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Milk as the proximal mechanism for behavioral change in the newborn

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Early experience in the context of suckling at the nipple is a crucial determinant of neurobehavioral development in mammals. In particular, milk has been recognized by developmental psychobiologists as an ecologically relevant sensory stimulus and should be viewed by clinicians as more than a source of nutrition in early human development. Gaining access to and processing milk during suckling serves as a primary focus of activity in the newborn. Because the rat fetus lacks prior exposure to milk or other suckling stimuli, it provides an excellent model system for investigating the development of milk-related responses. Fetal exposure to milk results in a cascade of behavioral, physiological and neurochemical consequences. Milk-induced activation of the endogenous opioid system plays an important role in reorganizing fetal motor activity, altering sensory responsiveness and supporting associative learning in the fetus. Subtle changes in contextual stimulation alter the ability of milk to engage different neurochemical systems. These findings suggest that the infant's first experiences with milk and other suckling stimuli may have lasting consequences for neurobehavioral development. □ *Fetus, milk, neurobehavioral development, newborn, opioids, plasticity, suckling*

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Milk produced by the lactating mother and the behavior expressed by the infant to gain access to milk is a central focus of early postnatal life in most mammals. A typical behavioral sequence involves motor activity that brings the infant in the proximity of the breast, orientation towards and attachment to the nipple, rhythmic movements of the head, mouth and tongue that stimulate milk availability and withdraw milk from the nipple, ingestion of milk and disengagement from the nipple and general quiescence of motor activity after milk consumption (1). This sequence of milk-related activity, which is referred to as nursing in humans and suckling in other mammals, is an important source of behavioral and physiological regulation in the mother–infant dyad (2, 3). Infant behavior during suckling has direct influences on maternal physiology, such as stimulating maternal neuroendocrine systems that function to sustain lactation and subserve maternal behavior in many species. Suckling also has the indirect effects of promoting episodic contact between the mother and infant and entraining maternal care-taking activity. Sensory experience with milk influences many neurochemical systems in the infant, including the endogenous opioid and dopamine systems (4). Exposure to milk also may serve to modulate behavioral state and infant attention, which can directly or indirectly influence early sensory responsiveness and learning. In a variety of mammals, experience with mother's milk and the suckling context has been documented to influence maternal, kin and species recognition, adult mate choice and reproductive behavior, and the development of dietary preferences (5). For these reasons, milk has been recognized as an ecologically relevant sensory stimulus by the developmental psychobiologist and should be viewed by the clinician as more than a source of nutrition in early human development.

Much of the recent evidence concerning the role of milk in regulating infant behavior and physiology derives from studies of non-human mammals. Research involving animal models does not necessitate the attempt to duplicate the human situation, but permits application of experimental and technical tools that can identify general issues and outline processes of behavioral development. In particular, research on non-human animals permits the use of true experimental designs in which subjects are assigned randomly to control and experimental groups and the application of experimental techniques (including invasive procedures and pharmacological manipulations) to tease apart the mechanisms of behavioral change. Findings obtained from animal research can suggest specific hypotheses and studies that can be addressed in clinical situations with human subjects.

The animal model discussed in this report is the rat fetus in vivo. Experimental access to the fetal rat is permitted by applying surgical techniques that result in spinal anesthesia in the pregnant rat, externalization of the uterus and fetuses into a physiologically supportive fluid medium and measurement of behavioral variables in individual fetal subjects (6). Fetuses prepared in this manner may be viewed directly by the experimenter, providing the opportunity to categorize and score fetal behavior in real time or they may be videotaped for later slow-motion or frame-by-frame analysis of action sequences. The direct access afforded by these techniques also enables the experimenter to manipulate the sensory or biochemical environment of fetal subjects through controlled presentation of tactile or chemosensory stimuli or administration of pharmacological agents. These procedures have provided a window on prenatal development that has contributed to a new conception of the mammalian fetus as an active organism that resides within and is responsive to changes in a unique environment (7, 8). In particular, prenatal behavioral study has documented that the fetal rat can express organized motor responses to stimuli that are relevant to the developmental ecology of the prenatal or neonatal periods.

