Emotion regulation and touch in infants: the role of cholecystokinin and opioids

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Abstract

Behavioral–pharmacological research in infant rats supports the role of cholecystokinin (CCK) and opioid peptides in mediating early learning of new associations with aspects of the nest and dam, such as maternal odor, milk, and contact. The current paper reviews research that examines the hypothesis that these neuropeptide systems are further involved in mediating emotion regulation in infants, thus playing a role in the emergence of stress-reactivity and other motivational systems. The beneficial effects of maternal proximity, handling, and touch on the development of emotion regulation have been demonstrated in both human and animal models. Interventions that promote tactile stimulation of the infant (“touch therapy”) and infant–mother contact (“skin-to-skin contact” or “kangaroo care”) have been shown to improve the infant’s ability to self-regulate, and to moderate the effects of some risk factors. Theoretical perspectives and empirical findings regarding emotion regulation in infants are first discussed. This is followed by a review of work providing evidence in animal models (and suggestive evidence in humans) for the importance of CCK and opioid neuropeptides in affecting infant emotion regulation and the impact of touch-based interventions, in particular in the context of infant–mother attraction, contact, separation, and attachment.

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1. Prospectus

Compared to adults, the repertoire of infants’ behavior is relatively restricted, as they are in the beginning phase of expanding behavioral development (infancy and childhood). Therefore, infant rats may be viewed, for purposes of psychobiological research, as a good research paradigm for the study of neurobiological mechanisms underlying ontogenetically emerging motivational–behavioral systems. Research in infant rats has shown that pairing a novel odor with administration of cholecystokinin (CCK) or with the opioid agonist morphine produces relative conditioned-odor preferences in preweanling rats. These conditioned preferences can be prevented by pretreatment with the respective receptor antagonists, devazepide and naltrexone. Furthermore, antagonists of CCK1 and mu-type opioid receptors prevent early learning. Specifically, the CCK1 antagonist devazepide blocked the conditioned preferences produced by pairing of novel odors with textures with aspects of the mother and the nest, such as contact with siblings or with the dam herself. Similarly, the opioid antagonist naltrexone blocked the conditioned preference produced by pairing novel odors with the taste of sucrose or corn oil in 6-day-old rats and the conditioned activity of the rat fetus in response to an artificial nipple, previously paired with intranasal infusion of milk. In addition, naltrexone blocked odor preference resulting from pairing of a shock with a novel odor, in young rat pups (older pups develop an odor-aversion following shock–odor pairing).

The involvement of CCK and opioids in early learning of rats is of special interest, as it offers testable hypotheses regarding the potential mediation of different aspects of the

Note that some other neuropeptides and classical neurotransmitters have similar effects. For instance, Nelson and Panksepp reported that an oxytocin antagonist blocked the development of a conditioned-odor preference, when the odor was paired with reunion with the mother on the previous day. Pairing a noradrenaline receptor agonist, isoproterenol, with a novel odor produced an odor preference. Furthermore, a noradrenergic receptor blocker prevented the odor preference produced by pairing of tactile stimulation and the novel odor. It is thus of importance to follow up these studies and explore the relative degree of redundancy in the impact of the different neuropeptides versus their unique roles in early affective learning.
learning process by these neuropeptides. In addition to the possibility of neuropeptide involvement in the associative process itself, neuropeptide mediation may be implicated in the degree of “reward”, or “incentive value” (cf. [5]) provided by the unconditioned stimuli (the cues from the mother and nest). This further suggests potential neuropeptide involvement in the hedonic aspects of the process, i.e. in “wanting” or “liking” (see ref. [4]), the mother- and nest-related rewarding stimuli. To illustrate, sucrose drinking can support, as reinforcement, the establishment of a conditioned place preference (CPP). A high dose of the opioid antagonist naloxone not only blocked CPP, but also reduced sucrose consumption. Furthermore, a low dose of naloxone, while still decreasing consumption, did not block CPP [2]. These results suggest that opioids are more important for the rewarding/liking of the sucrose than for the CPP-supporting reinforcement/ wanting.

