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Maternal inhibition of infant behavioral response following isolation in novel surroundings and Inflammatory challenge

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Abstract

During isolation in a novel environment, guinea pig pups gradually begin to display passive behavior that appears to be mediated by proinflammatory activity, i.e., “sickness behavior”. Administration of substances that increase proinflammatory activity [corticotropin-releasing factor (CRF), lipopolysacchride (LPS)] prior to isolation induces passive behavior from the beginning of the isolation episode. Here we show that reunion with the mother in the novel environment rapidly and potently suppresses the passive behavior of isolated pups (Experiment 1); inhibits the passive behavior of pups administered CRF (10 µg, subcutaneous; Experiment 2); and inhibits the passive behavior of male, though not female, pups administered LPS (250 µg/kg, intraperitoneal; Experiment 3). Together these findings suggest that the presence of the mother either recruits other processes that moderate the impact of proinflammatory processes on brain mechanisms mediating the passive response or initiates compensatory mechanisms that counter the effect of proinflammatory activity. Further, the results suggest that for physically ill animals of social species, the adaptive advantage that accrues from maintaining normal social interactions may sometimes outweigh the advantage gained by engaging in sickness behavior.

Keywords

Social separation; maternal separation; sickness behavior; proinflammatory activity; social buffering; corticotropin-releasing factor; CRF; corticotropin-releasing hormone; CRH; lipopolysacchride; guinea pig

INTRODUCTION

Mammalian young depend on the mother not only for nutrition and the specific caretaking activities that promote immediate survival, but also for learning about environmental resources and threats (Black-Rubio, Cibils, & Gould, 2007; Galef & Clark, 1972; Mateo, 2009) and for the various forms of stimulation that regulate neonatal physiological systems (Hofer, 1987; Schanberg, Ingledue, Lee, Hannun, & Bartolome, 2003; Levine, 2001), shape normal development (Harlow, 1962; Mason, 1978; Belay, Burton, Lovic, Meaney, Sokolowski, & Flemming, 2011; Moore, Dou, & Jusaska, 1992), and appear to facilitate adaptation to future environmental conditions (Bagot, van Hasselt, Champagne, Meaney, Krugers, & Joels, 2009; Cameron, 2011; Champagne & Curley, 2005; Sachser, Hennessy, &

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Kaiser, 2011; Sevelinges, Mouly, Raineke, Moriceau, Forest, & Sullivan, 2011). Given the mother's pervasive influence on the immediate and long-term survival and well-being of the young, it is not surprising that maternal separation evokes a variety of behavioral and physiological responses while reunion results in a rapid reduction of such reactions. The classic example is the vocalizing of separated infants (MacLean, 1985) and the rapid termination of vocalizations upon the mother's return (Shair, 2007). Although vocalizing and other active behaviors are typical of brief periods of maternal absence, more-prolonged separation often is associated with a distinctive profile, in which behavior is passive and appears disengaged (Colonnello, Iacobucci, Fuchs, Newberry, & Panksepp, 2011; Hofer, 2006; Kaufman & Rosenblum, 1967). In the guinea pig, an initial period of vocalizing and a tendency to increase locomotor activity gradually wanes over the course of the first hour of separation in a novel environment, and a second passive stage characterized by a crouched stance, closed eyes, and extensive piloerection begins to emerge (Hennessy, Long, Nigh, Williams, & Nolan, 1995).

Evidence suggests that the passive stage in guinea pigs is mediated by proinflammatory activity. For instance, any of three anti-inflammatory agents reduces the passive behavior of pups during a 3-hr isolation in novel surroundings (Hennessy, Schiml-Webb, Miller, Maken, Bullinger, & Deak, 2007; Perkeybile, Schiml-Webb, O'Brien, Deak, & Hennessy, 2009; Schiml-Webb, Deak, Greenlee, Maken, & Hennessy, 2006). Proinflammatory signaling is known to produce a behavioral reaction—typically referred to as “sickness behavior”—that involves responses like those observed in separated guinea pigs (i.e., a hunched posture, signs of sleepiness, piloerection, and a reduced propensity to explore their surroundings). This reaction appears to be part of a systemic behavioral and physiological adjustment to support fever, conserve energy, and in other ways combat pathogen exposure (Hart, 1988; Maier & Watkins, 1998). However, increased proinflammatory activity and its physiological and behavioral sequelae can be induced not only by pathogens, but also by stressors (Maier & Watkins, 1998), as appears to be the case for the separated guinea pig pup.