Although the fetus is not exposed to milk before birth, investigation of fetal responses to milk offers a number of experimental advantages. Fetal subjects can be studied at different gestational ages with different degrees of neural and behavioral development, yet the experimenter can be certain that all subjects are exposed to milk for the first time, providing control over the sensory experience of subjects. Fetal study also permits the conduct of experimental protocols without removing the subject from the physiological regulatory systems provided by the mother and the placenta. Study of altricial neonates often necessitates isolating infants to prevent behavioral interference that can result from normal care taking by the mother. Yet the mother is an important source of behavioral and physiological regulation for the infant; isolation from the mother can also produce unwanted experimental effects on infant nutritional, thermal, hormonal and behavioral state regulation. Because the fetal subject remains attached via the umbilical cord to the placenta within the uterus, physiological homeostasis is maintained without behavioral interference by the mother. Behavioral study of the rat fetus in vivo thus provides a means for controlled experimental investigation where ecologically relevant sensory stimuli are used to assess the integrated output of the developing nervous system.

Behavioral effects of milk in the rat fetus

Rat fetuses are capable of detecting a small volume of milk infused directly into the oral cavity, distinguishing this biologically important fluid from other chemosensory stimuli and expressing organized changes in sensory and motor behavior in response to milk. Because of its similarity in composition to mature rat milk, bovine milk (light cream) is the standard type of milk used in studies of suckling behavior in developing rats. On day 21 of gestation (E21, approximately 8–12 h before birth), a single 20-μl intraoral infusion of bovine light cream initiates a sequence of effects on the motor behavior of rat fetuses. The initial response of the fetus to milk infusion consists of a brief episode of mouth movements. Over a period of several minutes, mouthing and other general movements are replaced by activity involving the rear limbs. The selective increase in rear-limb activity culminates 3–5 min after infusion in the stretch response, a stereotypic action pattern that involves dorsiflexion of the back and caudal extension of the rear limbs. The fetal stretch response is very similar in form to the behavior expressed by newborn rats on milk let-down at the nipple, but is expressed on the fetus's first exposure to milk (9).

A brief experience with milk also affects physiological variables in the fetus, some of which are related to behavioral state organization. For example, heart rate in the E21 rat fetus typically exhibits episodes of high variability. Milk results in reduced heart rate variability that persists for several minutes after infusion. The period of stable heart rate is interrupted in some fetal subjects by a single, brief deceleration in heart rate; the return to baseline levels following this bradycardia is associated with the occurrence of the stretch response (4) and may be indicative of a transition between states. An infusion of milk also has effects on the form and temporal patterning of motor activity that can persist for up to 30 min. Different measures of motor behavior that vary independently in unmanipulated fetal subjects become more highly correlated and synchronized following milk infusion, suggesting that exposure to milk promotes changes in fetal behavior that may reflect underlying behavioral state organization (10).

Unmanipulated fetal rats show qualitatively different behavioral responses to other types of sensory stimuli, including infusion of chemosensory fluids (e.g. lemon odor extract) or tactile stimulation (e.g. application of a stiff bristle to the area around the mouth). Presentation of a perioral tactile probe, for example, typically evokes a facial wiping response in fetal subjects that involves contact between one forelimb and the face (11). Exposure to milk alters fetal responsiveness to perioral stimulation and reduces the expression of facial wiping behavior: whereas 80% or more of control fetuses exhibit the wiping response to the probe, less than 5% of fetuses express facial wiping to a perioral stimulus 1 min after milk infusion. The effect of milk on cutaneous responsiveness is transient, disappearing 3–5 min after infusion.

