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# Cholecystokinin modulation of maternal behavior

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## Abstract

Maternal behavior is regulated by several neurotransmitters, neuropeptides, and hormones. This mini-review focuses on the role of cholecystokinin (CCK), a neuropeptide and gut hormone best known as a satiety signal, in mediating maternal behavior. In addition to the role of CCK in the infant in mother-infant interactions, maternal CCK appears to also be important. We discuss maternal behavior research, mainly in rats, that has examined the effect of administering CCK to dams, CCK-opioid interactions, and maternal behavior in rats that lack CCK1 receptors. We discuss the possibility that CCK might play a role in neurological adjustments during pregnancy that ultimately influence behavioral adaptations by the offspring during lactation. Finally, we hypothesize that maternal CCK is also involved in maternal memory and reward. **Keywords**: cck, maternal behavior, opioid, lactation, nutrition.

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## Maternal Behavior in Rats

Maternal behavior in rats consists of several behaviors toward the litter that ensure the pups' survival and promote offspring development. These behaviors are often divided into pup-directed patterns and non-pup-directed patterns. Pup-directed patterns include retrieving, grouping, crouching-over, and licking young. Non-pup-directed patterns include protecting them against predators, which may include maternal aggression, and nest building. The duration and quality of early maternal care modulates the physiological and behavioral development of the offspring (for review, see Cummings, Clemens, & Nunez, 2010; Kaffman, & Meaney, 2007; Vasconcelos et al., 2012).

Research has characterized the central neurochemistry that mediates maternal behavior in rats (Kristal, 2009). The medial preoptic area, which is located in the rostral hypothalamus, and dopamine neural systems interact to regulate maternal behavior in rats (Numan, & Stolzenberg, 2009). The hormonally (i.e., estradiol, progesterone, and prolactin) primed medial preoptic area regulates the appetitive, proactive, and voluntary aspects of maternal behavior by activating mesolimbic dopamine inputs to the shell region of the nucleus accumbens (Silva, Bernardi & Felicio, 2001; Silva et al., 2003). Preoptic efferents also appear to suppress a central aversion system that includes an amygdala-to-anterior hypothalamic circuit, thus reducing pup aversion (Numan, 2006, 2007). By acting on these pathways, neural oxytocin facilitates the onset of both pup-directed and -non-directed maternal behavior (Neumann, 2008; Numan, & Stolzenberg, 2009).

This review focuses on the role of maternal cholecystokinin (CCK), a neuropeptide and gut-hormone, in mediating maternal behavior. We note that CCK in infants also plays a role in mother-infant interactions. This topic has been reviewed by Weller, & Feldman (2003), Weber, Manfredo, & Rinaman (2009), and Bosch, & Neumann (2012).

This manuscript discusses maternal behavior research that has examined the effect of administering CCK to rats, CCK-opioid interactions, and maternal behavior in rats that lack CCK1 receptors. Finally, we attempt to summarize the state of knowledge and perspectives of investigation in this field.

## Cholecystokinin

The discovery of CCK has much to do with the discovery of hormonal signaling itself in the early 20th century. Bayliss, & Starling (1902) described the discovery of a substance in extracts of the mucosa of the upper intestine. The question of whether the substance stimulates the liver similarly to stimulating the pancreas was answered by Viktor Mutt who purified and chemically characterized a peptide ($CCK_{33}$) that

