereas dotted lines represent delayed effects. ABN, arched back nursing; nurs, nursing.

presence in naïve, unsensitized females (Numan and Insel, 2003), which culminates even in infanticide (Pedersen et al., 1991). As soon as the switch from aversive to approach behavior has occurred - as seen in lactating or sensitized females – the behavioral effects of CRF-R activation is shifted from infanticide to reduced maternal care resulting in maternal neglect.

Acute central blocking of CRF-R by administration of a non-selective antagonist does not affect maternal care under basal conditions in lactating rats (Klampfl et al., 2013), implying that CRF-R activation is suppressed under basal conditions to assure adequate and sufficient levels of maternal care. This is supported by the lack of a behavioral effect after CRF-BP inhibition, which increases free endogenous levels of CRF/UCN1 (Westphal and Seasholtz, 2006; Behan et al., 1995a); under non-stress conditions, the CRF-BP seemingly has bound too low levels of CRF/UCN1 to elicit a behavioral effect upon release.

4.3.2. Intra-BNST CRF-R manipulations

In the BNST (Fig. 2), subtype-specific manipulations of CRF-R1 or CRF-R2 confirm previous findings obtained in the central approaches and, in addition, allow the assignment of behavioral effects to this limbic brain region (Klampfl and Bosch, 2018). Here, it is important to distinguish between the subdivisions of the BNST given their distinct cyto- and chemoarchitectonic differences (Bayer, 1987; Ju and Swanson, 1989; Ju et al., 1989).

In the medial-posterior BNST (mpBNST; Fig. 2, bottom half), acute activation of CRF-R reduces basal levels of ABN and nursing in a time-dependent manner (Klampfl et al., 2014); the effects of CRF-R1 activation with CRF are rapid, whereas those of CRF-R2 stimulation with UCN3 are delayed. In parallel to the decrease in maternal care, CRF-R1 activation increases locomotion and self-grooming, whereas CRF-R2 activation increases sleeping/resting. Heightened locomotor activity and grooming behavior by CRF-R1 activation is also described in studies utilizing male rats under basal conditions in the home cage (Dunn and Berridge, 1990; Koob et al., 1984; Sherman and Kalin, 1987; Sutton et al., 1982). The rise in sleeping/resting indicates sedative properties of UCN3 and the concomitant CRF-R2 activation, which is supported by a study in male rats demonstrating motor suppressive effects upon CRF-R2 stimulation (Ohata and Shibasaki, 2004).

In the anterior-dorsal BNST (adBNST; Fig. 2, top half), manipulations of CRF-R show a distinct picture (Klampfl et al., 2016b). While activation of CRF-R1 impairs ABN and total nursing similarly to what is seen for the mpBNST, activation of CRF-R2 in the adBNST impairs nursing but improves ABN, though with a delay. The behavioral changes following CRF-R activation in the adBNST might be mediated via an indirect pathway. Acute stimulation of CRF-R1 or CRF-R2 in the adBNST increases HPA axis activity including a rise in plasma CORT, which is insufficient to provide a feedback on maternal care (Klampfl et al., 2016b). However, chronic peripheral CORT application is potent enough to impair maternal behavior (Brummelte and Galea, 2010).

Inhibition of either CRF-R or of the CRF-BP as regulator of CRF-R signaling in both mpBNST and adBNST reveal no behavioral effects under basal conditions, supporting the results from previous ICV studies (Klampfl et al., 2013, 2014, 2016a). In fact, it strengthens the hypothesis of a down-regulated CRF system as an indispensable prerequisite for the occurrence of adequate maternal care.

When considering all those findings, we propose that CRF-R1 activation in the BNST, independent of anterior or posterior portion, is detrimental for maternal care and requires hypo-activation during lactation (Klampfl and Bosch, 2018). Here, CRF, but not UCN1, is most likely the endogenous ligand for CRF-R1 as CRF neuronal cell bodies and terminals are abundant (Swanson et al., 1983; Olschowka et al., 1982; Cummings et al., 1983; Moga et al., 1989; Morin et al., 1999) while UCN1 expression or projections have not been detected in the BNST (Vaughan et al., 1995; Kozicz et al., 1998; Bittencourt et al., 1999). In contrast, CRF-R2 appears to play a more complex role. While the time course of treatment-effectiveness is similar in both the adBNST and mpBNST, i.e. a slow, delayed behavioral change, CRF-R2 activation in the mpBNST impairs ABN, but improves it in the adBNST. This implies a facilitating role for CRF-R2 in the regulation of ABN in the adBNST, but a negative role in the mpBNST. Interestingly, CRF-R2 activation in the adBNST decreases total nursing, which is again similar to its effects in the mpBNST. This demonstrates that CRF-R2 activation causes less nursing promptly after infusion, which is reversed at the time when these dams display increased ABN. Further research is needed to determine the relevance of this dissociation.