Changes in motor activity and responsiveness to sensory stimulation involve the endogenous opioid system

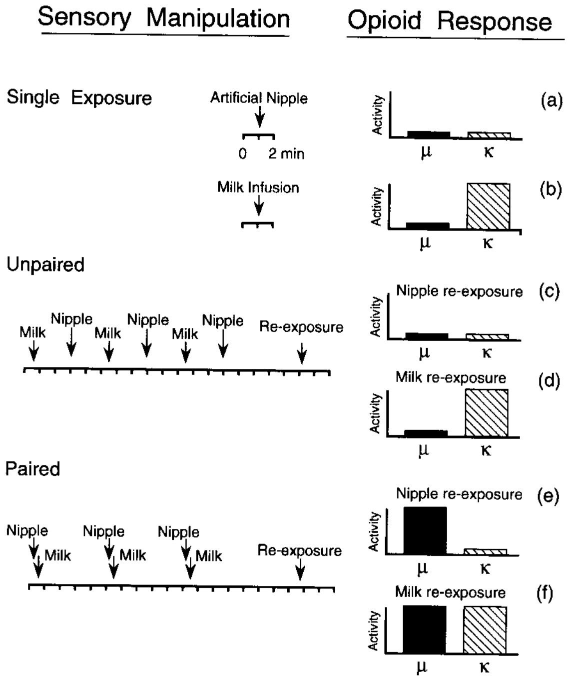

Fig. 1. Effects of sensory manipulations of suckling stimuli on endogenous opioid activity in the rat fetus. Fetuses exposed to an artificial nipple (a) show no evidence of increased opioid activity at either mu (μ) or kappa (κ) receptors. A single intraoral infusion of milk results in activation of the kappa system (b). After fetuses have received unpaired presentations of the artificial nipple and milk, re-exposure to the nipple has no influence on opioid activity (c) and milk continues to engage the kappa system (d). However, after receiving three paired presentations of the nipple and milk, re-exposure to the artificial nipple promotes conditioned activation of the mu opioid system (e), while re-exposure to milk after conditioning results in activity at both mu and kappa receptors (f). These findings provide evidence that exposure to suckling stimuli has different neurochemical effects that depend upon the subjects past experience with milk, the artificial nipple and the temporal configuration of these biologically relevant stimuli.

of the fetus (Fig. 1(a–f)). The transition to rear-limb motor activity, expression of the stretch response and reduction in responsiveness to perioral cutaneous stimulation that typically occur after milk infusion can be blocked by administration of naloxone, a non-selective antagonist of opioid receptors. The opioid system comprises a number of distinct classes of receptors and their associated endogenous ligands, including the mu and kappa systems, that appear to develop during the prenatal period. Administration of drugs that are selective for mu or kappa receptors has provided evidence that changes in fetal behavior evoked by milk involve activity at kappa receptors (Fig. 1b). For example, administration of U50,488 (a selective kappa agonist) results in changes in motor activity, organization of fetal movements, expression of the stretch response to non-milk fluids and reduced sensory responsiveness that resemble the effects of milk infusion. Conversely, norbinaltorphimine (BNI, a selective kappa antagonist) blocks the behavioral effects of milk; fetuses treated with BNI do not exhibit a stretch response to milk and show high levels of facial wiping in response to perioral cutaneous stimulation. Comparable effects are not evident after administration of mu agonists and antagonists. Experimental findings such as these suggest that the fetus's first experience with milk results in increased activity in the kappa opioid system, which has multiple effects on fetal behavior and physiology (4).

