Differential Calming Responses to Sucrose Taste in Crying Infants With and Without Colic

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ABSTRACT. Background. Colic is a behavioral syndrome of early infancy of unknown etiology whose core symptom is increased crying. Both clinical anecdotal descriptions and controlled observations converge in suggesting that a defining characteristic of the crying behavior is the longer duration of the crying bouts, especially during the second month of life when colic is at its peak. This implies that, once infants with colic begin crying, they do not calm as well as infants without colic. To investigate this difference objectively, we used response to sucrose taste as a probe of colic-normal differences in regulation of crying for three reasons. First, sucrose taste has been shown to be a potent regulator of crying in human newborns. Second, convergent evidence from studies in both nonhuman and human infants suggests that sucrose calming reflects the function of central distress regulatory systems that are opioid-dependent. Third, effectiveness of sucrose calming diminishes in normal infants by 4 to 6 weeks of age, consistent with the developmental increase in crying duration common to infants with and without colic. Consequently we predicted that, if the regulation of crying by sucrose taste is relevant to the crying of infants with colic, calming responses to sucrose taste should be less effective in 6-week-old infants with colic compared with those without.

Objectives. To investigate the clinical observation that infants with and without colic differ in their ability to regulate their crying behavior, our primary objective was to determine if there were differential crying responses to intraoral sucrose tastes (relative to water) in crying infants with and without colic. Based on previous studies of calming responses to sucrose taste, it was predicted that sucrose-specific calming before a feeding would be less effective in infants with colic than in those without. A secondary and more exploratory aim was to assess calming responses to sucrose (relative to water) on spontaneous crying after a feed in both groups.

Methods. Nineteen infants meeting modified West's criteria for colic were compared with 19 age- and sex-matched normal infants without colic in a within-subject controlled observation of calming and mouthing responses to both intraoral sucrose and water tastes. Both before and after two feedings on the same day, each infant was observed until she or he cried continuously for 15 consecutive seconds, at which time three 250-μL tastes of 48% sucrose solution or sterile water were administered 30 seconds apart, and infant responses videotaped. Outcome measures derived from second-by-second coding of the videorecordings were percent time crying per minute for 4 minutes and percent time mouthing per minute for 2 minutes after stimulus administration.

Results. As predicted, the crying of infants with colic was less affected than the crying of infants without colic after sucrose but not water tastes before feedings. After feedings, the crying of infants with colic was less affected than the crying of infants without colic for both sucrose and water tastes, and sucrose was more effective than water in both groups of infants. These calming differences could not be attributed to differences in mouthing responses because the calming effects persisted after mouthing ceased, and there were no differences in mouthing responses between groups before or after feedings.

Conclusions. As in newborns, a significant calming effect of sucrose taste that persisted beyond the cessation of mouthing could be elicited in crying 6-week-old infants, but it required a stronger taste stimulus to do so. As predicted, infants with colic were less effectively calmed by sucrose taste than infants without. These differential effects could not be accounted for by differences in crying when the stimulus was applied or by differences in mouthing behavior. Before a feed, these differences in calming were specific to sucrose taste. After a feed, infants with colic were calmed less by both sucrose and water. These results imply that a defining individual difference of infants with colic is that they are less able to regulate crying once started and that the regulatory effects of sucrose taste are reduced in infants with colic. In light of evidence that sucrose-induced calming may be mediated by central opioid-dependent systems, the reduced calming effectiveness may be indexing a functional difference in a central opioid-dependent calming system in infants with colic. Pediatrics 1999;103(5). URL: http://www.pediatrics.org/cgi/content/full/103/5/e68; colic, crying, sucrose, taste, mouthing.

Although there is disagreement as to details,1 classic colic syndrome is characterized by crying that: 1) increases ~2 weeks after birth, peaks during the second month, and resolves in the third or fourth month; 2) clusters in the late afternoon or evening; 3) is resistant to soothing, including feeding; 4) may be associated with behaviors of fist clenching, back arching, legs flexed over the abdomen, and a facial grimace (pain facies); and 5) that is unpredictable (paroxysmal).23 Whether and, if so, how often this behavioral syndrome of infant colic is
attributable to a pathologic process remains obscure. Organic disease can present as colic syndrome, but based on current evidence, organic disease probably accounts for <10% of cases depending on the definition and the clinical setting. Analogously, although some cases may be accounted for by preexisting personality disorders in the parents, postpartum depression, or inappropriate and nonoptimal caregiving, most infants with subsequent colic have mothers who do not differ in third trimester emotional lability (anxiety and depression) and who demonstrate the same sensitivity and affection with their infants as controls. Consequently, it is equally unlikely that most cases of colic syndrome can be accounted for in this way.