4.3.3. Intra-MPOA CRF-R manipulations

In the MPOA (Fig. 3), activation of CRF-R1 under basal conditions strongly decreases ABN and total nursing while CRF-R2 stimulation induces a more transient and less pronounced decline in ABN and nursing (Klampfl et al., 2018). At the same time, CRF-R1 or CRF-R2 activation significantly increases the display of non-maternal behaviors, i.e. off-nest behavior, locomotion, self-grooming. However, the CRF-BP does not seem to be involved in the regulation of basal levels of maternal care as its inhibition in the MPOA is ineffective, and, in addition, *Crhbp* mRNA expression is unchanged in lactating versus virgin rats (Klampfl et al., 2018). In support of the general assumption that under basal conditions the CRF system is not active enough to impair maternal behavior, inhibition of either CRF-R remains without effect on maternal care.

In conclusion, the CRF system in the MPOA together with the BNST is a potent regulator of maternal care. Interestingly, it seems to be highly sensitive to the variable presence of the different ligands due to its receptor subtype-, time-, and region-specific influences on maternal

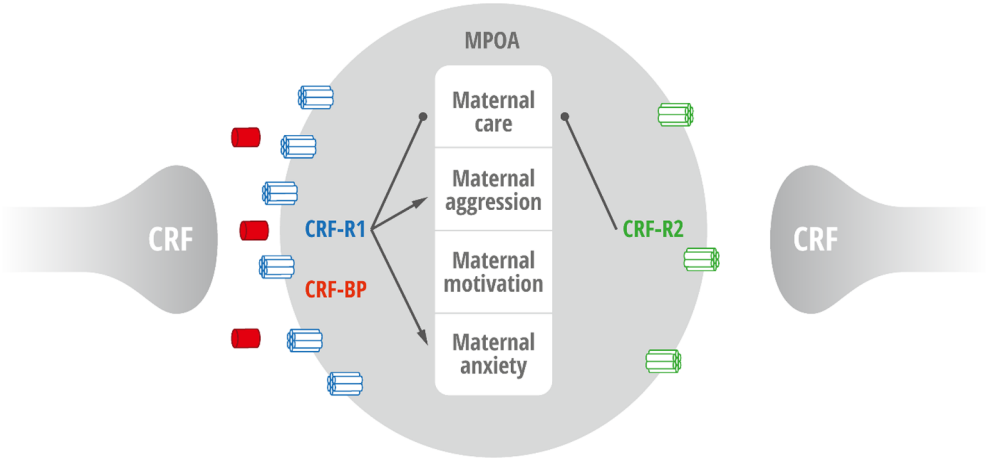

Fig. 3. Schematic representation of the effects of the CRF system within the MPOA on maternal behavior. The MPOA expresses CRF-R1 (left), CRF-R2 (right) and the CRF-BP (barrel). In the MPOA, both CRF-R1 and CRF-R2 are hypothesized to be stimulated mainly by CRF. CRF-BP does not act on CRF-modulated maternal behavior. Arrows indicate stimulating effects while blunted ends represent inhibiting effects.

care. This suggests a complex and precise regulatory system for this essential type of maternal behavior.

4.4. Blocking the CRF system rescues maternal care after stressor exposure

4.4.1. Central CRF-R manipulations

Maternal care is impaired immediately after termination of a stressful condition, i.e. exposure to the maternal defense test as psychosocial stressor, which results in an activated brain CRF system as reflected by a strong stimulation of the HPA axis (Neumann et al., 2001). Following ICV manipulation, the non-selective inhibition of CRF-R1/2 or of CRF-BP prior to the maternal defense test has no effect on subsequent maternal care in lactating rats (Klampfl et al., 2014, 2013) and mice (Gammie et al., 2004). This might be due to the global inhibition of the CRF-R and the CRF-BP, which most likely require region-specific manipulations to alter maternal care following stressor exposure as we demonstrate below.

4.4.2. Intra-BNST CRF-R manipulations

The two CRF-R subtypes play different roles depending on the type of behavior and division of the BNST as discussed in Section 4.3.2 for basal conditions. Under stress conditions, in the mpBNST blocking CRF-R1 prevents the stress-induced decrease in nursing behavior, whereas in CRF-R2 antagonist-treated dams also ABN returns rapidly to pre-stress levels (Fig. 2, bottom half) (Klampfl et al., 2014). This demonstrates that under stressful conditions, CRF-R2 activation mediates all important parameters of nursing while CRF-R1 activation affects only nursing behavior in general. In contrast, in the adBNST only the CRF-R1 antagonist recovers ABN, which - in turn - points to a crucial role of intra-adBNST CRF-R1 signaling in mediating stress-induced changes of maternal care (Fig. 2, top half). Together, the CRF-R2 subtype appears to be more important in modulating maternal care in the mpBNST whereas the CRF-R1 subtype most likely is the crucial receptor in the adBNST, especially in a stress context. This region-specific pattern is supported by the diverse *Crhr* mRNA expression levels; the more posterior in the BNST the more abundant CRF-R2 are expressed (Klampfl et al., 2014, 2016b). Interestingly, the CRF-BP has no functional implication in the regulation of maternal care under stressful conditions in the adBNST whereas in the mpBNST CRF-BP inhibition prolongs the stress-induced decrease of nursing (Klampfl et al., 2016a). Given that the CRF-BP binds mostly the endogenous ligands for CRF-R1, i.e. CRF and UCN1, it is surprising to see no effects in the adBNST, which seems to mediate its effect via CRF acting on CRF-R1. In contrast, the CRF-BP in the mpBNST appears to impact on maternal care, which is probably mediated via CRF-R2 activation by UCN3. However, UCN3 does not bind to the CRF-BP (Westphal and Seasholtz, 2006), which is why it is feasible that in this case CRF – instead of UCN3 – binds to CRF-R2 and induces further signaling. Nevertheless, more studies are needed to elucidate the respective ligand and exact molecular actions of the CRF-BP to gain insights in its functional role during lactation.

