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Naloxone-sensitive, Pregnancy-induced Changes in Behavioral Responses to Colorectal Distention: Pregnancy-induced Analgesia to Visceral Stimulation

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This study examined the feasibility of using colorectal distention as a noxious visceral stimulus in rat pregnancy-induced analgesia studies as well as the influence of naloxone on the pregnancy-induced changes in the behavioral response to a noxious visceral stimulus. In the first part of the study, we compared the effects of pregnancy on several forms of noxious stimulation (colorectal distention, hypertonic saline induced writhing, tail flick, and hot plate). After determination of prepregnant baseline values, one group of rats (n = 35) was mated and retested on days 7 and 21 of gestation and 1, 3, 5, 7, and 14 days after parturition. After baseline determinations on day 21 and postpartum day 1, the animals received a subcutaneous injection of naloxone 1.0 mg/kg and were retested. A nonpregnant control group of animals (n = 7) was tested in the same manner. On day 21 of gestation and postpartum days 1 and 3, significant changes (higher threshold or longer latency to response) were observed after all but the writhing test. High-dose naloxone (1.0 mg/kg) significantly reduced the increases observed on day 21 and postpartum day 1. Nonpregnant rats demonstrated no significant change on any test day. The second part of the study evaluated a possible influence of low-dose naloxone on pregnancy-induced analgesia to visceral stimulation (colorectal distention) in another group of pregnant rats (n = 44). The significant increase in threshold on day 21 of gestation was not changed by intravenous (iv) naloxone 1.0, 2.3, or 3.0 μg/kg, whereas 5.0 and 20.0 μg/kg naloxone significantly decreased the observed pregnancy-induced analgesia. We have confirmed that colorectal distention is a reproducible visceral stimulus that may be used in pregnant animal studies and that a naloxone-reversible analgesia to visceral stimulation exists late in pregnancy and the early postpartum period in rats. In addition, these results indicate that low doses of naloxone that were shown to produce paradoxical analgesia in an inflammatory pain model do not produce an additional analgesia beyond that seen as a result of pregnancy in rats. (Key words: Analgesia: pregnancy induced. Antagonist, opioid: naloxone. Pain: colorectal distension.)

PREGNANCY-INDUCED ANALGESIA is of interest to anesthesiologists because of the observation that parturients may require less anesthetic or analgesic drugs.[1,2] Previous studies have demonstrated a unique form of endogenous, naloxone-reversible analgesia that becomes activated late in pregnancy.[3] However, human psychophysical tests of pain thresholds in pregnant women have not always supported the concept of pregnancy-induced analgesia.[4,5] The majority of these studies typically assessed only somatic pain, which differs greatly from the visceral pain associated with labor and delivery.

In animals, intraperitoneal administration of irritating solutions has been widely used as a noxious visceral stimulus.[6] Those procedures, however, may produce inescapable, long-lasting visceral stimuli that are difficult to control and interpret in pregnant animals. Recent reports have indicated that the presentation of colorectal distention is a safe, well-controlled visceral stimulus that is aversive and associated with relevant behavioral responses by the animals.[7]

The first purpose of this study was to evaluate colorectal distention as an adequate visceral stimulus that could be used in pregnant animals to further examine the physiology and pharmacology of pregnancy-induced analgesia in the rat.

The second purpose of this study centers on reports of clinical administration of low-dose naloxone to parturients in conjunction with perispinal opioids in an attempt to avoid adverse opioid-induced side effects.[8–10] It has been reported that administration of very low doses of the opiate antagonist naloxone (generally believed to be a pure opiate antagonist[11,12]) produces analgesia in a model of experimental chronic pain in rats[13] and also, interestingly, in clinical postoperative pain in humans.[14] The paradoxical analgesic effects of low-dose naloxone have suggested possible involvement with endogenous opiate systems in the modulation of pain.[15–17]

We hypothesized that low-dose naloxone would create additional analgesic effects in pregnant animals, in which there may well be changes in endogenous opiate systems.

Materials and Methods

This protocol was approved by the Yale University Animal Care and Use Committee. Experiments were performed on female Sprague-Dawley rats, weighing 200–

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250 g at the start of the experiment. Animals were housed in individual cages, with free access to food and water, and were kept on a 12 h light/dark cycle, with lights on at 6:00 AM.

The estrous cycle of the rats was monitored to determine the appropriate time for mating. The first day of mating on which mucous plugs were detected in the cage was designated as day 1 of pregnancy. Animals were used for only one experiment. In order to reduce handling effects on nociceptive responses, all animals were handled and trained in the test situation for at least 3 days before testing and all measurements were made by the same experimenter.