If traditional pathologies are not implicated in most of these cases, those that are clinically unexplained could be infants whose crying is at the upper end of the spectrum of crying of normal infants. Developmental studies suggest that all of the defining clinical characteristics are also typical of crying in infants during normal behavioral development, but that they are exaggerated in infants with colic syndrome. Wessel and his colleagues noted in 1954 that "the time distribution and frequency of diurnal regularity are similar for the mild fussing periods of the ‘contented babies,’ and for the more prolonged periods of the ‘fussy infants.’" Subsequently, the early peak crying pattern and evening clustering were systematically described in normal infants by Brazelton and replicated in most subsequent samples of infants in Western societies. Similar features were also described in !Kung San hunter-gatherers and infants in Manali, India, despite radically different caregiving styles, and in age-corrected preterm infants whose postnatal experience is longer. These findings suggest that the early crying curve may be a behavior universal of infancy, rather than a defining characteristic of a distinct clinical syndrome. Further, St. James-Roberts et al demonstrated that unsoothable crying bouts were not specific to infants with colic, but that they occur in proportion to the overall amount of crying and fussing that infants do regardless of clinical grouping. Similarly, infants with colic exhibit more facial activity and pain facies, but these patterns are also common in infants without colic. Consequently, the defining characteristics of clinical colic syndrome are continuous with the crying of normal infants, rather than distinctively different. In that case, explanations implicate a central opioid-dependent calming system. Consequently, soothed crying and calming responses to sucrose provide a particularly appropriate test of colic-normal differences for a number of reasons. First, sucrose-induced calming provides measures of the ability to regulate distress in already crying infants. This permits tests of behavioral soothing under experimental control in an ethically acceptable way in a relatively simple paradigm. This is particularly important methodologically because differences in crying duration are defining characteristics of the groups being compared. Consequently, soothing differences in observational studies could be confounded by the fact that crying is more likely to occur in the excessive crying group. Second, convergent evidence from nonhuman infant mammals and two clinical samples of human infants suggest that sucrose calming implicate a central opioid-dependent calming system. Consequently, colic-normal differences might index putative central mechanisms underlying the manifest differences in crying behavior. Third, previous studies in normal infants indicate that the effectiveness of sucrose calming diminishes by 4 to 6 weeks of age. This is consistent with the developmental increase in crying duration common to infants with and without colic as previously described.

Our primary aim was to assess calming responses to sucrose taste (relative to water) on spontaneous crying occurring before a feeding. This standardizes...
the stimulus situation for both colic and control groups, and controls for any possible effects of recent feeds. We predicted that sucrose would be less effective in infants with colic, but that there would be no difference in response to water. A secondary and more exploratory aim was to assess calming responses to sucrose relative to water on spontaneous crying occurring after a feed. Predictions as to likely effects were not clear for the postfeed response. On the one hand, it is a common clinical observation in infants with colic that they are more likely to cry postfeed. This implies that the feeding would be ineffective and that sucrose calming would be unchanged for the infants with colic. In a previous study in normal 6-week-old infants, sucrose-water differences in calming were no longer present after a feeding. Consequently, sucrose-induced calming in normal infants might become less effective, and therefore more similar to, that in infants with colic. On the other hand, in a controlled clinical observation, there were no significant differences in postfeed crying in infants meeting Wessel’s criteria for colic.

If this is the case, colic-normal differences might still persist after the feed. Consequently, no clear prediction of outcome could be made a priori concerning differences in sucrose-induced calming after a feed.