Stress-induced impairment of maternal care is mediated predominantly by CRF-R1 in the adBNST and by CRF-R2 in the mpBNST, concomitantly assigning the main receptor subtype of signal transmission to either of the BNST subdivisions. Furthermore, the re-establishment of an adequate appearance of maternal care after stressor exposure requires immediate hypo-activation of CRF-R, which appears to be partially supported by the CRF-BP.

4.4.3. Intra-MPOA CRF-R manipulations

In the MPOA (Fig. 3), activation of CRF-R1 decreases nursing and increases LG of the pups in lactating rats (Klampfl et al., 2018). It is considered a positive and beneficial behavior directed towards the pups as it positively impacts the social and emotional development of the offspring (Champagne and Meaney, 2001). Therefore, an increase in LG by CRF-R1 activation might seem counter-intuitive. However, CRF is well-known to induce self-grooming in both males and females (Dunn et al., 1987; Wiersielis et al., 2016), referred to as displacement activity (Kalueff et al., 2016). During lactation, this activity seems to be redirected from self-grooming to pup-grooming, thus increasing LG after stressor exposure. In support, a similar effect has been reported in lactating rats following exposure to white noise stress (Windle et al., 1997b). In addition, blocking CRF-R1 prevents the stress-induced reduction of ABN, but not nursing (Klampfl et al., 2018). As suggested earlier (Klampfl et al., 2018), it is feasible that any stress-induced impairment in maternal care is mediated by CRF-R in more stress-responsive brain regions, such as the BNST (see Section 4.1).

In conclusion, exposure to a (social) stressor strongly impairs maternal care shortly after stressor exposure, which is partly regulated by activated CRF-R. Compared to the MPOA, the BNST plays a more prominent role in the stress-induced reduction of maternal care. However, different BNST subdivisions show different CRF-R activation profiles rendering the stress-induced regulation highly sensitive and complex.

4.5. The CRF system does not modulate maternal motivation

Maternal motivation expressed by retrieval of the pups is unchanged in CRF-R1 or CRF-R2 deficient mice (Gammie et al., 2007; D'Anna et al., 2008) and remains unaltered after acute central CRF or UCN3 infusion in lactating rats (Klampfl et al., 2013) or mice (D'Anna et al., 2005; D'Anna and Gammie, 2009), respectively. However, central UCN1 infusion tends to impair this appetitive behavior in rat mothers (Klampfl et al., 2014). On the one hand, it is feasible that UCN1's effects are artifacts of the global drug administration so that CRF-R signaling is not involved in the regulation of maternal motivation. On the other hand,

UCN1, but not CRF, might generally affect appetitive behavior in rats as has been seen, e.g. in feeding behavior (Spina et al., 1996). However, a causal relationship remains to be proven.

Local CRF-R subtype-specific manipulations in the mpBNST, adBNST (Fig. 2), MPOA (Fig. 3) or LS have no effects on pup retrieval behavior (Klampfl et al., 2014, 2016b, 2018; D'Anna and Gammie, 2009). This is anticipated for the BNST and LS; they have not been reported to mediate maternal motivation except after blocking OT receptors in the mpBNST, which reduces pup retrieval (Klampfl and Bosch, 2018). However, the MPOA is known to be a key brain area for maternal motivation (Numan and Insel, 2003; Numan and Woodside, 2010), but CRF-R manipulations are not capable of affecting this appetitive behavior. Hence, these findings support our assumption that the central CRF system is not taking part in the regulation of maternal motivation, at least in a direct manner (Klampfl and Bosch, 2018). However, it cannot be excluded that the CRF system in other brain areas might influence pup retrieval.

4.6. Activation of the CRF system affects maternal aggression in a receptor subtype- and brain region-dependent manner

In contrast to maternal care and maternal motivation, maternal aggression is directed toward an intruder to protect the pups. Importantly, the behavioral expression of maternal aggression in lactating rats and mice is mediated not only by the pro-maternal neuropeptide systems of OT and AVP (Bosch, 2013), but also the CRF system significantly modulates this behavior.

4.6.1. Central CRF-R manipulations

In lactating rats, maternal aggression remains unchanged after central inhibition of CRF-R1/2 (Klampfl et al., 2013, 2014) while their activation decreases this aggressive behavior (CRF: Klampfl et al., 2013; UCN1: Klampfl et al., 2014). A similar picture is seen in lactating mice (CRF: Gammie et al., 2004; UCN1: D'Anna et al., 2005), thereby supporting a species-independent negative effect of CRF-R activation on maternal aggression during lactation.