Four different tests were used to measure nociceptive response in rats. The colorectal distention apparatus and methods were modified from that of Anderson *et al.*[18] Colorectal distention involved inflation, with air, of a 7–8-cm long, pressure-monitored flexible latex balloon that had been inserted intraanally into the descending colon and rectum under light halothane anesthesia. Animals were awake during testing. Intracolonic pressure was continuously monitored *via* an in-line pressure transducer. Air pressure within the intracolonic balloon was steadily increased at a rate of 2–3 mmHg/s, beginning at 0 mmHg. The pressure at which abrupt constrictions of abdominal musculature were triggered by balloon distention was defined as the threshold response of colorectal distention. Ness and Gebhart[7] have shown that pressures of about 25 mmHg are aversive and produce cardiovascular and visceromotor changes suggestive of noxious stimulation in awake rats. A cut-off distention pressure was set at 60 mmHg to avoid tissue damage.

Abdominal writhing responses were induced by the intraperitoneal administration of 1.5 ml 4% saline. (This produces a short duration period of noxious stimulation.) Individual rats were scored every 10 s over a 3-min period after injection for the presence of characteristic changes in posture associated with writhing. The posture at the end of each 10-s time period was the value applied to that time period. The writhing score (0–3) was assigned as follows: 0 = normal body position of the rat, with paws flat on floor; 1 = leaning posture favoring one side of the body; 2 = stretching of the hind limbs and dorsiflexion of the hind paws, body stretched and flat on bottom, frequently with pelvis rotated sideways; and 3 = constriction of the abdominal muscles following by stretching of the body and extension of the hind limbs (described by Collier *et al.*[6].) Cumulative writhing scores were determined by averaging the ratings of two observers over the 3-min observation period, resulting in a maximum possible score of 54.

The tail-flick test was performed using a restraint box, and the response evoked by placing the animal's tail over a rectangular slit through which the light of a 50-W quartz bulb was focused. The position of a distal segment of the tail (about 2 cm from the tip) was changed systematically so that the same portion of the tail was not exposed repeatedly to the beam. Latency to withdrawal from the stimulus was monitored.

A hot-plate test, as described by Hargraeves *et al.*,[19] was also used to test pregnancy effects on somatic stimuli. Rats were placed under a clear plastic box (20 × 42 × 20 cm) on a thin glass floor. After an acclimation period, the radiant heat source (a 50W projector lamp bulb) was focused on the foot from under the glass floor directly beneath the hind paw. Latency to withdrawal from the stimulus was monitored.

Tail-flick and hot-plate response latencies were defined as the time required for the animals to withdraw from a radiant heat source focused on the tail or foot. In order to minimize tissue damage, the trials of tail-flick and hot-plate were terminated after 10 and 15 s, respectively.

In the first series of experiments, in which we evaluated the efficacy of colorectal distention, 42 rats were evaluated during baseline studies for their responses to the four tests. Animals were mated after baseline studies. One group of rats (n = 35), those that became pregnant, was retested on days 7 and 21 of gestation (delivery typically on day 22) and 1, 3, 5, 7, and 14 days after parturition. The other group of rats (n = 7), which did not become pregnant after mating, was retested in a similar fashion until what would have been postpartum day 3. After testing on day 21 of gestation and postpartum day 1, animals received a subcutaneous injection of either naloxone 1.0 mg/kg or an equal volume of normal saline, and were retested.

Each test (except writhing) was repeated ten times on each test day, with a 30-s intertrial interval. The threshold or latency at each time point was defined as the mean of the last five tests and was used for analysis. In the writhing test animals received intraperitoneal administration of hypertonic saline only once at each time point.

In the second series of experiments, in which we examined the influence of low-dose naloxone, all testing procedures for colorectal distention were identical to those described above. Forty rats were tested for baseline threshold levels to colorectal distention pressure that produced abdominal constriction. After determining the pain threshold before pregnancy, animals were mated. On day 21 of gestation, animals were again tested for their colorectal distention threshold. Immediately after determining threshold levels, animals were randomly divided into groups and received either one of the following doses of naloxone hydrochloride (1.0, 3.0, 5.0, and 20.0 μg/kg) or equal volumes of normal saline (n = 8) intravenously and were retested for threshold values 15 min later. The

doses of 1.0 (n = 5), 5.0 (n = 5), and 20.0 (n = 7) μg/kg naloxone were calculated by the mother's body weight on day 21 of gestation. In addition, animals in the 3-μg/kg test group were further subdivided based on the mother's body weight on either day 7 (n = 10) or day 21 (n = 9) of gestation. These doses were chosen because Kayser *et al.*[17] have reported that 3 μg/kg naloxone administered intravenously produces a peak paradoxical analgesic effect in chronic arthritic rats. The mean dose of naloxone that animals received when based upon their weight on day 7 was 2.3 ± 0.3 μg/kg.

