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The Role of Maternal Care in Shaping CNS Function

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Abstract

Maternal care involves the consistent and coordinated expression of a variety of behaviours over an extended period of time, and adverse changes in maternal care can have profound impacts on the CNS and behaviour of offspring. This complex behavioural pattern depends on a number of integrated neuroendocrine mechanisms. This review will discuss the use of animal models in the study of the role of maternal care in shaping CNS function, the contributions of corticosteroid releasing hormone, vasopressin, oxytocin, and prolactin in this process, the molecular mechanisms involved, and the translational relevance of this research.

Animal Models and the Study of Maternal Care and the CNS

The need for improved animal models of neuropsychiatric disorders has been an active topic of discussion (Kalueff et al., 2007; Nestler and Hyman, 2010). Despite the identification of this need and frequent calls for the development of new models for disorders such as depression and anxiety, many current studies still focus on traditional approaches which have limited potential for augmenting our understanding of CNS mediated disorders. One area that a great deal of potential for improvement is the construct validity, or etiological relevance, of animal models. While the role of stress in the development of neuropsychiatric disorders has been an active area of study for many years, the stressors commonly used are often not similar to the challenges associated with the clinical development of stress induced disorders. Two examples of such stressors would be restraint and chronic mild stress. Based on the limited effectiveness of clinical treatments developed using rodent restraint, chronic mild stress (CMS), and similar paradigms, it is concluded that these stress paradigms have poor predictive value (Kirsch et al., 2008). If a lack of construct validity is responsible for this ineffective translation, as has been postulated (Nestler and Hyman, 2010), more ethologically relevant stressors will have greater predictive value. Compared with studies using restraint and CMS, the use of social stressors in studies of depression and anxiety have generated results and conclusions which have greater overlap with clinical data in terms of behaviour, endocrinology, and physiology.

Ecologists and comparative behavioural endocrinologists have recognized the value and importance of ethological relevance in both field and associated laboratory studies for

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decades. In comparison, research on many CNS disorders has placed a greater value on the development of easily controlled manipulations and standardized behavioural tests. It is argued that ethological stressors can be used in well-controlled studies which will generate reliable and repeatable results. The best examples of this may be the numerous variations of social stressors that can be used in numerous species, both genders, and a wide range of contexts. Social stressors are especially useful in the study of stress associated disorders in females, as they are especially sensitive to the adverse effects of these types of stressors (Haller et al., 1999; Herzog et al., 2009). Social stress paradigms can be easily modified to suit specific needs based on species social structure and/or to target a specific social interaction, such as territorial aggression or maternal care. However, there can be logistical challenges in administering social stress studies that are often related to common animal husbandry practices in research facilities, such as large centralized animal rooms or limited cage space which make behavioural manipulations and recording difficult. These husbandry practices may represent a significant challenge to progress in the study of stress-induced CNS disorders.

The other area where focusing on ethological relevance may be advantageous in the study of the pathophysiology of neuropsychiatric disorders is the behavioural tests used to assess the impact of an animal model. The forced swim test (FST), tail suspension, and learned helplessness test are used to measure the development of a depression-like state in rodents. Studies using these tests have not had good predictive value at the clinical stage with most types of depression. One of the most popular tests to measure anhedonia, the lack of motivation to perform reward mediated behaviour which is a common symptom of depression, is the sucrose or saccharin preference test. It is argued that naturally occurring behaviours (social interaction, sexual behaviour) can be used to assess the motivation to perform a reward mediated behaviour and generate conclusions which are more ethologically and translationally relevant. For example, saccharin preference can be used to measure anhedonia in maternal animals, but it is suggested that maternal care is a better measure due to the common clinical observation of impaired maternal care in depressed and anxious mothers. While saccharin preference addresses anhedonia, maternal care is more specific to the behavioural pathology of the disorder, therefore having greater face validity. Furthermore, it is unclear if saccharine preference has a strong predictive value for maternal care in rodent models of postpartum depression and anxiety, and one of the main objectives of any animal model of these disorders should be to impair maternal care, as the adverse effects of postpartum depression and anxiety on offspring are often mediated through impaired maternal care.