4.6.2. Intra-BNST versus intra-LS CRF-R manipulations: similarities and differences

On a brain region level, the picture becomes more complex as CRF-R manipulations have different effects on maternal aggression depending on the targeted subdivision (Klampfl et al., 2014, 2016a; Klampfl and Bosch, 2018). In the mpBNST (Fig. 2, bottom half), inhibition of CRF-R2 signaling increases whereas activation decreases maternal aggression, but modulating CRF-R1 signaling has no effect on this behavior. These findings in lactating rats are in general supported by data from lactating mice where Gammie and colleagues studied the role of the CRF system in the LS for maternal aggression in detail. Here, CRF-R2 stimulation reduces and inhibition increases maternal aggression (D'Anna and Gammie, 2009). Furthermore, lactating mice deficient for CRF-R2 have deficits in the display of aggressive behavior towards the intruder (D'Anna et al., 2008). Together, these data indicate a potent role for CRF-R2 in regulating maternal aggression, at least within the mpBNST and LS.

Interestingly, when combining the knowledge from the studies on intra-mpBNST and central manipulations (see Section 4.6.1) a prominent role of UCN3-induced CRF-R2 activation in modulating maternal aggression evolves for the mpBNST. While infusion of UCN1 (ICV) or UCN3 (mpBNST) completely abolishes maternal aggression in lactating rats, CRF treatment (ICV or mpBNST) has a weaker effect on this behavior (Klampfl et al., 2014). This is further supported by the endogenous expression patterns of CRF-R2 ligands as studied in male rats; *Ucn3* mRNA is found in the BNST while *Ucn1* and *Ucn2* mRNA expression is restricted to the Edinger-Westphal nucleus and hypothalamic/hindbrain regions, respectively, at least in male rats (Vaughan et al., 1995; Reyes et al., 2001; Lewis et al., 2001; Hsu and Hsueh, 2001). However, it needs to be mentioned that the maternal aggression-abolishing effects of UCN1 and UCN3 are not necessarily ubiquitous as in lactating mice, infusion of the same ligands in the LS only impairs but does not prevent maternal aggression (D'Anna and Gammie, 2009). The difference in the strength of the effects might be due to the difference in animal models or the studied brain regions. Another explanation is that in the study investigating the mpBNST of lactating rats (Klampfl et al., 2014), a higher dose was used than in the study on the LS in lactating mice (D'Anna and Gammie, 2009). This suggests a potentially unsaturated CRF-R2 activation and, thus, incomplete reduction of maternal aggression in mice (Klampfl and Bosch, 2018). With respect to CRF-R1, lactating knock-out mice display slightly impaired maternal aggression (Gammie et al., 2007). In general, these mouse dams show a high variance in aggressive behavior toward the intruder; however, they fail to display constantly lower maternal aggression levels compared to wildtype mice over several experimental days. Additionally, if CRF-R1 activation affects maternal aggression along with CRF-R2, deletion of the CRF-R1 gene would rather improve but not impair maternal aggression. Therefore, the altered levels of aggressive behavior in lactating CRF-R1 deficient mice most likely result from compensatory mechanisms throughout development and adulthood (Nelson, 1997).

In the adBNST (Fig. 2, top half), selective manipulation of either CRF-R subtype has no effect on maternal aggression (Klampfl et al., 2016b). Assuming that in the BNST activation of CRF-R2, but not CRF-R1, mediates maternal aggression, and that *Ucn3* mRNA (Reyes et al., 2001; Hsu and Hsueh, 2001) and fibers (Li et al., 2002) are present in the mpBNST, but not adBNST, it is not surprising to detect no behavioral changes after CRF-R manipulation in the adBNST. Furthermore, the mpBNST heavily projects to the LS (Dong and Swanson, 2004), another vital regulating site for maternal (Bosch et al., 2013; D'Anna and Gammie, 2009) and male aggression (Wong et al., 2016), while the adBNST is lacking projections to the LS (Dong et al., 2001). Such projections to the LS might be involved in regulating the display of (maternal) aggression.

4.6.3. Intra-MPOA CRF-R manipulations

So far, only one study provides direct behavioral evidence for an involvement of the MPOA in maternal aggression (Fig. 3) (Klampfl et al., 2018). Here, contrary to the BNST, only CRF-R1 appear as the main modulator of this behavior. Acute inhibition of CRF-R1 robustly increases the display of aggression toward the intruder, whereas stimulation by CRF has no effect. Therefore, these findings suggest an activation of CRF-R1 under this stressful situation. In support, studies in lactating rats (Motta et al., 2013) and mice (Gammie and Nelson, 2001) show that exposure to an aggressive encounter increases the neuronal activation within the MPOA. Based on the expression patterns of the members of the CRF ligands, i.e. no expression of UCNs but of CRF in the MPOA, we propose that CRF is the main ligand mediating the effects of CRF-R1 signaling on maternal aggression.

In conclusion, three main brain regions for CRF-R-mediated maternal aggressive behavior are identified. Both the mpBNST and the LS impact on maternal aggression via CRF-R2 whereas CRF-R1 is the dominant receptor in the MPOA. These findings of the involvement of different receptor subtypes in distinct brain regions suggest a fine-tuned modulation of maternal aggression in the postpartum brain.