In the second set of experiments, the animals received six colorectal distention stimuli at 30-s intervals to determine the threshold values on each test day. We defined the threshold as the mean of the last three of these six measurements at each test point.

Data are expressed as mean ± standard deviation (SD). Differences between nonpregnant and pregnant animals on day 21 were evaluated using the Mann-Whitney U test. Differences between pregnant groups were evaluated using Kruskal-Wallis one-way analysis of variance. Differences were considered significant at the $P < 0.05$ level.

Results

All pregnant animals that were included in the analysis delivered normal litters. Intraanal insertion of the colorectal distention balloon was quite easy under light halothane anesthesia. Thirty-five of the 42 mated animals in the first study became pregnant. Seven mated animals, which did not become pregnant, were used as controls.

The observed changes in the mean data for the four behavioral tests (colorectal distention, writhing, tail-flick, and hot-plate) before and after parturition in pregnant rats and in nonpregnant animals are depicted in figures 1 and 2.

Prior to pregnancy, the thresholds for colorectal distention and the tail-flick and hot-plate latencies were 22.4 ± 3.0 mmHg, 4.9 ± 0.5 s, and 7.5 ± 0.7 s, respectively in rats that became pregnant and 24.1 ± 2.6 mmHg, 5.0 ± 0.5 s, and 6.9 ± 0.6 s, respectively in nonpregnant control animals. These baseline threshold and latency values in the two groups were not significantly different. On day 21 of gestation, the colorectal distention threshold (29.1 ± 4.6 mmHg), tail-flick and hot-plate latencies (6.1 ± 1.1 s and 9.3 ± 1.2 s, respectively) in pregnant animals were significantly greater than the prepregnant baseline values and also were significantly different from those observed in nonpregnant rats. These increased thresholds and latencies were maintained on postpartum day 1 and 3 for colorectal distension and hot-plate latency and returned to the prepregnant baseline values by postpartum day 5. Although the mean data demonstrate a pregnancy-induced analgesia, 20% of the pregnant animals did not show a change in pain threshold.

The pattern of alterations in distention thresholds and withdrawal latencies during repeated testing in pregnant animals was not seen over the same time span in nonpregnant animals.

Writhing responses were assessed by scoring the cumulative writhing activities over a 3-min period after intraperitoneal administration of 1.5 ml 4% saline in 24

