Melanin-Concentrating Hormone: Role in Nursing and Sleep in Mother Rats

Luciana Benedetto, Pablo Torterolo, and Annabel Ferreira

Abstract In mammals, the postpartum female undergoes the most important physiological and behavioral changes in life, which allow orchestrating two essential behaviors for survival: nursing and sleep. Although the melanin-concentrating hormone (MCH) is mainly found within the posterolateral hypothalamus and incerto-hypothalamic area, during lactation this neuropeptide is also expressed in the preoptic area (POA). Remarkably, this brain area controls key components not only of the maternal behavior repertoire but also is involved in the regulation of sleep and wakefulness. In this sense, when MCH is microinjected into the POA, this neuropeptide is capable to reduce the motivational aspects of maternal behavior in postpartum rats while increases sleep in male rats. This effect seems to oppose to one of the dopaminergic systems that promotes wakefulness while in postpartum rats stimulates motivational components of maternal behavior. How the MCHergic system controls maternal behavior and sleep within the POA is still an unresolved question.

In this chapter, we provide neuroanatomical and neurochemical evidences showing that MCHergic and dopaminergic systems interact within the medial POA (mPOA) to regulate maternal behavior and sleep. We suggest that the interplay among these and other neurotransmitter/neuromodulators modulates mother's physiology and behavior assuring not only pups' nutrition and development but also the mother's needs for rest and sleep during this highly demanding period of life. Finally, we discuss some useful directions for future research and some issues yet to be explored.

L. Benedetto (✉) · P. Torterolo
Department of Physiology, School of Medicine, University of the Republic, Montevideo, Uruguay
e-mail: lbenedet@fmed.edu.uy

A. Ferreira
Facultad de Ciencias, Sección de Fisiología y Nutrición, Universidad de la República, Montevideo, Uruguay

S. R. Pandi-Perumal et al. (eds.), *Melanin-Concentrating Hormone and Sleep*,
https://doi.org/10.1007/978-3-319-75765-0_9

1 Introduction

The postpartum period is a highly physically and emotionally demanding period for the mammalian female, characterized by a huge range of physiological and behavioral adaptations that allow the adequate development and survival of the offspring. We recently showed that the mother rat can sleep and nurse the pups at the same time, making possible to fulfill the pups' needs of nutrition together with the maintenance of an adequate homeostasis of her sleep physiology (Benedetto et al. 2017b). Interestingly, the melanin-concentrating hormone (MCH), a neuropeptide synthesized by neurons of the lateral hypothalamus and incerto-hypothalamic areas that project throughout the central nervous system (CNS) (Bittencourt et al. 1992), has been involved in the control of maternal behavior (Alachkar et al. 2016; Benedetto et al. 2014) and sleep (Torterolo et al. 2011). Thus, MCH microinjections into the medial preoptic area (mPOA), an essential area in the control of maternal behavior, reduce the active components of maternal behavior (Benedetto et al. 2014). Also, local delivery of MCH into the ventrolateral preoptic area (VLPO), a key player in the control of sleep, promotes NREM sleep (Benedetto et al. 2013).

In the present chapter, we describe the maternal and sleep behaviors of the lactating rat as well as the interplay between the MCHergic and dopaminergic system in specific brain areas related to the control of both behaviors. As most studies of the neurobiological basis of maternal behavior and sleep were done in rodents, we will focus on these animals.

2 Maternal Behavior

In the rat, newborn pups are altricial, that means that they are highly immature and totally dependent on the maternal care and nutrition for development and survival. They are born with eyes and ears closed (Fig. 1), are unable to regulate their own temperature, and are incapable of urinating and defecating without the anogenital stimulation provided from the mother (Fig. 2b) (Numan and Insel 2003). These characteristics of the pups require a constant maternal attention and care resulting in a highly demanding stage with important metabolic costs for the mother (Thornburg et al. 2006). Thus, the mother rat provides not only the nutritional requirements to the offspring through lactation but also care and protection, contributing to the establishment of the maternal-infant bonding which is crucial for the development and survival of the young (Numan and Insel 2003). As newborn rats grow up, the mother will be continuously accommodating her own physiology and behavior to the pups' requirements.

To fulfill the pups' needs, mother rats develop a wide variety of behaviors termed as maternal behavior that is aimed to provide food, heat, shelter, cleaning, nourishment, and affect to the offspring (Reisbick et al. 1975; Rosenblatt 1975; Pereira 2016). In rats, if the mother is reunited with the pups after a certain time of separation, she will display a sequence of maternal behaviors. She will transport

Fig. 1. Altricial rat pup. Note that the pup rat is born hairless with eyes and ears closed

materials to build a nest, retrieve the pups into it, and lick and rearrange them in the nest (Stern 1989) (Fig. 2a, b). As these behaviors precede and promote mother-infant contact, they are known as pronurturant or active behaviors (Hansen et al. 1991b; Stern 1989). Following the reunion of the pups, the mother stands over them (Fig. 2c), and with sufficient ventral stimulation, she will adopt quiescent nursing postures, referred as nurturant, passive, or nursing behaviors (Hansen et al. 1991a; Stern and Johnson 1990) (Fig. 2d). Nursing is the behavior that defines us as mammals and is present in all mammalian species. However, it presents a wide variability among species, from the rabbit that nurses a few minutes once a day to the rat that nurses during most of the day in the early period of lactation (Gonzalez-Mariscal et al. 2016; Grota and Ader 1969; Zarrow et al. 1965).

In the mother rat, upright crouching is the most typical nursing posture, also known as kyphosis (Stern and Johnson 1990). This posture is elicited by the sensory stimulation of the mother's ventral area provided by a sufficient number (at least four) of pups (Neville 2006; Stern and Johnson 1990; Wakerley 1996). In this posture, the dam stands still over the litter, in high- or low-arched back posture with its legs rigidly splayed (Fig. 2d). Only during quiescent nursing postures milk ejection occurs (Voloschin and Tramezzani 1979).

The postpartum period of the rat lasts approximately three weeks until weaning during which the mother continuously adapts her maternal responses to pups' needs. Thus, during the first days after parturition, mother rats spend 85% of the day with their pups, rarely leaving the nest. While pups grow older, maternal behavior diminishes toward weaning (Numan 1994; Pereira 2016; Rheingold 1963; Rosenblatt et al. 1985). Both active and nursing behaviors decline significantly from the 10th–12th days onward (Grota and Ader 1969; Pereira 2016; Reisbick et al. 1975).

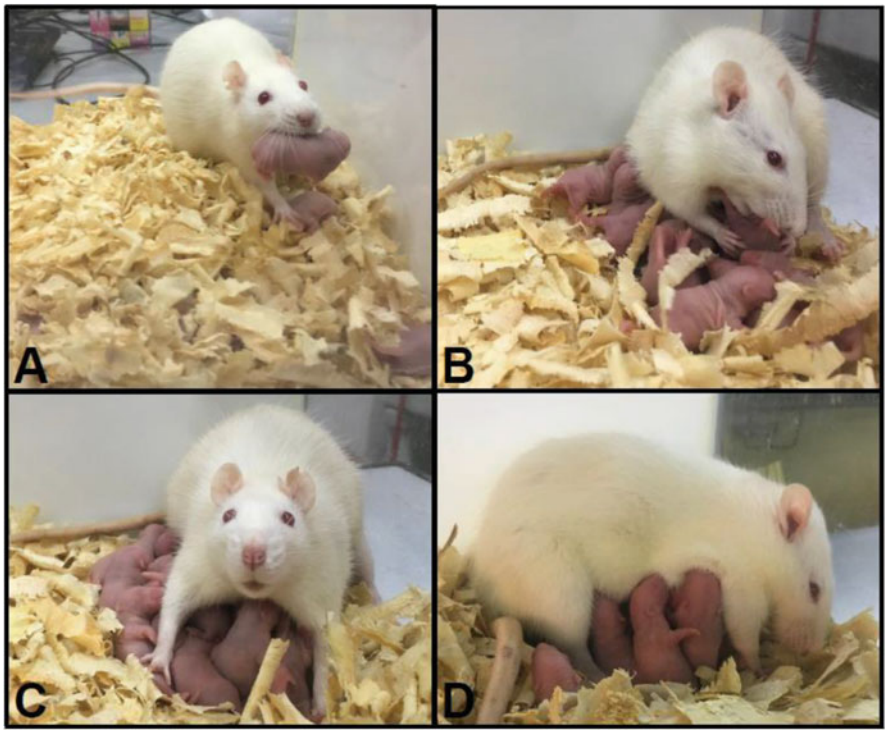

Fig. 2. Active and passive maternal behaviors in the rat. (**a**) Transporting or retrieving a pup. (**b**) Licking a pup. (**c**) Hovering over the pups. (**d**) Nursing the litter

3 Sleep During Postpartum Period

As mentioned, nursing is one of the most energy-consuming stages for the female (Krasnow and Steiner 2006; Thornburg et al. 2006; Zhao et al. 2010). In contrast, sleep is necessary for the conservation and restoration of energy. Although both processes are essential for the survival of the individual or the offspring, the strategies to reconcile both behaviors vary among species. Recently, we demonstrated that the mother rat can nurse and sleep at the same time (Benedetto et al. 2017b) (see Fig. 3). Thus, during the low upright crouching posture (also known as low kyphosis, the most common nursing posture), mother rats mostly sleep, particularly in NREM sleep, both at the light and dark phases of the cycle (see Fig. 4).

