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Developmental Changes in Responsivity to Threat are Stimulus-Specific in Rats

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ABSTRACT: *During early ontogeny, stimuli that pose a threat to an animal change. Unrelated adult male rats may kill young rats, but infanticide ends around weaning. Predation, on the other hand, may increase during early ontogeny when rats begin to extend their activity range. We investigated the developmental course of two defensive responses, immobility and analgesia, in young rats exposed to an adult male rat or to predator cues. Preweaning 14-day-old rats became immobile and analgesic when exposed to the male and showed immobility but not analgesia when exposed to cat odor. On Day 26, around weaning, the presence of the male rat no longer induced immobility and analgesia whereas cat odor produced higher levels of immobility and analgesia compared to control and male-exposed animals. This developmental change in responsivity may reflect the differences in the risk of being harmed by a male or a cat during different periods of ontogeny.* © *2001 John Wiley & Sons, Inc.* Dev Psychobiol 39: 1–7, 2001

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The young of altricial mammals are protected by their mother and other group members. Rodent pups in particular are raised in the safety of nests and burrows (Nowak, 1999). However, young mammals may be exposed to situations such as loss of parental care, climatic fluctuations, or predation that threaten their survival. These situations may pose a threat only during a limited period of development, when the animal's particular developmental stage makes it more vulnerable. Selection pressure specific to a developmental period has thus resulted in the design of behavioral, physiological, and morphological traits that allow the animal to successfully counter threats during that developmental period (Hofer, 1995; Oppenheim, 1981). One such ontogenetic adaptation is the ability of a young animal to selectively respond to stimuli that are potentially harmful.

For preweaning rats, an unrelated, adult male rat represents a deadly threat because adult males are infanticidal (Brown, 1986; Mennella & Moltz, 1988; Takahashi, 1982). Male threat is highest after birth (Paul & Kupferschmidt, 1975). The mother displays aggression towards intruders, and neonatal rats are

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thus especially vulnerable to infanticide in her absence (Flannelly, Flannelly, & Lore, 1986; Takushi, Flannelly, Blanchard, & Blanchard, 1983). Infanticide decreases during the preweaning period and is less of a threat during the weaning period between Days 21 and 25 (Paul & Kupferschmidt, 1975; Takushi et al., 1983). The change in infanticide can be explained by its function (Hausfater & Hrdy, 1984; vom Saal & Howard, 1982). Infanticide increases the male's reproductive success. A female that loses her offspring stops lactating and resumes cycling, which allows the male to mate with her and to produce his own offspring. Infanticide, therefore, is no longer necessary when the female comes back into estrus after weaning. Young rats have the ability to respond to male threat. When exposed to male cues, pups have elevated corticosterone levels (Tanapat, Galea, & Gould, 1998), which mobilizes energy supply (Johnson, Kamilaris, Chrousos, & Gold, 1992), and they become immobile and analgesic (Takahashi, 1994; Wiedenmayer & Barr, 1998). Developmentally, these responses are displayed in a graded fashion that parallels the changes in infanticidal threat during early ontogeny (Wiedenmayer & Barr, 1998). On postnatal Day 7, pups are quiescent and immobile in the huddle almost all of the time, and they do not change this behavior when a male is in close proximity to the nest. Rats are more active on Day 14, and when exposed to the male, they stop ongoing behaviors and become immobile and analgesic. On Day 21, rats show decreased male-induced immobility and no analgesia. At this age, some rats do not become immobile and instead approach the male.

Predation is another strong selection pressure that resulted in the evolution of defensive behaviors (Lima & Dill, 1990). Adult rats display a variety of behavioral responses such as withdrawal and immobility (Blanchard & Blanchard, 1989; Dielenberg & McGregor, 1999) that allow them to avoid predation. However, predation is not restricted to adulthood. Small mammals such as cats may access nest areas and harm preweaning rats. Little is known about the responses of young rats to predators. Twenty- and 50-day-old rats exposed to a caged cat were more immobile than unexposed animals (Bronstein & Hirsch, 1976), which indicates that immobility is a developmentally continuous response to cat threat.