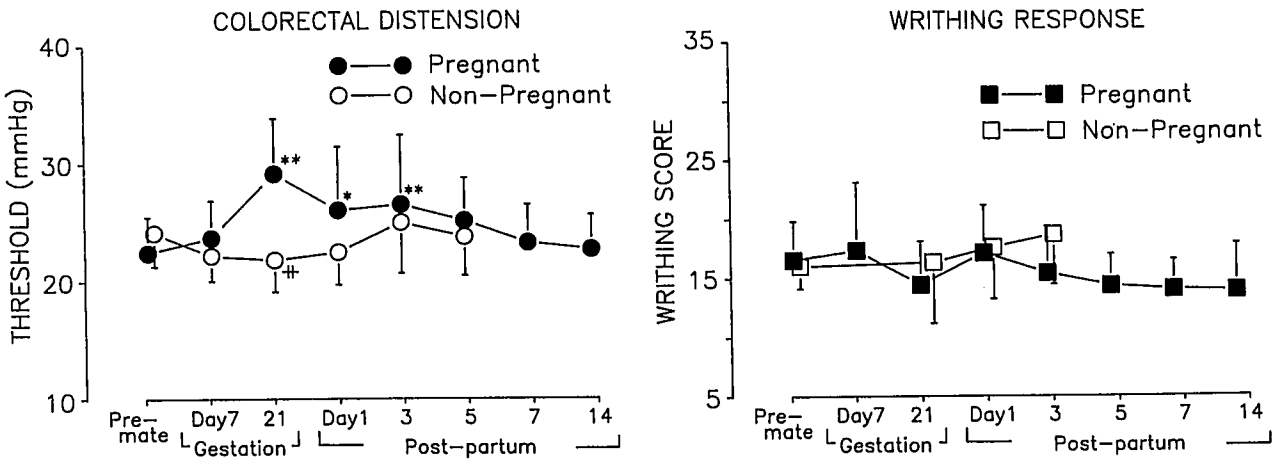

FIG. 1. Comparison of colorectal distention thresholds and writhing responses before and after parturition in pregnant rats (filled symbols) and in nonpregnant animals (open symbols). On day 21 of gestation, mean colorectal distention thresholds in pregnant rats (n = 35) were significantly different from those observed in nonpregnant animals (n = 7), whereas the prepregnant baseline thresholds in the two groups were not significantly different. Analgesia was also evident on postpartum days 1 and 3. In the writhing tests, no significant changes in the pregnant groups on any test day or between the two groups across the test points were observed. Each point is represented as the mean ± SD. $**P < 0.01$ compared to prepregnant baseline values. $*P < 0.05$ compared to prepregnant baseline values. $\dagger\dagger P < 0.05$ compared to pregnant animals.

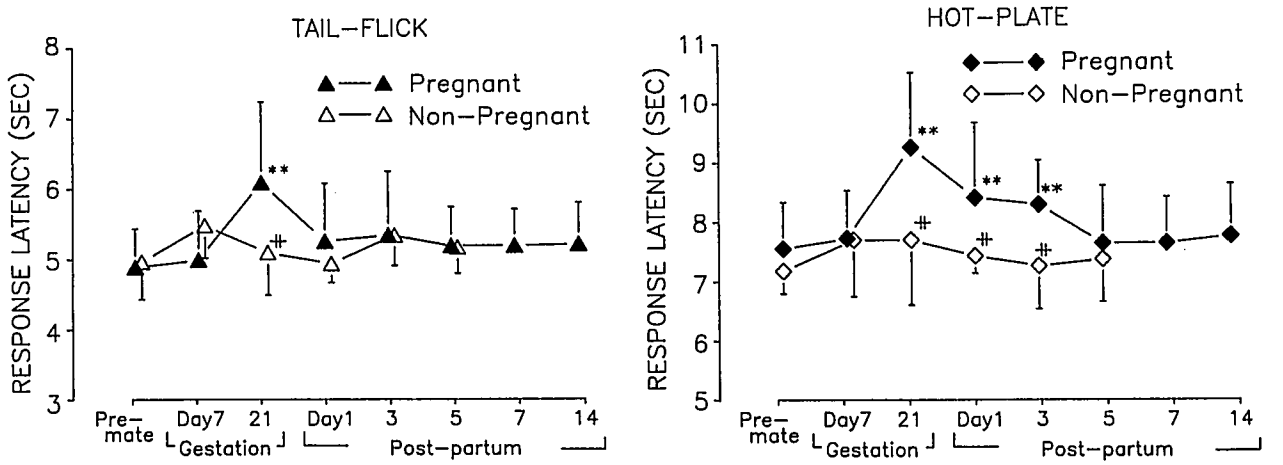

FIG. 2. Comparison of tail-flick and hot-plate latencies before and after parturition in pregnant rats (filled symbols) and in nonpregnant animals (open symbols). On day 21 of gestation, both tail-flick (n = 35) and hot-plate (n = 28) latencies were significantly greater than the prepregnant baseline values (n = 35, each test) and than those observed in nonpregnant animals (n = 7). These elevated hot-plate latencies in pregnant rats were maintained through postpartum day 3. Each point is represented as the mean ± SD. $^{**}P < 0.01$ compared to prepregnant baseline values. $\dagger\dagger P < 0.05$ compared to pregnant animals.

pregnant rats and in 7 nonpregnant animals. On day 21 of gestation, typical writhing responses were observed in only 14 pregnant animals, whereas all nonpregnant animals writhed after intraperitoneal hypertonic saline administration.

Prepregnant baseline writhing scores in pregnant rats and nonpregnant animals were 16.5 ± 3.2 and 16.0 ± 1.7, respectively. No significant difference of writhing responses was demonstrated between pregnant and nonpregnant rats across test days, and there was no significant suppression of writhing scores in pregnant animals on any test day (fig. 1), although some animals demonstrated an absence of writhing.

The effects of 1.0 mg/kg of naloxone or saline administered subcutaneously on pain thresholds and withdrawal latencies on day 21 of gestation are illustrated in figures 3 and 4. As expected, 1.0 mg/kg naloxone resulted in a significant reduction in colorectal distention thresholds and tail-flick and hot-plate latencies on day 21 of gestation (figs. 3 and 4), whereas saline administered in the same volumes as that used to deliver naloxone did not produce changes in colorectal distention thresholds in pregnant rats (fig. 3). The effect also was not seen when naloxone was administered to nonpregnant animals. On postpartum day 1, administration of 1.0 mg/kg naloxone produced a significant decrease of threshold in colorectal distention, from 26.6 ± 2.8 mmHg (n = 12) to 23.4 ± 2.9 mmHg, a value that was not significantly different from prepregnant baseline values (21.3 ± 2.8 mmHg).