Four key hormones in the study of the role of maternal care in shaping the CNS are corticotrophin releasing hormone (CRH), arginine vasopressin (AVP), oxytocin (OXT), and prolactin (PRL). These four hormones are involved in both the physiological and behavioural changes associated with maternal care, as well as also being mediators of the stress response. A number of recent studies conclude that these are primary mediators of the intergenerational effects of maternal care on CNS function.

CRH, Maternal Care, and CNS Function

Although there is a wealth of studies on the role of maternal care in shaping the HPA axis, most studies focus on corticosterone and central glucocorticoid receptors. CRH secreted by the paraventricular nucleus (PVN) is a primary modulator of the HPA axis through its actions on ACTH release into the circulation, and is also involved in gestation, parturition, and maternal care (table 1). It has been postulated that low CRH receptor activity is needed for the expression of typical maternal behaviour. Initial studies revealed that CRH decreased maternal care and increased infanticide in an induced virgin rodent model of maternal care

(Pedersen et al., 1991), and intracerebroventricular (icv) CRH also inhibits maternal aggression in mice (D'Anna and Gammie, 2009; Gammie et al., 2004; Gammie et al., 2008). The behavioural differences in the maternal care of rat and mouse strains bred for differing levels of anxiety (high anxiety behaviour/low anxiety behaviour, HAB/LAB) has been associated with differences in central CRH and AVP (Bosch et al., 2006; Kessler et al., 2011; Klampfl et al., 2013). PVN CRH is higher in HAB vs. LAB rats, and central CRH was found to be involved in maternal anxiety in multiple strains of rats (Klampfl et al., 2013). Icv injection of CRH and a CRH receptor antagonist indicated that CRH decreases both maternal care and aggression, and this effect on maternal care was partially rescued by a CRH antagonist (Klampfl et al., 2013). Both CRH and AVP are involved in the maladaptive effects of maternal separation stress, where females show greater changes in CRH (Desbonnet et al., 2008). Urocortin-1, a member of the CRH peptide family, is also affected by maternal separation (Gaszner et al., 2009). Given these strong connections between maternal care and CRH, it is likely that maternal care is involved in the intergenerational transmission of central CRH activity and anxiety. Variations in maternal care, working through changes in central CRH activity, may allow mothers to alter the behavioural and physiological stress responses of their offspring to match their environment. For example, a high risk of predation may decrease maternal care and increase predatory vigilance through elevated central CRH activity, with this modulation of CRH being epigenetically transmitted to offspring to increase survival in a similarly threatening environment. However it is likely that AVP, OXT, and PRL also have roles in this process.

AVP, Maternal Care, and CNS Function

AVP is another neurohormone involved in both stress and maternal behaviour (table 1), and AVP mRNA levels in the hypothalamus increase 2–3 fold during late pregnancy and lactation. Central AVP mediates both maternal care (Bosch and Neumann, 2008; Nephew and Bridges, 2008a; Nephew and Bridges, 2008b) and aggression (Nephew and Bridges, 2008b; Nephew et al., 2009; Nephew et al., 2010) in rodents. The blockade of V1a receptors around parturition impairs maternal memory, which is the ability of a maternal dam to return to maternal care following a prolonged separation from her pups (Nephew and Bridges, 2008a). Studies of HAB/LAB rodents have postulated that maternal nurturing is linked to innate anxiety and OXT and AVP activity, as low anxiety mice display lower levels of maternal care compared to high anxiety mice and acute icv injection of AVP increases maternal care and has anxiogenic effects (Kessler et al., 2011). While the association between maternal care and innate anxiety was not supported in another study of maternal mice, V1a receptors were correlated with pup grooming (Curley et al., 2012). Both AVP and V1a antagonist treatments attenuate maternal care during exposure to a male intruder, with the effects of AVP associated with increased self grooming and the effects of V1a antagonist associated with elevated maternal aggression towards the intruder (Nephew and Bridges, 2008b). In comparison to investigations focusing on maternal care in a benign environment (Bosch and Neumann, 2008), these results illustrate the importance of considering the behavioural context of neuroendocrine manipulations. Based on these studies of AVP and maternal care, and observed changes in central AVP activity which are associated with differential exposures to maternal care (Murgatroyd and Nephew, 2013), it is postulated that altered maternal care programs the developing behavioural mechanisms.