Remarkably, while suckling from the pups is sufficient to stimulate the upright crouching posture in the mother rat, this stimulus has to be preceded by a NREM sleep episode for milk ejection occurrence (Lincoln et al. 1980; Sutherland et al. 1987; Voloschin and Tramezzani 1979). In fact, sleep deprivation decreases lactation and impairs pups' weight gain (Voloschin and Tramezzani 1979). This is not the case for other animals, such as rabbits, where suckling is associated with a desynchronized electroencephalogram (Neve et al. 1982). However, as rabbit doe

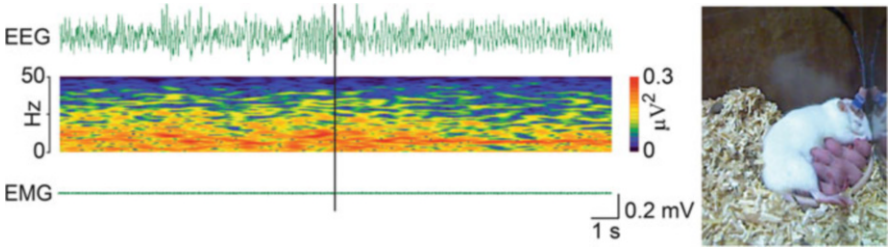

Fig. 3. Mother rat during the first postpartum week. The raw electroencephalogram (EEG), its correspondent spectrogram, and the electromyogram (EMG) of a mother rat during nursing in supine posture. The vertical line indicates the moment when the photograph was taken. Note the transition from NREM to REM sleep

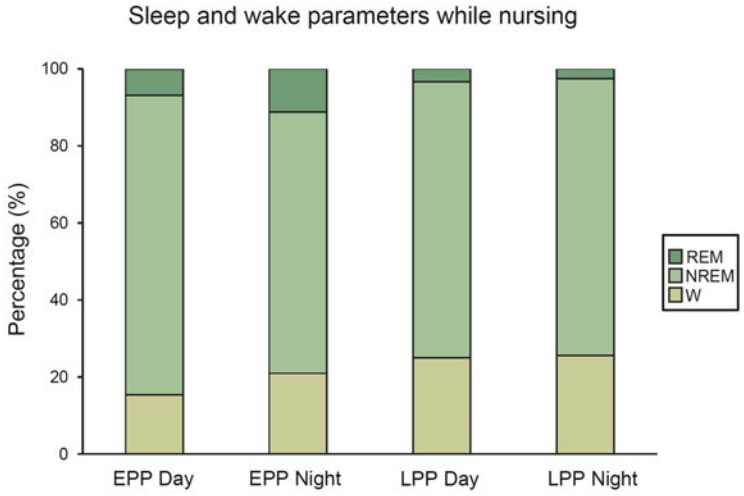

Fig. 4. Graphic charts showing the percentage of time spent in wakefulness (W), NREM, and REM sleep while nursing. Comparisons of the percentage of time of sleep and W during low kyphosis during the first and second postpartum weeks in the light and dark periods. [These data were published in Benedetto et al. (2017b).] *EPP* early postpartum, *LPP* late postpartum

usually nurses once a day (Gonzalez-Mariscal et al. 2016), nursing and pups' attention would not interfere with maternal sleep.

In some species, sleep deprivation and sleep fragmentation are consequences of the early stages of motherhood (Hunter et al. 2009; Lyamin et al. 2007). In the case of the human mother, partial sleep deprivation and sleep fragmentation have been reported; these sleep disturbances are compensated, at least partially, by a deeper sleep (Montgomery-Downs et al. 2010; Nishihara et al. 2004). Sleep deprivation and fragmentation may lead to maternal irritability and possible psychiatric disorders, with negative consequences for the care and welfare of the newborn (Lee 1998; Sharma and Mazmanian 2003). An extreme case is found in dolphins, where both the

mother and calf are sleep deprived during the first months after birth (Lyamin et al. 2007). In laboratory rat the antecedents are not conclusive, since Voloschin and Tramezzani (1979) reported no sleep deprivation during the second postpartum week, while Sivadas et al. (2016) showed that mother rats are sleep deprived during the day throughout the postpartum period. Our studies showed that NREM sleep during nursing is highly fragmented compared to that observed when the mother sleeps outside the nest (Benedetto et al. 2017b). In this sense, Sivadas et al. (2016) also showed that mother rats have fragmented sleep compared to non-maternal animals.

It is likely that different species have developed specific and unique strategies to conciliate nursing and sleep according to their habitat, ecology, and the degree of development of the young, among other factors. For instance, in mother dolphins, which do not have a burrow to protect their young from possible predators, it would not be adaptive that sleep has to be a prerequisite for milk ejection, as predation risk would increase dramatically during sleep. Also, for the rabbit doe, which usually nurses once a day and for a few minutes (Zarrow et al. 1965), nursing and sleep would not represent a conflict and sleep is not a prerequisite for milk ejection (Neve et al. 1982). Regardless of the strategy used by each species, adaptations have been developed to reconcile the maternal care and nursing of the newborn with mother's sleep physiology that assure the survival of the offspring without affecting the welfare of the mother.

4 Neural Circuits Shared by Maternal Behavior and Sleep

The rapid onset of maternal responsiveness relies on hormonal events that occur close to parturition. Specifically, the ovarian steroids, estrogen and progesterone, as well as lactogenic hormones and oxytocin initially activate the brain areas that control the maternal responsiveness to the newborn litter (Numan and Insel 2003; Rosenblatt 1980; Rosenblatt et al. 1988). Afterward, maternal behavior is maintained by the continued mother-infant interactions and seems to be relatively independent of endocrine regulation (Numan and Insel 2003; Rosenblatt 1980; Rosenblatt et al. 1988).

Experimental evidence has shown that the mPOA and its connections with the mesolimbic dopamine (DA) system play a predominant role in the control of active aspects of maternal behavior (Stolzenberg and Numan 2011). Interestingly, these brain areas are also key components of neural circuits for sleep generation and maintenance (Benedetto et al. 2017a; Kaushik et al. 2011; Mendelson 1996, 2000, 2001; Monti et al. 2016). Also, there is strong evidence that the MCHergic system is also involved in the regulation of both maternal behavior and sleep. Thus, we will focus on these brain areas and systems in this section.

4.1 The Preoptic Area Controls Maternal and Sleep Behaviors

4.1.1 Preoptic Area and Maternal Behavior

The first evidence that the POA was involved in maternal behavior was in 1956, when Fisher reported that chemical stimulation of this area with testosterone elicits active maternal behavior in male rats (Fisher 1956). Since then, many studies have demonstrated the involvement of mPOA in maternal behavior. For instance, mPOA damage interferes with all maternal behaviors (Numan et al. 1988) or mainly with the active maternal behavior (Numan and Callahan 1980; Terkel et al. 1979), while chemical stimulation with oxytocin (Pedersen et al. 1994), estrogen implants (Rosenblatt and Ceus 1998), dopaminergic agents (Miller and Lonstein 2005), and prolactin (Bridges et al. 1990) promotes full maternal behavior.

Thus, the mPOA is believed to act as a crucial area in the control of maternal behavior, integrating information from diverse modalities related to the pups and adjusting maternal responses to fulfill the pups' needs as they grow older (Pereira 2016; Pereira and Ferreira 2015; Risold et al. 1994; Simerly and Swanson 1986). Also, it is a key neural site where the hormones such as prolactin (Bridges et al. 1990), vasopressin (Bosch et al. 2010), and oxytocin (Pedersen et al. 1994) and a variety of neurotransmitters/neuromodulators such as DA (Miller and Lonstein 2005; Stolzenberg et al. 2007), hypocretin (Rivas et al. 2016), and MCH (Benedetto et al. 2014) modulate maternal behavior.

