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Naproxen attenuates sensitization of depressive-like behavior and fever during maternal separation

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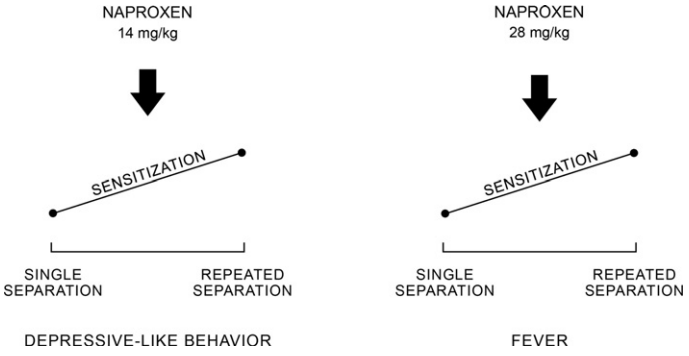
HIGHLIGHTS

- Guinea pig depressive-like response sensitized with repeated maternal separations
- Febrile response also sensitized with repeated maternal separation
- 14 mg/kg of naproxen reduced behavioral response to early and later separations
- 28 mg/kg of naproxen reduced febrile response to early separations
- Prostaglandins may mediate sensitization of maternal separation effects

GRAPHICAL ABSTRACT



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ABSTRACT

Early life stress can increase susceptibility for later development of depressive illness though a process thought to involve inflammatory mediators. Isolated guinea pig pups exhibit a passive, depressive-like behavioral response and fever that appear mediated by proinflammatory activity, and which sensitize with repeated separations. Treatment with an anti-inflammatory can attenuate the behavioral response during the initial separation and separation the following day. Here we used the cyclooxygenase inhibitor naproxen to examine the role of prostaglandins in mediating the depressive-like behavior and core body temperature of young guinea pigs during an initial separation, separation the next day, and separation 10 days after the first. The passive, depressive-like behavior as well as fever sensitized with repeated separation. Three days of injection with 14 mg/kg of naproxen prior to the initial separation reduced depressive-like behavior during all three separations. A 28 mg/kg dose of naproxen, however, had minimal effect on behavior. Fever during the early separations was moderated by naproxen, but only at the higher dose. These results suggest a role of prostaglandins in the behavioral and febrile response to maternal separation, and particularly in the sensitization of depressive-like behavior following repeated separation.

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1. Introduction

Disruption of attachment relationships and other childhood stressors can increase vulnerability for developing mental disorders,

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such as depression, in adolescence or adulthood [1–4]. Several lines of research suggest this effect can involve inflammatory mechanisms. First, it is well known that stressors can induce a systemic inflammatory reaction [5]. There also now is overwhelming evidence that systemic inflammation can promote depressive symptomatology [6–8]. Most importantly, an abundance of recent findings suggest that early-life psychosocial stress produces lasting elevations in inflammatory activity [e.g., 9–14], and that these effects may be linked to later depression. For instance, Danese et al. [15] found the severity of adult depression to be related to levels of the inflammatory marker, C-reactive protein, but only in individuals who had been exposed to childhood maltreatment. It has been suggested that early-life stressors may sensitize inflammatory processes, so that exposure to stressors in later life is more likely to evoke an inflammatory-mediated depressive episode [16, 17].

A variety of inflammatory factors have now been identified that influence neurotransmitter synthesis, release, and reuptake in ways that potentially could promote depression [8]. One class of mediators that may be particularly relevant for understanding lasting effects of early trauma are the prostaglandins, a group of lipid compounds derived from arachidonic acid largely through the action of cyclooxyenase (COX) isoenzymes. Prostaglandins not only subserve acute inflammatory reactions, but also appear to encourage the transition to, and maintenance of, chronic inflammation [18]. Further, COX inhibitors have been observed to reduce inflammatory mediated behavioral deficits, including depressive-like behavior, in rodents [19–21]. Heightened prostaglandin levels have been reported in depressed patients [22,23], and COX inhibitors have been found to have an antidepressant effect [24, 25]. Finally, there is evidence that negative long-term biobehavioral consequences of early psychosocial stress are mediated by prostaglandins and can be blocked with anti-inflammatory treatment. Brenhouse and Andersen [26] found repeated periods of maternal separation in infant rats produced cognitive impairment as well as evidence of a reduction in parvalbumin-containing GABAergic interneurons and increased levels of COX expression in prefrontal cortex during adolescence, but these effects were reversed if animals were administered a COX inhibitor during the period between the early separations and later testing.