Functional MRI has also been used to examine the role of V1a receptors in neural processing in the maternal brain when dams are exposed to a male intruder (Caffrey et al., 2010). Primiparous females were given an icv injection of vehicle or V1a receptor antagonist before imaging, and awake dams were presented with a male intruder while in the presence of their pups. The results indicated that neural activity was reduced in some regions with V1a receptor blockade, while increases were observed in other areas. Dams treated

with V1a antagonist showed significantly greater neural responses in the anterior olfactory nucleus, infralimbic prefrontal cortex, gustatory cortex, somatosensory cortex, and substantia innominata when presented with a novel male intruder. Neural responses were reduced in the cortical amygdala and ventromedial hypothalamus (Caffrey et al., 2010). These regions are involved in the processing of smell, taste and touch, emotional reactivity, aggression, and coordination between sensory inputs and motor outputs. It is postulated that AVP, acting through V1a receptors, may modulate sensory processing and perhaps coordinate sensory processing and visceromotor activity during the initial stages of maternal aggression and/or anxiogenic responses.

With respect to the stress response, AVP is especially sensitive to psychosocial stressors (De Goeij et al., 1992), and the primary signal for ACTH release may switch from CRH to AVP in the latter stages of exposure to chronic stress (Ma et al., 1997). In studies of early life stress, dams exposed to early life chronic social stress (CSS) as infants, which includes both depressed maternal care and conflict between a dam and a male intruder, display substantial decreases in nursing efficiency that are associated with attenuated vasopressin gene expression in the SON (Murgatroyd and Nephew, 2013). It was concluded that early life CSS has long term effects on central AVP, OXT, and PRL which results in decreased nursing efficiency in the adult dams. Overall, these animal studies suggest that AVP may be another worthwhile target for the study of translationally relevant interactions between maternal care associated disorders such as postpartum depression and anxiety and CNS development and function.

OXT, Maternal Care, and CNS Function

The social behaviour functions of OXT have been documented in numerous species (Donaldson and Young, 2008), and this neuropeptide is a particularly potent mediator of maternal care (table 1). The importance of OXT in the establishment of maternal care was initially reported in the late 70's and early 80's through icv injections of OXT (Pedersen et al., 1982; Pedersen and Prange Jr., 1979), and further supported by OXT antagonist administration (Pedersen et al., 1994; van Leengoed et al., 1987). In addition, the actions of OXT receptors in the nucleus accumbens have been implicated in spontaneous maternal care in prairie voles (Olazabal and Young, 2005). While OXT receptor knockout mice exhibit deficits in maternal care (Takayanagi et al., 2005), central OXT activity may not be a factor in all aspects of maternal care once it is initiated. Investigations in sheep have supported the hypothesis that OXT specifically mediates the induction of maternal care (DaCosta et al., 1996). OXT disrupting lesions to the PVN of sheep do not disrupt maternal care once it has been established, indicating that this neuropeptide is not essential for the ongoing display of maternal care (Kendrick, 1997). Comprehensive studies of natural variations in rodent maternal care indicate that OXT receptors mediate these differences, with high levels of OXT activity being associated with elevated levels of maternal care (Champagne et al., 2001; Francis et al., 2002). Furthermore, both OXT receptor levels and maternal care are altered by exposure to gestational stress (Champagne and Meaney, 2006). It is postulated that impairments in maternal care following gestational stress may be mediated by decreases in central OXT activity. OXT's role in maternal care induction parallels the importance of this peptide in lactation (Grosvenor et al., 1986; McNeilly et al., 1983; Uvnäs-Moberg and Eriksson, 1996), and there is clinical interest in this parallel (Steube et al., 2011). Future animal work which includes the behavioural and physiological effects of OXT in maternal animals may identify treatments for disorders involving deficits in both maternal care and lactation. Dams exposed to early life CSS as infants display substantial impairments in lactation and maternal care which are associated with attenuated oxytocin and oxytocin gene expression in the hypothalamus and amygdala (Carini and Nephew, 2013; Murgatroyd and Nephew, 2013). As with AVP, it is likely that the effects of early life CSS on adult central

OXT activity are mediated by the depressed maternal care experienced by the dams as infants. Another hormone intricately involved in both lactation and maternal care is PRL.