Particularly, this area is known to present important plasticity both during pregnancy and postpartum periods (Champagne and Curley 2016; Parent et al. 2017; Pereira and Morrell 2009; Rondini et al. 2010; Schrader et al. 2012) allowing the adaptation of maternal responsiveness to the changing needs of the offspring. Several studies point out a significant anatomical and functional reorganization of different brain areas across postpartum period that are crucial for maternal behavior (Driessen et al. 2014; Insel 1990; Pereira 2016; Pereira and Morrell 2009; Rondini et al. 2010). Specifically, the mPOA has been demonstrated to change its role throughout the postpartum period, from a facilitatory role during early lactation period (Jacobson et al. 1980; Lee et al. 2000; Numan et al. 1977; Pereira and Morrell 2009; Rosenblatt and Ceus 1998) to an inhibitory role during mid-lactation (Pereira and Morrell 2009). Interestingly, Schrader et al. (2012) show that the mPOA loses its daily rhythmicity of Fos activation in pregnant rats compared to diestrous females (Schrader et al. 2012).

4.1.2 Preoptic Area and Sleep

Since the early Von Economo's studies of the hypothalamus, the POA has been proposed as a sleep center (Von Economo 1930). Most studies have pointed out the crucial role of the VLPO and the median POA (MnPN) in the regulation of NREM sleep (Benedetto et al. 2012, 2013; Gong et al. 2004; Gvilia et al. 2006; Lu et al.

2000; Torterolo et al. 2009a), while the extended VLPO (eVLPO) has been involved in REM sleep regulation (Lu et al. 2002). Likewise, the mPOA, the same area that is critical for maternal behavior, has been also involved in the control of sleep (Kumar 2004). In fact, microinjections of different neuropeptides and substances, such as glutamate (Kaushik et al. 2011), triazolam (Mendelson and Martin 1992), pentobarbital (Mendelson 1996), and adenosine (Mendelson 2000), are known to promote NREM sleep. Although most studies relate mPOA to NREM sleep, there is also experimental data that spotlight the importance of this area also in the regulation of REM sleep (Asala et al. 1990; Suntsova and Dergacheva 2004). Particularly, most mPOA neurons increase their firing rate during REM sleep compared to W and NREM. In addition, electrical stimulation of the mPOA at low frequency during NREM sleep promotes the entrance to REM sleep (Suntsova and Dergacheva 2004). Moreover, Asala et al. (1990) induced a reduction of NREM sleep and an increase in REM sleep after mPOA lesions.

4.2 Dopaminergic System Modulates Maternal and Sleep Behaviors

4.2.1 Dopaminergic System and Maternal Behavior

The mesocorticolimbic system has been recognized for its central role in several motivated behaviors (Berridge 2004; Salamone and Correa 2012), including maternal behavior (Stolzenberg and Numan 2011). This system is comprised of dopamine (DA)-containing cell bodies in the midbrain ventral tegmental area (VTA) and its major targets, the nucleus accumbens (NAc) and prefrontal cortex (PFC) (Fallon and Moore 1978; Lindvall and Bjorklund 1974; Lindvall et al. 1974; Moore and Bloom 1978). The NAc has been considered as a neural interface between the limbic and motor systems allowing the transition from motivation to motor action (Mogenson et al. 1980). In addition, this nucleus is one of the main projection sites of the MCHergic neurons and has an important MCHergic receptor density (Bittencourt et al. 1992; Hervieu et al. 2000). The interconnection between the mPOA and the mesocorticolimbic DAergic system is known to regulate the motivational aspects of maternal behavior (Numan and Insel 2003; Stolzenberg and Numan 2011).

The central role of the DAergic system in the control of maternal behavior has initially been shown by the actions of systemic DA antagonists that reduced active maternal behavior but enhanced nursing and milk ejection (Stern 1991; Stern and Keer 1999). Interestingly, active maternal behaviors, such as licking the pups, are linked to an elevated DA release and increased DA receptor levels in the NAc (Champagne et al. 2004; Hansen et al. 1993). In accordance, DA receptor antagonism in the NAc inhibits maternal retrieval and licking, but promotes nursing behavior (Keer and Stern 1999). In addition, lesions of DAergic neurons of the VTA also impair pup-directed maternal behavior, but nursing was unaffected (Hansen et al. 1991b).

The administration of DA D1 receptor antagonist (SCH-23390) into mPOA impairs the retrieval and licking of pups but no other components of the maternal behavior (Miller and Lonstein 2005; Numan et al. 2005a), while the infusion of the D2 receptor antagonist raclopride into this area increases nursing, leaving intact active maternal behaviors (Miller and Lonstein 2005). These data suggest that different DA receptors within the mPOA are involved in distinct aspects of maternal behavior, where D1 receptors would control active maternal behavior, while D2 receptors would regulate nursing postures.

4.2.2 Dopaminergic System and Sleep

Interestingly, the DAergic system also plays a critical but complex role in the control of sleep and wakefulness (W). DAergic neurons, mostly present in the VTA and substantia nigra pars compacta (SNc), do not change their mean firing rate across the sleep-wake cycle (Miller et al. 1983; Trulson 1985; Trulson and Preussler 1984; Trulson et al. 1981). However, the temporal pattern of the discharge is strongly modulated during the sleep-wake cycle. Accordingly, during W, DAergic neurons in VTA discharge in burst in response to salient stimuli (Schultz et al. 1993). This increase in bursting activity is accompanied by a substantial increase in DA extracellular levels in striatal regions (Wightman and Robinson 2002). In this regard, microdialysis studies by Lena et al. (2005) have shown that DA release is greater during W in comparison to sleep, both in the prefrontal cortex and the NAc (Lena et al. 2005). In addition, Dahan et al. (2007) demonstrated that there is a prominent burst firing increase in VTA DAergic neurons during REM sleep that resembles the bursting induced by the consumption of palatable food (Dahan et al. 2007). This is in line with previous findings that described an increase in the number of Fos-immunoreactive neurons in the VTA during REM sleep (Maloney et al. 2002). In addition, the release of DA, both in the NAc and prefrontal cortex, increases during REM sleep in comparison to NREM sleep (Lena et al. 2005). In this regard, it has been shown that DAergic VTA neurons participate in the promotion of theta rhythm, a prominent feature of REM sleep (Orzel-Gryglewska et al. 2015).

4.2.3 Dopamine and POA Regulating Maternal Behavior and Sleep Together

In spite of the bunch of evidence that POA modulates both sleep and maternal behavior, there were no studies focused on determining how this brain area acts to promote these two behaviors together.

Based on the findings that (1) nursing and NREM sleep can be co-expressed (Benedetto et al. 2017b), (2) mPOA stimulation increases the time spent in NREM sleep (Kaushik et al. 2011), and (3) the local delivery of a dopaminergic D2 antagonist raclopride increases nursing duration without interfering with active maternal behavior (Miller and Lonstein 2005), we posit that raclopride into mPOA would also be associated with an increase in NREM sleep. Contrary to our expectations, we find

neither an increase in nursing nor in NREM sleep after the microinjection of raclopride within the mPOA. Surprisingly, REM sleep and its transitional stage from NREM were significantly reduced in time after this microinjection procedure. Regarding maternal behavior, the latency to reunite the entire litter into the nest was increased, while the time to the start of nursing was reduced, suggesting that some aspects of the maternal sequence were affected (Benedetto et al. 2017a). Thus, we are carrying out more experiments to elucidate how the dopaminergic system acts to integrate sleep and maternal behavior within the mPOA.

4.3 The MCHergic System

The general feature of this system has been described in preceding chapters. Briefly, MCH is an inhibitory neuropeptide synthesized by neurons that are primarily located in the posterolateral hypothalamus and incerto-hypothalamic area (Bittencourt et al. 1992). The MCHergic neurons project widely throughout the central nervous system (CNS).

MCH acts via neurons expressing the MCH receptor 1 (MCHR1) and MCH receptor 2 (called MCHR2) (Macneil 2013; Saito and Nagasaki 2008). The latter has been described in primates (including humans), cats, and dogs but seems to be absent in rodents (Tan et al. 2002).

There is a widespread distribution of the MCHR1 mRNA along with the MCHergic fibers including critical areas for sleep and maternal behavior (Bittencourt et al. 1992; Saito et al. 2001).

4.3.1 MCH and Sleep

The role of MCH as a sleep-promoting factor has been assessed in previous chapters of this book and reviewed in detail (Konadhode et al. 2015; Monti et al. 2013; Torterolo et al. 2011, 2015). Briefly, the intracerebroventricular administration of MCH in the rat produces an increase in REM sleep and a moderate enhancement in the time spent in NREM sleep, while the systemic administration of MCHR1 antagonists both decreases sleep and increases wakefulness (Verret et al. 2003; Ahnaou et al. 2008). Microinjection of MCH into the REM-off neuronal areas, such as the dorsal raphe and the locus coeruleus of the rat, facilitates the generation of REM sleep (Lagos et al. 2009; Monti et al. 2015). MCH also promotes REM sleep when microinjected into either the basal forebrain of the rat or the NPO of the cat (Lagos et al. 2012; Torterolo et al. 2009b). In contrast, the administration of MCH into the VLPO, a NREM sleep-promoting area, induced NREM sleep (Benedetto et al. 2013).