The absence of the mother clearly is crucial for triggering the passive response in young guinea pigs. If the pup is placed into the novel environment together with the mother, the passive response is greatly suppressed (Hennessy & Morris, 2005; Hennessy et al., 2004). Although it is clear that the presence of the mother from the beginning of the test inhibits the onset of passive behavior, the effect of maternal reunion in pups already exhibiting passive behavior has not been systematically investigated. Informal observations of pups returned to the mother and home cage following isolation suggest that reunion rapidly suppresses passive behavior. One purpose of the present study was to experimentally test this effect of reuniting pup and mother.

The passive response of guinea pigs can also be elicited pharmacologically. Pups injected with either corticotropin-releasing factor (CRF; 7–14 µg, subcutaneous; Becker & Hennessy, 1993; Hennessy et al., 1995) or lipopolysaccharide (LPS; 50–250 µg/kg bw, intraperitoneal; Hennessy, Deak, Schiml-Webb, Wilson, Greenlee, & McCall, 2004), show a rapid onset of passive behavior when subsequently separated so that passive behavior predominates during the first hour of separation when pups typically are in the active phase of responding. Both drugs appear to stimulate passive behavior via activation of proinflammatory activity. Peripheral CRF is known to have a variety of proinflammatory effects (Baker, Richards, Dayan, & Jessop, 2003; Chowdrey, Lightman, Harbuz, Larsen, & Jessop, 1984; Hagan, Poole, & Bristow, 1993; Karalis, Muglia, Bae, Hilderbrand, & Majzoub, 1997; Leu & Singh, 1992; Paschos, Kolios, & Chatzaki, 2009; Singh & Leu, 1990; Stengel & Tache, 2009; Webster, Elenkov, & Chrousos, 1997), and injection of LPS, which is derived from the cell wall of gram negative bacteria, potently elicits an inflammatory cascade and increases central inflammatory signaling in guinea pig pups

(Hennessy et al., 2004). Moreover, the effect of both CRF and LPS on passive behavior can be attenuated with administration of an anti-inflammatory agent (Hennessy et al., 2007, Hennessy, Fitch, Jacobs, Deak, & Schiml, 2011; Schiml-Webb, Miller, Deak, & Hennessy, 2009).

The influence of the mother on pharmacologically elicited passive behavior in guinea pig pups has not been studied. At first glance, it might appear that if the physiological mechanisms underlying passive behavior were directly activated by injection of CRF or LPS, the presence of the mother would not be expected to moderate the behavioral response of the pup to the illness-inducing challenge. However, social stimuli can have powerful influences on inflammatory processes and health. Social housing reduces ischemic damage and mortality to experimentally induced stroke in rats, an effect that appears mediated by observed changes in the underlying inflammatory reaction (Karelina, Norman, Zhang, Morris, Peng, & DeVries, 2009). Moreover, a number of findings indicate that the *behavioral* reaction to an inflammatory challenge can be modified by the environmental context. For instance, a dose of Interleukin-1 (IL-1) that disrupted the motor activity of male rats in an open field had no effect on the male's sexual behavior when presented with an estrous female (Yimiri, Avitsur, Donchin, & Cohen, 1995). Likewise, the maternal behavior of lactating mice injected with LPS was found to depend on ambient temperature. When temperature was lowered, and consequently posed a threat to the litter, deficits in maternal behavior observed at a higher temperature were normalized (Aubert, Goodall, Dantzer, & Gheusi, 1997). Similarly, sickness behavior induced by IL-1 and LPS in macaque monkeys was rapidly replaced with attentive and agonistic behavior upon the appearance of a threat (human in the room; Friedman, Reyes, & Coe, 1996; Willette, Lubach, & Coe, 2007). Overall, these behavioral findings suggest that when a conflicting motivation is of sufficient strength, sickness behavior can be inhibited to permit appropriate responding to the new condition (Aubert, 1999). Nonetheless, the results do not directly address the potential ability of the mother to ameliorate sickness behavior produced by inflammatory challenge in her pups. Accordingly, the second purpose of the present study was to determine if the presence of the mother would reduce the passive behavioral response to CRF and LPS.

