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# Predator-induced opioid and non-opioid mediated analgesia in young meadow voles: sex differences and developmental changes

Lisa M. Saksida [a], Liisa A.M. Galea [b] and Martin Kavaliers [b]

[a] *Department of Psychology, University of British Columbia, Vancouver, BC (Canada) and* [b] *Neuroscience Program, Department of Psychology and Division of Oral Biology, University of Western Ontario, London, Ont. (Canada)*

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The present study examined developmental changes in the nociceptive responses of male and female meadow voles, *Microtus pennsylvanicus*, exposed to a garter snake, a natural predator of young voles. After 15 min of exposure to the presence of a garter snake, neonatal-juvenile voles (5–20 days of age) displayed naloxone (1.0 mg/kg)-sensitive opioid mediated analgesic responses, while after a brief 30-s exposure to the snake, voles displayed a higher amplitude, non-opioid analgesia that was insensitive to naloxone and blocked by the serotonin-1A (5-$HT_{1A}$) agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin. The levels of opioid and non-opioid mediated analgesia declined during development as the threat presented by the snake decreased. Young female voles also displayed a significantly greater non-opioid, 5-$HT_{1A}$ sensitive analgesia than males, with no significant sex differences in the lower amplitude opioid analgesia. These results indicate that young (neonatal) meadow voles that are exposed to a naturally threatening stimulus display sexually dimorphic analgesic responses. These findings also illustrate the need to consider the ecological context when examining environmentally-induced analgesia.

## INTRODUCTION

Exposure to a variety of aversive laboratory stimuli has been shown to produce a reduction in pain reactivity and induce analgesia[1,2,3]. Ecologically relevant stimuli associated with aggression and predation have also been shown to activate endogenous antinociceptive mechanisms[7,15,17–19,22,24,32,33]. These intrinsic analgesic systems are proposed to have a fundamental role in the organization of defensive responses and the expression of species specific defense patterns[6].

Depending on the characteristics of the stimuli, the antinociceptive responses have been shown to be mediated by either endogenous opioid or non-opioid mechanisms[23,36]. In both laboratory bred and wild adult rodents brief predator exposures can induce non-opioid mediated analgesia, while more prolonged exposures result in opioid analgesia[17–19]. There is evidence suggesting that the non-opioid mediated responses observed after the brief, more ecologically appropriate exposures, may involve anxiety-related serotonergic mechanisms[4,5,18].

Sex differences in nociception, antinociception, and responses to aversive stimuli have also been observed in adult rodents[18,34]. Adult male rodents display higher levels of exogenous opiate and endogenous opioid-mediated stress-induced analgesia than do adult females. Conversely, there is evidence for greater anxiety related, serotonergic mediated, responses in adult females than males[18]. Adult female rodents also display greater levels of serotonergic (5-$HT_{1A}$) mediated predator-induced analgesia and associated anti-predator responses than males[4,5,14,16,20].

These demonstrations of opioid and non-opioid mediated predator-induced analgesia, along with their gender dependency, have been limited to adult rodents. Relatively little is known about the ontogeny of anti-predator responses and the responses of young male and female rodents to natural predators. There are indications that both opioid and non-opioid anal-

*Correspondence:* M. Kavaliers, Division of Oral Biology, Faculty of Dentistry, University of Western Ontario, London, Ont., Canada N6A 5C1. Fax: (1) (519) 661-3875.

gesic systems are functional in young rodents[10,13,21,35]. However, whether or not these systems display any sexual dimorphism, or subserve responses to ecologically relevant stimuli, such as those associated with predators is not known.

In the present study we examined developmental changes (5–35 + days of age) in the nociceptive responses of meadow voles, *Microtus pennsylvanicus*, following either a brief (30 s) or more prolonged (15 min) exposure to a garter snake, which is a natural predator of young voles[25]. In addition, we describe the effects of the prototypic opiate antagonist, naloxone, and the 5-$HT_{1A}$ agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT)[9], on the predator-induced responses of the young voles.

## MATERIALS AND METHODS

*Experimental animals*

Sexually mature breeding meadow voles (35–55 g; 2–12 months of age) were housed as mixed-sex pairs in polyethylene cages with a hardwood (Beta-chip) substrate and cotton bedding at 20 + 2°C under a natural, approximately 14-h light–10-h dark cycle. Food (Purina Rat Chow 5015 and Prolab Guinea Pig Feed) and water were available ad libitum. The adults were laboratory born offspring derived from locally trapped animals.