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contained 33 amino acids and had both cholecystokinetic and pancreozyminic activities. Thus, both pancreatic secretion and contraction of the gall bladder are mediated by the same peptide, CCK, which is found in endocrine and neural cells in the periphery and central neurons. Cholecystokinin is a gastrointestinal hormone, neurotransmitter, and neuromodulator. It is abundant in the brain and intestine. It is one of the most abundant peptides in the brain, particularly in the cerebral cortex, striatum, and hippocampus (Mutt , 1994). Additionally, CCK is co-localized with various classic neurotransmitters. It is involved in reproductive behaviors and modulates thermo- and cardiovascular regulation, analgesia, learning, memory, satiety, anxiety, and most neurological and psychiatric issues that involve dopaminergic neurotransmission (Crawley, & Corwin, 1994). Formerly, CCK receptors were designated $CCK_A$ and $CCK_B$ (type A, "alimentary," and type B, "brain"; Moran et al., 1986; Noble et al., 1989; Noble et al., 1999). The $CCK_A$ receptor was first characterized in pancreatic acini from rodents, whereas the $CCK_B$ receptor was first found in the brain. The former $CCK_A$ and $CCK_B$ receptor nomenclature was generally accepted by investigators. Nevertheless, according to recommendations of the International Union of Pharmacology (IUPHAR) committee, the $CCK_A$ receptor was renamed the $CCK_1$ receptor, and the $CCK_B$ receptor was renamed the $CCK_2$ receptor. These receptors belong to the family of G-protein coupled receptors, and the two types show 50% homology. Cholecystokinin receptors have been pharmacologically classified based on their affinity for the endogenous peptide agonists CCK and gastrin, which share the same COOH-terminal pentapeptide amide sequence but differ in sulfation at the sixth (gastrin) or seventh (CCK) tyrosyl residues. The $CCK_1$ and $CCK_2$ receptor subtypes have been shown to differ with regard to their relative affinity for natural ligands, differential distribution, and molecular structure. The $CCK_1$ receptor binds sulfated CCK with 500- to 1000-fold higher affinity than sulfated gastrin or nonsulfated CCK. The $CCK_2$/gastrin receptor binds gastrin and CCK with almost the same affinity and discriminates poorly between the sulfated and nonsulfated CCK analogues (Saito, Williams, & Kanno, 1980). The distribution of $CCK_1$ and $CCK_2$/gastrin receptors is tissue-dependent.

## Late pregnancy influences maternal behavior

Physiological and neuroendocrine adaptive changes during late pregnancy stimulate the rapid onset of maternal behavior. The serum levels of CCK octapeptide increase during pregnancy and lactation in rats (Frick, Bremme, Sjögren, Lindén, & Uvnäs-Moberg, 1990). Serum progesterone levels that remain high during pregnancy start dropping before parturition. Serum estrogen and prolactin levels increase before parturition. Other hormones, such as oxytocin and opioids, also participate in either the induction or maintenance of maternal behavior. Puerperal treatment with morphine has been shown to lead to sensitization to this drug, increasing the inhibitory effects of opioids in ongoing rat maternal behavior (Miranda-Paiva et al., 2001; 2003). Behaviorally meaningful morphine treatment during late pregnancy also induces an increase in serum progesterone levels, without significantly altering corticosterone, estradiol, or prolactin levels (Sukikara et al., 2011). A morphine-induced increase in progesterone levels during late pregnancy might play a role in the tardive effects described for this treatment. Nevertheless, progesterone also has stimulating effects on appetite. The possible role of CCK in maternal nutritional adjustment during pregnancy fits this theory. Pretreatment with a CCK antagonist during late pregnancy increased opioid inhibitory effects on maternal behavior (Miranda-Paiva, Nasello, Yim, & Felicio, 2002). These data suggest that CCK and opioid interactions may mediate prepartum adjustments that ultimately influence the expression of maternal behavior. This influence is expressed through counterbalanced, multi-peptidergic control, in which CCK and morphine (representing the activation of endogenous opioid peptides) act antagonistically on maternal behavior. Such peptidergic control appears to be plastic and adaptive and may be important for optimizing behavioral versatility during lactation.

The sensitivity of offspring development to the maternal phenotype predisposes the offspring to potentially adverse effects through various pathways. For example, the offspring may be exposed to a postnatal diet or environment that may be mismatched with nutritional and metabolic experience *in utero* (Nederhof, & Schmidt, 2012; Wells 2007). Thus, developing mechanisms that help the conceptus anticipate the postnatal environment have great adaptive value. Interactions with other neuropeptides and neurotransmitters and the role of this peptide in other fields, such as immunology, in this context are worth future investigations. Cholecystokinin may thus participate in the adaptation of the mother's behavior toward optimally fitting to the post-partum environment.