In sum, Experiment 1 examined the effect of reunion with the mother following isolation under non-drug conditions. Therefore, this experiment assessed the mother's influence when mechanisms underlying the passive behavior were already activated physiologically at the time the mother was encountered. Experiments 2 and 3 examined the effect of the mother following administration of CRF and LPS, respectively. In these experiments, then, mechanisms underlying the passive response were activated pharmacologically at the time testing with the mother began.

GENERAL METHOD

Subjects

Albino guinea pigs (*Cavia porcellus*) were bred in our laboratory. Each mother and her litter were housed in opaque plastic cages (73 × 54 × 24 cm) with wire fronts and sawdust bedding. Water and guinea pig chow were available *ad libitum*. Lights were maintained on a 12:12 light:dark cycle, with lights on at 0700 hr. Cages were changed twice per week. As in earlier studies (e.g., Hennessy, 2011; Schiml-Webb et al., 2009) testing was conducted near the time of natural weaning, which occurs around Day 25 (König, 1985; Schiml & Hennessy, 1990). It should be noted, however, that young guinea pigs continue to show a strong attraction to the mother, as well as behavioral and physiological reactions to her presence and absence, for weeks thereafter (Hennessy, Maken, & Graves, 2002; Hennessy & Morris, 2005; Hennessy, Young, O'Leary, & Maken, 2003). All procedures were approved by the Wright State University Laboratory Animal Care and Use Committee.

Procedure

For testing, pups were carried in a transport cage (< 10 s) from the colony room to the testing room, where they were placed into an empty, clear plastic cage (47 × 24 × 20 cm), either alone or together with their mother, on a table top under full room lighting. Because passive behavior typically occurs over an extended period of time, these responses were scored with one-zero sampling as in previous studies (e.g., Schiml-Webb, et al. 2009). That is, a trained observer (85% or better inter-observer reliability) behind 1-way glass recorded the number of 1-min intervals in which pups exhibited the characteristic crouched posture in which the feet are tucked beneath the body, complete or near complete closure of one or both eyes (> 1 s), and extensive piloerection (over half the body). However, because the mother often occluded the observer's view of the infant's eyes, the measure of eye-closing was dropped from the study. Therefore, our measure of passive behavior was the number of 1-min intervals in which crouch and piloerection both occurred. When pups were tested with the mother, the number of 1-min intervals in which the pup was in physical contact with the mother also was noted. As in previous work (e.g., Hennessy et al., 2007; Hennessy et al., 2011), all pups were tested in two separate conditions, with the first and second tests occurring on Days 20–24 and 23–27, respectively, at the same time of day. There were at least 3 days between tests. The test cage was cleaned with detergent prior to each use.

Data analysis

Because of non-normal distributions (large numbers of “zero” and maximum scores), data were analyzed with non-parametric tests (Mann-Whitney *U* tests for between-subject comparisons and Wilcoxon matched-pairs, signed-ranks tests for within-subject comparisons). Central tendency is represented with median values and variation with the semi-interquartile range. SPSS was used for calculations. In all experiments, preliminary analyses examined possible sex differences. Unless otherwise noted, these comparisons were all non-significant and males and females were combined for further analyses. A probability of $p < 0.05$ (2-tailed) was accepted as significant throughout.