To investigate the development of responsivity to threat during early ontogeny, young rats were presented with two different types of stimuli, an adult male rat and cat odor. The two stimuli differ in their potential to induce or signal harm depending on the age of young rats. Male threat is limited to the preweaning period whereas cat threat extends through weaning into adulthood. Weaning is considered here as the period during which mother–infant interactions gradually decline and during which suckling is replaced by solid food intake. Weaning occurs in the 3rd and the 4th postnatal week (Cramer, Thiels, & Alberts, 1990; Hall & Williams, 1983; Thiels, Alberts, & Cramer, 1990). We hypothesized that male exposure induces immobility and analgesia in the preweaning 14-day-old rat, but not in the weaning 26-day-old rat. We hypothesized that, in contrast, exposure to cat cues induces immobility and analgesia in both age groups.

METHODS

Animals and Housing

Long-Evans hooded rats were housed in standard laboratory cages in a colony room maintained at 22 to 24°C on a 12:12 hr light:dark cycle with light onset at 0700 hr. Cages were checked twice daily at approximately 0900 and 1700 hr. Pups found at either time were designated as 0 days of age. Litters were culled to 7 pups and kept with the mother until testing was completed. Young rats were tested on postnatal Days 14 and 26. A sexually experienced unrelated adult male was housed under identical conditions. Treatments were according to the guidelines of the Institutional Animal Care and Use Committee of Columbia University.

Test Procedure and Behavioral Measurements

Rats were tested in small huddles to decrease isolation-induced stress and to investigate a situation when an adult male intrudes into a nest area. Rats were tested at one of the two ages and either exposed to the male or to cat odor. On the day of testing, 3 rats (both sexes represented) were taken randomly from a litter, marked with a nontoxic marker on their fur, and placed in one compartment of the testing cage. The testing cage ($46 \times 25 \times 21$ cm) was subdivided by a wire-mesh partition positioned in the middle of the cage, thereby forming two equal compartments. The compartment, into which the young rats were placed, contained home-cage bedding to simulate the nest area. The other compartment of the testing cage was empty. The rats were allowed to acclimate for 15 min. Then, a nociceptive reactivity test was carried out. The forepaw of a rat was put on one of three electric resistors, in a random order. The resistors were heated by current and maintained at nominal temperatures of 39, 44, and 49°C. The latency to withdraw the paw was recorded with a timer (Lafayette Instruments, Lafayette, IN) operated by a foot pedal. The timer was activated when the pup's forepaw touched the resistor and was terminated when the pup removed its paw from the resistor. To prevent tissue damage, the test was stopped after 20 s if the paw was not withdrawn. The different temperatures were chosen to produce a wide range of latencies (Wiedenmayer & Barr, 1998). Previous work in our laboratory has shown that repeated testing across temperatures and time does not affect paw withdrawal latencies. Afterward, the adult male was placed in the adjacent compartment, and the behavior of the young rats was recorded for 5 min by scan sampling. Every 15 s, each rats' behavior was recorded on a checklist of behavioral categories including "immobile." Immobile was defined as any posture in which the animal did not exhibit any movement except that necessary for respiration and was expressed as a percentage of the scans. After removal of the male, nociceptive reactivity was again assessed. Three young rats from the same litter were used as control animals. They were submitted to the same procedure, but were tested without a male in the adjacent compartment. The order of testing male-exposed and control animals was alternated. The same procedure was used with cat odor. Cat bedding (approximately 100 g) soiled with urine was taken out of the litter boxes in our animal facility the same day as testing and put in a plastic container with a cover ($11 \times 12 \times 8$ cm). After acclimation, the container was placed in the adjacent compartment of the testing cage and opened. As a control, a container with clean bedding impregnated with 0.2 ml of lemon oil (Humco Laboratory, Texarkana, TX) was put in the adjacent chamber for 5 min. Rat pups do not show preference or aversion to lemon oil, thus it can be considered a neutral odor (Barr & Wang, 1992). All tests were conducted in the first half of the light cycle.

Data Analysis

Rats from eight litters were used for each of the two conditions, male and cat odor exposure, and for both ages, Days 14 and 26, totaling 24 litters. No sex differences were found for immobility and nociceptive reactivity. Therefore, data of the 3 littermates in each condition were pooled and treated as one data point. Data were analyzed by factorial analyses of variance (ANOVA). For the immobility data, the two conditions (male and cat odor) and age of the rats (Days 14 and 26) were between-subjects variables, and the control conditions (no stimulus and lemon odor) were within-subject variables. For the nociceptive reactivity data, the two conditions and the two ages were between-subjects variables, and the control conditions, the temperatures, and two time points during a test (before and after exposure) were within-subject variables. Afterwards, Fisher's least significant difference tests were used for planned pairwise comparisons.