## Cholecystokinin and maternal behavior in rats

cholecystokinin is released in the mother rat and cow but not in humans in response to suckling, together with other peptides, such as oxytocin and prolactin (Holst, Jenssen, Burhol, Jorde, Maltau, & Haug, 1986; Linden, Eriksson, Hansen, & Uvnas-Moberg, 1990; Lupoli, Johansson, Uvnäs-Moberg, & Svennersten-Sjaunja, 2001). Accordingly, acute CCK injection has been shown to activate magnocellular oxytocin-producing cells in the hypothalamus, resulting in increased plasma levels of oxytocin (Renaud, Tang, McCann, Stricker, & Verbalis, 1987). Furthermore, lesioning of the pathways from the brain stem to the periventricular nucleus in lactating rats inhibited the suckling-related, vagally dependent release of CCK (Linden et al., 1990), suggesting that central oxytocin pathways are involved in

the suckling-related, vagally mediated release of gastrointestinal hormones, such as CCK.

However, the role of exogenously administered CCK in the onset of maternal behavior is uncertain. Treatment with estradiol benzoate in combination with peripherally administered CCK octapeptide (CCK8) rapidly stimulated maternal behavior within 4 h of exposure to newborn pups in ovariectomized rats (Linden, Uvnas-Moberg, Eneroth, & Sodersten, 1989). However, one of us, together with another group, failed to replicate this effect in a series of experiments (Mann, Felicio, & Bridges, 1995). Furthermore, Wager-Srdar, & Levine (1991) reported that maternal behaviors, such as mother-pup interactions and nursing, were unaltered by CCK8 administration. In this review, we discuss the hypothesis that CCK might modulate maternal behavior by interacting with other neurotransmitters and neurohormones, such as opioids, and "preparing" or sensitizing the parental brain for optimal adaptive post-partum behavior.

The action of CCK on maternal behavior appears to be associated with the reproductive state and hormonal profile of female rats and depend on the neuroanatomical place of action. After chronic intracerebroventricular infusions of CCK-8, the onset of maternal behavior was unaltered in previously steroid-primed virgin female rats (Mann et al., 1995). The same study, however, showed that CCK-8 prevent β-endorphin's inhibitory action on maternal behavior when the infusions occurred in the medial preoptic area in lactating rats.

## Effect of cholecystokinin-opioid interactions on maternal behavior in rats

Cholecystokinin appears to influence maternal behavior while the brain is preparing to express this behavior during pregnancy. Studies have also demonstrated that both endogenous opioids and CCK are involved in the control of maternal behavior during lactation. In this context, CCK's most important effect appears to be its ability to antagonize the inhibitory effects of opioidergic transmission.

### *Role for effect of CCK-opioid balance in late pregnancy on maternal behavior*

Unilateral infusions of CCK octapeptide into the lateral periaqueductal gray (PAG) but not the nearby reticular formation are able to restore the normal expression of maternal responsiveness in morphine-treated dams (Miranda-Paiva, Canteras, Sukikara, Nasello, Mackowiak, & Felicio, 2007). These data suggest that opioidergic PAG activation plays a functional role in the inhibition of maternal behavior during lactation, supporting the hypothesis that CCK interacts with endorphins at more than one site that controls maternal behavior in lactating rats. Subcutaneous injections of antagonists selective for both CCK1 and CCK2 receptor subtypes increase the inhibitory effects of morphine on maternal behavior in lactating rats (Miranda-Paiva, & Felicio, 1999). These studies support the role of CCK-opioid ligand interactions in the maintenance of maternal behavior.

Morphine disrupts and naloxone restores maternal responsiveness in female rats (Bridges, & Grimm, 1982; Grimm, & Bridges, 1983; Rubin, & Bridges, 1984). Acute morphine injections at very low doses do not inhibit maternal behavior *per se*. Puerperal treatment with morphine may lead to sensitization to this drug, ultimately influencing the effects of these opioids on maternal behavior during lactation. Repeated administration of morphine increases the subsequent inhibitory effects of this drug on maternal behavior. Puerperal treatment with morphine may lead to sensitization to this drug, influencing the effects of opioids on maternal behavior, and CCK may antagonize these sensitization effects (Miranda-Paiva et a., 2001; 2003; 2007).

Cholecystokinin-opioid interactions in the control of maternal behavior appear to play a role in the tardive effects of late pregnancy, demonstrated by pharmacological treatments with a CCK antagonist. Pretreatment with low doses of the CCK1 receptor antagonist lorglumide inhibited maternal behavior in lactating rats. This inhibition was even more intense in animals acutely treated with a morphine dose that was not sufficient to significantly inhibit maternal behavior *per se*. The 7-day-long puerperal blockade of CCK1 receptors resulted in the inhibition of maternal care on day five of lactation. Puerperal treatment with lorglumide has long-lasting inhibitory effects on maternal behavior. Opioid receptors may be particularly sensitive to pharmacological manipulations during late pregnancy, with long-term consequences for maternal care. The antagonism of CCK receptors during the puerperal period may facilitate the inhibitory actions of endogenous opioids on maternal care during lactation (Miranda-Paiva et al., 2002).