EXPERIMENT 1: EFFECTS OF REUNION ON PASSIVE BEHAVIOR

Method

Eleven pups (5 males, 6 females, from 7 litters) were tested for 3 hr on two occasions. On each occasion, the pup was alone for the first 2 hr. In the With Mother condition, the mother was placed into the test cage with the pup for the third hour. In the Alone condition, the pup was exposed to the same disturbance at 2 hr (experimenter entering the room and reaching into the cage), but the pup remained alone for the final hour. Two males and three females were tested first alone and then with the mother, while the other three males and three females were exposed to the conditions in the reverse order. In both conditions, behavior was observed during the final hour of the test.

Results

As expected based on previous studies, passive behavior was common during the third hr of isolation. Ten of eleven pups exhibited passive behavior when alone, with four exhibiting both the crouched stance and extensive piloerection during 50 or more of the 60 min of observation. In contrast, when reunited with their mother in the test cage, only a single pup displayed passive behavior during the final hour, and in that case, only for a single minute ($p < 0.01$; Table 1). When the mother was returned to the cage, pups spent most of the observation period in physical contact with her. All 11 pups were in contact during at least 50 of the 60, 1-min intervals of the final hour.

EXPERIMENT 2: MATERNAL INFLUENCES ON PASSIVE BEHAVIOR INDUCED BY CRF

Method

Pups were tested twice, with each test occurring 60 min following subcutaneous injection of either CRF (10 µg) or saline vehicle. Eleven pups (7 males, 4 females from 8 litters) were tested alone on each occasion and 11 pups (7 males, 4 females, from 10 litters) were tested together with their mother for the entire test. In both the Alone and With Mother conditions, three or four males and two females were injected first with CRF and then with saline, and the other three or four males and two females were injected with the substances in the reverse order. Behavior was observed throughout the 1-hr test.

Results

In the Alone condition, injection of CRF greatly enhanced passive, sickness behavior during a first hour of separation ($p < 0.01$; Fig. 1) as in previous studies (e.g., Hennessy et al., 1995). However, in pups tested with the mother, the effect of CRF on passive behavior was abolished. Passive behavior following injection of CRF was reduced to the level observed following saline injection when in the presence of the mother. Direct comparisons between pups tested with the mother and those tested alone showed that the mother reduced passive behavior both when pups were injected with saline and when they were injected with CRF (p 's < 0.01 ; Fig. 1).

In the With Mother condition, mother and pup remained in almost constant physical contact regardless of the injection substance. Eight of 11 pups were in contact during all 60 min of observation following injection with saline, and 10 of 11 were in contact during every min after injection with CRF.

EXPERIMENT 3: MATERNAL INFLUENCES ON PASSIVE BEHAVIOR INDUCED BY LPS

Methods

Pups were tested twice, with each test occurring 90 min following intraperitoneal injection of either LPS (250 µg/kg bw) or saline vehicle. Eleven pups (6 males, 5 females, from 11 litters) were tested alone on each occasion and 12 pups (6 males, 6 females, from 12 litters) were tested together with their mother for the full test period. In the Alone and With Mother conditions, three males and two or three females were injected first with LPS and then with saline, and three males and three females were injected with the substances in the reverse order. Behavior was observed throughout the 1-hr test.

Results

LPS increased passive behavior both in pups tested alone ($p < 0.01$) and in pups tested with the mother ($p < 0.01$, Fig. 2). Following injection with either substance, the presence of the mother reduced the time pups spent exhibiting passive behavior (p 's < 0.01). Although the mother reduced passive behavior of pups when they were administered LPS, other aspects of the findings raise questions of interpretation. Because the absolute amount that the mother reduced passive behavior was similar following injection of LPS and saline, and because passive behavior in the With Mother condition was more common following injection of LPS than following injection of saline, it is possible that the mother's effect following LPS injection was on that portion of passive behavior that pups would have occurred in the absence of LPS.

Considering that passive behavior gradually increases over time in pups under non-drug conditions, but the effect of LPS on passive behavior is present essentially from the beginning of isolation, a shorter observation period might permit assessment of the effect of the mother on LPS-induced passive behavior without potential confounding due to her influence on passive behavior not elicited by LPS. For this reason, we performed additional analyses of data from the first 30 min of testing. At this time, we would expect to still see high levels of passive behavior of Alone pups injected with LPS, but minimal passive behavior of Alone pups treated with saline.