4.7. An activated CRF system facilitates maternal anxiety

Anxiety-related behavior is reduced in lactation as part of the peripartum adaptations (Lonstein, 2007; Bosch, 2011), which appears to be essential for the mother's acceptance of and attraction to unfamiliar and potentially anxiogenic neonates (Fleming and Luebke, 1981). Furthermore, reduced anxiety is necessary for the mother to display increased aggression toward potentially dangerous conspecifics (Bosch, 2013; Hansen et al., 1985), and both are associated with an increased activity of the OT system (Bosch, 2011, 2013; Neumann and

Landgraf, 2012). Additionally, the CRF system supposedly plays a role in the regulation of maternal anxiety (Lonstein, 2007), though there is no evidence from studies on lactating mice deficient for CRF-R1 (Gammie et al., 2007), CRF-R2 (D'Anna and Gammie, 2009; Gammie et al., 2005) or CRF-BP (Gammie et al., 2008). However, the CRF system in male mice and rats is well studied and has been linked to anxiety-related behavior (reviewed elsewhere (Reul and Holsboer, 2002; Deussing and Wurst, 2005; Reul and Holsboer, 2002; Henckens et al., 2016; Dedic et al., 2018).

4.7.1. Central CRF-R manipulations

Acute central CRF-R inhibition results in different effects on anxiety in lactating rats, depending on the experimental approach. While in both studies D-Phe as CRF-R1/2 antagonist is infused, this inhibition of CRF-R signaling acts anxiolytic in the one study (Klampfl et al., 2013) but not in the other (Klampfl et al., 2014). Exposure to the elevated plus-maze (EPM), a widely used test for anxiety-related behavior (Pellow et al., 1985), is a mild stressor to the animals (Neumann et al., 1998), thereby probably causing elevated endogenous CRF/UCN levels. In turn, these can be antagonized by central CRF-R blockade causing anxiolysis. However, in the above-mentioned studies with contrary results, exposure to the EPM might have stressed the mothers to different degrees, which would explain the anxiolytic effects in the (potentially more stressed) mothers of the first compared to the (potentially less stressed) mothers of the second study (Klampfl et al., 2014).

With respect to central, non-selective activation of CRF-R, acute infusion of UCN1, but not of CRF, significantly increases anxiety-related behavior in lactating rats (Klampfl et al., 2014) similar to males (Spina et al., 1996; Jones et al., 1998; Moreau et al., 1997). Additionally, UCN1 is able to dissociate CRF from the CRF-BP, thus elevating endogenous CRF levels (Behan et al., 1996), which could potentiate the anxiogenic effects of UCN1. Interestingly, inhibition of the CRF-BP is ineffective in altering maternal anxiety (Klampfl et al., 2016a) but supports the lack of effect following central CRF infusion (Klampfl et al., 2014). However, given that inhibition of the CRF-BP can also increase endogenous levels of UCN1 (Behan et al., 1996), but is not as anxiogenic as central infusion of UCN1 itself (Klampfl et al., 2014), it can be speculated that the slight elevation of 'free' UCN 1 by CRF-BP inhibition is insufficient to induce an anxiogenic phenotype. In support, in male rats central CRF-BP inhibition does not act anxiogenic either (Behan et al., 1995a), thereby suggesting that central manipulations of CRF-BP are not potent enough to alter anxiety-related behavior.

4.7.2. Intra-BNST CRF-R manipulations

The BNST is an important regulator of anxiety-related behavior in males (Sahuque et al., 2006; Lee and Davis, 1997; Liang et al., 2001; Ciccocioppo et al., 2003; Greenwell et al., 2004; Jasnow et al., 2004) as it is in females. In lactating females, maternal anxiety is modulated by subtype-selective CRF-R manipulation (Fig. 2). Administration of CRF into the mpBNST is anxiolytic (Klampfl et al., 2014), which is confirmed by the anxiogenic phenotype following CRF-BP inhibition (Klampfl et al., 2016a). Furthermore, intra-mpBNST administration of either a selective CRF-R1 or CRF-R2 antagonist acts strongly anxiolytic in lactating rats. Interestingly, this effect of either antagonist is also present in virgin rats, suggesting that both receptor subtypes mediate anxiety-related behavior in females independent of their reproductive status. In contrast, in males only a combined infusion of CRF with a CRF-R1, but not CRF-R2, antagonist reveals anxiolytic properties (Sahuque et al., 2006). These findings suggest that females have at least slightly elevated CRF-R signaling in the mpBNST, possibly to enable them to react more immediately to an anxiogenic situation compared to males. In contrast, in the adBNST maternal anxiety remains unchanged following any selective CRF-R1 or CRF-R2 manipulation (Klampfl et al., 2016b) nor has CRF-BP any effects on maternal anxiety (Klampfl et al., 2016a).

4.7.3. Intra-MPOA CRF-R manipulations

Within the MPOA of lactating rats, increased signaling of CRF-R1, but not of CRF-R2, heightens anxiety-related behavior (Fig. 3) (Klampfl et al., 2018). In contrast, inhibition of CRF-R1 in the MPOA does not alter maternal anxiety (Klampfl et al., 2018), which is different from studies demonstrating an anxiolytic effect of CRF-R1 blockade either ICV (Klampfl et al., 2013) or intra-BNST (Klampfl et al., 2014). On the one hand, this discrepancy might be explained by a floor effect in the CRF-R1 antagonist group as the mothers' anxiety levels were generally very low in that study (Klampfl et al., 2018). On the other hand, this could point to an indirect effect of CRF-R1 activation on anxiety through reduced locomotion (Donner and Lowry, 2013). Interestingly - and in contrast to the mpBNST - inhibition of the CRF-BP in the MPOA does not influence maternal anxiety. However, the anxiogenic effect of increased CRF-R1 signaling might be unique to lactating rats as it has neither been studied in male or virgin female rodents nor has the MPOA in general been described to mediate anxiety-related behavior.