The PAG is an important site for the opioidergic inhibition of ongoing maternal behavior. This site is also an important neuroanatomical structure for the development of opioid tolerance, and CCK has been proposed to be involved in tolerance mechanisms (Tortorici, Nogueira, Salas, & Vanegas, 2003). Infusions of CCK into the PAG reestablish maternal behavior in morphine-pretreated dams. Similar to animals pretreated and challenged only with saline, animals treated with 1.0 and .2 nmol CCK exhibited shorter latencies in all maternal behavior parameters. Opioid stimulation actively inhibited maternal behavior, whereas CCK reestablished it. The inhibitory effect of morphine on maternal behavior was blocked by a unilateral CCK injection in the PAG but not in nearby regions of the mesencephalic reticular nucleus (Miranda-Paiva et al., 2007).

### *Cholecystokinin-opioid antagonist action on maternal behavior*

Cholecystokinin reverses the β-endorphin-induced inhibition of maternal behavior in lactating

rats when injected both intracerebroventricularly and into an important site for reproductive behaviors, the medial preoptic area (Felicio, Mann, & Bridges, 1991; Mann et al., 1995). Central co-infusion of CCK and β-endorphin into the brain blocks the disruptive effect of the opioid on maternal behavior in post-partum rats (Felicio et al., 1991). Specifically, the administration of CCK8 into the lateral ventricles (i.e., intracerebroventricularly) in lactating rats prevented the inhibitory effects of β-endorphin (also administered intracerebroventricularly) on the maintenance of maternal behavior. This result was replicated by Mann et al. (1995), who found a similar effect when both peptides were administered directly into the medial preoptic area at doses that were 10-times lower. Furthermore, the nonspecific CCK antagonist proglumide, administered centrally or systemically, significantly increased the latencies of lactating dams to retrieve and crouch over their pups (Mann et al., 1995).

## Role for CCK receptors in the control of maternal behavior

Cholecystokinin receptor subtypes may differentially modulate maternal behavior and the opioid modulation of ongoing maternal behavior. CCK1 and CCK2 receptor blockers potentiated the inhibitory effects of morphine on maternal behavior. The influence of peripheral injections of CCK1 (lorglumide) and CCK2 (L-365,260) receptor blockers on the effects of maternal behavior during lactation are the following. Both CCK receptor antagonists at 10 mg/kg (but not 1 mg/kg) potentiated the inhibitory effects of morphine on maternal behavior. Additionally, treatment with 10 mg/kg L-365,260 alone had the same action (Miranda-Paiva, & Felicio, 1999). These data suggest that the CCK antagonism of the opioid-induced disruption of maternal behavior occurs because of the action of CCK on both CCK1 and CCK2 receptor subtypes.

### *Interactions in mother-single-infant dyads*

To examine the involvement of CCK1 receptors in maternal care, we observed maternal behavior in mother-infant dyads, in which the dam or pup (or both or neither) were from a line of rats that lack CCK1 receptors (Lavi-Avnon, Malkesman, Hurwitz, & Weller, 2004). The Otsuka Long-Evans Tokushima Fatty (OLETF) rat is a selectively bred line characterized by deletion of the CCK1 receptor gene, resulting in the absence of functional CCK1 receptors (Nakamura et al., 1998). OLETF rats and their control line (Long-Evans Tokushima Otsuka [LETO]) have been studied as a rat model of non-insulin-dependent diabetes mellitus, and lately they have been recognized as a model of early-onset hyperphagia-induced obesity (Moran, 2008; Lavi-Avnon et al., 2004; Schroeder et al., 2009c; Schroeder, Schechter, Fride, Moran, & Weller, 2009a; Schroeder, Shbiro, Zagoory-Sharon, Moran, & Weller, 2009b).