**METHODS**

**Overall Design**

The study was designed as a controlled colic versus normal between-groups comparison with a sucrose versus water within-subjects comparison of calming in response to introral sucrose taste. Infants were considered to have colic if they met modified Wessel’s criteria for clinically significant crying. Infants were tested in their homes. They were randomized in blocks of 4 to receive sucrose or water tastes before and after two consecutive feedings in one of two orders: sucrose before the first feed, water after the first feed, water before the second feed, sucrose after the second feed; or water before the first feed, sucrose after the first feed, sucrose before the second feed, water after the second feed. Because sucrose stimuli are less effective in older infants than in newborns, the taste stimuli were more concentrated and more frequent than those provided in our original study. The taste stimuli were 250 mL of 48% sucrose solution or sterile water given through the nipple 30 seconds apart. As in our previous study, infants were observed until a sustained cry occurred, defined as continuous crying for at least 15 consecutive seconds. At that point, the assigned liquid (sucrose solution or sterile water) was delivered to the anterior portion of the tongue by pipette and the infant was observed for up to 6 minutes. For ethical reasons, the infant was picked up and soothed before 6 minutes if it cried continuously for 2 minutes. The study was undertaken with the approval of the Institutional Review Board of the Montreal Children’s Hospital.

**Study Participants**

Forty-three infants were recruited from two primary care pediatric practices and from the newborn clinic at Ste Justine’s Hospital. Eligible infants with colic (n = 20) were those up to 7 weeks of age who had uncomplicated prenatal and perinatal histories, a normal postnatal course, and whose parents presented with a primary complaint of crying seen as a problem but without evidence of other illness accounting for the complaint. Control infants (n = 23) were eligible if they met the same criteria, but did not complain of colic or excessive crying. When referred to the study, they were telephoned by a research assistant who described the study in detail and obtained oral parental consent. Only control infants who matched a previously recruited colic infant by sex and age (within 7 days) were recruited.

**Procedure**

A home visit was arranged to include two afternoon and/or evening feedings on the same day to maximize the likelihood of capturing any potential time of day effects. Research assistants arrived one-half hour before an expected feeding. During the visit, written informed consent was obtained, demographic information gathered, prefeed and postfeed responses to sucrose and water around the feedings observed and videotaped, and the mother provided with a 1-week diary. Use of the diary was demonstrated, accompanied by a written set of instructions. The diaries were mailed to the laboratory 1 week later in a self-addressed stamped envelope or picked up by a research assistant.

**Taste Testing**

The infant’s diaper was checked, and changed if not clean. The infant was then placed in a bassinet on the floor. The bassinet included a mirror placed to the right of the infant’s head. A rolled blanket was tucked on the infant’s right side so that the infant was supine but tilted slightly away from the mirror. A Panasonic (Secaucus, NJ) VHS model AG 170 videocamera was positioned ~6 feet away to the left side of the infant and adjusted to provide an optimal view of the infant’s facial features and hands. The mirrored reflection provided a two-dimensional view permitting more accurate judgments of the occurrence of facial grimaces and mouthing, and reducing blind spots or out-of-view judgments.

Baseline recordings of up to 40 seconds (mean ± 1 standard deviation) were obtained for all but two sessions. The infant was then observed for up to 15 minutes. After a sustained 15 seconds of crying, the infant received 250 mL of 48% sucrose solution (w/v) or sterile water three times 30 seconds apart for a total of 90 seconds. The stimulus situation was a sustained 15 seconds of crying, the infant received 250 mL of 48% sucrose solution (w/v) or sterile water three times 30 seconds apart for a total of 90 seconds. The stimulus situation was a sustained 15 seconds of crying, the infant received 250 mL of 48% sucrose solution (w/v) or sterile water three times 30 seconds apart for a total of 90 seconds.

**Videotape Analysis**

The videotapes were analyzed second-by-second for crying and mouthing by coders blind to the infant’s group assignment and to
TABLE 1. Characteristics of Study Sample*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Colic (n = 19)</th>
<th>Noncolic (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (days)</td>
<td>38 ± 4</td>
<td>41 ± 5</td>
</tr>
<tr>
<td>Parity (first born)</td>
<td>6 (32%)</td>
<td>6 (32%)</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>8:11</td>
<td>8:11</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3374 ± 525</td>
<td>3459 ± 466</td>
</tr>
<tr>
<td>Feeding type (breastfeeding only)</td>
<td>10 (56%)</td>
<td>11 (61%)</td>
</tr>
<tr>
<td>Pacifier use</td>
<td>8 (44%)</td>
<td>5 (28%)</td>
</tr>
</tbody>
</table>

| Parent                         |               |                   |
| Age (y)                        |               |                   |
| Mother                         | 31 ± 3        | 30 ± 5            |
| Father                         | 33 ± 6        | 33 ± 5            |
| Education                      |               |                   |
| Mother                         | 16 ± 5        | 15 ± 3            |
| Father                         | 16 ± 4        | 15 ± 3            |
| Marital status                 | 19 (100%)     | 16 (89%)          |
| (couples)                      |               |                   |
| Ethnicity                      | 13 (72%)      | 15 (83%)          |
| (white North American)         |               |                   |
| Parental smoking               | 6 (33%)       | 7 (37%)           |
| (at least one parent)          |               |                   |

* Results are mean ± 1 standard deviation or number of infants (percent) with designated characteristic in each group. There were no significant differences for any infant or parent characteristic (all P > .10).