In conclusion, maternal anxiety is mediated in the mpBNST, but not adBNST, by both CRF-R1 and CRF-R2, whereas in the MPOA it is only via CRF-R1 activation. Therefore, to fulfill the essential postpartum-associated reduction of maternal anxiety, both CRF-R subtypes need to by hypo-activated in the BNST and MPOA. The characteristic hypo-anxious state in lactation is likely supported and maintained by the CRF-BP, at least in the mpBNST, while there must be a different mechanism in the MPOA.

5. Potential interactions of the CRF system with other neuropeptide systems

Complex behaviors, such as maternal behavior, are mediated not only by single neurotransmitter systems but are triggered by a variety of neuronal circuits often interacting with each other. Indeed, important neuropeptide systems in the postpartum period like OT and AVP act in concert to mediate maternal behavior (Bayerl and Bosch, 2019; Neumann and Landgraf, 2012; Bosch and Neumann, 2012). Thus, it is highly feasible that CRF and UCNs not only act alone, but also are capable of influencing the release patterns of other neurotransmitters or vice versa. Central CRF neurons may not be regarded as a homogeneous cell population even though they share a common neuropeptide phenotype (Dabrowska et al., 2013). For example, CRF neurons co-localize with serotonin in the raphe nuclei (Valentino et al., 2010), noradrenaline (NA) in the LC (Valentino et al., 2010; Valentino et al., 1983), and glutamate (Ziegler et al., 2002; Lin et al., 2003; Hrabovszky and Liposits, 2008; Hrabovszky et al., 2005) and OT in the PVN (Dabrowska et al., 2013).

5.1. Interaction of the CRF system with GABA neurons

Within the BNST, CRF neurons co-localize mainly with GABA, the major neurotransmitter phenotype in the BNST (Dabrowska et al., 2013). Additionally, CRF-R are predominantly expressed on GABAergic neurons (Dabrowska et al., 2011) and their activation, particularly of CRF-R1, is known to induce inhibitory postsynaptic currents (Zhiguo et al., 2009; Harlan et al., 2018). Due to this prominent co-expression, signaling via a GABA-mediated mechanism might be essentially involved in the regulation of maternal behavior. For instance, the negative effects of CRF and UCN3 on maternal care might be indirectly mediated via an increased HPA axis activity (Klampfl et al., 2016b) (see Section 4.1), which could be triggered by a GABAergic-mediated disinhibition of the PVN. Moreover, it is reasonable that ligand-induced CRF-R activation in the BNST increases GABAergic signaling in other brain regions such as the PAG, where enhanced GABA release reduces nursing behavior in lactating rats (Stern and Lonstein, 2001). Furthermore, systemic activation of GABA(A) receptors increases maternal aggression in lactating mice, which seems to be related to neuronal changes in the LS and PAG (Lee and Gammie, 2007). This proves a

direct interaction of the GABA system with maternal behavior and adds to our theory on local interactions of the CRF and GABA systems in the regulation of maternal behavior.

5.2. Interaction of the CRF system with OT neurons

Exposure to stress not only activates the HPA axis with CRF neurons in the PVN being the main driver, but also triggers peripheral and central OT release (for review see Winter and Jurek, 2018). Furthermore, OT fibers express CRF-R2, at least in the PVN, BNST (rats: Dabrowska et al., 2013, 2011) and nucleus accumbens (prairie voles: Bosch et al., 2016). So far, only few studies have investigated a direct link between CRF-R manipulation and the resulting changes in local OT release (male rats: Martinon and Dabrowska, 2018; lactating rats: Klampfl et al., 2016a; Klampfl and Bosch, 2018; prairie voles: Bosch et al., 2016). In male rats, local inhibition of CRF-R2 in the dorsolateral BNST increases OT release in this brain area, which is discussed to be caused by a parallel activation of CRF-R1 (Martinon and Dabrowska, 2018). In lactating rats, local CRF-R2 inhibition in the mpBNST does not affect OT release suggesting that these effects are BNST subregion- or even postpartum-specific (Klampfl and Bosch, 2018). However, central CRF-R2 antagonism increases local OT release in the mpBNST (Klampfl and Bosch, 2018). This shows that the impact of the CRF system on OT neurons is not necessarily localized within the mpBNST directly but rather a secondary effect upstream of this brain region. Importantly, in lactating rats blocking OT receptors in the mpBNST (Klampfl and Bosch, 2018), but not the anterior BNST (Consiglio et al., 2005), impairs pup retrieval without affecting any other maternal behavior. Thus, central CRF-R2 activation might lead to reduced OT release in the mpBNST, thereby suppressing maternal motivation.