PRL, Maternal Care, and CNS Function

Prolactin is a key mediator of both mammalian lactation (Freeman et al., 2000; McNeilly et al., 1983; Powe et al., 2010) and maternal care (Bridges, 1994; Bridges et al., 1997; Grattan, 2002; Grattan et al., 2001; Lucas et al., 1998)(table 1), although less is known about its role in non-maternal social behaviour. It also has inhibitory actions on HPA activity following stress exposure which may be related to its' role in maternal care (Torner and Neumann, 2002). Study of early life CSS exposed females indicates that plasma PRL concentrations are decreased in early life CSS exposed maternal females (Carini and Nephew, 2013), and this decrease in peripheral PRL is associated with impaired maternal care and lactation and decreased expression of the long form of the PRL receptor in the PVN (Carini and Nephew, 2013; Murgatroyd and Nephew, 2013). Interestingly, the decrease in peripheral PRL was associated with an increase in corticosterone concentrations. The decreased levels of PRL and elevated corticosterone in dams support the hypothesis presented by Torner and Neumann that PRL mediates the suppression of the HPA axis during lactation (Torner and Neumann, 2002). PRL's role in maternal care may be a key mediator of the effects of maternal care on the development of the HPA axis. Low plasma levels of PRL are associated with maternal depression, supporting research on PRL as a treatment target for treating stress related disorders that affect both maternal care and lactation, such as postpartum depression and anxiety (Stuebe et al., 2012; Watkins et al., 2011). Considering the related involvement of AVP, OXT, and PRL in both maternal care and lactational physiology, there is a need for more integrative investigations of maternal care and CNS related disorders that include nursing assessments.

Molecular Mechanisms that Affect Maternal Care and Offspring Behaviour

An important avenue in delineating the neurological basis of maternal behaviours is identifying genes that contribute to individual differences. As previously mentioned, some animal models with mutations in key genes have provided key evidences for their involvement. In the clinic several association studies further support key roles of the previously discussed CRH, OXT, AVP and PRL signaling pathways. Recently, Mileva-Seitz and colleagues (Mileva-Seitz et al., 2013), studying 187 mothers at 6 months postpartum, found single nucleotide polymorphisms (SNPs) in the vicinity of the OXT gene that had effects on maternal vocalizing to the infant though no associations with maternal sensitivity, highlighting the importance of exploring multiple dimensions of human maternal behaviour in such genetic association analyses. A follow-up study by the same group revealed that one of the OXT SNPs furthermore interacted with early life adversity to predict variation in breastfeeding duration (Apter-Levy et al., 2013). Further studies on an OXTR SNP by the authors found no effects on maternal behaviour but an association with pre-natal (but not post-natal) depression score. This maternal depression finding has been supported by several other association studies involving different SNPs within the OXTR locus (Jonas et al., 2013). Importantly, mothers with a genotype for a different SNP in the third intron of OXTR showed lower levels of sensitive responsiveness to their toddlers (Bakermans-Kranenburg and van IJzendoorn, 2008). Numerous association studies have investigated genetic variation in the vasopressinergic system in mood disorders (Dempster et al., 2009). Further studies have demonstrated an impact of a polymorphism in the AVPR1A promoter region, previously associated with autism, on a mother's structure and support when interacting with their infants (Avinun et al., 2012) and maternal sensitivity (Bisceglia et al., 2012).

It is worth noting however that the effect sizes of single SNPs are usually small. Thus in addition to genetic studies, which are concerned with effects due to the direct alterations of the DNA sequence, other factors influencing expression of key genes should be taken into account. One such additional layer of genetic information that has recently become the target of considerable interest is epigenetic regulation of gene activity, where gene expression changes occur in the absence of changes to the DNA sequence. Several mechanisms involved in the control of gene expression have been described, including DNA methylation and chromatin modification. DNA methylation involves the direct chemical modification of cytosines in cytosine-guanine (CpG) dinucleotides. This can inhibit gene transcription by interfering with the recruitment of transcription factors or by recruiting methylated-DNA binding proteins. Chromatin refers to a complex of DNA wrapped around histone proteins. These proteins are extensively modified at their N-terminal tails by methylation, phosphorylation, acetylation, and ubiquitination as part of a histone signature serving to define accessibility to the DNA as to whether it is “closed” or “open” to translation (Jenuwein and Allis, 2001). Histone acetylation is known to be a predominant signal for active chromatin configurations while some specific histone methylation reactions are associated with either gene silencing or activation.