Data Analyses

Crying time was calculated for each infant and expressed as percent time crying per period for the baseline before the sustained cry, the sustained cry 15 seconds before liquid administration, and the postliquid administration period divided into 1-minute segments. Analogous measures of mouthing were also derived.

Because infants were permitted to be picked up after 2 minutes of crying, complete data are missing for 11.3% of the fourth minute and occasionally part of the third minute for some infants. To optimize the sample and description of the time course, two conservative extrapolation rules were used. This was considered justifiable, because infants tend to increase crying after the taste, are unlikely to calm without intervention, and if they do, it is not likely to be because of delayed taste effects. If data were present for 30 seconds or more of the 1-minute bracket, percent time crying was prorated for the remainder of that minute. If more than 30 seconds were missing, then percent time crying (in minute X) was extrapolated from the trend in the previous 2 minutes by the formula: percent time crying in minute X = ([percent time crying in minute X−1]− [percent time crying in minute X−2]) + (percent time crying in minute X−1). These rules were less likely to bias in favor of group differences than substituting group means for missing values. Because the trends were not nearly so clear for mouthing, equivalent extrapolations were not performed, and complete data were available only for 2 minutes. In addition, mouthing responses were not able to be scored in 3 cases (1 normal, 2 colic) before the feed and in 3 cases (all colic) after the feed because of blocked views.

To assess the crying responses, percent time crying measures were first submitted to a condition (colic versus control) × feeding (prefeed versus postfeed) × solution (sucrose versus water) × period (minutes 1–4) overall analysis of variance in which condition was a grouping factor and the other factors were repeated measures. Because there was a main effect for feeding (F(1,36) = 10.6; P < .002) unqualified by any interactions with group, location of group differences were followed-up by further repeated measures analysis of variance for prefeed and postfeed responses separately. Repeated measures data were examined for sphericity, and when present, Greenhouse-Geiser e values were used. As a protection against differences in initial state, all analyses were rerun entering baseline percent time crying values as a covariate, but neither the levels nor the pattern of significance were affected. Because the distributions were occasionally skewed when crying approached 100%, all data were arcsine square root transformed, and the analyses rerun. Again, virtually identical results were obtained, and no results involving groups were affected. Mouthing measures were treated similarly, but included only two periods (minutes 1 and 2).

RESULTS

Before Feed Responses

Crying

Mean percent time crying responses to sucrose and water for both colic and control groups before a feed are shown in Fig 1. By design, infants in both groups cried more than 90% of the time before liquid administration. After water, crying diminished transiently in both groups to ~82% in minute 1 and returned to 99% by minute 3. As expected, percent time crying was reduced in normal infants after sucrose to 40% in minute 1, and then remained reduced at between 64% and 69% for minutes 2 through 4. In infants with colic, however, percent time crying was reduced to 55% but increased to 94% by minute 3.

Consequently, regardless of group, sucrose effectively reduced crying relative to water (solution main effect, F(1,36) = 28.4; P < .001). In addition, there was a significant difference between the responses of the infants with and without colic (group main effect, F(1,36) = 3.95; P = .05). However, the solution effect was different depending on whether the infant did or did not have colic (solution × group interaction, F(1,36) = 6.7; P < .01). This difference was significant in minutes 3 F(1,36) = 10.4; P < .003 and 4 (F(1,36) = 9.7; P < .004), but not in minutes 1 and 2 (both P > .16). It was attributable to more crying after sucrose in infants with colic than without (95% confidence intervals: minute 3 colic 89% to 99% versus controls 48% to 94% time crying; minute 4 colic 92% to 100% versus controls 51% to 87% time crying). There were no
group differences in crying responses after water at any time point.