Preliminary analyses revealed a sex difference in one of four comparisons, i.e., LPS had a greater effect on females than males in the With Mother condition ($p < 0.01$). Therefore, we analyzed the data from the first 30 min separately for males and females. For males, LPS increased passive behavior in pups tested alone ($p < 0.05$), but not in those tested with their mother. Further, the presence of the mother reduced the passive behavior of males when injected with LPS ($p < 0.01$), but not when injected with saline (Fig. 3). For females, the effect of LPS was as great for pups tested with the mother as for those tested alone (Fig. 3). That is, in both the Alone and With Mother groups, females showed more of the passive behavior when injected with LPS than when injected with saline (p 's < 0.05) and there was no difference in the passive behavior of females tested alone versus with the mother, regardless of whether the females were injected with LPS or saline. In sum, the 0–30-min data indicate that the mother was capable of reducing the passive, sickness behavior resulting from LPS injection at this dose in male, but not female, pups.

DISCUSSION

The findings of Experiment 1 demonstrate that reunion with the mother following 2-hr of isolation in a novel environment rapidly abolishes the passive behavior of guinea pig pups. When the mother was placed into the test arena, passive behavior was almost immediately and uniformly terminated. Experiments 2 and 3 show that the mother also is capable of reducing passive behavior induced pharmacologically. This effect was especially clear for injection of CRF. For pups injected with LPS, a moderating effect of the mother on passive behavior was observed only for males. The reason for this sex difference is not clear. No sex differences in the passive responding of pups during isolation have been apparent in our previous studies. Still, up to this point we have not assessed the *mother's influence* on passive responding. Further, earlier studies of isolated pups, like the present one, have generally used relatively small sample sizes of males and females (usually 4–6), so that the statistical power to detect sex differences has been limited. Sex differences in the behavioral response to inflammatory challenge are not uncommon, though the direction and nature of those differences can be complex and appear to shed little light on the present findings (Stucky, Gregory, Winter, He, Hamilton, McCarron, & Berman, 2011; Yee & Prendergast, 2010). It may be that females were more sensitive to LPS than were males in the present study so that the presence of the mother was insufficient to moderate the sickness behavior of females at this dose of LPS. In any event, the findings for males injected with LPS, and for pups of both sexes administered CRF, indicate that increases in passive behavior induced pharmacologically via manipulations that enhance proinflammatory activity can be reversed by reunion with the mother.

If, under non-drug conditions, it is the stress evoked by the absence of the mother in the novel environment that initially triggers a proinflammatory response, then it would be reasonable to expect that reunion with her would terminate processes leading to increased proinflammatory activity (e.g., conversion of monocytes to macrophages, secretion of proinflammatory cytokines) in short order, if not immediately. Yet, it would seem to require some time for the enhanced activity (e.g., heightened cytokine levels) to return to pre-

separation values. If this is the case, the almost instantaneous inhibition of passive behavior of reunited pups observed in Experiment 1 (as opposed to the gradual onset of passive behavior following separation) must involve some process other than simple cessation of the source of heightened proinflammatory activity. The return of the mother might either reduce the impact of proinflammatory activity on downstream mechanisms affecting behavior or activate compensatory mechanisms of some other sort that counter the proinflammatory influence. Experiments 2 and 3 are consistent with this suggestion. When substances were administered that increased passive behavior pharmacologically—so that reunion with the mother would not remove the stimulus for increased proinflammatory action—the mother still was capable of moderating the behavioral response.