Fos and electrophysiological studies have shown that MCHergic neurons are active mostly during sleep (mainly during REM sleep) in the rat (Verret et al. 2003; Hassani et al. 2009). However, Gonzalez et al. (2016) by means of fiber-optic recordings have recently shown that these neurons are active during novelty exploration.

The concentration of MCH in the CSF of rats increases during the light phase, when the animals are predominantly asleep, and is affected by sleep deprivation or sleep restriction (Pelluru et al. 2013; Dias Abdo Agamme et al. 2015). By means of in vivo microdialysis, Blouin et al. (2013) have shown that the release of MCH in the amygdala of patients reaches a maximum level at sleep onset.

Studies of ppMCH and MCHR1 KO mice indicate that the sleep of these animals is altered (Ahnaou et al. 2008; Willie et al. 2008; Takase et al. 2014). Recent optogenetic and chemogenetic studies have confirmed the role of MCH in sleep generation. Optogenetic stimulation of MCHergic neurons increased both REM and NREM sleep at night, whereas during the day only REM sleep was increased (Konadhode et al. 2013; Blanco-Centurion et al. 2016). In addition, delta power (an indicator of sleep intensity) was also increased (Blanco-Centurion et al. 2016). Optogenetic activation of MCH neurons at the onset of REM sleep extended the duration of REM sleep episodes (Jego et al. 2013). Also, the acute silencing of these neurons reduced hippocampal theta rhythm during REM sleep without affecting the duration of the episodes. Tsunematsu et al. (2014) showed that the acute optogenetic activation of MCH neurons at 10 Hz induced transitions from NREM to REM sleep and increased REM sleep time. Also, Vetrivelan et al. (2016) have shown that the selective chemogenetic activation of the MCHergic neurons causes specific increases in REM sleep without altering wakefulness or NREM sleep.

4.3.2 MCH and Maternal Behavior

A recent review by Diniz and Bittencourt (2017) described that MCH is involved in motivated behaviors such as feeding, drinking, and mating and also active maternal behavior. In fact, not only MCHergic neurons project toward regions involved both in active maternal behavior, such as the mPOA, VTA, and NAc (Bittencourt et al. 1992), but also mRNA for the MCHR1 has been recognized in these regions (Saito et al. 2001).

The importance of this neuropeptide in the postpartum period is evidenced by the fact that in males and cycling females most MCHergic neurons are located within the lateral hypothalamus and incerto-hypothalamic area, while during lactation, neurons of the mPOA express pre-pro-MCH mRNA and MCH, being most of them GABAergic (approximately 95%) (Knollema et al. 1992; Rondini et al. 2010). Remarkably, the number of MCHergic neurons in the mPOA varies along lactation (Alvisi et al. 2016; Knollema et al. 1992; Rondini et al. 2010). Taken together, these interesting results suggest that the number of MCH neurons within the mPOA varies according to a curve in which: their number is very low on PPD5, moderated at PPD12, and maximum at PPD15–16, starts to decrease at PPD17–19 (but is higher than at PPD12), at PPD21, has a similar number as in PPD12, finally disappearing after weaning (Alvisi et al. 2016; Knollema et al. 1992; Rondini et al. 2010). This changing pattern in the number of mPOA MCHergic neurons is likely associated to maternal behavior, such that these cells are maximal when active maternal behaviors begin to decrease, as the pups grow older, become more

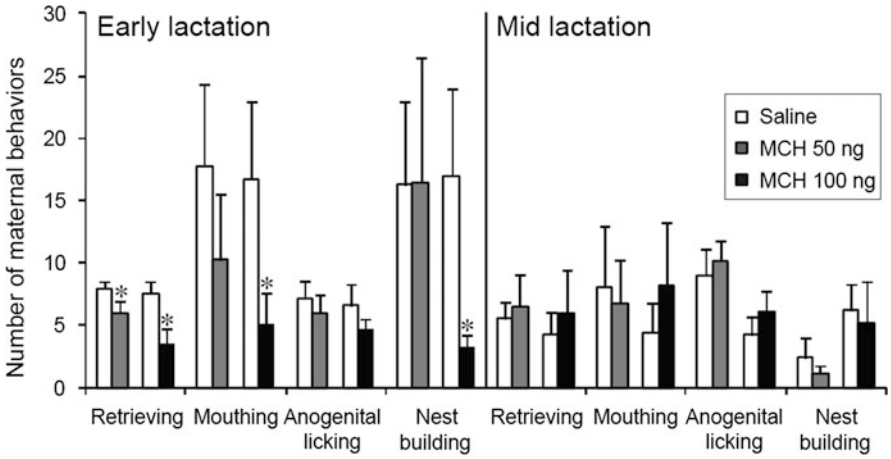

Fig. 5. Effects of MCH microinjections into the mPOA on active components of maternal behavior during early and mid-lactation. Graphic chart showing the number of different active maternal responses after bilateral administration of saline and MCH (50 and 100 ng) in a 30-min maternal test. All values are presented as means ± SEM; significant differences are indicated by asterisks ($*p < 0.05$). Part of the early lactation results was published in Benedetto et al. (2014)

independent, and start to consume food (Hall and Rosenblatt 1978; Reisbick et al. 1975), and decline at the end of lactation. However, these changes could be also related to hormonal variations along lactation (Ferreira et al. 2017).

Benedetto et al. (2014) have shown that bilateral microinjections of MCH into the mPOA decrease active maternal behaviors during the early postpartum period (PPD5–6) to levels characteristic of the late postpartum period (Benedetto et al. 2014). The fact that only active maternal behaviors but not huddling and nursing were reduced after MCH treatment agrees with published evidence showing that interference with mPOA function mainly affects these active components (Jacobson et al. 1980; Numan 1974; Numan and Insel 2003; Pereira and Morrell 2009; Terkel et al. 1979). Interestingly, the same procedure during the PPD14–15, the period in which MCH reaches its maximum levels, did not provoke any change in maternal behavior compared to control saline microinjections (Fig. 5). It could be speculated that during this latter stage, external MCH does not significantly change maternal behavior, such that increasing its levels exogenously does not potentiate the inhibitory effect of the high endogenous levels at this moment. It would be interesting to explore if MCHR1 varies within the mPOA along lactation, promoting these functional changes. These differential results found according to the postpartum stage are in line with the knowledge of the mPOA as a plastic area that changes its functionality during the postpartum period (Champagne and Curley 2016; Pereira 2016; Pereira and Morrell 2009).

It has also been shown that MCHR1 KO mother mice show a decrease in the survival of the pups during PPD1–2 compared to pups from wild-type mothers (Adams et al. 2011; Alachkar et al. 2016). However, beyond the PPD2 pups' mortality did not differ between these two groups. Authors hypothesized that

MCH would be important for the initiation of maternal behavior, but not for its maintenance (Alachkar et al. 2016). Although these results might seem contradictory with Benedetto et al. (2014), it can be speculated that the requirement of MCH may fluctuate at the different stages of the postpartum period to display an appropriate maternal behavior that matches with the changing characteristics and needs of the offspring; when MCH is outside its normal range, the maternal care of the pups could be altered.

The MCHergic system seems to be linked also to an endocrine function during lactation. Recent evidences presented by Ferreira et al. (2017) show that the number of mPOA-MCH neurons is positively correlated with the litter size (Ferreira et al. 2017), likely caused by the suckling stimulus from pups that also promotes the release of prolactin and oxytocin (Wakerley 1996). In this sense, Parkes and Vale (1993) found that MCH directly stimulates the release of oxytocin acting on neurohypophysis cell cultures (Parkes and Vale 1993). On the contrary, MCH was significantly decreased in a model of hyperprolactinemia compared to control rats (Garcia et al. 2003). Thus, prolactin seems to be inversely related to MCH levels. Further experiments are needed to understand the functionality of these mPOA-MCH neurons.

4.4 MCH and DAergic System Interaction in the Control of Sleep and Maternal Behavior

As described before, it can be proposed that the DAergic system promotes motivation and arousal, while the MCHergic system stimulates consummatory behaviors and sleep. Hence, it could be speculated that DAergic and MCHergic systems have opposite functions. Based on this idea, it could be hypothesized that MCH may decrease motivation and arousal, at least in part, by inhibiting the DAergic system.