We examine the effect of maternal separation in the guinea pig, a precocial rodent in which the young display evidence of a selective filial attachment [e.g., 27–29], and the response to maternal separation resembles that of primate infants in a number of ways [30]. One of these similarities is that the behavioral reaction occurs in two stages. An initial active stage, marked primarily by vocalizing, is followed by a passive, depressive-like stage characterized by a crouched posture, prolonged eye-closure, and extensive piloerection [31]. These stages are reminiscent of the "protest" and "despair" of separated macaques [32], though the transition to the second stage develops over the course of hours rather than days. Several sets of findings indicate that this second stage of responsiveness in guinea pigs is mediated by inflammatory processes: (1) direct activation of an inflammatory reaction with lipopolysaccharide hastens the onset of the passive stage [33]; (2) separation elicits physiological signs of an inflammatory reaction, specifically fever and increased proinflammatory cytokine expression [34,35]; and, (3) three different anti-inflammatory agents (including the COX inhibitor indomethacin) reduce the passive response to separation [36–38].

Both the passive behavioral response and the fever sensitize with repeated separations. Hennessy et al. [39] found that pups separated on two consecutive days showed more of the depressive-like passive behavior and a more-distinct and rapid fever response during the second separation than during the first. Since an increase in fever likely reflects an increase in underlying proinflammatory signaling, the results suggest that inflammatory factors may have promoted the behavioral sensitization. To examine this possibility, pups were administered the anti-inflammatory cytokine interleukin-10 (IL-10) through an intracerebroventricular cannula prior to the first of two separations that occurred on consecutive days. Whereas vehicle controls showed sensitization of depressive-like behavior during the second separation, pups receiving IL-10 prior to the first separation did not [40]. Subsequent work revealed that the sensitization would persist for more than just 24 h. For instance, Schneider et al. [41] found that pups separated on two consecutive days, and then again 10 days after the first, exhibited more of the passive depressive-like behavior during both of the later separations, as well as a larger and more-rapid fever response, particularly during the last separation.

In all, results to this point support the notion that sensitization of inflammatory factors contributes to the sensitization of the depressive-like response. However, we have only evaluated the effects of anti-inflammatory treatment on short-term behavioral sensitization (i.e., over a 24-h period). Effects of this treatment on fever or its sensitization have not been investigated. In addition, nothing is known about which inflammatory factors might mediate the sensitization process. Therefore, in the present study we examined the role of prostaglandins in the short-term and more-prolonged sensitization of behavior and fever. The common, nonspecific COX inhibitor naproxen was administered prior to an initial separation. The pups were separated on two consecutive days and again 10 days after the first using the paradigm of Schneider et al. [41]. We measured both passive depressive-like behavior and core temperature during all separations. For comparison, we also scored the primary behavior of the active stage of separation—vocalizing. Finally, we monitored locomotor activity to rule out the possibility that increases in core temperature were secondary to increased exertion rather than to true fever.

2. Method

2.1. Animals and experimental design

Albino Hartley guinea pigs (*Cavia porcellus*) were bred and housed in our laboratory. Each mother and litter were maintained in an opaque plastic cage (73 × 54 × 24 cm) with wire front and sawdust bedding. Food and water were available *ad libitum*. The colony room was kept at ~70° on a 12:12 light–dark schedule, with lights on at 0700 h. Cages were changed twice per week. Pups were kept continuously with the mother with the exception of surgery, brief post-operative management procedures (e.g., inspection and weighing of pups), injections, and behavioral testing. All procedures were in compliance with NIH guidelines and were approved by the Wright State University Laboratory Animal Care and Use Committee.

In a first experiment, six male and six or seven female pups were tested in each of three experimental conditions. In the non-injected (NI) condition, pups were not injected prior to testing. Those in the vehicle (VEH) condition received three daily, subcutaneous injections of saline vehicle all prior to the first of the three separations. In the naproxen (NAP) condition, pups were administered three subcutaneous injections of naproxen (14 mg/kg; Sigma Aldrich) in sterile saline with carboxymethyl cellulose (.25%) according to the same schedule as VEH pups. In light of core temperature results in the first experiment, a second experiment was conducted in which six male and six female pups were tested in the VEH and NAP conditions, but with the dose of naproxen increased to 28 mg/kg. Because there were no significant differences between NI and VEH animals in passive behavior or core temperature in the first experiment, only the VEH controls were included in the second experiment. No more than one pup from a litter was assigned to any condition in either experiment.

2.2. Surgery and telemetry

Telemetry probes (PD 4000 Emitter, Philips Respironics) were surgically implanted into the abdominal cavity under isoflurane anesthesia (2–4%) using aseptic procedures between 15 and 18 days of age. Pups

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