In the laboratory rat, particular forms of stimulation associated with care-taking behavior by the mother have been found to have a remarkable range of often unexpected influences on specific biobehavioral characteristics of the young (Hofer, 1987; Levine, 2001; Schanberg et al., 2003). But while energetic, active maternal engagement characterizes the treatment of rat pups by the mother, and such intervention is necessary for the survival and normal development of the altricial pups, guinea pigs are much more developed at birth and require little in the way of direct care. Indeed, maternal behavior in guinea pigs is extremely passive in nature, and the active behavior that does occur—primarily licking—largely ceases by a week of age (König, 1985). Pups in the present study were tested at about 3 weeks of age, a time at which they have excellent thermoregulatory capabilities (Blatteis, 1975), readily consume solid food, and generally appear fully physically independent from the mother. Therefore, it seems very unlikely that specific maternal behaviors can account for her effect on the pup's behavior in the present study. An alternative explanation is that it was simply the detection a significant social partner—the pup's attachment figure—that inhibited passive responding, both when the passive behavior was elicited by prolonged separation, and when it was elicited pharmacologically. From nearly the time of birth, it is the strong attraction of the guinea pig pup for its mother that is responsible for maintaining physical proximity with her (Hennessy & Jenkins, 1994; König, 1985). This attraction persists well after the time pups can care for themselves (Hennessy et al., 2003), as reflected by the high degree of physical contact between mother and pup that we observed. Because we did not test pups with an adult other than the mother, we do not know if the ability to reduce passive behavior following reunion or inflammatory challenge is limited to the maternal attachment object. However, in a previous study in which pre- and post-weaning offspring maintained with the mother were then exposed to a novel environment for 3 hr, the presence of the mother for the duration of the test significantly reduced passive behavior whereas the presence of an unfamiliar adult female did not (Hennessy & Morris, 2005).

Although increased proinflammatory activity can be produced by stress, it more commonly is associated with exposure to a pathogen. The results of Experiments 2 and 3 suggest that the mother can inhibit sickness behavior during actual infection. Particularly instructive here may be the findings from Experiment 3 in which sickness was produced by a process that mimics the way that pathogen exposure triggers a proinflammatory response. Under these conditions, males at least showed a clear, though not complete, suppression of the behavioral sickness response. Sickness behavior facilitates recuperation by supporting fever and conserving energy in ill animals (Hart, 1988). It is viewed as a motivated response pattern, rather than the simple result of debilitation, because sickness behavior can be abandoned in favor of different patterns of response when immediate needs appear more pressing than recuperation (Aubert, 1999). Our results certainly support the notion of behavioral adaptability during sickness, and they indicate that social stimuli alone can inhibit the behavioral response. In some species, signs that the health of the young is compromised may prompt the mother to reject them (Hrdy, 1979). While this potential explanation for the behavior of weanling age guinea pigs seems remote, there may still be an

adaptive advantage in suppressing sickness behavior in the presence of the mother. The tendency for even post-weaning guinea pigs to follow the mother is strong (Hennessy et al., 2003). For a young, sick guinea pig, it may be more adaptive to maintain contact with and follow the mother from a threatening environment to a place of safety than to exhibit a passive, immobile pattern of responding, even if the latter does support fever and conserve energy.

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Figure 1.

Median number and semi-interquartile range of 1-min intervals in which pups injected with either CRF or saline, and tested either while alone or with their mother, exhibited passive behavior consisting of a crouched stance and extensive piloerection during 60 min in a novel environment.

** $p < 0.01$

Figure 2.

Median number and semi-interquartile range of 1-min intervals in which pups injected with either LPS or saline, and tested either while alone or with their mother, exhibited passive behavior consisting of a crouched stance and extensive piloerection during 60 min in a novel environment.

** $p < 0.01$

Figure 3.

Median number and interquartile range of 1-min intervals in which male and female pups injected with either LPS or saline, and tested while either alone or with their mother, exhibited passive behavior consisting of a crouched stance and extensive piloerection during 30 min in a novel environment.

* $p < 0.05$; ** $p < 0.01$

Table 1

Median level and semi-interquartile range (SIR) of the measure of passive behavior, and proportion of pups showing passive behavior, in Experiment 1.

	Median	SIR	Proportion
Alone	22.0 **	21.0	.91
With Mother	0.0	0.0	.09

**
 $p < 0.01$ vs With Mother