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Differential effects of prenatal morphine exposure on analgesia produced by vaginocervical stimulation or systemic morphine administration in adult rats

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Abstract

The present study investigated the effects of prenatal morphine exposure on the magnitude of analgesia produced by vaginocervical stimulation (VS) or systemic morphine injection in adult rats. In Experiment 1, an acute subcutaneous morphine (1 mg/kg) injection induced a 124% greater increase in tail-flick latency (TFL) in adult rats exposed prenatally to saline than to morphine. By contrast, in Experiment 2, VS induced a 196% greater increase in TFL in adult rats exposed prenatally to morphine than to saline. Female rats exposed prenatally to morphine also had a greater VS-produced increase in vocalization threshold (VOC-T) to tail shock than those exposed prenatally to saline. Thus, the present study demonstrates that prenatal morphine exposure exerts diametrically opposite effects on analgesia that is produced in adulthood by morphine or VS, attenuating the former while potentiating the latter. These findings provide evidence that the mechanisms underlying the two types of analgesia differ fundamentally.

Keywords: Prenatal morphine exposure; Morphine- and VS-induced analgesia

1. Introduction

In rats, receptors for neurotransmitters and neuromodulators that play a role in nociception, such as opioids, catecholamines, and gonadal steroids, begin to appear in the central nervous system (CNS) during the second half of gestation (Antelman and Caggiula, 1977; Clendeninn et al., 1976; Coyle and Pert, 1976; McEwen et al., 1978; Vito and Fox, 1981). Mid- to late-gestational exposure to morphine could potentially influence the development of those systems that play a role in nociception. In fact, prenatal exposure to opiates has already been shown to either increase (Gagin et al., 1996; Kirby et al., 1982; Zagon and McLaughlin, 1984) or decrease (Hovious and Peters, 1985; Johannesson and Becker, 1972; O'Callaghan and Holtzman, 1976) the analgesic response to opiate challenge later in life. Further, early postnatal morphine treatment exerts sex-specific, highly selective effects on analgesic responses on spinally mediated tail-flick (TF; Arjune and Bodnar, 1989).

Vaginocervical stimulation (VS) in adult rats induces analgesia. It differentially attenuates somatosensory thalamic neuronal responses to noxious, but not innocuous, sensory stimulation (Komisaruk and Wallman, 1977). Behaviorally, VS increases the latency to flick the tail away from radiant heat (TFL) and increases the vocalization threshold to electrical tail shock (VOC-T) (Komisaruk, 1974, 1991). The VS-induced VOC-T elevation is directly proportional to the force exerted on the cervix, and is strongly potentiated by estrogen treatment (Crowley et al., 1976).

The vaginal stimulation that occurs during mating in rats strongly potentiates their lordosis responses (Rodriguez-Sierra et al., 1975), but females that were exposed to

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morphine prenatally rarely show the lordosis response to male mounts (Vathy and Kátay, 1992; Vathy et al., 1985). Therefore, the present study was designed to test the hypothesis that prenatal morphine treatment reduces analgesic response to both a systemic morphine injection and VS. Consequently, we assessed analgesic responses using TFL and VOC-T in adult, prenatally morphine- and saline-exposed female rats, first to a systemic subcutaneous morphine injection and second to VS.

2. Methods

2.1. Animals

Timed pregnant Sprague–Dawley rats were purchased from Taconic Farms (Germantown, NY) on Postconception Day 8. The day of conception was considered Day 0. On the day of arrival, animals were weighed, housed individually in maternity pans ($47 \times 25 \times 15$ cm) with food and water available ad libitum, and maintained on a 14/10-h, reversed light/dark cycle with lights off at 1100 h. Pregnant females were randomly assigned to an experimental morphine- or a control saline-treated group.

2.2. Materials and injections

Morphine sulfate was obtained from the National Institute on Drug Abuse (Research Technology Branch, Rockville, MD) and was dissolved in physiological saline. As in all our works (Vathy, 1995; Vathy and Kátay, 1992; Vathy et al., 1985), on Postconception Days 11–18, pregnant rats were injected subcutaneously with 5–10 mg/kg morphine sulfate two times per day (0800 and 2000 h). To expose the animals gradually to a high dose of morphine, the first three morphine injections was 5 mg/kg, and the subsequent higher dose of morphine (10 mg/kg) was used (see Litto, 1983; Vathy et al., 1983). Control females received physiological saline injections at the same time.