In the study by Lavi-Avnon et al. (2004), 10 mothers from each strain were tested for 10 min on day 6-9 of lactation for maternal behavior toward one OLETF fostered pup and one LETO fostered pup (postnatal day 6-9). The pups were presented in a counterbalanced order, and each pup was tested only once. Based on previous reports that suggested a positive role for CCK in maternal behavior (Felicio et al., 1991; Mann et al., 1995), we hypothesized that OLETF dams will show less maternal behavior compared with LETO dams, although differences in locomotor activity were not anticipated, based on a report in adult males (Beinfeld, Connolly, & Pierce, 2001). The design used in this study, in which dams from each strain were tested with pups from both strains, allowed us to distinguish OLETF-LETO differences in the behavior of the pup and foster mother, separately. This current review focuses exclusively on the dams, so only the results regarding maternal strain differences are described here.

The dams showed different profiles, specifically in the variables of carrying pups and nursing position, but not in body licking or anogenital licking. OLETF dams carried pups from both strains less than LETO dams. Seven of the 10 OLETF dams also showed a nursing position, whereas no LETO dam did. Of the total 20 interactions between OLETF dams and pups observed, 11 nursing positions were seen, with two cases in which there was more than one nursing position in a single interaction. Of the 11 pups that were attached, six were OLETF pups, and the other five were LETO pups. No significant differences were found between the OLETF and LETO dams in horizontal and vertical activity levels, measured when the mother was alone. This mixed pattern of results (i.e., less retrieval and more nursing postures) in OLETF *vs*. LETO dams may be interpreted as the following. The OLETF dams were less "maternal" as predicted on the retrieval variable, suggesting a pro-maternal behavior effect of CCK in this aspect of maternal behavior. Following the report that female OLETF rats displayed (moderately) more anxiety-like behaviors than LETO controls (Schroeder, & Weller, 2010), we interpret the strain difference in settling down to "nurse" a single pup in the Lavi-Avnon et al. (2004) study as reflecting strain differences in anxiety more than differences in maternal care *per se*. However, as discussed in the following sections, studies of maternal care with complete, disturbed and undisturbed litters showed that OLETF dams often show altered patterns of nursing pups compared with LETO controls.

### *Undisturbed maternal observations during the day*

In separate studies, we observed maternal behavior in undisturbed OLETF and LETO litters. No overall significant differences in general behavioral patterns were found in the first post-partum week, but OLETF dams were significantly less active and engaged in less self-grooming behavior. This pattern was repeated over the following two post-partum weeks. OLETF dams showed significantly less self-grooming over the entire period and reduced activity in the first and third post-

partum weeks. In the second post-partum week, the OLETF dams slept more frequently and self-groomed less frequently than LETO dams. OLETF dams were found in a nursing posture more frequently than LETO controls, but this did not reach statistical significance. Surprisingly, OLETF dams exhibited less non-nutritive contact toward the pups than LETO dams. During the third post-partum week, OLETF females showed significantly increased nursing behavior compared with controls. The expected decrease in nursing behavior across the postnatal weeks, reflecting a transition from nursing to weaning, was present only in the LETO control strain. Instead, OLETF dams' nursing frequency was slightly increased over lactation (Schroeder, Zagoory-Sharon, Lavi-Avnon, Moran, & Weller, 2006).

### *Undisturbed maternal observations in the day and night*

In post-partum week 1, OLETF dams nursed significantly more during the day than controls, and that difference derived from longer nursing bouts and not from an increased number of nursing bouts. At night, LETO dams tended to show more total nursing time and significantly more supine nursing than OLETF dams. In post-partum week 1, postures slightly differed between the strains during the night. This difference did not reflect who took the initiative to start the nursing bouts. LETO dams presented kyphotic and supine postures, and OLETF dams only presented kyphotic postures. The nursing initiative did not differ between the strains. In post-partum week 3, OLETF dams engaged in significantly more nursing in the day and night. This time, the difference resulted from an increased number of nursing bouts rather than the length of the nursing episodes. The analysis of nursing postures at the beginning of the nursing bouts and bout initiative revealed that OLETF dams presented significantly more supine nursing and that OLETF pups took most of the initiative in starting the nursing bouts compared with controls. As expected, we found slight differences between the percentages of the dams' supine postures and pups' initiative; in general, however, the results were very similar, and both parameters were clearly related.