As mentioned, the NAc is a main target of the mesolimbic DAergic neurons and is an essential area for a proper care of the offspring (Hansen et al. 1993; Mogenson et al. 1980; Numan et al. 2005a, b). This nucleus is also one of the main projection sites of the MCHergic neurons and has an important MCHR1 density (Bittencourt et al. 1992; Hervieu et al. 2000). MCHR1 is co-expressed with DAergic receptors in the shell of the NAc, which raises the possibility that MCH and DA interact in NAc shell during motivated responses (Chung et al. 2009; Georgescu et al. 2005). This idea has been explored using a whole-cell patch-clamp recording from the NAc shell where the administration of MCH alone had no effect on spike firing, but the discharge rate showed an increase when MCH was applied in combination with D1 or D2 agonists (Chung et al. 2009; Hopf et al. 2013). Furthermore, biochemical analysis in NAc shell explants showed that MCH signaling blocks DA-induced phosphorylation of the AMPA glutamate receptor (Georgescu et al. 2005).

In addition, MCHR1 KO mice present hyperactivity that may be explained by interactions between MCHergic and DAergic systems (Lalonde and Qian 2007; Marsh et al. 2002). In fact, MCHR1 KO mice are supersensitive to the locomotor activating effects of d-amphetamine and D1 agonists as compared to wild-type animals. Besides, deletion of MCHR1 results in an upregulation of mesolimbic DA receptors, and the lack of MCH leads to an increase in DA release and in limbic DA transporter levels, indicating that MCH may negatively modulate mesolimbic monoamine function (Mul et al. 2011; Smith et al. 2005).

From these data, it could be expected that during highly aroused motivated behaviors, such as maternal behavior, the DAergic system may inhibit the MCHergic neurons. In fact, DA hyperpolarizes MCHergic neurons by activating G-protein-activated inwardly rectifying K+ (GIRK) channels by means of the activation of alpha-2a noradrenergic receptors (Alberto et al. 2011; Conductier et al. 2011). Conductier et al. (2011) also showed that MCH neurons receive both GABAergic and glutamatergic inputs and that DA modulates these inputs in a complex manner. At low concentrations, DA activates D1-like receptors promoting presynaptic activity, while at higher concentrations, DA activates D2-like receptors that inhibits presynaptic activity. Overall, DA leads to a decrease in the excitability of MCHergic neurons.

Regarding sleep and lactation from these data described above, we hypothesize that the DAergic and MCH system may interact to decrease the activity of the motivational system to promote sleep, thus allowing milk ejection.

5 Conclusions and Future Directions

In the present report, we analyzed data that support the interconnection between sleep and maternal behavior, two crucial behaviors for survival of mammals. We also propose a possible mechanism by which the MCHergic system modulates both behaviors together. We show that MCH induces sleep and reduces active maternal behaviors, thus promoting energy conservation for the mother. As mPOA is a critical area for the modulation of both behaviors, it is possible that MCH, acting in this area, will enhance sleep during nursing, thus promoting milk ejection occurrence. We are currently assessing this possibility.

As the stimulus of sucking from the pups induces not only nursing postures (and thus immobility) but also the synthesis and release of prolactin, hormone known to promote sleep and milk production (Wakerley 1996), mPOA-MCH cells might also have an endocrine function that indirectly promotes sleep and milk ejection, assuring the welfare of the pups and also of the mother (Alachkar et al. 2016). Also it would be important to explore the putative relationship between MCH and oxytocin in the control of both behaviors, as this hormone is stimulated by the sucking from the pups and promotes milk ejection.

Although MCH is expressed in mPOA neurons during the postpartum period, its functionality in lactating rats is still not clear. Also, behavioral experiments during

the postpartum period focused on the effect of MCH agents on both maternal behavior and sleep are still needed to fully understand the complex interaction between both behaviors and its relation with the MCHergic system.

References

Adams AC, Domouzoglou EM, Chee MJ, Segal-Lieberman G, Pissios P, Maratos-Flier E (2011) Ablation of the hypothalamic neuropeptide melanin concentrating hormone is associated with behavioral abnormalities that reflect impaired olfactory integration. Behav Brain Res 224(1): 195–200

Ahnaou A, Drinkenburg WH, Bouwknecht JA, Alcazar J, Steckler T, Dautzenberg FM (2008) Blocking melanin-concentrating hormone MCH1 receptor affects rat sleep-wake architecture. Eur J Pharmacol 579(1–3):177–188

Alachkar A, Alhassen L, Wang Z, Wang L, Onouye K, Sanathara N, Civelli O (2016) Inactivation of the melanin concentrating hormone system impairs maternal behavior. Eur Neuropsychopharmacol 26(11):1826–1835

Alberto CO, Trask RB, Hirasawa M (2011) Dopamine acts as a partial agonist for alpha2A adrenoceptor in melanin-concentrating hormone neurons. J Neurosci 31(29):10671–10676

Alvisi RD, Diniz GB, Da-Silva JM, Bittencourt JC, Felicio LF (2016) Suckling-induced Fos activation and melanin-concentrating hormone immunoreactivity during late lactation. Life Sci 148: 241–246

Asala SA, Okano Y, Honda K, Inoue S (1990) Effects of medial preoptic area lesions on sleep and wakefulness in unrestrained rats. Neurosci Lett 114(3):300–304

Benedetto L, Chase MH, Torterolo P (2012) GABAergic processes within the median preoptic nucleus promote NREM sleep. Behav Brain Res 232(1):60–65

Benedetto L, Rodriguez-Servetti Z, Lagos P, D'Almeida V, Monti JM, Torterolo P (2013) Microinjection of melanin concentrating hormone into the lateral preoptic area promotes non-REM sleep in the rat. Peptides 39:11–15

Benedetto L, Pereira M, Ferreira A, Torterolo P (2014) Melanin-concentrating hormone in the medial preoptic area reduces active components of maternal behavior in rats. Peptides 58C: 20–25

Benedetto L, Rivas M, Cavelli M, Pena F, Monti J, Ferreira A, Torterolo P (2017a) Microinjection of the dopamine D2-receptor antagonist Raclopride into the medial preoptic area reduces REM sleep in lactating rats. Neurosci Lett 659:104–109

Benedetto L, Rivas M, Pereira M, Ferreira A, Torterolo P (2017b) A descriptive analysis of sleep and wakefulness states in different maternal behaviors in lactating rats. Arch Ital Biol 155(3):99–109

Berridge KC (2004) Motivation concepts in behavioral neuroscience. Physiol Behav 81(2): 179–209

Bittencourt JC, Presse F, Arias C, Peto C, Vaughan J, Nahon JL, Vale W, Sawchenko PE (1992) The melanin-concentrating hormone system of the rat brain: an immuno- and hybridization histochemical characterization. J Comp Neurol 319(2):218–245

Blanco-Centurion C, Liu M, Konadhode RP, Zhang X, Pelluru D, van den Pol AN, Shiromani PJ (2016) Optogenetic activation of melanin-concentrating hormone neurons increases non-rapid eye movement and rapid eye movement sleep during the night in rats. Eur J Neurosci 44(10): 2846–2857

Blouin AM, Fried I, Wilson CL, Staba RJ, Behnke EJ, Lam HA, Maidment NT, Karlsson KAE, Lapierre JL, Siegel JM (2013) Human hypocretin and melanin-concentrating hormone levels are linked to emotion and social interaction. Nat Commun 4:1547

Bosch OJ, Pfortsch J, Beiderbeck DI, Landgraf R, Neumann ID (2010) Maternal behaviour is associated with vasopressin release in the medial preoptic area and bed nucleus of the stria terminalis in the rat. J Neuroendocrinol 22(5):420–429

Bridges RS, Numan M, Ronsheim PM, Mann PE, Lupini CE (1990) Central prolactin infusions stimulate maternal behavior in steroid-treated, nulliparous female rats. Proc Natl Acad Sci U S A 87(20):8003–8007

Champagne FA, Curley JP (2016) Plasticity of the maternal brain across the lifespan. New Dir Child Adolesc Dev 2016(153):9–21

Champagne FA, Chretien P, Stevenson CW, Zhang TY, Gratton A, Meaney MJ (2004) Variations in nucleus accumbens dopamine associated with individual differences in maternal behavior in the rat. J Neurosci 24(17):4113–4123

Chung S, Hopf FW, Nagasaki H, Li CY, Belluzzi JD, Bonci A, Civelli O (2009) The melanin-concentrating hormone system modulates cocaine reward. Proc Natl Acad Sci U S A 106(16): 6772–6777

Conductier G, Nahon JL, Guyon A (2011) Dopamine depresses melanin concentrating hormone neuronal activity through multiple effects on alpha2-noradrenergic, D1 and D2-like dopaminergic receptors. Neuroscience 178:89–100