2.3. Fostering and weaning

The day of birth was counted as postnatal day (PND) 0. On PND 1, pups were sexed, weighed, and morphine-exposed pups were tattooed with black India ink on one footpad for identification. Morphine- and saline-exposed litters were cross-fostered so that each mother raised half of her own and half of the adopted pups receiving the opposite prenatal treatment. Each mother raised a maximum of 10 pups. Pups were weaned on PND 25, weighed and housed individually with access to food and water ad libitum.

2.4. Postnatal surgeries and treatment

Female rats were ovariohysterectomized (OVX) at 60 days of age under Metofane (Pitman-Moore, Atlanta, GA) anesthesia leaving the uterine cervix intact. Following recovery, animals were transported to Rutgers University and were allowed to habituate 7–10 days prior to behavioral testing. Estradiol benzoate (EB; 3 μg) and progesterone (P; 500 μg), purchased from Steraloids (Wilton, NH), were injected subcutaneously 48 and 4 h prior to TFL or VOC-T testing, respectively. Acute subcutaneous morphine (1 mg/kg) was administered 30 min prior to TFL testing.

2.5. Behavioral measurements and nociceptive threshold determinations

All behavioral tests were conducted during the dark phase of the light cycle, between 1030 and 1400 h. For nociceptive threshold, two behavioral indices were utilized: TFL to radiant heat and VOC-T to a mild electric shock of the tail. These behavioral procedures have been described in our previous studies (i.e., Cunningham et al., 1991). Briefly, each female rat was placed in a Plexiglas restrainer for a 15-min period to habituate prior to baseline and VS-influenced TFL and VOC-T. For all experiments, four separate analgesia trials were conducted, two baseline trials and two test trials during VS. A 90-s intertrial interval was used for all behavior tests.

Additionally, TFL was also investigated following an acute subcutaneous injection of 1 mg/kg morphine. TFL was measured to assess whether prenatal morphine exposure (1) alters the analgesic effect of systemic morphine administration in adulthood and (2) differentially affects the analgesia produced by VS compared with systemic morphine administration in adulthood. The TFL tests to assess the effects of systemic morphine were conducted several hours after the TFL and VOC-T tests to assess the effects of VS. The tests to assess the effects of VS were performed during the application of the VS (starting approx. 5 s after the initiation of the VS). The tests to assess the effects of morphine were initiated approximately 1 h after the systemic injection.

2.6. Vaginocervical stimulation

Mechanostimulation was applied as continuous force against the uterine cervix (100 or 300 g) using a calibrated Force Dial Hand Held Dynamometer (Wagner Instruments, Model FD 300, Greenwich, CT) that was fitted with a soft rubber tip and lubricated with petroleum jelly.

2.7. Statistical analysis

All data are expressed as mean percent change from baseline. Baseline values were subtracted from test values, and this difference was divided by baseline values and multiplied by 100. Differences between groups were assessed by Student t tests in Experiment 1. Two-way analysis of variance (ANOVA) and Scheffe's post hoc

comparisons were used for comparison of treatment groups in Experiment 2.

3. Results

3.1. Experiment 1: effect of prenatal morphine exposure on an acute morphine-induced analgesia in adult female rats

As shown in Fig. 1, the effect of an acute subcutaneous injection of 1 mg/kg morphine (30 min prior to testing) on TFL was significantly lower in rats that were prenatally exposed to morphine than in the controls that were prenatally exposed to saline ($t = 2.85$, $P < .01$).

3.2. Experiment 2: effect of prenatal morphine exposure on VS-produced analgesia in adult female rats

3.2.1. Tail-flick latency

As shown in Fig. 2A, both the 100 and 300 g force of VS increased TFL in prenatally morphine-exposed females. There was a significant main effect of prenatal drug [$F(1,18) = 21.5$, $P < .001$]. Morphine-exposed rats had significantly elevated TFL regardless of the force of VS. Saline-exposed females, however, responded with increased TFL to VS when the stimulation force was increased to 300 g [$F(1,17) = 4.21$, $P < .05$]. No significant interaction was observed between these factors [$F(1,37) = 3.3$, $P = .08$].