Pregnant females (those greater than 50 g and with swollen abdomens) were checked daily until parturition at which time adult males were removed. Litters were monitored starting at 4–5 days of age to determine eye opening. At this time individuals could be reliably sexed by anal–genital distance, with males having a noticeably greater distance than females. Handling of litters was limited to every second day to minimize possible developmental disturbances[30]. Young were weaned at approximately 16 days of age and kept with their littermates until sexual maturity. Care was taken to exclude sibling and parent–offspring matings.

*Experimental procedures*

During the mid to late photoperiod individual male and female voles of various age classes (neonatal: 5–9 days; juvenile (pre-weaning): 10–14 days; weaning: 15–19 days; adults (immature): 20–24 days; adults: 25–29 and 30–35 days of age) were exposed for either 30 s or 15 min to either a common garter snake, *Thamnophis sirtalis*, or a plastic model of a snake. Exposures took place in an aquarium (40 × 20 × 25 cm) in which the snake and vole were separated by wire mesh screening. The voles were provided with a hardwood substrate on their side of the aquarium. Although there was no direct physical contact, the voles were exposed to the visual, auditory and chemosensory cues associated with the snake. The snake was aware of the presence of the voles and initially expressed an active interest in each vole.

Nociceptive responses of the voles ($n = 6$, for males and females of the various age groups) were recorded prior to and directly (15–30 s), 15, 30, 45 and 60 min after exposure to the snake or model. Nociception was measured as the latency of a foot-lifting response to an aversive thermal stimulus (50 ± 1°C; hot-plate, Omni-Tech, OH). The voles were previously acclimated to the exposure chamber and thermal testing procedures. In the wild adult female meadow voles will typically leave the young unattended in the nest for up to 1 h, with the young voles displaying minimal distress[26,29].

Either immediately, or 15 min, before being exposed for 15 min and 30 s, respectively, to the snake or model, different groups of male and female voles (10–14, 15–19, 20–24 days of age: $n = 6$, in all cases) received intraperitoneal (i.p.) injections of either naloxone hydrochloride (1.0 mg/kg; Sigma, MS), 8-OH-DPAT (0.50 mg/kg; Research Biochemicals, MA), or isotonic saline vehicle (10 ml/kg). Thermal response latencies of individual voles were recorded prior to injection and predator or non-predator exposure and directly, 15, 30 and 45 min after exposure. The thermal response latencies of additional unexposed male and female voles (15–19 and 30–35 days of age; $n = 6$) i.p. injected with either naloxone (1.0 mg/kg), 8-OH-DPAT (0.50 mg/kg) or saline (10 ml/kg) were also determined. The doses of naloxone and 8-OH-DPAT used were based on the results of previous investigations and pilot studies, where these doses were shown to have no evident effects on basal locomotor activity and nociceptive responses of rodents[11].

Data were analyzed by repeated measures multifactorial analysis of variance and post-hoc comparisons were done with the Newman–Keuls test with the significance levels set at 0.05.

## RESULTS

Young male and female voles exposed to the snake were analgesic, displaying significant ($P < 0.01$ for 30-s exposure males and females 5–19 days of age and females 20–24 days of age; $P < 0.05$ for 15-min exposure males and females 5–19 days of age) increases in their thermal response latencies (Figs. 1A, B). In all cases, maximum analgesia ($P < 0.01$ for 30 s, and $P < 0.05$ for 15-min exposures for males and females 10–14 days of age) was evident directly after exposure to the snake, with a decline to basal levels by 15–30 min (Fig. 2A, B). Male and female voles (5–9 and 10–14 days of age) exposed to the snake for 30 s displayed a signifi-

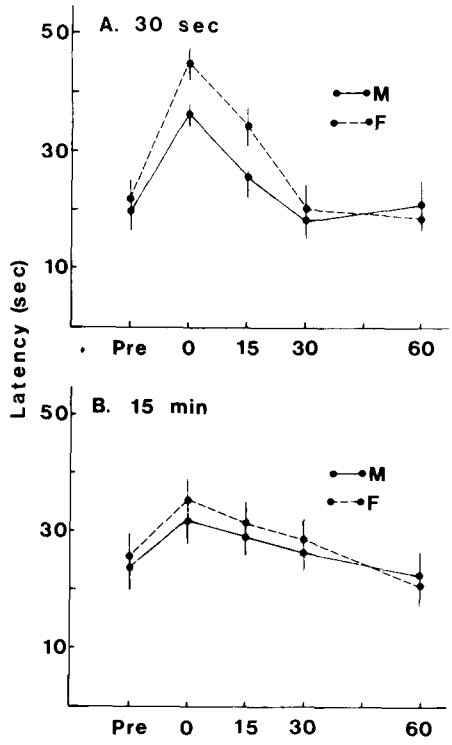


Fig. 1. A, B: effects of a 30 s (A) and 15 min (B) exposure to a predator, a garter snake, on the thermal (50°C) response latencies of male (M) and female (F) pre-weaning (10–14 days of age) meadow voles. The nociceptive responses of the voles 15 min prior (Pre) to the exposure are also shown. $n = 6$, in all cases. Vertical lines denote a standard error of the mean.