Dahan L, Astier B, Vautrelle N, Urbain N, Kocsis B, Chouvet G (2007) Prominent burst firing of dopaminergic neurons in the ventral tegmental area during paradoxical sleep. Neuropsychopharmacology 32(6):1232–1241

Dias Abdo Agamme AL, Aguilar Calegare BF, Fernandes L, Costa A, Lagos P, Torterolo P, D'Almeida V (2015) MCH levels in the CSF, brain preproMCH and MCHR1 gene expression during paradoxical sleep deprivation, sleep rebound and chronic sleep restriction. Peptides 74: 9–15

Diniz GB, Bittencourt JC (2017) The melanin-concentrating hormone as an integrative peptide driving motivated behaviors. Front Syst Neurosci 11:32

Driessen TM, Zhao C, Whittlinger A, Williams H, Gammie SC (2014) Endogenous CNS expression of neurotensin and neurotensin receptors is altered during the postpartum period in outbred mice. PLoS One 9(1):e83098

Fallon JH, Moore RY (1978) Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. J Comp Neurol 180(3):545–580

Ferreira JGP, Duarte JCG, Diniz GB, Bittencourt JC (2017) Litter size determines the number of melanin-concentrating hormone neurons in the medial preoptic area of Sprague Dawley lactating dams. Physiol Behav 181:75–79

Fisher AE (1956) Maternal and sexual behavior induced by intracranial chemical stimulation. Science 124(3214):228–229

Garcia MC, Lopez M, Gualillo O, Seoane LM, Dieguez C, Senaris RM (2003) Hypothalamic levels of NPY, MCH, and prepro-orexin mRNA during pregnancy and lactation in the rat: role of prolactin. FASEB J 17(11):1392–1400

Georgescu D, Sears RM, Hommel JD, Barrot M, Bolanos CA, Marsh DJ, Bednarek MA, Bibb JA, Maratos-Flier E, Nestler EJ, DiLeone RJ (2005) The hypothalamic neuropeptide melanin-concentrating hormone acts in the nucleus accumbens to modulate feeding behavior and forced-swim performance. J Neurosci 25(11):2933–2940

Gong H, McGinty D, Guzman-Marin R, Chew KT, Stewart D, Szymusiak R (2004) Activation of c-fos in GABAergic neurones in the preoptic area during sleep and in response to sleep deprivation. J Physiol 556(Pt 3):935–946

Gonzalez JA, Iordanidou P, Strom M, Adamantidis A, Burdakov D (2016) Awake dynamics and brain-wide direct inputs of hypothalamic MCH and orexin networks. Nat Commun 7:11395

Gonzalez-Mariscal G, Caba M, Martinez-Gomez M, Bautista A, Hudson R (2016) Mothers and offspring: the rabbit as a model system in the study of mammalian maternal behavior and sibling interactions. Horm Behav 77:30–41

Grota LJ, Ader R (1969) Continuous recording of maternal behavior in Rattus Norvegicus. Anim Behav 17:722–729

Gvilia I, Xu F, McGinty D, Szymusiak R (2006) Homeostatic regulation of sleep: a role for preoptic area neurons. J Neurosci 26(37):9426–9433

Hall WG, Rosenblatt JS (1978) Development of nutritional control of food intake in suckling rat pups. Behav Biol 24(4):413–427

Hansen S, Harthon C, Wallin E, Lofberg L, Svensson K (1991a) The effects of 6-OHDA-induced dopamine depletions in the ventral or dorsal striatum on maternal and sexual behavior in the female rat. Pharmacol Biochem Behav 39(1):71–77

Hansen S, Harthon C, Wallin E, Lofberg L, Svensson K (1991b) Mesotelencephalic dopamine system and reproductive behavior in the female rat: effects of ventral tegmental 6-hydroxydopamine lesions on maternal and sexual responsiveness. Behav Neurosci 105(4): 588–598

Hansen S, Bergvall AH, Nyiredi S (1993) Interaction with pups enhances dopamine release in the ventral striatum of maternal rats: a microdialysis study. Pharmacol Biochem Behav 45(3): 673–676

Hassani OK, Lee MG, Jones BE (2009) Melanin-concentrating hormone neurons discharge in a reciprocal manner to orexin neurons across the sleep-wake cycle. Proc Natl Acad Sci U S A 106(7):2418–2422

Hervieu GJ, Cluderay JE, Harrison D, Meakin J, Maycox P, Nasir S, Leslie RA (2000) The distribution of the mRNA and protein products of the melanin- concentrating hormone (MCH) receptor gene, slc-1, in the central nervous system of the rat. Eur J Neurosci 12(4):1194–1216

Hopf FW, Seif T, Chung S, Civelli O (2013) MCH and apomorphine in combination enhance action potential firing of nucleus accumbens shell neurons in vitro. PeerJ 1:e61

Hunter LP, Rychnovsky JD, Yount SM (2009) A selective review of maternal sleep characteristics in the postpartum period. J Obstet Gynecol Neonatal Nurs 38(1):60–68

Insel TR (1990) Regional changes in brain oxytocin receptors post-partum: time-course and relationship to maternal behaviour. J Neuroendocrinol 2(4):539–545

Jacobson CD, Terkel J, Gorski RA, Sawyer CH (1980) Effects of small medial preoptic area lesions on maternal behavior: retrieving and nest building in the rat. Brain Res 194(2):471–478

Jego S, Glasgow SD, Herrera CG, Ekstrand M, Reed SJ, Boyce R, Friedman J, Burdakov D, Adamantidis AR (2013) Optogenetic identification of a rapid eye movement sleep modulatory circuit in the hypothalamus. Nat Neurosci 16(11):1637–1643

Kaushik MK, Kumar VM, Mallick HN (2011) Glutamate microinjection at the medial preoptic area enhances slow wave sleep in rats. Behav Brain Res 217(1):240–243

Keer SE, Stern JM (1999) Dopamine receptor blockade in the nucleus accumbens inhibits maternal retrieval and licking, but enhances nursing behavior in lactating rats. Physiol Behav 67(5): 659–669

Knollema S, Brown ER, Vale W, Sawchenko PE (1992) Novel hypothalamic and preoptic sites of prepro-melanin-concentrating hormone messenger ribonucleic acid and peptide expression in lactating rats. J Neuroendocrinol 4(6):709–717

Konadhode RR, Pelluru D, Blanco-Centurion C, Zayachkivsky A, Liu M, Uhde T, Glen WB Jr, van den Pol AN, Mulholland PJ, Shiromani PJ (2013) Optogenetic stimulation of MCH neurons increases sleep. J Neurosci 33(25):10257–10263

Konadhode RR, Pelluru D, Shiromani PJ (2015) Neurons containing orexin or melanin concentrating hormone reciprocally regulate wake and sleep. Front Syst Neurosci 8:244

Krasnow SM, Steiner RA (2006) Physiological mechanisms integrating metabolism and reproduction. In: Neill JD (ed) Knobil and Neill's physiology of reproduction. Elsevier, St. Louis, MO, pp 2553–2625

Kumar VM (2004) Why the medial preoptic area is important for sleep regulation. Indian J Physiol Pharmacol 48(2):137–149

Lagos P, Torterolo P, Jantos H, Chase MH, Monti JM (2009) Effects on sleep of melanin-concentrating hormone (MCH) microinjections into the dorsal raphe nucleus. Brain Res 1265: 103–110

Lagos P, Monti JM, Jantos H, Torterolo P (2012) Microinjection of the melanin-concentrating hormone into the lateral basal forebrain increases REM sleep and reduces wakefulness in the rat. Life Sci 90(23–24):895–899

Lalonde R, Qian S (2007) Exploratory activity, motor coordination, and spatial learning in Mchr1 knockout mice. Behav Brain Res 178(2):293–304

Lee KA (1998) Alterations in sleep during pregnancy and postpartum: a review of 30 years of research. Sleep Med Rev 2(4):231–242

Lee A, Clancy S, Fleming AS (2000) Mother rats bar-press for pups: effects of lesions of the mpoa and limbic sites on maternal behavior and operant responding for pup-reinforcement. Behav Brain Res 108(2):215–231

Lena I, Parrot S, Deschaux O, Muffat-Joly S, Sauvinet V, Renaud B, Suaud-Chagny MF, Gottesmann C (2005) Variations in extracellular levels of dopamine, noradrenaline, glutamate, and aspartate across the sleep–wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. J Neurosci Res 81(6):891–899

Lincoln DW, Hentzen K, Hin T, van der Schoot P, Clarke G, Summerlee AJ (1980) Sleep: a prerequisite for reflex milk ejection in the rat. Exp Brain Res 38(2):151–162