The current article discusses some of the implications of these possibilities. Sensory aspects of the mother, nest, and siblings are not only “rewarding”, in the sense meant in associative learning literature, but also serve as a basis for the infant’s developing attachment and security, in the sense discussed extensively by Bowlby [11,12]. According to this approach, the ways in which the individual will deal with stressful situations (“coping”, “stress-reactivity”, “emotion regulation”), physiologically, e.g. changes in heart rate and activation of the hypothalamic-pituitary-adrenal (HPA) axis, and behaviorally, e.g. crying, or seeking social support and contact, are shaped within the early infant–mother “attachment” system [56,31,32,107,108]. The main hypotheses to be discussed in this article is that CCK and opioids mediate the infant’s emotion-regulatory capacities, as seen by reactivity to stress, tendency to approach maternal stimuli when separated, and the “quieting/calming” response to maternal-related stimuli and maternal touch. Data from studies in human infants, rats, and lambs will be presented.

2. Emotion regulation: risk factors and interventions

Emotion regulation, defined as the “extrinsic and intrinsic processes involved in monitoring, facilitating, and inhibiting heightened levels of positive and negative affect” [15] has recently become a major focus in the study of early development, psychopathological conditions, and neurobehavioral growth [101,119]. The development of emotion regulation abilities appears to be an important prerequisite for the organism’s growing abilities to handle stress, develop coping skills, mediate attentional and learning processes, and achieve optimal functioning [108]. Emotion regulation processes are multilevel [19] and develop within the context of early infant–mother interactions. The importance of attachment processes for shaping the infant’s emerging patterns of reactivity and regulation has been shown in studies of animals and humans. Accordingly, the potential for emotional dysregulation has been demonstrated when the mother (or caregiver) is physically and/or emotionally unavailable (cf. [38,39,57]). Panksepp [96] describes four early-emerging “emotional systems of the mammalian brain.” Very briefly, these include the appetitive SEEKING system, the RAGE system that mediates anger, the FEAR system that mediates fight or flight responses and pain reactivity, and the PANIC system, dealing with social distress, and assessed mainly by crying and vocalization. Behaviors within each system gradually become more refined and task-specific and the various emotional systems work in concordance to appraise environmental stimuli and form appropriate reaction. In the following paragraphs, we will discuss empirical findings regarding risk factors and touch-based interventions that affect the development of emotion regulation.

The human infant’s emotion-regulatory capacities may potentially be compromised by several risk factors that are accompanied by infant–mother separation or unavailability, such as premature birth or intrauterine growth retardation (IUGR) (accompanied typically by days to weeks of infant hospitalization during the important post-birth period), and maternal depression. Research has shown that maternal touch and contact have the potential to reverse some of the negative impact of maternal separation (due to infant biological conditions or maternal unavailability) on the infant’s emotion regulation capacities. This may be evident on the structural, neurochemical, and behavioral levels. It is of both clinical and scientific importance that interventions that provide the infant with contact and touch have been shown to alleviate many of these adverse effects on emotion dysregulation.

2.1. Maternal separation and infant emotion regulation

Maternal separation in the first period of life is shown to have a negative and lasting effect on the development of arousal regulation and behavior organization in animal models (e.g. [57,76]). Anand and Scalzo [3] describe two pathways by which prematurity disrupts behavior organization. Maternal separation leads to apoptosis (programmed cell-death) in multiple areas of the immature brain, while pain exposure causes excessive excitatory amino acid activation resulting in excitotoxic damage to developing neurons. On the behavioral level, both conditions are expressed in disturbed reactivity, difficulties in sustained attention, and inability to self-regulate. Rodents separated from their mothers showed changes in the prelimbic prefrontal areas, causing increased excitation and hyper-reactivity [99], and undergoing a complex adaptive response that includes a reduction in DNA synthesis index of cell multiplication, a suppression of cell responses to growth hormone, prolactin and insulin, three major growth hormones, and abnormal patterns of neuroendocrine secretion [76]. Furthermore, interventions that provide separate components of the “maternal proximity” complex, such as touch, smell, or body heat, during the post-natal period may be sufficient to induce lasting improvement in growth and self-regulation [76,78]. Weizman
et al. [121] found increased exploratory behaviors in handled rats, better regulation of the HPA axis, improved functioning of the renin-angiotensin system—the system implicated in attention and memory processes as well as in sleep–wake cyclicity [130]—and better autonomic regulation.