The LETO dams appeared to exhibit a reduction of the number of nursing bouts in the third week, without reducing their relative initiative. Their pups simultaneously were less interested in suckling. This pattern, rather than dam-initiated suckling blockade (such as ''press-posture''), appears to characterize the LETO weaning process. In contrast, although OLETF dams exhibited a decrease in their nursing initiative, OLETF pups did not give up suckling. Additionally, nursing bouts that contained more than one postural change were associated with a long duration of the nursing episode, which usually lasted longer than 40 min. This pattern was more frequently observed in the third post-partum week in both strains but was especially frequent in the OLETF strain, in which the pups initiated most of the episodes and probably induced the dam to adopt the kyphotic posture through strong stimulation.

### *Frequency results*

OLETF dams nursed significantly more frequently in the first week during the day, whereas LETO dams showed a tendency to be more active during the day, which did not reach statistical significance. In contrast, OLETF dams were found at night to engage in significantly more active self-directed behaviors than controls, whereas LETO dams showed a tendency to present more nursing frequency (Schroeder, Lavi-Avnon, Zagoory-Sharon, Moran, & Weller, 2007).

### *Nursing/retrieval tests*

A further study was performed, in which the maternal parameters examined included nursing time, pup retrieval latency, and the latency to start nursing in nursing/retrieval tests performed once every lactating week after 3-4 h separation from the dam. In post-partum week 3, OLETF pups were frequently found outside the nest, possibly indicating a deficit in pup retrieval on the side of the dams that could reflect a deficit in maternal behavior. No differences in retrieval time were observed between the strains in this study, and that concern was discarded. Although the latency to start nursing tended to be shorter in the OLETF strain, it did not reach statistical significance. The duration of the nursing episodes was significantly longer in the OLETF strain in postnatal week 3. The significant difference found between the strains with regard to the average nursing time showed that OLETF dams presented a gradual increase, rather than the expected gradual decrease, in nursing time over weeks, potentially reflecting a response to the pups' nutritional demands (Schroeder et al., 2007).

### *Undisturbed maternal observations: cross-fostering study*

In this study, pups were switched to dams of the opposite or same strain on postnatal day 1 to examine the maternal *vs*. infant interaction in determining nursing and maternal behavior in this strain. We also milked the dams in the first and third postnatal weeks for milk lipid analysis. OLETF milk was found to contain large amounts of fat, both in the first and third postnatal weeks. Thus, the efficient nursing of OLETF pups from their natal OLETF dams' high-fat milk can potentially contribute to their pre-obese profile (Schroeder et al., 2009a).

LETO females did not significantly alter their behavior when rearing obese pups instead of lean pups in the first postnatal week. However, an interesting increase in eating frequency was observed when rearing OLETF pups, a finding that might reflect higher energy demands by the pups. In the second postnatal week, LETO females provided more nonnutritive contact to LETO pups compared with OLETF pups. No further differences were observed in the LETO dams' behavior. OLETF dams also behaved almost equally when raising

OLETF pups *vs*. LETO pups during the first two postnatal weeks. Again, the only significant difference consisted of increased nonnutritive contact toward the LETO pups compared with the OLETF pups. In contrast, a different profile occurred during the third week. OLETF females nursed less frequently when rearing LETO pups *vs*. OLETF pups, an outcome that was strongly supported by our previous findings, in which OLETF pups were found to be responsible for the increased nursing time and frequency during this specific postnatal week. When rearing "lean" pups that do not initiate so many nursing episodes by themselves, OLETF dams spent less time nursing and more time in self-directed behaviors, such as self-grooming and sleeping (Schroeder et al., 2009a).

Despite the initial hypothesis that OLETF dams take less care of their pups as a result of the absence of functional CCK1 receptors, the experiments described above demonstrated that this is not always the case. The changes are directly related to the week of lactation and stage of the light/dark cycle. OLETF mothers express more maternal behavior in the third week of lactation compared with wildtype LETO rats. In the first week of lactation, Wistar and Long Evans rats usually express more maternal care during the light phase of the cycle. Interestingly, rat mothers are generally more responsive to their offspring around the fifth and sixth days of lactation. As the offspring grow and become able to regulate their body temperature and feed themselves, the dams become less responsive to them. Generally, maternal care is clearly expressed during the light cycle. In the dark cycle, the dams prioritize their own food and general activity (Hughes, Harlan, & Plaut, 1978). Self-grooming could optimize lactation processes (Roth, & Rosenblatt 1966; Serafim, & Felicio, 2002). OLETF dams showed less self-grooming behavior, and this could interfere with the lactation process.