The behavioral consequences of infusing bovine milk to the fetal rat appear to be highly specific to this fluid. Intraoral infusion of other chemosensory stimuli, including isotonic saline, sucrose, lactose or vegetable oil, is ineffective in evoking distinctive behavioral responses or changes in cutaneous sensitivity in fetal subjects. It is interesting that infusion of soy or milk-based human infant formula (Similac, Ross Laboratories, Columbus, OH, USA or ProSobee, Mead-Johnson Nutritionals, Evansville, IN, USA) is also ineffective in promoting the behavioral effects evoked by bovine milk. Novel olfactory stimuli, such as lemon or mint, consistently elicit behavioral activity and action patterns such as facial wiping, but do not produce the same behavioral changes as milk. Only one other stimulus—dimethyl disulfide (DMDS)—has been identified that exerts milk-like effects on fetal behavior. Intraoral infusion of a low concentration of DMDS promotes rear-limb activity and reduces fetal responsiveness to perioral stimulation. Both of these behavioral effects are dependent on kappa opioid activity and can be reversed by selective antagonism of kappa receptors (12). DMDS is noteworthy because it is present in the saliva of the newborn rat pup. Immediately after birth, the first attachment of newborn pups to nipples is promoted by two factors: the odor of amniotic fluid deposited by the mother on her ventrum during parturition and the tactile qualities of the nipple itself (3). During the first suckling episode, pup saliva is deposited on nipples and the odor of DMDS helps to direct subsequent nipple attachments. The effects of milk and DMDS on behavior and opioid activity are evident in the fetus, indicating that they do not depend on specific experience with these stimuli. The ability to evoke suckling responses in the fetus with naturally occurring chemosensory stimuli provides an experimental tool for studying the sensory and neurochemical determinants of behavioral development in the newborn.

Implications for the first suckling episode

Suckling behavior in mammals is a highly organized activity that consists of a sequence of events. After attaching to the nipple, infant rats engage in rhythmic mouthing movements (sucking), fore-limb movements that press against the maternal ventrum (treadling) and rear-limb movements against the substrate (pushing) that appear to maintain mouth–nipple contact. Sucking and treadling activity provide tactile stimulation to the ventrum of the lactating female, which eventually triggers the release of oxytocin and elicits a milk let-down response. Milk let-down is associated with distension of the nipples, which evokes a change in pup behavior. Pups perform a stretch response, which appears to facilitate withdrawal of milk from the nipple by the pup. Immediately after milk ingestion, pups typically disengage from the nipple, exhibit a brief increase in motor activity and reattach, often to a different nipple ("nipple-shifting"), to re-initiate the suckling sequence.

Many of the same behavioral events are evident in rat fetuses that receive an intraoral infusion of milk, including mouthing, rear-limb activity and stretching. One of the most notable differences in the behavior of infant rats at the nipple and rat fetuses after infusion is the timing of events relative to the moment of milk delivery (4, 13). In the rat pup, rhythmic mouthing and limb activity occur after nipple attachment, but before milk let-down; in the fetus, mouthing and rear-limb movements are evoked by milk infusion. In the pup, the stretch response occurs within seconds of milk let-down; in the fetus, stretching occurs after a cascade of other behavioral changes and can be delayed for 3–5 min after infusion. Because many of the behavioral changes evoked by milk in the fetus, including the stretch response, are dependent on opioid activity, differences in the timing of events in the neonatal suckling sequence imply that pups exhibit increased opioid activity before they are exposed to milk. Differences in the timing of the suckling sequence in the fetal and infant rat imply discontinuity in the behavioral effects of milk between the prenatal and postnatal periods. However, it should be noted that the information available on the behavior of infant rats is drawn almost entirely from studies of pups at least 24 h after birth; little is known of the behavior of newborn pups during the first suckling episode. Because newborn pups can receive dozens of individual milk let-downs per day, the suckling sequence may be considerably modified through experience with the nipple, milk and other stimuli present in the suckling situation.

If mouthing, fore-limb treadling, rear-limb pushing and the prompt occurrence of the stretch response are promoted by endogenous opioid activity before milk let-down, then what might be responsible for activating the opioid system? One possibility is that newborn rats exhibit classical conditioning of opioid activity during the first few experiences with milk at the nipple. Sensory cues present in the suckling situation may serve as conditioned stimuli (CS) that are reliably associated with milk let-down (the unconditioned stimulus (US)) and evoke opioid activity and a sequence of behavioral responses (the unconditioned response (UR)). Over a series of let-downs, the CS provides a signal that predicts the imminent availability of milk, eliciting a conditioned response (CR) before the pup actually receives milk. Studies of learning in infant rats have demonstrated that milk can support both classical conditioning and appetitive learning (14). Similarly, pharmacological treatments that promote opioid activity can serve as a US to support conditioning in young animals (15); re-exposure to a CS paired earlier with opioid activation results in conditioned activity in the opioid system. Indeed, the fact that milk or opioid drugs can support learning in young animals has led to the suggestion that the reinforcing properties of milk derive from the ability of milk to evoke opioid activity.