Recently, research is revealing that epigenetic modifications are more plastic than previously assumed. Indeed, the epigenome seems sensitive to a wide variety of environmental influences, including diet, toxins, and stress (Faulk and Dolinoy, 2011). Epigenetics has thus been embraced by behavioural and developmental neuroscientists as a biological mechanism for the link between environmental influences and persisting changes in physiology and behaviour (Kumsta et al., 2013). As previously discussed, the quality of maternal care that an infant receives is a crucial factor in the development of behaviour and psychopathology. Therefore, an attractive hypothesis for how maternal care could be programmed, and intergenerationally transmitted, is through environmentally induced epigenetic alterations of those genes important to maternal behaviour within key brain regions known to play prominent roles.

A seminal paper by Michael Meaney and colleagues in 2004 first demonstrated a mechanism for the epigenetic programming of gene function by maternal care during early life (Weaver et al., 2004). They studied a well-characterized model established to investigate the effects of early life environment on stress programming through variations in the quality of early postnatal maternal care, as measured by levels of licking and grooming. Previous work revealed that rat pups receiving high levels of maternal care during early life developed sustained elevations in glucocorticoid receptor (GR) expression within the hippocampus and decreased hippocampal sensitivity to glucocorticoid hormones (Liu et al., 1997). In addition, these rats showed decreased hypothalamic CRH levels and reduced HPA axis responses to stress (Francis et al., 1999) when compared to animals reared by mothers showing low levels of maternal care. Analysis of the molecular mechanisms underlying the long-lasting programming of the GR revealed enhanced hippocampal GR expression in animals receiving high levels of maternal care associated with lower DNA methylation and increased histone acetylation at the GR promoter in the hippocampus. These epigenetic modifications facilitated binding of the transcriptional activator nerve growth factor-inducible protein A (NGF1a) to this region, providing a plausible mechanism (Weaver et al., 2004). Subsequent studies detected altered GR promoter methylation in human postmortem hippocampal tissue of depressed suicide patients who suffered from a history of early life abuse and neglect (McGowan et al., 2009). Indeed, there do appear to be relatively conserved epigenetic patterns between rats and human in the hippocampal GR gene with analogous cross-species epigenetic regulatory responses at the level of the genomic region to early-life experience (Suderman et al., 2012). Oberlander and colleagues (Oberlander et al., 2008) studied this same region of the GR promoter in blood cells of infants exposed to

prenatal maternal depression and found increased DNA methylation that further correlated with salivary cortisol responses to stimulation. A more recent study also found that prenatal maternal emotional state, particularly pregnancy related anxiety, associated with methylation changes in promoter regions of the glucocorticoid receptor gene NR3C1 in the child (Hompes et al., 2013).

A growing number of studies are revealing epigenetic mechanisms regulating neuroendocrine gene expression. Prenatal stress during early gestation led to decreased DNA methylation at the CRH promoter in the hypothalamus of the offspring in adulthood (Mueller and Bale, 2008) while chronic social stress in adult mice caused a hypomethylation of the CRH promoter in the PVN of a subset of animals displaying subsequent social avoidance (Elliott et al., 2010). A more recent study by the group of Aguilera showed that maternal deprivation led to reduced DNA methylation at this same promoter that correlated with increased CRH expression in the PVN and HPA axis hypersensitivity (Chen et al., 2012). Early life stress in mice has been further demonstrated to lead to decreased DNA methylation at the AVP gene underpinning sustained expression and increased HPA axis activity (Murgatroyd et al., 2009).

A very recent study has been able to support the functional importance of differential methylation of a CpG island in the OXTR promoter with OXTR expression (Mamrut et al., 2013). Changes in methylation at this region have been observed in childhood disorders characterized by impairments in social recognition (for review, see (Kumsta et al., 2013)). OXTR promoter methylation has also been linked in one study to autism (Gregory et al., 2009). Studies of PRL have identified regulatory regions demonstrating tissue-specific differences in methylation that correlate with expression. However, it remains to be seen if differential methylation of OXTR and PRL might be important in explaining differences resulting from variations in maternal behaviour.