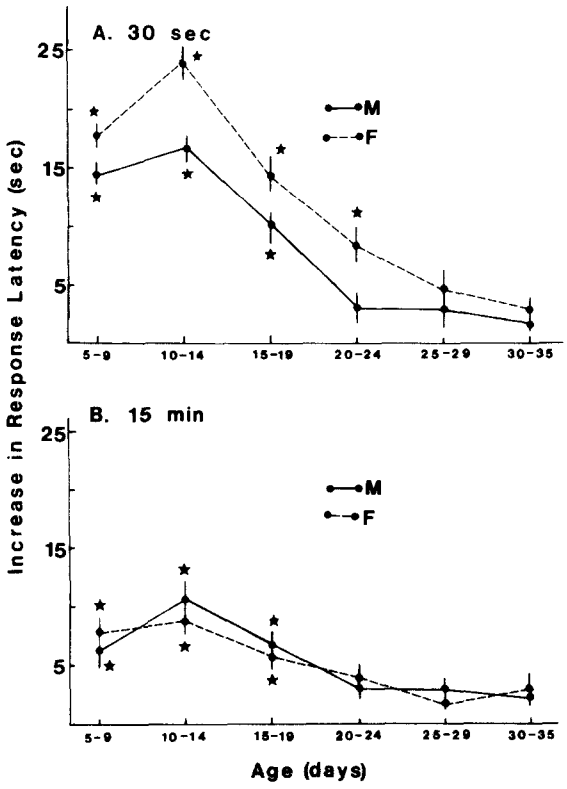


Fig. 2. A, B: effects of a 30 s (A) and 15 min (B) exposure to a predator, a garter snake, on the thermal (50°C) response latencies of various ages of male (M) and female (F) meadow voles. Increases in basal response latencies recorded directly after exposure to the snake are shown, with stars (*) denoting a significant ($P < 0.05$) increase in response latency. $n = 6$, in all cases. Vertical lines denote a standard error of the mean.

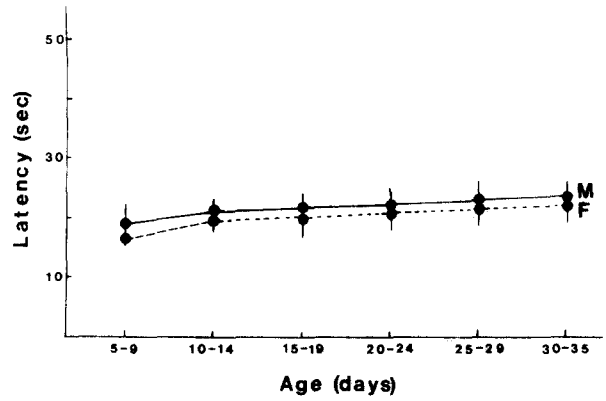


Fig. 3. Latency of response to an aversive thermal surface (50° C) of male (M) and female (F) meadow voles of various ages. Similar nociceptive responses were displayed by the various age classes of meadow voles that were exposed for either 30 s or 15 min to a model of a snake. $n = 6$, in all cases. Vertical lines denote a standard error of the mean.

cantly ($P < 0.05$) greater amplitude of analgesia than did animals that were exposed for 15 min. In both cases response, latencies were not significantly different from pre-exposure levels by 30 min post-exposure.

The degree of analgesia induced by a 30 s exposure to the snake declined during the course of development, with male and female voles 15–19 and 20–24 days of age displaying significantly ($P < 0.05$) lower levels of analgesia than 10–14 day old voles (Fig. 1A, B). There was also a non-significant developmental