## Future directions: CCK, cognition, and maternal behavior

Endogenously increasing appetite cues during late pregnancy could make the organism more willing to display hunting/foraging behavior during the post-partum period. Maternal abilities to save and retrieve valuable information are important elements of the parental repertoire. Because CCK plays a role in both feeding and cognition, we may hypothesize that maternal CCK plays a role in mediating these essential behavioral patterns during lactation. Such CCK-mediated metabolic-behavioral interactions should be investigated in depth.

Specifically, CCK receptors mediate both anxiety and memory processes (e.g., Cohen, Kaplan, Matar, Buriakovsky, Bourin, & Kotler, 2004; Huston, Schildein, Gerhardt, Privou, Fink, & Hasenöhrl, 1998). Cholecystokinin may also be involved in maternal memory. This hypothesis is based on the following findings: (1) selective CCK receptor antagonists alter social memory between adult male rats (Lemaire et al., 1994a; Lemaire, Böhme, Piot, Roques, & Blanchard, 1994b), suggesting that CCK1 receptors mediate mnemonic effects, whereas CCK2 receptors mediate amnestic effects (Hadjiivanova, Belcheva, & Belcheva, 2003), (2) CCK1 and CCK2 receptor antagonists prevented the appearance of conditioned preferences based on rewards that represent aspects of the dam and nest (Weller, Tsitolovskya, Gispan, & Rabinovitz, 2001), and (3) CCK receptor antagonists alter learned maternal preference in lambs. For example, lambs treated with a CCK2 antagonist and controls preferred their mother at 24 h postnatally, but the CCK1 antagonist devazepide prevented maternal preference at both 24 and 48 h postnatally (Goursaud, & Nowak, 2000; Nowak et al., 1997). 2-NAP, an antagonist of peripheral CCK1 receptors, also blocked the expression of maternal preference (Goursaud, & Nowak, 2000; Nowak, Breton, & Mellot, 2001). Thus, the possibility that maternal CCK plays a role in maternal-infant memory deserves further investigation.

Both feeding and peripherally administered CCK-8 enhance memory in mice. This gastrointestinal hormone appears to produce its effect on memory by activating ascending vagal fibers. A link may have evolved between the release of gastric peptides and memory processing in the central nervous system because of the survival advantages conferred to an animal that remembers the details of a successful food-foraging expedition (Flood, Smith, & Morley, 1987). Feeding is important for mothers to promote the lactation process, and a link between memory and feeding could be established by studying the role of the CCK hormone in maternal memory and how it can improve the lactation process and development of the offspring.

The central administration of CCK8 receptor antagonists produced marked memory deficits, and CCK8 administration prevented experimental amnesia in rodents (Flood, Garland, & Morley, 1992). The intracerebroventricular administration of CCK8 suppressed the analgesic effects of β-endorphin (Faris, Komisaruk, Watkins, & Mayer, 1983). It would be interesting to determine whether the effects of the stimulation and blockade of opioid receptors using β-endorphin and naloxone, respectively, on memory processes that have been shown to be affected by CCK8 (Itoh, & Lal, 1990; Itoh, & Katsuura, 1982), mainly in pregnant rats near the partum period, are influenced by endogenous opioids and their interactions with the neuroendocrine system.

Cholecystokinin is intimately involved in multiple processes related to cognitive function and food intake regulation. Cholecystokinin knockout mice showed normal food intake, fat absorption, body weight, and body mass and ate more food during the light period compared with wildtype controls. They spent more time in the closed arms of an elevated plus maze, reflecting an increase in anxiety-like behavior, and were as active as wildtype controls. These results suggest that CCK may be involved in several metabolic processes that can directly influence memory and exploration (Lo et al., 2007). Nevertheless, studies that would allow

more specific manipulation of these receptors, such as activating them more temporally specifically and in microregions of the brain, will provide important information about this complex issue. Finally, because every mother must balance her own subsistence and reproduction, specific cues might be essential for mother and offspring survival. The potential relevance of central CCK in these processes is indisputable.

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