During periods of maternal separation, contact and touch function to improve the infant's emotion regulation capacities. Meaney and others have reported that post-natal handling of rat pups increased levels of licking and grooming of the pups and the frequency of arched-back nursing posture [79]. This change in pattern of maternal care resulted, in turn, in adult offspring with improved affect regulation: milder behavioral and physiological responses to stress and novelty and less anxiety. Several studies have examined the behavioral manifestations of emotion regulation in handled rats. As compared to non-handled controls, post-natally handled rats exhibit, as adults, reduced startle responsivity, increased exploration in a novel open field and decreased novelty-induced feeding suppression [18]; less “resistance to capture” in an “emotional reactivity” test and less time freezing in a “punished drinking” test [95]; more time in the open arms and less time in the closed arms of the elevated plus maze and less immobility upon re-exposure to a box in which they previously received a foot shock [83]. This appears to be, in general, a less anxious behavioral profile than that exhibited by controls. Similar results were obtained when physiological indicators of emotion regulation were examined. As compared to non-handled controls, post-natally handled rats exhibit in adulthood reduced plasma ACTH and corticosterone responses to stress, increased expression of glucocorticoid receptors in the hippocampus, enhanced glucocorticoid feedback sensitivity, and decreased levels of corticotropin-releasing factor (CRF) expression in the hypothalamus [79]. Handled rats also display altered levels of GABA_A and central benzodiazepine receptor levels in specific brain sites [18], less intense hormonal responses (ACTH, corticosterone, and prolactin) during and after an open-field test [95], lower adrenaline, corticosterone, and prolactin responses to a novel cage and smaller changes in the latter two hormones after re-exposure to the shock box [83].

Consistent with the results of animal models, studies of premature infants suggest that touch and contact increase emotion and behavior regulation. Prematurity is a condition that involves maternal separation, as infants are placed in incubators and full body contact is precluded for medical reasons. Premature infants who received massage showed improved state organization, habituation, and motor control following tactile stimulation [40,105].

2.2 Maternal depression and infant emotion regulation

Maternal depression is among the central mother-related antecedents of maternal physical and emotional unavailability to her infant. In general, depressed mothers typically show low, flat affect and provide their infant with less stimulation, and less contingent responsivity during interactions [43]. Such mothers tend to exhibit decreased awareness or sensitivity to their infant’s emotional cues and negative perceptions of the infant’s behavior, resulting in a general mismatch between infant signals and maternal response [36]. The interactions of depressed mothers with their infants have been characterized by two distinct behavioral profiles—the withdrawn, understimulating profile and the intrusive, overstimulating one [41]. Both profiles appear to be discordant, “out of synchrony” with the infant’s behavior and emotional bids. Both acute (more transient) post-partum depression and more chronic, long-term maternal depression have a negative impact on the infant’s affect regulation, typically leading to a withdrawn, “depressed-like” behavior of the infant. Maternal depression in the first months of life has the potential to carry long-term negative impacts on the infant’s growth and development, in particular on the behavioral and physiological indices of emotion regulation (for a review, see refs. [38,50]). In particular, children of depressed mothers are at risk for problems in regulation of vagal tone and EEG, and in motor, affective, and mental development (e.g. [42,44,65]). The risk appears to come from multiple sources, including a genetic predisposition, effects of the prenatal, in utero environment, and in addition post-natal environmental and experiential effects [38,50].

2.3 Maternal contact and infants’ emotion regulation

Hofers [58] model of “hidden regulators” underscores the role of maternal proximity and contact in the post-birth period for the infant’s physiological regulation. Maternal milk, touch, smell, body heat, and biological rhythms in the first post-birth period provide a set of bio-behavioral regulators for the infant’s autonomic, thermo-regulation, feeding, and anxiety-management systems [59]. In a recent longitudinal study, we examined the effects of infant–mother skin-to-skin contact (kangaroo care [KC]) provided to low-birthweight premature infants in the neonatal period, on the development of physiological and emotional regulation among 146 premature infants. Mothers and infants remained in the KC position for at least an hour a day for at least a 2-week period. Intervention was targeted to a period when infants were incubated and skin-to-skin contact was the only way to maintain full body contact between the mother and her infant. Early contact was found to positively affect infants’ emotion regulation, stress-reactivity, and social and cognitive development [33–35].