The classical conditioning hypothesis yields a number of testable predictions concerning the learning capacities of fetal and neonatal subjects and the early organization and development of suckling behavior. First, experimental promotion of opioid activity before exposure to milk should alter the timing of behavioral responses in subjects, such as fetuses, that lack prior suckling experience. Second, the hypothesis implies that newborn rats, and most likely term fetuses, can exhibit classical conditioning with a small number of learning trials. Third, conditioning should be promoted by using milk as the US. Fourth, conditioning with a milk US should be evident with a CR that includes activation of the endogenous opioid system. Each of these predictions have been investigated in the rat fetus. Administration of selective agonists of the kappa opioid system, such as U50,488 or U69,593, are effective in promoting behavioral changes that are similar to the responses evoked by milk. Agonist-treated fetal subjects exhibit a disproportionate increase in rear-limb movements, a reduction in sensitivity to a perioral cutaneous stimulus and express the fetal stretch response, with a significantly shorter latency than evoked by milk, after infusion of non-milk stimuli such as saline or lemon (4, 16). Milk infusion can also support classical conditioning of opioid activity in the fetal rat. A series of three pairings of a CS (intraoral infusion of sucrose) with a milk US results in a conditioned decrease in perioral cutaneous sensitivity after re-exposure to the CS. Administration of opioid antagonists after the series of CS–US pairings, but before re-exposure to the CS, has confirmed that the conditioned change in cutaneous sensitivity is the result of opioid activity evoked by the CS (5). These conditioning experiments complement other studies of learning in the rat fetus and demonstrate that fetuses can exhibit conditioned changes in opioid activity after only a few experiences with a milk US. Because the timing of milk-evoked responses can be shifted with opioid treatments and fetuses can exhibit conditioned changes in opioid activity, it is plausible that differences in the organization of suckling behavior in the fetus and infant rat are due to learning that occurs during the first few suckling episodes.

Plasticity in fetal responses to milk

Many of the behavioral elements of suckling behavior have been referred to as simple reflexes (e.g. sucking, rooting, stretching). Reference to these activities as reflexes implies a high degree of stereotypy and minimal specificity in underlying neural control. The functional expression of suckling behavior is crucial to the health and continued growth of the infant, yet suckling occurs during a period of development associated with rapid changes in sensory systems, motor systems, central nervous system structure and environmental features that contribute to early learning. Rather than representing "hard-wired" circuits that must be maintained in the face of these changes, recent evidence suggests that the mechanisms that govern suckling behavior change considerably over the course of development. Plasticity in suckling behavior, which may be mediated by experience with milk, is likely to be an important factor that contributes to the rapid development of the nervous system and behavior during the neonatal period.

Some of the experimental findings summarized above indicate that brief exposure to milk is sufficient to activate the endogenous opioid system of the fetus or newborn rat (Fig. 1b). Experience with milk also has effects on other neurochemical systems, including the dopamine system. Measurement of dopamine release in perinatal rats by different techniques has suggested that milk infusion results in changes in the regulation of the dopamine system. Further, the effects of infusion on dopamine activity change rapidly over a series of experiences with milk. Milk-induced changes in dopamine activity may also be involved in the ability of milk to engage the endogenous opioid system of the fetal rat. Pharmacological studies conducted with fetal subjects have established that changes in dopamine activity evoked by milk infusion promote activity in the kappa opioid system (4). Functional interaction between the dopamine and opioid systems, triggered by infusion of milk, develops rapidly over the last few days of gestation and is evident at term, at the time of the newborn's first experience with milk in the suckling context.