**Mouthing**

Prefeed mouthing responses are shown in Fig 2. Mouthing responses to both sucrose and water were virtually identical in each group. As expected, mouthing increased in the first minute and then rapidly declined in the second (periods main effect, \( F(1,33) = 110.6; P < .001 \)). Consistent with the increased salience of sucrose, mouthing is greater for sucrose than for water (solution main effect, \( F(1,33) = 22.0; P < .001 \)); however, there is a more rapid decline for sucrose in the minute 2 (periods \( \times \) solution interaction, \( F(1,33) = 11.4; P < .002 \)). There is no significant main effect or interaction with group (all \( P > .53 \)).

**After Feed Responses**

**Crying (Fig 3)**

As indicated previously, the patterns of crying response after a feed were different. Sucrose again effectively calmed infants relative to water regardless of group (solution main effect, \( F(1,36) = 20.8; P < .001 \)). The reduction in crying was greater for infants without colic than for those with, but not as reliable statistically as the effect due to solution (group main effect, \( F(1,36) = 3.3; P = .08 \)). Being an infant with or without colic did not affect the sucrose-water difference in calming (group \( \times \) solution interaction, \( F(1,36) = 0.1; P = .78 \)).

**Mouthing (Fig 4)**

The postfeed mouthing responses were essentially identical with those before the feed. The increased mouthing in the first minute declined significantly in the second minute (periods main effect, \( F(1,33) = 34.6; P < .001 \)), was significantly greater for sucrose than water (solution main effect, \( F(1,33) = 17.2; P < .001 \)), and the decline was greater for sucrose than water (periods \( \times \) solution interaction, \( F(1,33) = 10.1; P < .003 \)). There were no group main effects or interactions (all \( P > .54 \)).

**DISCUSSION**

There are a number of straightforward significant findings. The first is that, regardless of colic status, sucrose tastes applied to the anterior tongue exerted a significant calming effect in crying 6-week-old infants. This was in addition to effects due to contact with a liquid, because the effect was less with a water stimulus. Furthermore, the response pattern was similar to that previously reported in newborns. The calming effect occurred rapidly and was sustained for minutes after cessation of the taste stimulus. Mouthing was elevated in the first minute, but more stimulus bound, decaying quickly in the second minute, consistent with the time course of sucrose removal from the mouth. However, the results were also consistent with previous findings indicating that sucrose’s effectiveness is diminished relative to that seen in the newborn period. Zeifman et al. reported that repeated doses of 0.5 mL of

![Fig 2](http://www.pediatrics.org/cgi/content/full/103/5/e68/5o) of 9

![Fig 3](http://www.pediatrics.org/cgi/content/full/103/5/e68/5o)

![Fig 4](http://www.pediatrics.org/cgi/content/full/103/5/e68/5o)
12% sucrose solution were effective in newborns, but had no effect in 4-week-old infants. In our studies, 250 μL of 24% sucrose solution reduced crying in newborns to <10% in the first minute, with effectiveness continuing for >5 minutes. However, the same dose reduced crying to only 50% in 6-week-old infants, and the effect persisted for only 1 minute. In the current study, the sucrose concentration was doubled and the dose was given three times. Despite this increase, crying time was reduced to only ~50%. However, in response to the more concentrated, more frequent sucrose stimulus, relative calming was maintained for at least 4 minutes. In summary, the newborn pattern of a prolonged calming response that persists beyond the cessation of mouthing can also be elicited in 6-week-old infants, but it requires a stronger stimulus to do so.

The second main finding is that, as predicted, infants with colic did demonstrate a diminished sucrose-induced calming response relative to normals. This was statistically reliable before a feeding, and similar but not quite so statistically reliable after a feeding. This is an important experimental demonstration of colic-normal differences in soothing, because the calming effects cannot easily be accounted for by differences in crying when the soothing stimulus was applied. Protections against such a bias were that the stimulus situations, percent time crying at the time of stimulus application, and baseline crying at the beginning of the observation sessions were similar. Further, there were no changes in the results when baseline crying was entered as a covariate in the analyses. Colic-normal differences in soothing cannot be accounted for by differences in mouthing behavior. As judged by the presence of mouthing movements, the sucrose taste sensation was equally salient and lasted for the same amount of time in both groups. This also rules out colic-normal differences because of the extent to which mouthing might predispose to calming by competitively blocking the crying response. Colic-normal differences in calming persisted after the increased mouthing had ceased. Indeed, in the prefeed situation, the differences were specific to the period following the decline in mouthing.