A study by Stolzenberg and colleagues demonstrated an important role for epigenetic mechanisms in regulating maternal behaviour through the use of a chromatin-modifying drug (Stolzenberg et al., 2012). Treating virgin female mice with a histone deacetylase inhibitor (sodium butyrate) increased maternal responsiveness and the expression of several genes in the medial preoptic area (MPOA), including OXT, AVP and AVP1a. The group of Champagne studying the MPOA of rats during postnatal development found increased estrogen receptors (ER) α and ER β and OXTR RNA levels by postnatal day 21 in female offspring of high licking and grooming dams. This correlated with decreased DNA methylation and histone H3K9 tri-methylation and increased H3K4 tri-methylation at the ER α gene promoter (Esr1) in these offspring. Cross-fostering revealed that maternal sensitization and MPOA ER α levels are sensitive to maternal care experienced before but not after postnatal day 10 with differential windows of plasticity for ER β and OXTR mRNA levels (Peña et al., 2013). This all brings us closer to understanding mechanisms in which variation in maternal behaviour can be transmitted from one generation to the next.

Focusing on Maternal Care to Model Disorders that Affect Offspring Behaviour and CNS Function

After identifying associations between variations in maternal care and CNS function and manipulating maternal care through central treatments, the next step is the development of models for disorders such as depression and anxiety which affect CNS development and function through changes in maternal care. Studies focusing on the use of ethologically relevant manipulations of maternal care, such as those resulting from exposure to chronic social stress, have reported substantial changes in both maternal care, CNS gene expression, and related peripheral endocrinology which parallels changes observed in clinical

populations (Brunton, 2013; Brunton and Russell, 2010; Carini et al., 2013; Carini and Nephew, 2013; Murgatroyd and Nephew, 2013; Nephew and Bridges, 2011). One of the major symptoms of postpartum depression/anxiety, and the primary mediator of the detrimental effects of these disorders on children, is depressed maternal care.

As previously mentioned, chronic social stress during lactation decreases maternal care, increases maternal aggression, and impairs overall growth in both the dam and offspring (Nephew and Bridges, 2011). When the F1 offspring of the stressed dams are studied as maternal females, deficits in lactation efficiency and/or maternal care have been described, and these changes are associated with robust decreases in central OXT, AVP, and PRL receptor mRNA expression, as well as decreased plasma prolactin and elevated plasma corticosterone (Carini and Nephew, 2013; Murgatroyd and Nephew, 2013). In contrast to maternal care, non-maternal activities such as locomotion, nest building, and self grooming increase, suggesting an increase in restless and anxiety, which are common in postpartum mood disorders (Carini and Nephew, 2013). The roles of these hormones may be gender specific, and it is possible that treatments aimed at decreasing anxiety in maternal females may negatively affect maternal care. For example, although V1 receptors are a target for the treatment of anxiety disorders (Griebel et al., 2005; Landgraf, 2006; Simon et al., 2008; Surget and Belzung, 2008), AVP is an important mediator of typical maternal care (Bosch and Neumann, 2008; Nephew and Bridges, 2008a; Nephew and Bridges, 2008b), and icv AVP has been found to increase maternal care in dams exposed the CSS model of postpartum depression and anxiety (Coverdill et al., 2012). It is possible that V1a antagonists may increase anxiety, or decrease both anxiety and maternal care. The neuroendocrine and behavioural data from the F1 dams suggest that OXT is a particularly potent mediator of the intergenerational effects of early life CSS, and a clear understanding of gender and behavioural context specific effects is also needed in the development of OXT based treatments (Bartz et al., 2011; Parker et al., 2010).

One important potential mediator of the effects of altered maternal care on CNS function, but one that has been neglected in both basic and clinical studies, is nursing. Deficient nursing is often reported in women suffering from disorders associated with a lack of overall maternal care, and offspring may be faced with both depressed maternal care and impaired nutrition (Stuebe et al., 2012). Decreases in nursing that result in underweight infants increases the risks for numerous CNS disorders due to developmental effects (Murray, 1992; Murray and Cooper, 1997). Even if infant nutrition is not significantly affected in terms of overall growth, as is often seen in developed countries, there is evidence that breastfeeding has beneficial effects on general cognitive development (Anderson et al., 1999; Lucas et al., 1992) and behaviour (Al-Farsi et al., 2012; Hinde and Capitanio, 2010; Sullivan et al., 2011). Although PRL is an important mediator of both lactation and maternal care, and lactation is often impaired in depressed mothers, there has been little focus on PRL as a potential treatment target for disorders that affect maternal care. Both clinical and pre-clinical research indicate that PRL, in addition to studies of CRH, AVP, and OXT, may be a productive target in the search for safe and effective treatments for postpartum depression and anxiety associated lactational difficulties. Rodent models of the connection between maternal care and offspring behaviour, especially those which focus on maximizing construct and face validity with respect to clinical work, will generate consistent and translationally significant data.