RESULTS

There was a significant interaction effect for immobility between male-exposed, cat-odor-exposed, and control animals, and between the two age groups, $F(1, 28) = 8.13$, $p < 0.01$. Control animals (no stimulus, lemon odor) did not differ from each other. Lemon-odor-exposed animals, however, were less immobile on Day 26 than on Day 14 ($p < 0.05$). On Day 14, male-exposed and cat-odor-exposed pups were more immobile than control pups (Figure 1, $p < 0.001$), and male-exposed pups were more immobile than cat-odor-exposed pups ($p < 0.01$). On Day 26, male-exposed rats did not differ from control animals whereas cat-odor-exposed rats were significantly more immobile than controls (Figure 1, $p < 0.05$).

The highest temperature (49°C) caused rapid forepaw withdrawal unaffected by any manipulation; these data are not shown. There was a significant interaction effect for paw-withdrawal latencies for the conditions, the two age groups, and time, $F(1, 28) = 20.54$, $p < 0.001$. Although paw-withdrawal latencies differed between 39 and 44°C (mean control 39°C: 3.5 ± 0.15; 44°C: 2.59 ± 0.1), there were no interaction effects. For subsequent comparisons, therefore, latencies for the two temperatures were combined. Baseline paw-withdrawal latencies did not differ between conditions and age. On Day 14, male-exposed rats had longer latencies than controls (Figure 2, $p < 0.001$) and than cat-odor-exposed rats ($p < 0.001$). On Day 26, male-exposed rats did not differ from controls whereas cat-odor-exposed rats had longer latencies than lemon controls ($p < 0.001$) and male-exposed rats ($p < 0.001$).

DISCUSSION

Young rats responded to the two types of stimuli, cues from an adult male rat and from a cat, in an age-specific way. On postnatal Day 14, they became immobile and analgesic to male exposure and became immobile to cat odor whereas on Day 26 they only showed these responses to cat odor. These findings support and extend a previous study that demonstrated

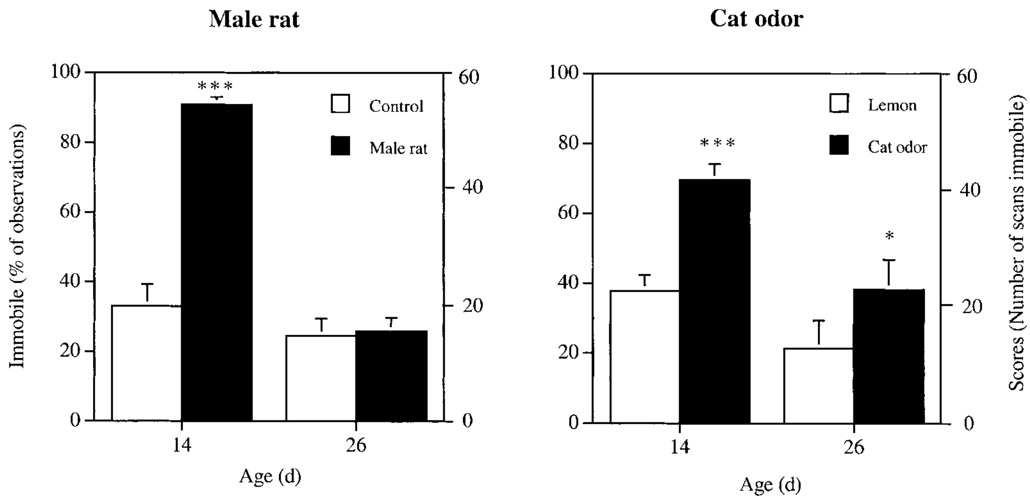

FIGURE 1 Development of threat-induced immobility in young rats. Rats were exposed to an adult male rat or to cat odor and their respective controls (control, lemon odor) before weaning, on Day 14, and around weaning, on Day 26 (*$p < 0.05$, ***$p < 0.001$).

immobility and analgesia in 14-day-old rats, and reduced immobility and no analgesia in 21-day-old rats exposed to an adult male (Wiedenmayer & Barr, 1998). Although most of the 21-day-old rats became immobile, one third were not immobile and even approached the male. The present study demonstrates that by Day 26, the male no longer elicits immobility, but that a different type of stimulus, predator odor, induces immobility and analgesia.