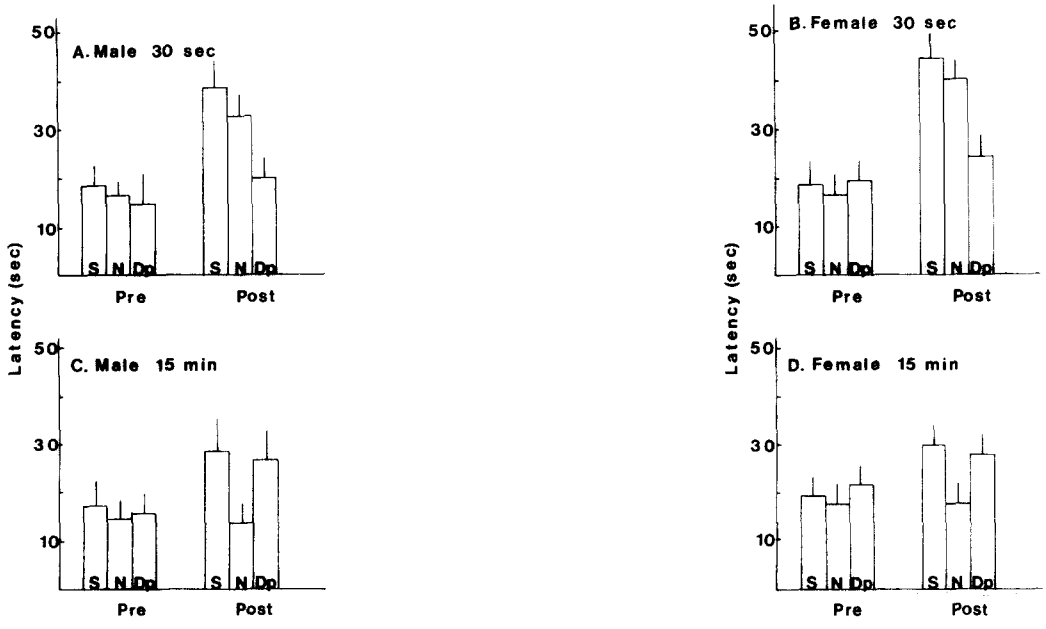


Fig. 4. A, D: effects of intraperitoneal (i.p.) injections of either naloxone (N; 1.0 mg/kg), 8-OH-DPAT (Dp; 0.50 mg/kg), or saline vehicle (S; 10 ml/g) on the thermal (50°C) response latencies of pre-weaning (10–14 days of age) male and female meadow voles exposed to a predator, a garter snake, for: 30 s, male (A); 30 s, female (B); 15 min, male (C); and 15 min, female (D). In all cases, nociceptive response were determined 15 min after injection (Post), as well as 15 min prior (Pre) to predator exposure and injection. $n = 6$, in all cases. Vertical lines denote a standard error of the mean.

decline in the lower level analgesia following a 15-min exposure to the snake. The presence of the garter snake (30 s or 15 min) had no significant effects on the nociceptive response of subadult and adult (25 + days of age) voles.

There were also sex differences in the levels of predator-induced analgesia displayed by the young voles. The analgesia induced by 30 s of exposure to the snake was significantly ($P < 0.05$, directly after exposure for 5–24 days of age groups) greater in the female than the male voles. There were no significant sex differences in the lower amplitude analgesia evident after 15 min of exposure to the snake. Exposure to a model snake for 30 s–15 min (stationary or manually 'wiggled' and in additional controls snake odor) had no signifcant effects on the nociceptive responses of either the male or female voles. Across all exposure conditions, there were no consistent, significant ($P > 0.05$) developmental changes or sex differences in the nociceptive responses of male and female meadow voles (Fig. 3)

The significant analgesia induced by 30 s of exposure to the snake was blocked ($P < 0.01$, for 10- to 14-day-old voles) by 8-OH-DPAT in both male and female voles (Fig. 4A, B). Neither naloxone nor saline had any significant effects on the analgesia arising from 30 s of exposure. There were no significant differences between the analgesic responses recorded from uninjected mice (Fig. 2A), naloxone and saline-injected voles (Fig. 4A, B), with in all cases female voles displaying significantly greater 8-OH-DPAT sensitive analgesia than male voles.

In both male and female voles, naloxone blocked ($P < 0.05$, for males and females 10–14 days of age) the analgesia induced by a 15-min exposure to the snake, and the response latencies of naloxone injected mice were equivalent to those of unexposed animals (Fig. 4C, D). Neither 8-OH-DPAT nor saline had any significant effects on the analgesic responses arising from 15 min of exposure to the snake. There were no significant differences between the analgesic responses recorded from uninjected mice (Fig. 2B), 8-OH-DPAT, and saline injected animals (Fig. 4C, D). Neither naloxone, 8-OH-DPAT nor saline had any significant effects (not shown) on the basal response latencies of control unexposed male and female voles.

## DISCUSSION

The results of the present study demonstrate that exposure to a natural predator, a garter snake, induces opioid and non-opioid mediated analgesia in young (neonatal-juvenile) meadow voles. After a brief (30 s) exposure to the snake, young (5 + days of age) meadow voles displayed non-opioid, 5-$HT_{1A}$ mediated, 8-OH-DPAT-sensitive analgesia, whereas a prolonged (15 min) exposure to the predator induced naloxone-reversible, opioid-mediated analgesia.