The prompt response to milk infusion in unmanipulated subjects consists of a brief bout of mouthing behavior. In adult animals, mouthing is thought to be involved in stimulus sampling and is an important early link in a chain of events leading to ingestion. Although the amount of mouthing evoked by milk demonstrates that fetuses can distinguish this fluid from other chemosensory solutions, the expression of mouthing to milk can be influenced by variables both internal and external to the subject. For example, pharmacological manipulation of activity in neurochemical systems, such as the opioid or dopamine systems, can influence the number of mouthing movements evoked by milk. Sensory events that precede infusion also influence the mouthing response to milk. Rat fetuses exhibit a variety of behavioral responses when an artificial nipple is presented to the perioral area, including fore-limb treadling, mouthing, licking and oral grasping of the nipple (17). Presentation of the artificial nipple 15 s before intraoral infusion has the effect of increasing the number of mouthing movements elicited by milk. Other aspects of the suckling sequence also appear to be influenced by the state of the subject at the time of exposure to milk. Some fetal rats that receive an intraoral infusion of milk ultimately express a stretch response, whereas others do not. Close examination of fetal behavior in these two groups during the minute prior to infusion has suggested that the pattern of motor activity at the time of infusion is predictive of whether the stretch response will be expressed. Although all fetuses showed similar initial responses to milk infusion, subjects that showed decreasing activity over the minute before infusion ultimately exhibited the stretch response, whereas fetuses that showed increasing activity before infusion failed to stretch. Together, these examples of mouthing and stretching imply that fetal responses to milk are not rigidly constrained, but can be modified by environmental conditions and levels of behavioral and neural activity at the time of exposure to this biologically relevant fluid.

Exposure to milk and stimuli associated with milk are events that are involved at many different levels of behavioral and neural regulation during early development. Milk can activate different neurochemical systems in the fetus and neonate. Sensory manipulations prior to infusion can alter behavioral responsiveness to milk and thus are likely to modify the way milk is processed initially. Finally, most of the important effects of experience during the neonatal period occur in the context of suckling, immediately before, during or after exposure to milk. These facts suggest that exposure to milk may serve as a focal event that mediates the effects of recent sensory experience on the central nervous system. This hypothesis has gained recent experimental support from studies of associative learning in the fetal rat (5). Fetuses that receive a series of paired presentations of an artificial nipple (CS) followed by intraoral infusion of milk (US) show altered sensory responsiveness on representation of the nipple. Associative learning supported by using milk as a reinforcer results in conditioned activation of the endogenous opioid system and a consequent reduction in perioral cutaneous sensitivity when subjects are re-exposed to the artificial nipple CS (Fig. 1c). An unexpected finding of this research is that the CS does not evoke activity in the same opioid system as the US. Initial infusions of milk promote opioid activity at kappa receptors, but re-exposure to the artificial nipple after pairings with milk results in activity in the mu, not kappa, opioid system (Fig. 1c). The ability of the CS to elicit a conditioned opioid response in the mu rather than the kappa opioid system is dependent upon the contiguous presentation of the artificial nipple and milk during conditioning trials. Control fetuses that have equal exposure to both the nipple and milk during three trials, but receive presentations of these stimuli separated from one another, fail to exhibit conditioned changes in cutaneous sensitivity or opioid activity after re-exposure to the nipple (Fig. 1e). Therefore, the temporal relationship between stimuli during the fetus's first experiences with milk and the nipple dictate subsequent behavioral and neurochemical consequences.

In light of other studies of learning during the perinatal period, it may be unremarkable that fetal rats can learn quickly an association between a stimulus that mimics an important feature of the postnatal suckling environment (the nipple) and another stimulus that has important consequences for neonatal biology (milk). However, another surprising finding to emerge from this research is that associative learning also affects the behavioral and neurochemical consequences produced by milk. Fetal subjects that receive a series of three nipple–milk pairings continue to exhibit increased opioid activity upon a fourth infusion of milk. However, this milk-evoked opioid response is not blocked by administration of either a kappa or a mu antagonist. Rather, it is necessary to administer antagonists of both kappa and mu receptors to reverse the effects of milk on cutaneous sensitivity. This observation indicates that milk, after its presentation with another stimulus (the nipple), promotes activity in both the mu and kappa opioid systems (Fig. 1d). Similar to the basic conditioning effect, the altered opioid response of milk is evident only in fetuses that receive contiguous presentations of the nipple and milk, and not in control subjects that receive unpaired presentations of these stimuli (Fig. 1f). The implication of this fetal research is that subtle changes in sensory stimuli at the time of initial experiences with milk can alter the ability of milk to engage different neurochemical systems. It implies further that long-term consequences for neurobehavioral development may accrue from the availability and juxtaposition of stimuli in relation to milk during the neonatal period.