Immobility and analgesia are not limited to early ontogeny. Various stimuli such as cat exposure, electric shock, reexposure to a stimulus previously paired with a shock, or to the environment in which conditioning took place induce immobility and analgesia in adult rats (Canteras, Chiavegatto, Ribeiro do Valle, & Swanson, 1997; Helmstetter & Fanselow, 1987; Kalin, Sherman, & Takahashi, 1988; Lichtman & Fanselow, 1990). Both responses are therefore developmentally

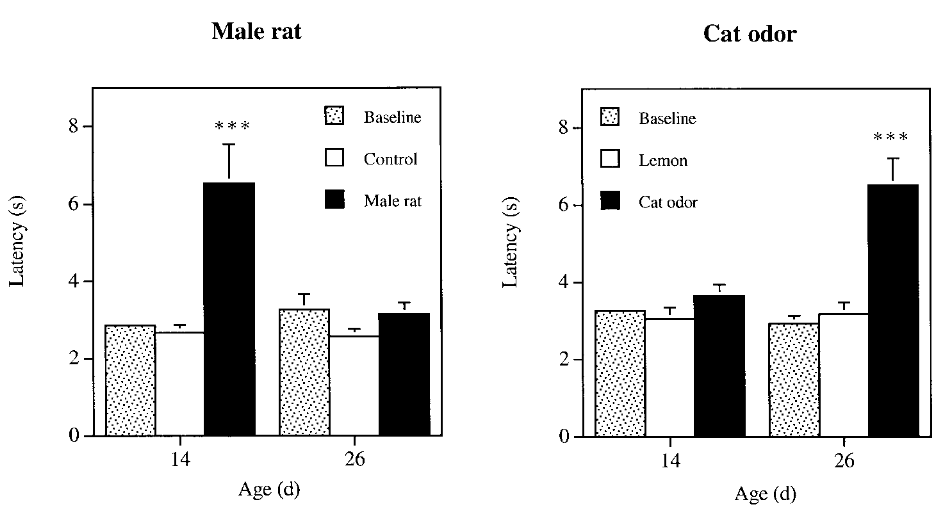

FIGURE 2 Development of threat-induced analgesia in young rats. Paw-withdrawal latencies from a heated surface were measured before (baseline) and after exposure to an adult male rat or to cat odor and their respective controls (control, lemon odor) before weaning, on Day 14, and around weaning, on Day 26. Baselines did not differ between conditions and are pooled (***$p < 0.001$).

continuous throughout ontogeny. Although immobility and analgesia can be induced throughout ontogeny, the intensity of these responses and the likelihood that they are displayed depend on the type of stimulus at any particular developmental stage.

Differences in the quality of the two stimuli could explain, on the proximate level, differential responsivity to male and cat cues. On Day 14, the male was more effective than cat odor in inducing both immobility and analgesia. The freely moving male was the origin of a variety of cues whereas urine-soiled bedding was the source of odor cues only. Other studies, however, have shown that odor cues emitted by a male are sufficient to induce defensive responses in preweaning rats. Twelve-day-old rat pups that were made anosmic did not become immobile in contact with a male (Shair, Masmela, & Hofer, 1999), and an anesthetized male which only provided odor cues induced immobility in 14-day-old and younger rats (Gould & Cameron, 1997; Takahashi, 1992). Whether other cues such as sound combined with odor made the male more effective than cat odor remains to be investigated.