Lindvall O, Bjorklund A (1974) The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method. Acta Physiol Scand Suppl 412:1–48

Lindvall O, Bjorklund A, Moore RY, Stenevi U (1974) Mesencephalic dopamine neurons projecting to neocortex. Brain Res 81(2):325–331

Lu J, Greco MA, Shiromani P, Saper CB (2000) Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. J Neurosci 20(10):3830–3842

Lu J, Bjorkum AA, Xu M, Gaus SE, Shiromani PJ, Saper CB (2002) Selective activation of the extended ventrolateral preoptic nucleus during rapid eye movement sleep. J Neurosci 22(11): 4568–4576

Lyamin O, Pryaslova J, Kosenko P, Siegel J (2007) Behavioral aspects of sleep in bottlenose dolphin mothers and their calves. Physiol Behav 92(4):725–733

Macneil DJ (2013) The role of melanin-concentrating hormone and its receptors in energy homeostasis. Front Endocrinol (Lausanne) 4:49

Maloney KJ, Mainville L, Jones BE (2002) C-Fos expression in dopaminergic and GABAergic neurons of the ventral mesencephalic tegmentum after paradoxical sleep deprivation and recovery. Eur J Neurosci 15(4):774–778

Marsh DJ, Weingarth DT, Novi DE, Chen HY, Trumbauer ME, Chen AS, Guan XM, Jiang MM, Feng Y, Camacho RE, Shen Z, Frazier EG, Yu H, Metzger JM, Kuca SJ, Shearman LP, Gopal-Truter S, MacNeil DJ, Strack AM, MacIntyre DE, Van der Ploeg LH, Qian S (2002) Melanin-concentrating hormone 1 receptor-deficient mice are lean, hyperactive, and hyperphagic and have altered metabolism. Proc Natl Acad Sci U S A 99(5):3240–3245

Mendelson WB (1996) Sleep induction by microinjection of pentobarbital into the medial preoptic area in rats. Life Sci 59(22):1821–1828

Mendelson WB (2000) Sleep-inducing effects of adenosine microinjections into the medial preoptic area are blocked by flumazenil. Brain Res 852(2):479–481

Mendelson WB (2001) The sleep-inducing effect of ethanol microinjection into the medial preoptic area is blocked by flumazenil. Brain Res 892(1):118–121

Mendelson WB, Martin JV (1992) Characterization of the hypnotic effects of triazolam microinjections into the medial preoptic area. Life Sci 50(15):1117–1128

Miller SM, Lonstein JS (2005) Dopamine d1 and d2 receptor antagonism in the preoptic area produces different effects on maternal behavior in lactating rats. Behav Neurosci 119(4): 1072–1083

Miller JD, Farber J, Gatz P, Roffwarg H, German DC (1983) Activity of mesencephalic dopamine and non-dopamine neurons across stages of sleep and walking in the rat. Brain Res 273(1): 133–141

Mogenson GJ, Jones DL, Yim CY (1980) From motivation to action: functional interface between the limbic system and the motor system. Prog Neurobiol 14(2–3):69–97
Montgomery-Downs HE, Insana SP, Clegg-Kraynok MM, Mancini LM (2010) Normative longitudinal maternal sleep: the first 4 postpartum months. Am J Obstet Gynecol 203(5):465 e461–465 e467
Monti JM, Torterolo P, Lagos P (2013) Melanin-concentrating hormone control of sleep-wake behavior. Sleep Med Rev 17(4):293–298
Monti JM, Lagos P, Jantos H, Torterolo P (2015) Increased REM sleep after intra-locus coeruleus nucleus microinjection of melanin-concentrating hormone (MCH) in the rat. Prog Neuro-Psychopharmacol Biol Psychiatry 56:185–188
Monti JM, Pandi-Perumal SR, Chokroverty S (2016) Dopamine and sleep: molecular, functional, and clinical aspects. Springer, Switzerland
Moore RY, Bloom FE (1978) Central catecholamine neuron systems: anatomy and physiology of the dopamine systems. Annu Rev Neurosci 1:129–169
Mul JD, la Fleur SE, Toonen PW, Afrasiab-Middelman A, Binnekade R, Schetters D, Verheij MM, Sears RM, Homberg JR, Schoffelmeer AN, Adan RA, DiLeone RJ, De Vries TJ, Cuppen E (2011) Chronic loss of melanin-concentrating hormone affects motivational aspects of feeding in the rat. PLoS One 6(5):e19600
Neve HA, Paisley AC, Summerlee AJ (1982) Arousal a prerequisite for suckling in the conscious rabbit? Physiol Behav 28(2):213–217
Neville MC (2006) Lactation and its hormonal control. In: Knobil E, Neill JD (eds) The physiology of reproduction. Elsevier, New York, pp 2993–3054
Nishihara K, Horiuchi S, Eto H, Uchida S, Honda M (2004) Delta and theta power spectra of night sleep EEG are higher in breast-feeding mothers than in non-pregnant women. Neurosci Lett 368(2):216–220
Numan M (1974) Medial preoptic area and maternal behavior in the female rat. J Comp Physiol Psychol 87(4):746–759
Numan M (1994) Maternal behavior. In: Knobil E, Neill JD (eds) The physiology of reproduction. Raven, New York, pp 221–302
Numan M, Callahan EC (1980) The connections of the medial preoptic region and maternal behavior in the rat. Physiol Behav 25(5):653–665
Numan M, Insel TR (2003) The neurobiology of parental behavior. Springer, New York
Numan M, Rosenblatt JS, Komisaruk BR (1977) Medial preoptic area and onset of maternal behavior in the rat. J Comp Physiol Psychol 91(1):146–164
Numan M, Corodimas KP, Numan MJ, Factor EM, Piers WD (1988) Axon-sparing lesions of the preoptic region and substantia innominata disrupt maternal behavior in rats. Behav Neurosci 102 (3):381–396
Numan M, Numan MJ, Pliakou N, Stolzenberg DS, Mullins OJ, Murphy JM, Smith CD (2005a) The effects of D1 or D2 dopamine receptor antagonism in the medial preoptic area, ventral pallidum, or nucleus accumbens on the maternal retrieval response and other aspects of maternal behavior in rats. Behav Neurosci 119(6):1588–1604
Numan M, Numan MJ, Schwarz JM, Neuner CM, Flood TF, Smith CD (2005b) Medial preoptic area interactions with the nucleus accumbens-ventral pallidum circuit and maternal behavior in rats. Behav Brain Res 158(1):53–68
Orzel-Gryglewska J, Matulewicz P, Jurkowlaniec E (2015) Brainstem system of hippocampal theta induction: the role of the ventral tegmental area. Synapse 69(11):553–575
Parent C, Wen X, Dhir SK, Ryan R, Diorio J, Zhang TY (2017) Maternal care associates with differences in morphological complexity in the medial preoptic area. Behav Brain Res 326: 22–32
Parkes DG, Vale WW (1993) Contrasting actions of melanin-concentrating hormone and neuropeptide-E-I on posterior pituitary function. Ann N Y Acad Sci 680:588–590

Pedersen CA, Caldwell JD, Walker C, Ayers G, Mason GA (1994) Oxytocin activates the postpartum onset of rat maternal behavior in the ventral tegmental and medial preoptic areas. Behav Neurosci 108(6):1163–1171

Pelluru D, Konadhode R, Shiromani PJ (2013) MCH neurons are the primary sleep-promoting group. Sleep 36(12):1779–1781

Pereira M (2016) Structural and functional plasticity in the maternal brain circuitry. New Dir Child Adolesc Dev 2016(153):23–46

Pereira M, Ferreira A (2015) Neuroanatomical and neurochemical basis of parenting: dynamic coordination of motivational, affective and cognitive processes. Horm Behav 77:72–85

Pereira M, Morrell JI (2009) The changing role of the medial preoptic area in the regulation of maternal behavior across the postpartum period: facilitation followed by inhibition. Behav Brain Res 205(1):238–248

Reisbick S, Rosenblatt JS, Mayer AD (1975) Decline of maternal behavior in the virgin and lactating rat. J Comp Physiol Psychol 89(7):722–732

Rheingold H (1963) Maternal behavior in mammals. Wiley, New York

Risold PY, Canteras NS, Swanson LW (1994) Organization of projections from the anterior hypothalamic nucleus: a Phaseolus vulgaris-leucoagglutinin study in the rat. J Comp Neurol 348(1): 1–40

Rivas M, Torterolo P, Ferreira A, Benedetto L (2016) Hypocretinergic system in the medial preoptic area promotes maternal behavior in lactating rats. Peptides 81:9–14