From Nest to Bedside, and Back Again

A well-described approach to stimulate increased maternal care is to separate pups from their mother for short (e.g., 15 min) periods of times during early life. Seemingly in support the so called “maternal mediation” hypothesis (Smotherman et al., 1974) whereby the

emotional state of the mother imprints the one of the offspring (Champagne and Meaney, 2001; Milgrom et al., 2004). Continuous refinements of translational animal models are needed to tease out the impacts of environmental interactions and the multitude of facets underlying maternal behaviour and its impacts. The ultimate aim is to allow us to foster appropriate preventative measures in the management of early-life care and mood disorders effecting mothers and infants. An excellent recent example of this is the work of Sharp and colleagues (Sharp et al., 2012). They examined whether maternal stroking over the first weeks of life modified associations between prenatal depression and physiological and behavioural outcomes in infancy, hence mimicking previously described effects of rodent licking and grooming (Weaver et al., 2004). Interestingly, increasing maternal depression was only associated with decreasing physiological adaptability and increasing negative emotionality in the presence of low maternal stroking. This suggests that maternal stroking in infancy strongly resembles the effects of observed maternal behaviour in animals. It remains to be seen if at the molecular level conserved epigenetic mechanisms, identified by Meaney and colleagues in the rats, are also underlying these effects in human populations.

Maternal care involves the consistent and coordinated expression of a variety of behaviours over an extended period of time, and adverse changes in maternal care can have profound impacts on the CNS and behaviour of offspring. This complex behavioural pattern depends on a number of integrated neuroendocrine mechanisms. It is suggested that investigations which attempt to simulate, measure and/or manipulate several behavioural and or neuroendocrine mechanisms may generate novel findings that have greater translational relevance in the study of maternal care disorders that involve altered CNS function in mothers and their offspring.

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	icv administration	Antagonists	Knock-out findings	Natural variations	Clinical SNP findings
CRH	↓ maternal care and aggression (, Pedersen, Caldwell et al. 1991; Klampfl, Neumann et al. 2013)	N/A	CRHR2 ↓ maternal aggression (Gammie, Hasen, Stevenson, Bale, & D'Anna, 2005)	↑ in HAB/LAB differing in maternal care (Bosch, Krömer et al. 2006; Kessler, Bosch et al. 2011; Klampfl, Neumann et al. 2013)	N/A
AVP	↑ maternal care (Kessler, Bosch et al. 2011)	V1a antagonist ↓ maternal care (Nephew and Bridges, 2008)	N/A	↑ in HAB/LAB differing in maternal care	V1a - maternal sensitivity (Bisceglia, Jenkins et al. 2012).
OXT	↑ maternal care (Pedersen and Prange Jr. 1979; Pedersen, Ascher et al. 1982)	↓ maternal care (van Leengoed, Kerker et al. 1987; Pedersen, Caldwell et al. 1994)	OXT ↓ maternal care (Takayanagi, Yoshida et al. 2005) though some studies report normal maternal behaviors (Macheth et al., 2010; Nishimori et al., 1996).	↑ associated with ↑ maternal care (Champagne, Diorio et al. 2001; Francis, Young et al. 2002). OXTR receptor levels and maternal care are altered by exposure to gestational stress (Champagne and Meaney 2006).	OXT - maternal vocalizing, breastfeeding duration (Apter-Levy, Feldman et al. 2013). OXTR - sensitive responsiveness to offspring (Bakermans-Kranenburg and van IJzendoorn 2008), maternal depression (Jonas, Mileva-Seitz et al. 2013)
PRL	↑ maternal behaviour (Bridges, Numan et al. 1990).	↓ onset of maternal behaviour (Bridges, Rigerio et al. 2001).	PRL Receptor ↓ maternal care (Lucas, Ormandy et al. 1998)	↓ plasma concentrations in stress associating with ↓ maternal care (Carini and Nephew, 2013)	N/A