3.2.2. Vocalization threshold

As shown in Fig. 2B, prenatal morphine exposure significantly increased VS-produced elevation in VOC-T relative to control females. There was a significant main effect of prenatal drug treatment [$F(1,18) = 11.22$, $P < .01$].

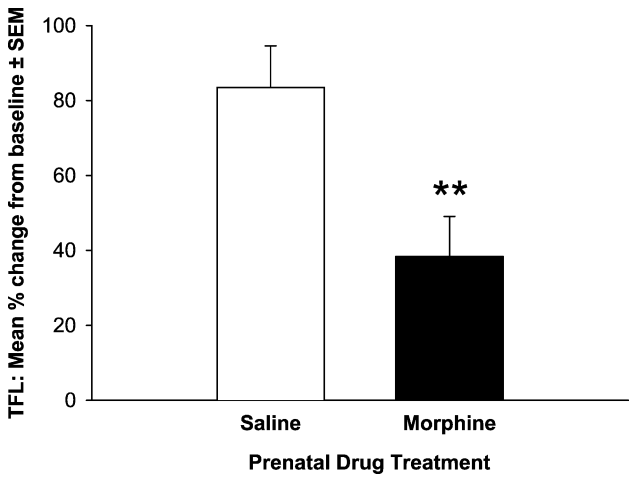

Fig. 1. Response to an acute subcutaneous morphine injection (1 mg/kg) was attenuated by prenatal morphine treatment. TFL = tail-flick latency. $N = 9–10$. $**P < .01$ vs. saline.

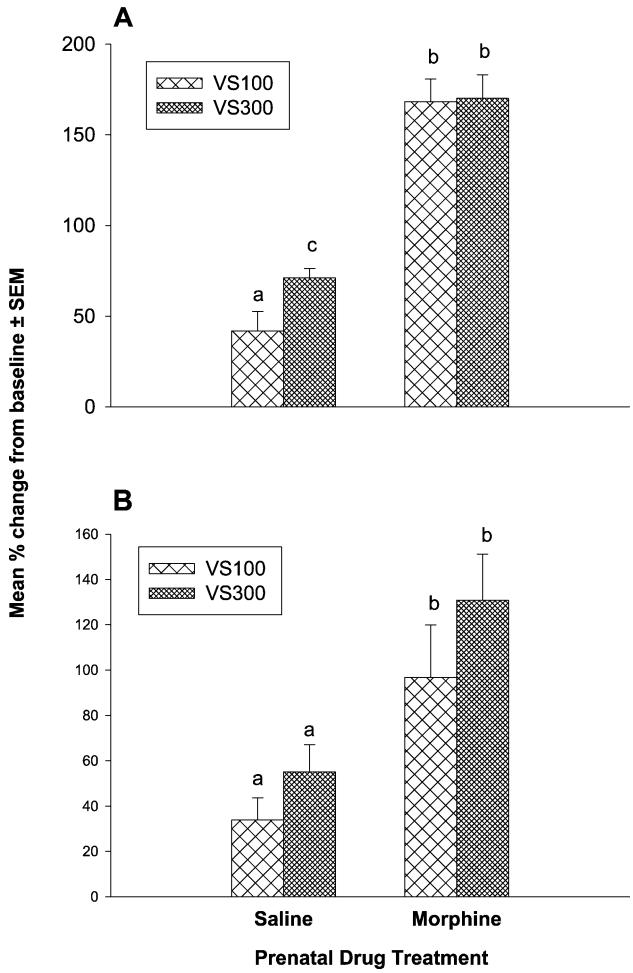

Fig. 2. Response to VS was potentiated by prenatal morphine treatment on TFL (A) and VOC-T (B). TFL = tail-flick latency. $N = 9–10$. Bars that do not share the same letter differ significantly from each other ($P < .05$). VOC-T = vocalization threshold; VS100 = VS 100g; VS300 = VS 300g.

Neither morphine-exposed nor control females responded differently to the different forces of VS.