Rondini TA, Donato J Jr, Rodrigues Bde C, Bittencourt JC, Elias CF (2010) Chemical identity and connections of medial preoptic area neurons expressing melanin-concentrating hormone during lactation. J Chem Neuroanat 39(1):51–62

Rosenblatt JS (1975) Prepartum and postpartum regulation of maternal behaviour in the rat. Ciba Found Symp 33:17–37

Rosenblatt JS (1980) Hormonal and nonhormonal regulation of maternal behavior: a theoretical survey. Reprod Nutr Dev 20(3B):791–800

Rosenblatt JS, Ceus K (1998) Estrogen implants in the medial preoptic area stimulate maternal behavior in male rats. Horm Behav 33(1):23–30

Rosenblatt J, Mayer A, Siegel H (1985) Maternal behavior among nonprimate mammals. In: Adler N, Pfaff D, Goy RW (eds) Handbook of behavioral neurobiology. Plenum, New York, pp 229–298

Rosenblatt JS, Mayer AD, Giordano AL (1988) Hormonal basis during pregnancy for the onset of maternal behavior in the rat. Psychoneuroendocrinology 13(1–2):29–46

Saito Y, Nagasaki H (2008) The melanin-concentrating hormone system and its physiological functions. Results Probl Cell Differ 46:159–179

Saito Y, Cheng M, Leslie FM, Civelli O (2001) Expression of the melanin-concentrating hormone (MCH) receptor mRNA in the rat brain. J Comp Neurol 435(1):26–40

Salamone JD, Correa M (2012) The mysterious motivational functions of mesolimbic dopamine. Neuron 76(3):470–485

Schrader JA, Smale L, Nunez AA (2012) Pregnancy affects FOS rhythms in brain regions regulating sleep/wake state and body temperature in rats. Brain Res 1480:53–60

Schultz W, Apicella P, Ljungberg T (1993) Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J Neurosci 13(3):900–913

Sharma V, Mazmanian D (2003) Sleep loss and postpartum psychosis. Bipolar Disord 5(2):98–105

Simerly RB, Swanson LW (1986) The organization of neural inputs to the medial preoptic nucleus of the rat. J Comp Neurol 246(3):312–342

Sivadas N, Radhakrishnan A, Aswathy BS, Kumar VM, Gulia KK (2016) Dynamic changes in sleep pattern during post-partum in normal pregnancy in rat model. Behav Brain Res 320: 264–274

Smith DG, Tzavara ET, Shaw J, Luecke S, Wade M, Davis R, Salhoff C, Nomikos GG, Gehlert DR (2005) Mesolimbic dopamine super-sensitivity in melanin-concentrating hormone-1 receptor-deficient mice. J Neurosci 25(4):914–922

Stern JM (1989) Maternal behavior: sensory, hormonal and neural determinants. In: Brush FR, Levine S (eds) Psychoendocrinology. Academic, New York, pp 103–226

Stern JM (1991) Nursing posture is elicited rapidly in maternally naive, haloperidol-treated female and male rats in response to ventral trunk stimulation from active pups. Horm Behav 25(4): 504–517

Stern JM, Johnson SK (1990) Ventral somatosensory determinants of nursing behavior in Norway rats. I. Effects of variations in the quality and quantity of pup stimuli. Physiol Behav 47(5):993–1011

Stern JM, Keer SE (1999) Maternal motivation of lactating rats is disrupted by low dosages of haloperidol. Behav Brain Res 99(2):231–239

Stolzenberg DS, Numan M (2011) Hypothalamic interaction with the mesolimbic DA system in the control of the maternal and sexual behaviors in rats. Neurosci Biobehav Rev 35(3):826–847

Stolzenberg DS, McKenna JB, Keough S, Hancock R, Numan MJ, Numan M (2007) Dopamine D1 receptor stimulation of the nucleus accumbens or the medial preoptic area promotes the onset of maternal behavior in pregnancy-terminated rats. Behav Neurosci 121(5):907–919

Suntsova NV, Dergacheva OY (2004) The role of the medial preoptic area of the hypothalamus in organizing the paradoxical phase of sleep. Neurosci Behav Physiol 34(1):29–35

Sutherland RC, Juss TS, Wakerley JB (1987) Prolonged electrical stimulation of the nipples evokes intermittent milk ejection in the anaesthetised lactating rat. Exp Brain Res 66(1):29–34

Takase K, Kikuchi K, Tsuneoka Y, Oda S, Kuroda M, Funato H (2014) Meta-analysis of melanin-concentrating hormone signaling-deficient mice on behavioral and metabolic phenotypes. PLoS One 9(6):e99961

Tan CP, Sano H, Iwaasa H, Pan J, Sailer AW, Hreniuk DL, Feighner SD, Palyha OC, Pong SS, Figueroa DJ, Austin CP, Jiang MM, Yu H, Ito J, Ito M, Ito M, Guan XM, MacNeil DJ, Kanatani A, Van der Ploeg LH, Howard AD (2002) Melanin-concentrating hormone receptor subtypes 1 and 2: species-specific gene expression. Genomics 79(6):785–792

Terkel J, Bridges RS, Sawyer CH (1979) Effects of transecting lateral neural connections of the medial preoptic area on maternal behavior in the rat: nest building, pup retrieval and prolactin secretion. Brain Res 169(2):369–380

Thornburg KL, Bagby SP, Giraud GD (2006) Maternal adaptation to pregnancy. In: Neill JD (ed) Knobil and Neill's physiology of reproduction. Elsevier, St. Louis, MO, pp 2899–2924

Torterolo P, Benedetto L, Lagos P, Sampogna S, Chase MH (2009a) State-dependent pattern of Fos protein expression in regionally-specific sites within the preoptic area of the cat. Brain Res 1267:44–56

Torterolo P, Sampogna S, Chase MH (2009b) MCHergic projections to the nucleus pontis oralis participate in the control of active (REM) sleep. Brain Res 1268:76–87

Torterolo P, Lagos P, Monti JM (2011) Melanin-concentrating hormone: a new sleep factor? Front Neurol 2:14

Torterolo P, Scorza C, Lagos P, Urbanavicius J, Benedetto L, Pascovich C, Lopez-Hill X, Chase MH, Monti JM (2015) Melanin-concentrating hormone (MCH): role in REM sleep and depression. Front Neurosci 9:475

Trulson ME (1985) Activity of dopamine-containing substantia nigra neurons in freely moving cats. Neurosci Biobehav Rev 9(2):283–297

Trulson ME, Preussler DW (1984) Dopamine-containing ventral tegmental area neurons in freely moving cats: activity during the sleep-waking cycle and effects of stress. Exp Neurol 83(2):367–377

Trulson ME, Preussler DW, Howell GA (1981) Activity of substantia nigra units across the sleep-waking cycle in freely moving cats. Neurosci Lett 26(2):183–188

Tsunematsu T, Ueno T, Tabuchi S, Inutsuka A, Tanaka KF, Hasuwa H, Kilduff TS, Terao A, Yamanaka A (2014) Optogenetic manipulation of activity and temporally controlled cell-

specific ablation reveal a role for MCH neurons in sleep/wake regulation. J Neurosci 34(20): 6896–6909
Verret L, Goutagny R, Fort P, Cagnon L, Salvert D, Leger L, Boissard R, Salin P, Peyron C, Luppi PH (2003) A role of melanin-concentrating hormone producing neurons in the central regulation of paradoxical sleep. BMC Neurosci 4:19
Vetrivelan R, Kong D, Ferrari LL, Arrigoni E, Madara JC, Bandaru SS, Lowell BB, Lu J, Saper CB (2016) Melanin-concentrating hormone neurons specifically promote rapid eye movement sleep in mice. Neuroscience 336:102–113
Voloschin LM, Tramezzani JH (1979) Milk ejection reflex linked to slow wave sleep in nursing rats. Endocrinology 105(5):1202–1207
Von Economo C (1930) Sleep as a problem of localization. J Nerv Ment Dis 71:249–259
Wakerley JB (1996) Milk ejection and its control. In: Knobil E, Neill JD (eds) The physiology of reproduction. Academic, New York, pp 3129–3191
Wightman RM, Robinson DL (2002) Transient changes in mesolimbic dopamine and their association with "reward". J Neurochem 82(4):721–735
Willie JT, Sinton CM, Maratos-Flier E, Yanagisawa M (2008) Abnormal response of melanin-concentrating hormone deficient mice to fasting: hyperactivity and rapid eye movement sleep suppression. Neuroscience 156(4):819–829
Zarrow MX, Denenberg VH, Anderson CO (1965) Rabbit: frequency of suckling in the pup. Science 150(3705):1835–1836
Zhao ZJ, Chi QS, Cao J (2010) Milk energy output during peak lactation in shaved Swiss mice. Physiol Behav 101(1):59–66