Relevance for the human newborn and preterm infant

The evidence from animal experimentation clearly indicates that the initial exposure to milk is responsible for a number of behavioral, physiological and neurochemical effects in both the fetus and neonate. Although invasive procedures, such as administration of selective receptor agonists and antagonists, is not feasible with human subjects, available information suggests that experience with sapid fluids, such as milk, has broad ranging behavioral consequences in the human infant also. Nursing at the breast is well known for its calming effects on human infants. Delivery of a small volume of sucrose into the mouth of a 1–2 day-old human newborn promotes calming and reduces crying after a heel lance (used for blood collection). The calming effect of sucrose persists for several minutes, suggesting that it may be mediated by activation of the opioid system, as has been demonstrated in infant rats (3). A parsimonious way to view the reduction in infant responsiveness is that sucrose or milk delivery results in opioid activity that is associated with a change in behavioral state. In other words, sensory-evoked opioid activity results in a reorganization in attentiveness and the way the infant interacts with its environment (4).

If exposure to milk and its neurobehavioral consequences can be generalized to human infants, then the experimental results of studies with fetal rats point to early feeding interactions at the breast as a proximal mechanism for promoting behavioral and neural development in the newborn. Not only may exposure to milk be a critically important event for the newborn, but the context in which this fluid is first experienced may alter trajectories for neural development, with lasting consequences for behavior. This importance of milk and early feeding interactions may be most evident in the NICU, which houses premature and small-for-date infants that must be sustained on artificial nutritional regimens. A common practice in the clinical care of preterm infants is gavage feeding, by which specially formulated diets are introduced directly into the stomach, bypassing the sensory and motor systems normally engaged during nursing behavior. Another group that exhibits atypical early feeding includes high-risk infants that have been exposed during gestation to drugs of abuse, such as cocaine or heroin, that exert their effects through alterations in the dopamine or opioid systems. Cocaine-exposed infants, for example, have been reported to exhibit deficits in feeding behavior and behavioral state organization (18). Variation in how infants are exposed to milk is common, even in unremarkable full-term newborns: infants may be breast fed or bottle fed with milk expressed by the lactating mother or with milk- or soy-based infant formula. Although a number of studies have sought to identify developmental differences among infants in these groups, few have addressed possible mechanisms that lead to altered developmental end-points.

Data obtained from animal models have suggested that alterations in the sensory contexts in which milk is first experienced, alterations in the composition of the diet during early feeding interactions or alterations in the neurochemical systems that are activated during early feeding, may result in different patterns of behavioral and neural development. This possibility raises a number of questions for human infants in the clinical situation. Are milk- or soy-based infant formulas as effective as mother's milk in engaging neurochemical and behavioral systems in the infant (because they appear to be ineffective in the fetal rat (4))? Does prenatal exposure to drugs of abuse alter the way biologically relevant sensory stimuli associated with nursing activate the nervous system of the infant? How persistent are the behavioral and neurochemical effects produced by the infant's first experiences with milk? Do gavage feedings that provide a source of nutrition for preterm infants engage orosensory systems normally active during feeding, and if not, do they result in different consequences on exposure to milk or alternative diets when more normal feeding is initiated? If any of these questions are answered in the affirmative, then clinicians will be faced with the additional problem of designing therapies to correct developmental trajectories that have been altered through the infant's first experiences with milk or alternative diets.

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