4. Discussion

The present findings provide evidence that prenatal morphine exposure reduces the analgesic effect of an acute systemic morphine injection in adult female rats when tested at 75–80 days of age. This is consistent with findings that repeated morphine administration in adult rats diminishes an acute morphine-induced analgesia (Weinstein et al., 1988), and with earlier studies challenging prenatally opiate-exposed animals with an acute dose of morphine (Hovious and Peters, 1984; Huidobro and Huidobro, 1973; Johannesson and Becker, 1972; O'Callaghan and Holtzman, 1976; Steele and Johannesson, 1975). Perhaps a common mechanism underlies the morphine analgesic tolerance that results from prenatal morphine exposure and repeated mor-

phine administration in adulthood. There are, however, several reports that show increased analgesic effects on TFL in prenatally opiate-exposed animals (Gagin et al., 1996; Kirby et al., 1982; Zagon and McLaughlin, 1984). Such inconsistency could be attributed to variance in the schedules of drug administration. For example, Kirby et al. (1982) reported that an identical dose of morphine had different effects on the fetus, depending on whether it was given two vs. four times daily. It has been suggested that variation in the effects of prenatal morphine may be attributed to drug withdrawal experienced by fetus between injections (Lichtblau and Sparber, 1984).

Based on the attenuation of morphine-induced analgesia by prenatal morphine exposure in Experiment 1, we expected that VS-produced analgesia as measured by TFL might also be attenuated by prenatal morphine exposure. However, in Experiment 2, surprisingly, there was an augmented VS-induced analgesia, measured by both TFL and VOC-T in the prenatally morphine-exposed rats. The opposite effects of prenatal morphine exposure, potentiating VS-produced analgesia while attenuating acute morphine-induced analgesia, suggest that different mechanisms are responsible for opiate- and VS-produced analgesia. Two previous studies (Hill and Ayliffe, 1981; Steinman et al., 1982) showed that naloxone significantly attenuated the ability of VS to elevate the TFL, but only partially (by approx. 30%), thus implicating any endogenous opiate component to this effect of VS in addition to a nonopiate component. Further evidence of an opiate-independent component to VS-produced analgesia is that cold water swim-induced analgesia, which is opiate-independent, showed functional similarities to VS-produced analgesia in that repeated cold water swims produced tolerance to both VS- and cold water swim-produced analgesia (Bodnar and Komisaruk, 1984). By contrast, neither naloxone nor morphine tolerance attenuated the ability of VS to elevate VOC-T, thus indicating that this effect of VS is opiate-independent. Therefore, VS-produced analgesia is predominantly independent of endogenous opiates.

In the present study, the TFL test was used because it had been shown to be responsive to an endogenous opiate-mediated component of VS as well as to morphine itself (Hill and Ayliffe, 1981; Steinman et al., 1982). The objective of the present study was to ascertain whether prenatal morphine exposure would alter two different forms of opiate-mediated analgesia (morphine-induced and VS-induced) in adulthood. Our rationale for performing the VOC-T test in response to VS was to ascertain whether this test, previously shown to be unaffected by manipulation of VS-related endogenous opiates, would respond to VS in a pattern different from or similar to the TFL test responses to VS. The present findings that prenatal morphine exposure differentially increased both the opiate and the opiate-independent forms of VS-produced analgesia, whereas the prenatal morphine attenuated the morphine-induced analgesia, suggest that the prenatal morphine exerted effects on a nonopiate mechanism underlying VS-produced analgesia in addition to the morphine-sensitive analgesia system.

There are studies that demonstrated differential effects of prenatal opiate exposure on the TFL response to opiates in adults. Offspring of morphine- or methadone-pretreated dams displayed reduction in morphine- and methadone-reduced analgesia at prepubertal ages and in adulthood on the TFL test (Hovious and Peters, 1984; Huidobro and Huidobro, 1973; Johannesson and Becker, 1972; O'Callaghan and Holtzman, 1976; Steele and Johannesson, 1975). In contrast, Zagon and McLaughlin (1978, 1981) observed that offspring of methadone-treated dams displayed potentiation of methadone analgesia. These responses to adult treatment with methadone were more pronounced in females than in males, suggesting that females are more sensitive to a prenatal opiate insult.