Of particular interest in the present context is the treated and control infants’ response to aversive stimuli at 3-month corrected age. Infants were tested with a modified version of the Behavioral Response Paradigm (BRP; [46]), which involves the presentation of increasingly aversive stimuli, with predetermined periods of presentation and rest for each stimulus. Infants who received KC during the time they spent in the incubator showed higher thresholds to negative emotionality. This was expressed in the finding that the latency
of 3 movements/s was reported to be soothing [14]. The infant's stress-reactivity was more optimal, as they were more resilient or less sensitive than controls, over 3 months after receiving the touch intervention.

Another finding related to emotion regulation capacities was observed in the level of infants' reactivity to the presentation and termination of the stimuli. We coded, on a micro-level, infants' low, mid-range, and high reactivity to the BRP stimuli during period of stimulus "on" and "off" and the differences between groups were computed with conditional probabilities (e.g. mid-range reactivity given stimulus "on"). Infants who received KC in the neonatal period showed more optimal reactivity (mid-range) while the stimulus was "on", and were more adept at using the "off" periods for rest (no reactivity). These data point to the role of early maternal contact in the development of appropriate mechanisms for stress-reactivity and responsivity to challenging environmental stimuli. The beneficial role of infant-maternal contact was further demonstrated by the findings that during infant-mother face-to-face interactions, infants who received KC showed less negative emotionality, and their mothers were more synchronous and less intrusive, pointing to the bi-directional effects of early co-regulation on the mother and the child (for further details, see ref. [34]).

An additional contribution of infant-maternal skin-to-skin contact is to increasing the rate of maternal lactation [61]. Comparing premature infants who were primarily fed on their mothers' breast milk with those who mainly received formula, Feldman and Eidelman [31] found that infants in the breast-milk group showed better emotion regulation and cognitive growth, in terms of better state regulation, orientation to the environment, and social alertness, and mental and motor development at 6 months.

Finally, KC had an impact on infants' autonomic functioning and the regulation of the vagal break. Following KC, infants showed higher vagal tone as compared to controls [32]. As vagal tone is a physiological index of the infant's ability to orient to the environment and adapt to changing inputs [100], early maternal contact appears to function on physiological as well as behavioral-regulatory mechanisms.

Recent collaborative research [37] has further indicated that a scheduled maternal touch bedtime massage ritual, applied to term infants in the early post-natal period, has a beneficial effect not only on infant growth rates [36], but also a few months later on the phase adjustment of the infant's activity-rest cycle (8 weeks) and on melatonin rhythms during the nocturnal period (12 weeks). The massage protocol, performed at home, involved touching the infant's head with one hand, and lightly stroking his back with the other, in a rhythm of 3 movements/s. This rhythm of 3 movements/s was reported to be soothing [14]. The massage therapy was performed, in this study, daily for 14 days. Similarly, impressive effects of touch therapy on growth and maturation in premature infants have been reported. For example, Kuhn et al. [77] reported that compared to controls, preterm infants that received tactile-kinesthetic stimulation showed significantly increased urine levels of noradrenaline and adrenaline, while levels of cortisol and dopamine in urine and growth hormone in serum were not different from controls. In our laboratory, Ferber et al. [36] have similarly shown that administration of massage therapy to preterm infants enhanced their growth rates. In this study, the massage was administered for three 15-min trials on 3 successive hours, for 10 days of treatment, through the portholes of the incubator.

3. Emotion regulation, touch, and neuropeptides

Several neurochemical systems have been implicated in mediating infant emotional reactivity and the positive effects of touch (cf. [17,18,45,59,64,82,96,106]). Here, we will focus on two relatively well-studied systems, the gut-brain peptide CCK (a neuropeptide and gut hormone, for which there are two receptor sub-types: CCK1 and CCK2) and opioids (of which there are several peptides and receptor types, the most studied in the current context are beta-endorphin and the mu-receptor sub-type).