Intriguingly, both the CRF and OT system within the BNST and PVN (Dabrowska et al., 2011) could presumably influence each other also reversely, i.e. OT modulates CRF synthesis / release via OT receptors expressed by CRF neurons (Dabrowska et al., 2013, 2011). In the PVN, OT release might have suppressing effects on CRF neurons given that central OT administration attenuates the stress-induced increase of *Crh* mRNA in the PVN (Windle et al., 2004), which is important for the blunted stress response postpartum. Even though such an interaction is also possible in the BNST, no studies have been performed to date investigating such physiological or behavioral effects.

Local OT release within the MPOA of lactating rats is also triggered by the CRF system (Klampfl et al., 2018), but in a different manner than in the BNST. In the MPOA, the release of OT increases after central acute infusion of CRF, but not of UCN3. Hence, activation of CRF-R1, but not CRF-R2, facilitates the effect of CRF on OT neurons. Furthermore, and in confirmation of the results after central infusion, local retrodialysis of CRF within the MPOA increases local OT release, which suggests a direct effect of CRF on OT neurons in this brain region. While this finding seems to be surprising and unanticipated - local CRF-R1 activation impairs maternal care (Klampfl et al., 2018) whereas OT facilitates it (Bosch and Neumann, 2012; Pedersen et al., 1994) - it is reasonable that the increased OT release after CRF-R1 activation serves to counterbalance the stress-induced drop of maternal care (see Section 4.4.3). One explanation is based on a direct mechanism within the MPOA via OT (Bosch and Neumann, 2012; Pedersen et al., 1994). Another possibility is a rather indirect mechanism with OT acting on the HPA axis to dampen the stress response (Windle et al., 1997a; Neumann et al., 2000) and, thus, looping back to down-regulate CRF neuron activity thereby increasing maternal care (Klampfl et al., 2018). A similar mechanism is known in female prairie voles after termination of immobilization stress; consolidated grooming by the male partner, termed social buffering, increases OT release within the PVN, thereby inducing faster recovery from the stressor (Smith and Wang, 2014). In fact, the CRF system in the PVN can be triggered by OT on multiple levels: (i) it reduces *Crh* mRNA expression (Windle et al., 2004; Bulbul et al., 2011), (ii) it delays the stress-induced increase of *Crh* transcription (Jurek et al., 2015), and (iii) it modulates excitability of CRF neurons (Jamieson et al., 2017). However, less is known for the MPOA; at least in male rats, cells or fibers of OT and CRF neurons do not co-localize (Simerly and Swanson, 1988). Hence, this suggests that the release of OT and CRF does not occur from the same neurons nor does it happen in parallel in response to the same stimuli. However, CRF-R1 activation triggers OT release in the MPOA (Klampfl et al., 2018), which implies a co-localization of CRF-R and OT. Support comes from a study in male prairie voles (Bosch et al., 2016; Pohl et al., 2018); increased central CRF-R2 signaling impairs the activity of OT neurons arising from the PVN and projecting to the nucleus accumbens where local OT release is dampened.

These data once again demonstrate the complexity of the interactions of the CRF and OT system as well as the significance of a healthy OT signaling for the maternal brain. Therefore, more studies are needed to advance our understanding of how the CRF and OT system might influence each other in brain regions relevant for stress and maternal behavior, for example in the PVN and the LS.

5.3. Interaction of the CRF system with AVP neurons

In contrast to the feedback loop between the OT and CRF system, interactions with the AVP system seem to be not as prominent. CRF neurons in the BNST and PVN express AVP V1b receptors (Dabrowska et al., 2013), which probably promote HPA axis activity by forming heterodimers with CRF-R1 (Young et al., 2007). In a behavioral context, AVP potentiates CRF's effects on stress-induced fighting in male rats (Elkabir et al., 1990), indicating a link of the two systems in the regulation of aggressive behavior. Therefore - and due to AVP's essential role in the regulation of maternal behavior (Bayerl and Bosch, 2019; Bosch and Neumann, 2012) - it is intriguing to speculate about possible interactions with the CRF system also during lactation. However, maternal behavior is predominantly facilitated by AVP (Bosch et al., 2010; Bayerl et al., 2014) acting on V1a, but not V1b, receptors in the BNST and MPOA (Bayerl et al., 2016). AVP V1a receptors are not expressed on CRF neurons in the BNST (Dabrowska et al., 2013), which is why an interaction appears unlikely. Still, AVP V1a receptors might be expressed on UCN3 neurons in the BNST, but this has not been investigated so far. Also, studies on a potential co-localization in the MPOA are missing. Thus, to date, we can only speculate that the AVP and CRF systems in the BNST and MPOA do not mediate maternal behavior via a common feedback loop.