The third main finding is that proximity of a feeding does affect the pattern of calming (but not mouthing) responses. The importance of controlling for feeding proximity in 6-week-old infants was suggested by our earlier observation that the small calming effect achieved by a single, less concentrated, sucrose taste in crying infants before a feeding was eliminated after a feeding. This may be different in newborns. Blass et al reported no statistical association between time since last feed and sucrose-induced calming of spontaneous crying, but this question has not been carefully addressed experimentally in newborns. Perhaps surprisingly in the current study, however, sucrose-induced calming was, if anything, more rather than less effective postfeed both in infants with and without colic.

Potentially more illuminating for the purposes of this study, however, was the fact that the pattern of colic-normal differences in calming was not the same before and after a feed. Before a feed, the colic-normal difference in calming was sucrose-specific; that is, there was a group difference for sucrose but not for water. This is what was predicted on the assumption that sucrose taste has a specific calming effect and that reduced ability to calm is characteristic of infants with colic. After a feed, the colic-normal difference resulted in a decrease in responsivity that was generalized; that is, infants with colic tended to be calmed less than infants without colic by both sucrose and water. By controlling for postfeed crying in infants with and without colic, this demonstrates that colic-normal differences in responsivity are also present after a feed. However, they seem to be present for sucrose and not water before a feed, and present for both sucrose and water after a feed.

The reasons for the sucrose-only calming difference before and the more general sucrose and water calming differences after feeds is open to a number of interpretations. One is that sucrose-specific calming differences are seen only when hunger is a stimulus. This assumes that hunger was present before a feed and absent after a feed. Presumably, the crying stimulus before the feed was a combination of the infant being separated from its caregiver and being hungry, whereas after the feeding, separation from its caregiver was the most obvious crying stimulus. A second interpretation is that, regardless of the number or classes of stimuli, the infant was simply more aroused before than after a feeding. Consequently, the apparent sucrose-specific difference may simply reflect the fact that water was generally less soothing than sucrose, and the colic-normal differences in calming to water were not able to be elicited because the higher arousal produced a ceiling effect for the less effective water stimulus. Because by design the infants were crying the same amount when the taste stimuli were given, this possibility cannot be confirmed in this study. It is possible that differences in crying intensity might have been reflected in acoustic analyses of fundamental frequency or other acoustic parameters but these were not available for this study. A third interpretation is that the prefeed stimulus unmask operations of a sucrose-specific system that is otherwise indistinguishable from the more nonspecific soothing in the postfeed setting. Water is commonly used as a control for the effects of presence of a liquid in the mouth. However, it too is a taste, albeit a less salient one than sucrose, as indicated by the differences in mouthing. The prefeed stimulus situation may have inadvertently controlled for the nonspecific calming of water taste, permitting the sucrose-specific taste differences to become manifest. These interpretations cannot be confirmed or ruled out within this study, but all should be amenable to experimental test in subsequent studies.

These results also have implications for the understanding of, and possibly the treatment of, colic syndrome. One implication is that, consistent with many other lines of evidence, an important and possibly defining individual difference predisposing to colic syndrome is an infant’s ability to regulate its responses to everyday stimuli. Although the stimulus in this study was a nutrient taste, other observations...
imply that regulatory differences may be more general. Clinically, inability to soothe is the most commonly cited behavioral characteristic other than differences in crying itself to describe infants with colic. A number of controlled observational studies support this clinical finding. As previously mentioned, based on diary data, duration of crying once started, rather than frequency of crying bouts, characterized infant crying behavior in infants with colic. St. James-Roberts and colleagues showed that infants withpersistent crying were more likely to have unsoothable crying bouts and that when they occurred, more calming maneuvers were required to stop these crying bouts. Furthermore, in randomized controlled trials, increased carrying was effective in reducing duration but not frequency of crying and fussing in normal infants but was ineffective in infants with colic. The results of this study experimentally demonstrate reduced ability to regulate crying while controlling for the likelihood and amount of crying, and suggests that this reduced soothing ability extends to nutrient as well as contact caregiving stimuli.