3.1. Neuropeptides, touch, and emotion regulation in human infants

To our best of knowledge, there has so far been only one study in preterm infants of plasma CCK levels during skin-to-skin contact [118]. This study assessed the influence of KC with or without nasogastric tube feeding on concentrations of CCK and another gut hormone, somatostatin. One group of 18 infants experienced KC for at least an hour. In this group, plasma CCK levels decreased by 12.5% (a small, yet statistically significant amount), from before to after the KC session. CCK levels did not change from before to after feeding, in a group of infants that received routine nasogastric tube feeding (N = 67). The dramatic result in this study was that CCK levels more than doubled (a 120% increase) from before to after feeding, in a third group of eight infants that were fed by nasogastric while being maintained in skin-to-skin contact with their parents [118]. It is also relevant to note here that CCK levels increase in plasma immediately after suckling well before any gastrointestinal effects (human baby [120]; calf [28]), suggesting activation by the contact of non-nutritive sucking. Note that non-nutritive sucking has been shown to: (A) be rewarding, supporting early learning of the infant rat and rabbit (e.g. [13,60,75]); (B) support the establishment of mother preference within 24 h after birth in the newborn lamb in the absence of nutrition and suckling the ewe [111]; and (C) enhance maturation and reduce distress in human preterm infants (e.g. [29,48,49,98,131]).
Opioids, well-known analgesic agents, have also been implicated in mediating the effects of infant–maternal contact. This was the conceptual framework behind the findings that skin-to-skin contact had an analgesic effect during and following painful medical procedures [47,53]. Gray et al. [53] studied 30 newborn infants during a standard heel-lance procedure. Half of the infants were assigned randomly to be held by their mothers in skin-to-skin contact during the procedure, while the other half were left swaddled in the crib. Skin-to-skin contact was associated with a lower heart rate, as well as dramatically lower levels of crying (82%) and grimming (65%). Gazzolo et al.’s [47] study examined the effect of skin-to-skin contact in the painful context of cardiac post-operative intensive care. KC was performed at 2-h intervals in the first 12 post-operative hours (after extubation), in five infants after open heart surgery. In addition to reducing heart rate, KC also influenced several other cardiorespiratory measures (e.g., decreased respiratory rate and increased oxygen saturation).

In the only study, to our knowledge, to measure opioids directly in the context of touch therapy in human infants, Mooney et al. [84] assessed plasma concentrations of beta-endorphin and cortisol in preterm infants, before and after a 20-min period of KC. Samples from the same infants taken on another day, without KC, served as within-subject controls. Concentrations of beta-endorphin dropped significantly after the touch session, and did not change on the control day (cortisol levels dropped on both days). These results suggest an attenuation of the stress response, at least in terms of its opioid component. Taken together, the results of the studies on KC, pain, and beta-endorphin, are consistent with the hypothesis that opioids mediate touch-induced calming and analgesia in human infants.

These findings in human infants show that the opioid and CCK systems respond to relevant, touch-based interventions. We note that this type of research is limited, for obvious ethical reasons, and is further restricted to monitoring peripheral, plasma levels of the peptides. These may (more or less) reflect central neuropeptide functional levels. But it is clear that for more detailed information, work with (more or less) reflect central neuropeptide functional levels.

In a separate line of research, antagonists of CCK1 and CCK2 receptors have been shown to increase natural preference levels of infant rats towards stimuli that appear to represent important aspects of the nest and dam, such as maternal odor, rug texture, and warm temperature [110,122]. Taken together, we can interpret these results as indicating an involvement of CCK in affect regulation. It appears that CCK may mediate part of the naturally soothing, calming aspects of milk and touch. In addition, CCK may mediate the processes of attraction, approach-motivation, and reward value of these types of stimuli.

Research in infant rats has shown that the opioid neuropeptide system mediates infant emotional reactivity and regulation, distress and calming, by various aspects of the mother, siblings, and nest. Briefly, morphine reduced levels of isolation-induced USV, an effect blocked by naltrexone [27,69,123]; while naltrexone alone increased USV levels in some studies [70,123], but not in others [26]. Miu and delta opioid-receptor agonists reduced USV, while kappa receptor agonists increased USV and disrupted contact with littermates [20–22,71]. In isolated compared to control rat pups, significant decreases were reported in opioid peptides in the midbrain, but not in the hypothalamus, septum, or amygdala [114]. Naltrexone blocked USV reduction produced by the presence of an anesthetized littermate [23], and partially blocked the gradual reduction in USV over a series of repeated isolations [51], but did not effect USV reduction by the benzodiazepine chloridiazepoxide [24]. Interestingly, an opioid antagonist did not affect USV when the test pup was in the home cage with its littermates [21] and was ineffective (except at a high dose; [25]) against USV reduction produced by contact with an anesthetized dam [6]. However, reduction of USV by sucrose, corn oil, or (the more naturalistic stimulus) milk, administered orally to an isolated pup, was reversed by an opioid-receptor antagonist [7,8,112]. Overall, one of the implications of these data is that opioids apparently mediate a portion or some of the pathways underling infant separation—and calming responses in rats.