On Day 26, the rats showed lower levels of immobility than on Day 14. Preweaning rats seem to be more responsive to odor than older rats (Takahashi, 1994). In adult rats, predator odors do not necessarily suppress locomotion and induce immobility (Morrow, Redmond, Roth, & Elsworth, 2000; Perrot-Sinal, Ossenkopp, & Kavaliers, 1999). Only in combination with other stimuli may odor inhibit activity. For example, a cat behind a wire-mesh screen elicited immobility in adult rats only when moving, and anesthetized or dead cats were less effective (Blanchard, Mast, & Blanchard, 1975). It seems that the combination of stimuli and context determine whether an animal becomes immobile or performs other defensive behaviors (Blanchard & Blanchard, 1971; Blanchard, Flannelly, & Blanchard, 1986). However, cat odor was very effective on Day 26 in inducing analgesia whereas the male was no longer effective. The differential effects of the two stimuli therefore cannot be explained solely by their properties. Rather, roperties of the animals themselves, how their neural organization processed the stimuli, could have contributed to the differences in responsivity.

Interconnected brain areas constitute pathways that process aversive signals and generate defensive responses (Alheid & Heimer, 1996; Charney, Grillon, & Bremner, 1998a; Charney, Grillon, & Bremner, 1998b; Holstege, 1992). The pathways that mediate immobility and analgesia are neurochemically and neuroanatomically distinct. Immobility involves areas of the fear circuit (Fendt & Fanselow, 1999; LeDoux, 2000) whereas analgesia is mediated by descending spinopedal inhibitory pathways (Fields & Basbaum, 1999). In 14-day-old rats, male exposure activates the endogenous opioid system in the midbrain periaqueductal gray that mediates analgesia but not immobility (Wiedenmayer & Barr, 2000). The two separate pathways that generate immobility and analgesia seem to differ in their properties to respond to male and cat cues. For example, cat odor did not activate the pathways that induce analgesia in preweaning rats, but did so in weaning rats. Specific brain areas such as the amygdala (Alheid & Heimer, 1996; Holland & Gallagher, 1999) may assess the biological relevance of male and cat cues at a particular age. Male cues activated different nuclei of the amygdala on Days 14 and 21, which indicates that male cues are processed differently at different ages (Wiedenmayer & Barr, in press). The neural substrates that underlie age-dependent male- and cat-odor-induced responses need further investigation.

On the ultimate level, stimulus and age specificity of the two responses can be explained by differences in selection pressure. As discussed earlier in the context of male threat (Wiedenmayer & Barr, 1998), the two responses may increase chances of surviving threatening situations. Immobility reduces auditory and visual cues to an approaching male or cat and therefore makes the huddled rats less detectable. Analgesia may be adaptive in two different ways. Before detection, pain suppression allows the young rat to remain immobile, and when detected and attacked, pain suppression may facilitate escape (Bolles & Fanselow, 1980; Walters, 1994). Responsivity to male cues declined during the postnatal period whereas responsivity to cat cues increased. This development in responsivity parallels the changes in male and cat threats. Males stop infanticide around weaning (Paul & Kupferschmidt, 1975). The decrease in male-induced immobility and analgesia could therefore reflect reduced infanticidal risk. In evolutionary terms, male-imposed selection pressure does not seem to have impacted on weaned rats, which resulted in the temporally limited responsivity to male cues. There are no data available on cat predation on young rats, but rodents in general experience strong predation pressure (Hendrie, Weiss, & Eilam, 1996). Neonatal rats in their nests may be preyed upon by cats, and by weaning when they leave the burrow and nest area and extend their activity range (Barnett, 1958; Bolles & Woods, 1964), predation pressure may even increase. The occurrence of cat-odor-induced immobility before and after weaning and the appearance of analgesia after weaning indicate that cat predation also imposed selection pressure on young rats.

Laboratory rats have been bred in captivity for dozens of generations. Domestication, or artificial selection, has changed certain traits such as levels of aggression (Blanchard et al., 1986), but the species-specific behavioral organization remains largely unaltered (Boice, 1981; Dewsbury, 1994). When given the opportunity in more structured environments, laboratory rats dig complex burrow systems and perform other species-specific behaviors (Blanchard & Blanchard, 1989; Boice, 1977; Fokkema, Koolhaas, & van der Gugten, 1995; Price, 1977). The present study demonstrates that young laboratory rats still have the ability to recognize and respond to stimuli that imposed selection pressure on their ancestors. Additionally, these responses are unlearned, as the rats did not have previous exposure to adult males or cats. Because threat-induced immobility and analgesia are resistant to domestication and rats still show them long after being removed from their natural environment, it seems that these responses had high survival values in rat ancestors.

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