5.4. Interaction of the CRF system with NA neurons

Another candidate neurotransmitter system for an interaction with the CRF family postpartum is the NAergic system. Its signal transmission in the BNST and MPOA strongly influences maternal behavior in lactating rats; NAergic α2 receptor activity in the ventral BNST and MPOA needs to be down-regulated during lactation to guarantee adequate maternal behavior (Smith et al., 2012, 2013). In general, NA is a potent suppressor of neuronal activity in the anterior BNST (Forray et al., 1999) and MPOA (Leung et al., 1981). Furthermore, the adBNST, mpBNST and MPOA, where a hypo-activation of the CRF system guarantees appropriate levels of maternal behavior, receive very dense NAergic innervations through the ventral NAergic bundle from the A1 and A2 cell groups in the nucleus of the solitary tract (Forray and Gysling, 2004; Ricardo and Koh, 1978; Woulfe et al., 1988; Park et al., 2009) or the LC (Ungerstedt, 1971; Anselmo-Franci et al., 1997). Even though the NAergic system in these subdivisions of the BNST is not implicated in the regulation of maternal behavior, it is tempting to suggest a similar down-regulation of NAergic activity in the adBNST and mpBNST. Here, NA is speculated to induce the release of endogenous CRF through the activation of α1-adrenergic receptors (Forray and Gysling, 2004), which would be detrimental for maternal behavior (Klampfl et al., 2013, 2014, 2016b) and also similar to the

neuronal interactions in the ventral BNST (Smith et al., 2012, 2013). Thus, it is quite reasonable that interactions between the NAergic and CRF system are responsible for changes in the occurrence of maternal behavior following manipulation of either receptor. In the MPOA, there is no evidence to date that the CRF and NAergic systems interact to regulate maternal behavior. Importantly, both the NAergic and CRF system need to be down-regulated during lactation to guarantee the appearance of adequate maternal behavior.

In conclusion, there is strong evidence that the CRF system interacts with various neurotransmitter systems in brain regions such as the BNST and MPOA, which are implicated in maternal behavior. These interactions appear to be fine-tuned and complex in order to facilitate the display of adequate maternal behavior in the lactating brain.

6. Translational aspects

During the last decades, the CRF system emerged as an important factor in the development of psychopathologies such as depression and anxiety disorders in humans, with women facing an almost doubled risk to be affected (Kessler, 2003; Marcus, 2009) especially in the years of potential reproduction (Dickens and Pawluski, 2018). Dysregulations leading to postpartum mood disorders have mostly been associated with a disturbed hormonal balance and hyperactivity of the HPA axis (Dickens and Pawluski, 2018; Brummelte and Galea, 2010; Slattery and Neumann, 2008). However, recent studies strongly indicate that the CRF system also plays an important role in the pathogenesis of postpartum mood disorders. In healthy mothers, the reduced activity of the brain CRF system is a prerequisite for adequate physiological and behavioral adaptations and may represent a protective mechanism of the maternal brain to cope with the essential alterations in various hormonal systems during motherhood (Slattery and Neumann, 2008). In the present review, we provide clear evidence from animal studies supporting this hypothesis. Furthermore, we demonstrate the detrimental effects on maternal behavior during the unfavorable, maybe even pathological condition of CRF-R (hyper-)activation in lactating rats. Indeed, CRF-R activation, especially within the BNST and MPOA, impairs not only pup-directed but also reduces pup-protective behaviors, i.e. maternal aggression. These outcomes most likely represent a form of infant neglect, which is often observed in depressed mothers (Adamakos et al., 1986; Bifulco et al., 2004; Friedman and Resnick, 2009). The development of such aversive tendencies toward the child could at worst culminate in filicide, which is almost exclusively seen in psychotic mothers (Appleby et al., 1998; Porter and Gavin, 2010). Interestingly, in animal models pup-killing is found following central activation of the CRF system in virgin rats naïve to pups (Pedersen et al., 1991). As discussed, these effects are most likely mediated by a potentiation of the aversive circuit stimulated by pups in non-lactating females. Even though this effect is not present in lactating females following CRF application, it needs to be considered that all studies are conducted using acute pharmacological approaches. Chronic CRF-R activation, in contrast, might not only result in infant neglect but could affect dams and, consequently, the young even more severely.

Taken together, previous and current data certainly indicate that a massive dysregulation of the CRF system postpartum, among others, leads to infant neglect and filicide (Appleby et al., 1998; Porter and Gavin, 2010). Unfortunately, the therapeutic possibilities are not well advanced in the treatment of postpartum mood disorders. Given that most current antidepressants or anxiolytics have been developed in males, and that psychopathologies are differentially regulated in females (Valentino et al., 2013; Solomon and Herman, 2009), suitable treatment options are essential for lactating mothers, but still missing (Pawluski et al., 2017). Therefore, a better understanding of the underlying mechanisms is absolutely required and would certainly advance the development of suitable medication for postpartum mood disorders.

7. Conclusion

We demonstrate that hypo-activation of CRF-R in early lactating rats is inevitable to express the full repertoire of maternal behavior. This finds evidence by the fact that (hyper-)activation of CRF-R, especially in the BNST (Fig. 2) and MPOA (Fig. 3), cause detrimental effects on the occurrence of maternal care, maternal aggression, and maternal anxiety. However, maternal motivation appears to be not affected by changes in CRF system signaling. Importantly, both CRF-R subtypes are differently involved in the regulation of maternal behavior depending on the brain area and the implicated behavior. The findings certainly have translational value to human mothering and postpartum mood disorders. In conclusion, over the recent years our knowledge of the role of the CRF system during the postpartum period has significantly advanced. This takes us closer to understanding the complex basis of postpartum mood disorders and the implications of the CRF system therein. However, further experiments are needed to unravel particularly cellular and neuronal mechanisms underlying the natural down-regulation and even the mood disorder-related upregulation of the CRF system during lactation.

Declarations of interest

None.

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