In another study, to our knowledge, to measure opioids directly in the context of touch therapy in human infants, Mooney et al. [84] assessed plasma concentrations of beta-endorphin and cortisol in preterm infants, before and after a 20-min period of KC. Samples from the same infants taken on another day, without KC, served as within-subject controls. Concentrations of beta-endorphin dropped significantly after the touch session, and did not change on the control day (cortisol levels dropped on both days). These results suggest an attenuation of the stress response, at least in terms of its opioid component. Taken together, the results of the studies on KC, pain, and beta-endorphin, are consistent with the hypothesis that opioids mediate touch-induced calming and analgesia in human infants.

Exogenous CCK decreased USV [123]. Devazepide, a selective pharmacological antagonist of CCK1 receptors blocks the USV reduction produced by milk (or corn oil, but not sucrose) ingestion [10,127]. Most recently, we found further convergent validation: OLETF rat pups, lacking CCK1 receptors because of a selective genetic “natural knockout”, emitted significantly more USV compared to LETO controls, in a number of testing conditions [62,80]. Interestingly, while the CCK1-receptor antagonist was ineffective against USV reduction by a passive, anesthetized dam [127], pups treated with this antagonist produced significantly more USV than controls when interacting with an active dam [126]. The latter finding was further supported by finding, under similar testing conditions, that OLETF pups emitted significantly more USV than LETO pups, when interacting with an active dam [80]. Overall, one of the implications of these data is that CCK apparently mediates a portion or some of the pathways underlying infant separation—and calming responses in rats.

3.2. Neuropeptides, touch, and emotion regulation in infant rats

Research with rat pups supports the role of CCK in infant emotional reactivity (as assessed by separation-induced ultrasonic vocalization [USV]) and subsequent “calming” and infant contact comfort. The abbreviation USV, as used in the current manuscript, is a shorthand for the vocal response of the infant rodent (in the ultrasonic range) to acute separation/isolation. This is essentially an animal model of infant separation-anxiety.

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The “brain opioid theory of social attachment” postulates that opiate receptor blockade facilitates an emotional state of social need (for review, see ref. [86]). This has been supported by research on infant–mother attachment in young various species. For example, naloxone treatment was found to increase the rat pup’s motivation for maternal care [87]. Herman and Panksepp [55] reported that morphine decreased approach attachment (offspring/maternal proximity time) in juvenile guinea-pigs, suggesting that opiate drugs could have equally affected the interest in the other social stimuli, thus affecting maternal “reward” indirectly.

The mother–young relationship in sheep is characterized by the individual recognition and rapid development of an exclusive bond. By interacting with its mother, the newborn lamb becomes attached on the basis of its ability to discriminate the mother from alien mothers, and this results in higher survival rates for the young [92]. The first few hours after birth are considered to be a sensitive period during which suckling plays a key role for the establishment of mother preference within 24 h after birth [94]. The ability of the newborn lamb to prefer its mother appears to be based on post-natal learning, as the performance of the neonates improves rapidly with age. Between 12 and 18 h of age, most lambs are attracted to post-parturient ewes, but by the age of 24 h they show a strong preference for their mothers over alien ewes [88]. The ability of a 24-h-old lamb to display such discriminative behavior appears to depend mainly on the first suckling interactions, in addition to visual and auditory cues [89,93]. Preventing lambs from suckling for the first 6 h after birth affects the establishment of the mother–young relations: the formation of a preference for the mother is delayed and they do not show any discrimination at the age of 24 h. This effect is unique to the first 6 post-natal hours and cannot be obtained if suckling is temporarily prevented later in life [93]. Thus, it appears that within the hours following birth, the newborn lamb associates the occurrence of the rewarding suckling with its mother’s features and consequently develops a preference to the mother.