In addition, early postnatal opiate exposure (Arjune and Bodnar, 1989), or prenatal stress increases TFL in adult animals in response to a morphine treatment (Kinsley et al., 1988). In these studies, females displayed greater analgesia to a morphine treatment in adulthood than did males (Arjune and Bodnar, 1989; Kinsley et al., 1988). These sex-dependent alterations on opiate analgesia suggest that endogenous opioids must interact with several central systems possibly converging on some common neuronal pathways. Endogenous opioids are important regulators of neural ontogenesis (Hammer et al., 1989; McLaughlin et al., 1997; Ricalde and Hammer, 1990), and the neuroregulation of adenohypophyseal functions including gonadal stimulation (Barraclough and Wise, 1982) and adrenocortical-stimulating activities (Martinez-Pinero et al., 1994) are regulated by catecholamines, particularly norepinephrine (NE). Thus, it is possible that the alterations in TFL of adult animals exposed to prenatal stress, or pre- or early postnatal morphine, result from alterations in the sensitivity of brain opioid and/or NE systems to opioids in adulthood. It has already been suggested that pre- and perinatal exposure to drugs, including opiates, affects those systems that are developing at the time of drug administration (Kellogg, 1992; Zagon and Slotkin, 1992).

Although the present study did not test the effects of NE on VS-produced analgesia, prenatal morphine exposure might have altered the NE system in the spinal cord as it does in the hypothalamus and locus coeruleus (Vathy and Kátay, 1992; Vathy et al., 1994, 2000a). The same schedule of prenatal morphine exposure as in the present study reduces hypothalamic NE content and turnover in adult female rats and attenuates their sexual receptivity to steroid priming (Vathy and Kátay, 1992; Vathy et al., 1994). VS releases NE into the spinal cord, and the NE receptor antagonist, phentolamine, administered directly to the spinal cord, attenuates VS-produced analgesia, providing evidence that NE is a mediator of VS-produced analgesia (Steinman et al., 1982). In the hypothalamus, NE action is necessary for lordosis behavior in steroid-primed animals (Etgen et al., 1999). Thus, it is possible that the effect of prenatal

morphine exposure on ovarian steroid–NE–opioid interaction is similar to that of an acute morphine injection (Vathy and Etgen, 1989). That is, after an acute morphine injection, normal adult female rats fail to display lordosis responses to stimulus males and have no increased hypothalamic NE release to the appropriate steroid priming (Vathy and Etgen, 1989).

The mechanisms underlying the opposite effects of the prenatal morphine exposure on the analgesic effects of VS vs. acute morphine are difficult to explain. What is clear from the present findings is that the analgesia produced by VS is subject to mechanisms that differ markedly from those affecting analgesia to morphine. Thus, it is possible that prenatally morphine-exposed females rarely exhibit lordosis responses to the mounting attempts of stimulus males not because mounting may elicit pain in these females, but because mounting stimulation is not adequate to induce sexual behavior in these females. Perhaps VS-produced analgesia utilizes opioid receptor subtypes that are different from those mediated by acute morphine-induced analgesia. A similar suggestion has been made by Crowley et al. (1977) who showed that in rats pretreated with naloxone, or made tolerant to the analgesic effect of morphine, VS produced just as strong an analgesic response (VOC-T elevation) as it did in saline-treated or nontolerant controls. They also suggested (Crowley et al., 1977) that either the analgesic effect of VS is not mediated by an opiate-sensitive neural system, or that VS- and morphine-produced analgesia may converge onto a common analgesic system, but at different sites in the nervous system.

It has been shown that morphine- and NE-produced analgesia could be reversed by the same dose of naloxone, whereas a much larger dose of naloxone was necessary to reverse serotonin-produced analgesia (Yang et al., 1994). It was suggested by Yang et al. (1994) that analgesic responses to morphine, NE, or serotonin might be through different opioid receptor subtypes. Thus, it is possible that the differential effects of prenatal morphine exposure on VS- vs. acute morphine-produced analgesia result from alterations in different opioid receptor subtypes. We have already shown that the same prenatal morphine exposure as in the present study affects the binding characteristics of all three major opioid receptor subtypes (μ, δ, and κ) in the brain of adult progeny (Rimanóczy and Vathy, 1995; Rimanóczy et al., 2001; Vathy et al., 2000b). These alterations in μ, δ, and κ receptor binding in female rats are receptor subtype- and site-specific (Rimanóczy and Vathy, 1995; Rimanóczy et al., 2001; Vathy et al., 2000b). It would be informative to investigate the involvement of opioid receptor subtypes in VS-produced analgesia in morphine-exposed adult female rats.

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