These findings may also implicate specific central mechanisms that could account for colic-normal soothing differences. Convergent evidence from studies in other infant mammalian species and infant humans suggests that sucrose taste-induced calming requires a functioning central opioid-dependent system, whereas other forms of tactile calming do not. In infant rats, distress vocalizations are reduced by morphine injections, an effect that is blocked by intraventricular naloxone injections. The same effect is produced by intraoral sucrose and blocked by opioid antagonists. Panksepp et al reported that the opioid system had the most specific and powerful effect on distress vocalizations in a comparison of 18 drugs aimed at modifying brain opioid, serotonin, norepinephrine, dopamine, and acetylcholine activity. By contrast, orotactile and whole body contact have effects on a variety of behaviors including distress vocalizations, latency to nipple attachment, and milk intake, but these are not blocked by opioid receptor antagonists. In normal human infants, sucrose taste and pacifier-induced calming are functionally separable in terms of their time courses. Pacifier calming is stimulus bound, in the sense that previously crying infants calm when the pacifier is in place but return to crying soon after the pacifier is removed. By contrast, sucrose calming is persistent, continuing for minutes after cessation of the sucrose stimulus. Findings from two groups of clinical infants support the argument that these functional differences reflect opioid-dependent mechanisms in the case of sucrose calming, and non-opioid but still unspecified mechanisms in the case of pacifier calming. Infants born to methadone-dependent mothers and infants with postmature syndrome show no or much reduced calming to sucrose taste but normal calming responses to pacifiers.

Consequently, the reduced calming effectiveness to sucrose described in this study may be indexing a functional difference in a central opioid-dependent calming system of infants with colic. This finding could have even more significance if infants with colic calm to the orotactile stimulation of a pacifier as do normal infants, in which case the opioid-dependent calming system might be specifically implicated. Although pacifiers are claimed to be effective in infants with colic, the only study supporting their use was uncontrolled and provided no measures of crying. However, based on diary recordings, infants with colic have been reported to have similar rates of soothing to pacifiers as those without. Consequently, a direct comparison of colic-normal differences in both sucrose and pacifier calming might be useful to determine if specific or more general cry reduction systems were implicated.

These findings may also contribute to our ability to explain nonpathologic cases of colic syndrome in terms of individual differences in otherwise normal infants. These findings support earlier observations that a stronger sucrose taste stimulus is required to achieve a calming effect in normal infants at 6 weeks of age than at birth. Thus, this developmental decrease in effectiveness of sucrose-induced calming is characteristic of otherwise normal infants and may contribute to the normal developmental increase in crying duration during the first 2 months of life. This reduced ability to calm in response to sucrose taste seems to be shared, but exaggerated, in infants with colic syndrome.

**CONCLUSIONS**

Finally, the results suggest some caution concerning promissory notes about the use of sucrose tastes as a therapeutic modality in infants with colic. On the one hand, the soothing effectiveness of sucrose tastes is clearly less effective in 2-month-old infants than in newborns, and less effective in infants with than without colic. Furthermore, if the prefeed versus the postfeed differences are because of more aroused crying, sucrose may be less effective for the extremely unsoothable crying bouts that so distress parents than for less extreme fussing bouts. Finally, 48% sucrose is a fairly concentrated and very sweet taste stimulus. On the other hand, sucrose tastes may be more effective if delivered in association with other caregiving stimuli. In normal newborns, crying after heel lance was reduced substantially more when the infant was both given sucrose and held during the procedure than when it was only given sucrose or only held. In normal 4-week-old infants, Zeifman et al reported that giving sucrose while at the same time engaging the eyes of the infant was substantially more effective than giving sucrose with deliberate avoidance of eye contact. These findings may help to explain the positive results reported in a sucrose treatment trial in infants with colic, despite the fact that a smaller dose of sucrose was used. Markestad reported improvement in 63% of infants whose parents were asked to provide 2 mL of less concentrated 12% sucrose solutions in a crossover trial during unsoothable crying bouts. However, the sucrose was to be provided while holding the infant in their arms. Although not explicitly described, it seems likely that eye contact, holding contact, or both

http://www.pediatrics.org/cgi/content/full/103/5/e68
may have contributed to the effects of sucrose administration at least in some cases.

In summary, sucrose taste has a persistent calming effect in crying infants in the second month of life, but infants with colic are less effectively soothed than infants without colic. Reduced soothing effects were manifest for sucrose but not water before a feed, and for both sucrose and water after a feed. These findings are consistent with evidence that infants with colic are less able to regulate crying once started, and that these regulatory differences may represent a nonpathologic individual difference reflective of the functioning of central soothing systems in infants with colic syndrome. Responses to sucrose taste may be a useful and ethically acceptable biobehavioral probe of mechanisms implicated in clinically significant behavioral crying syndromes of infancy. They may also contribute to modestly effective therapeutic strategies, possibly in association with other caregiving modalities.

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