Nowak et al. [94] showed that a 9-h fasting period significantly reduced plasma CCK levels (measured by RIA). Suckling was followed by a significant increase of CCK levels, over the 20- to 50-min period assessed post-suckling. Nowak et al. [93] showed that unrestricted access to the udder starting from birth is necessary for the development of a preferential relationship with the mother. Focusing on the CCKergic system, they reported that only lambs whose CCK plasma levels increased in the first 6 post-natal hours displayed a preference for their mothers at 24 h. Plasma CCK levels were low at birth, rising slowly, only in response to suckling [93]. These findings suggested that the post-natal rise in CCK may be part of the physiological mechanisms involved in the learning of maternal cues by the newborn. The study examining this hypothesis showed that while lambs treated with a CCK2 antagonist and controls preferred their mother at 24 h, the CCK1 antagonist devazepide prevented maternal preference at both 24 and 48 h postnatal [91]. This effect of devazepide was replicated in a second study, which further showed that 2-NAP, an antagonist of peripheral CCK1 receptors, blocked the expression of maternal preference at 24 h, but not at 48 h [52]. A follow-up study showed that the effect of 2-NAP was evident when this antagonist was administered at birth or 6 h later, but not when administered 12 h postnatal. In this study [90], the effect of the antagonist persisted at 48 h, in lambs treated at birth. We conclude that the findings in sheep showed that CCK mediated the development of the preference of the newborn lamb for its mother via peripheral CCK1 receptors, while CCK2 receptors were not shown to be involved; the role of central CCK1 receptors is not clear [52,90,91].
Recently, we examined the role of opioids as an additional possible neurochemical mechanism in the establishment of a preference by the lamb for its mother [109]. Lambs received naltrexone (1.5 mg/kg, Nalt1.5, or 3 mg/kg, Nalt3) or saline (control) within minutes following birth. As above, ewes and their newborn lambs were left undisturbed until 24 and 48 h of age, when lambs were tested for their choice between their mother and an alien ewe. At 24 h, control lambs spent significantly more time near the mother than near the alien ewe, while no significant difference was obtained for Nalt1.5- and Nalt3-treated lambs. The effect of naltrexone persisted at 48 h. No other significant difference in the behavior of the lambs was observed during both tests. Overall, these results support the hypothesis that opioid systems are involved in the establishment of preference for the mother and are consistent with the view that the positive affect associated with social attachment and maternal care may be modulated by opioid receptors.

An additional observation from this study [109] supports the role of opioids in emotion regulation. We recorded the emission of fewer low-pitched bleats in naltrexone (1.5 mg/kg)-treated lambs, compared to controls. This supports the hypothesis of an emotional state of social need. Our unpublished observations indicated that the lamb emits low-pitched bleats mainly during interaction with its mother. Similarly, low-pitched bleats in the ewe have been shown to act as a contact and recognition sign, helping to establish a firm attachment between the ewe and its lamb [30]. Opioid receptor blockade by naltrexone in parturient ewes reduces mean frequencies of low-pitched bleats, together with a reduction in other specific maternal behaviors, such as sniffing, licking, and approaching the lamb [16,74]. Thus, low-pitched bleats, occurring almost exclusively within infant-mother interactions, are consistently reduced by naltrexone in ewes and lambs. Further study is needed to assess whether the function of opioid-mediated low-pitched bleats is similar in infants and adults.

The findings in sheep may still be viewed as preliminary. Nevertheless, overall they support the hypothesis that CCK and opioids both take part in the neuropeptide basis of early learning of discriminative maternal aspects, and in the establishment of the infant-mother bond, the basis for infant emotion regulation. The possibility of CCK-opioid interactions (suggested by studies in rats; e.g. [123]), deserves further examination in sheep.

4. Conclusions

Taken together, the results from research in human, rats, and sheep imply that touch in the post-natal period provides the conditions to promote self-regulation and alleviate (at least partially) potential risk factor-induced emotion dysregulation. The results further support the hypothesis that CCK and opioids are an important portion of the underlying physiological mechanisms.

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