These findings of snake-induced analgesia are consistent with, and extend to an ecologically valid situation, previous demonstrations of opioid and non-opioid, 5-$HT_{1A}$-mediated analgesic responses in young rodents exposed to laboratory stressors[10,13,21,35]. The present observations are also consistent with the suggestion that serotonergic and opiate mechanisms and/or their interactions have a role in the mediation of neonate antinociception. Functional opiate receptors and exogenous opiate agonist-mediated responses have been demonstrated early in rodent postnatal development[10,21,27], while 5-HT receptors sensitive to 8-OH-DPAT have been reported on postnatal day 1 in rats[8]. This supports the presence of functional opioid and serotonergic mechanisms early in development. In this regard, it should also be noted that meadow voles display relatively rapid post-natal development[12,31] and minimal isolation-induced distress, being in the wild normally separated from the mother for extended periods of time[26,29].

The present results also agree with previous findings from several species of adult wild and laboratory bred rodents exposed to predators. In those studies it was observed that prolonged (15 min + ) predator (cat or weasel) exposures led to a naloxone- or naltrexone-sensitive, endogenous opioid-mediated analgesia; whereas brief exposures induced immediate non-opioid-mediated antinociceptive responses[17,19]. The opioid mediated analgesia was related to stress and passive defense responses, while the non-opioid-mediated antinociceptive responses were associated with anxiety, fear, and accompanying more active defense responses[4,5,17–19]. A similar dichotomy in analgesic responses and control mechanisms is also evident in adult rodents under conditions of social conflict, with brief exposures to an aggressive dominant conspecific leading to an immediate 5-$HT_{1A}$ sensitive response, and extended interactions leading to opioid-mediated responses[32,35].

The results of the present study also demonstrate sex differences in the predator-induced responses of postnatal-juvenile meadow voles. Young female voles displayed a significantly greater non-opioid 5-$HT_{1A}$ sensitive analgesia than young males, with no significant sex differences in the lower amplitude opioid-mediated analgesia. Sex differences in predator-induced responses have been previously reported in adult rodents, with females displaying greater non-opioid, 5-$HT_{1A}$ mediated analgesia and other anxiety-related

responses, than males[18]. Sex differences in the responses of laboratory mice to a rat snake (*Elaphe obsoleta*) have also been reported, with females displaying markedly greater aversive responses than males[37]. The present findings with meadow voles suggest that sex differences in 5-HT mediated responses may be present at an early (day 5 + postnatally) developmental stage. This may reflect an early organizational effect of gonadal steroids[2,3,28] on serotonergic systems and the establishment and functional display of sexually dimorphic serotonergic-related anxiety responses under environmentally appropriate conditions.

The ability of the prototypical 5-$HT_{1A}$ agonist, 8-OH-DPAT, to reduce predator-induced analgesia supports a role for 5-$HT_{1A}$ receptor mechanisms in the mediation of predator-induced analgesia. The antagonistic effect of the anxiolytic, 8-OH-DPAT, may be related to the inhibition of transmission by an agonist action on somatodendritic 5-$HT_{1A}$ autoreceptors[9]. This does not, however, preclude, a role for other serotonergic receptor types or, the involvement of additional non-opioid mechanisms, in the mediation of behavioral responses to other durations of predator exposures.

Non-opioid-mediated analgesic consequences of brief predator exposure have not always been reported[24]. The extent of opioid and non-opioid mediation is likely sensitive to the antinociceptive test employed and dependent on the context of the predator–prey interaction. It should, however, be noted that in pilot studies it was observed that the analgesic responses evident after the 30-s exposure to the garter snake were insenisitve to specific delta and kappa opiate antagonists along with that of naloxone.

Adult rodents exposed to either a predatory cat or a weasel have been shown to display significantly greater opioid than non-opioid-mediated analgesia[17–19], whereas in the present study snake-exposed young voles displayed greater non-opioid than opioid-mediated responses. This difference in response may reflect differences in the threat posed by the predators. The garter snake displayed marked threatening activity and interest in the voles only during the initial portions of the interaction, while the cat and weasel displayed continuous threat. In addition, the amplitude of the snake-induced analgesia declined during development, decreasing as the risk posed by the garter snake declined. Adult (25 + days of age) voles, which are generally too large to be captured by garter snakes, displayed non-significant antinociceptive responses to the snake. Whether or not other behavioral responses to the snake display similar decreases during development remains, however, to be determined. These observations do, however, further illustrate the need to take into account the ecological-ethological context, including sex differences and developmental stage, when examining environmentally-induced analgesia.

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