In the second experiment, possible effects of low-dose naloxone on pregnancy-induced analgesia to colorectal distention were examined on day 21 of gestation in pregnant animals. As was shown in the first experiment, on day 21 of gestation, colorectal distention thresholds were significantly increased as compared with the prepregnant baseline values. On day 21 of gestation, neither saline nor 1.0, 2.3, or 3.0 μg/kg naloxone caused a statistically significant change in the mean of colorectal distention threshold values (neither an increase nor a decrease) (fig. 5). In contrast, 5.0 and 20.0 μg/kg naloxone produced a significant reduction in the thresholds obtained on day 21 of gestation (fig. 5).

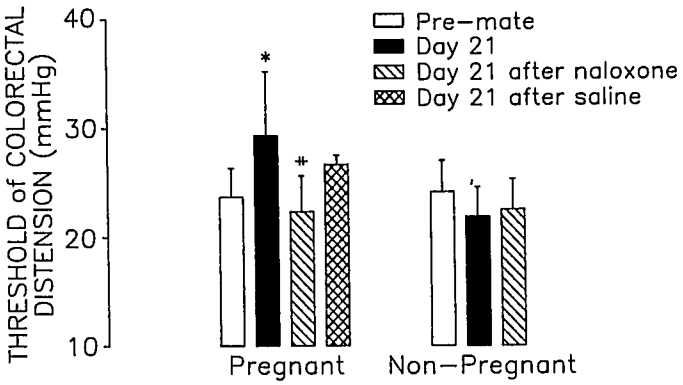

FIG. 3. Effects of subcutaneous administration of either naloxone 1.0 mg/kg or saline on the colorectal distention thresholds in pregnant (n = 29) and nonpregnant animals (n = 7) rats. On day 21 of gestation, elevated thresholds in pregnant rats were significantly decreased after naloxone (n = 22), whereas the same volume of saline (n = 7) did not produce a significant change. No significant change was observed after the administration of 1.0 mg/kg naloxone in nonpregnant animals on day 21 of gestation. Vertical bars indicate the mean ± SD. $^{*}P < 0.05$ compared to prepregnant baseline values. $\dagger\dagger P < 0.05$ compared with values on day 21 of gestation.

Discussion

Although in both human[20] and animal studies,[3] using only somatic stimuli, results have demonstrated pregnancy-induced analgesia, other studies[4,21] do not support its existence. Results of this study confirm the existence of pregnancy-induced, naloxone-reversible changes in behavioral responses to noxious visceral and somatic stimulation that are active late in pregnancy and the early postpartum period in rats. In addition, the adequacy of colorectal distention as a visceral stimulus for use in the study of pregnancy-induced analgesia has been confirmed.

The question of the presence or absence of pregnancy-induced analgesia in any single individual is likely to be complex. In this study, 20% of the animals did not demonstrate changed thresholds or latencies on day 21. Although the mean data demonstrated a statistically significant effect for the sample, it is likely that, as a result of biologic variability, some individuals will not experience pregnancy-induced analgesia.

A major part of labor is associated with nonsomatic nociception from uterine, cervical, and peritoneal afferent fibers. However, because of the difficulty in defining a reliable, noninvasive natural noxious visceral stimulus in pregnant animals, visceral pain has not been widely investigated. Widely used visceral pain models such as writhing tests have a questionable relationship with the pathology of human visceral pain and also raise concerns about the presentation of inescapable, long-lasting noxious stimuli. Moreover, in pregnant animals, the intraperitoneal administration of an irritating solution proves to be an unreliable way of studying visceral pain because of the difficulty of appropriate intraperitoneal administration.§ In fact, about 40% of pregnant rats tested on day 21 of gestation in this study did not show a typical writhing response. There is no way to know, however, if the absence of writhing was due to true analgesia or to mechanical factors resulting from the mass of the uterus. Furthermore, hypertonic-saline-induced writhing responses were not associated with analgesia on day 21 of gestation, despite our previous observations,¶·** using the same writhing test, of endogenous visceral pain tolerance prior to delivery.

In contrast, there is clinical as well as experimental evidence that distention of hollow organs such as the colon or gall bladder is closely related to a natural noxious stimulus that occurs in pathologic conditions causing pain. The adequacy and reliability of colorectal distention as a noxious visceral stimulus in nonpregnant rats have been carefully evaluated by Ness and Gebhart,[7] and the mean threshold value in this study (22.4 ± 3.0 mmHg) corresponds well with aversive threshold values reported by

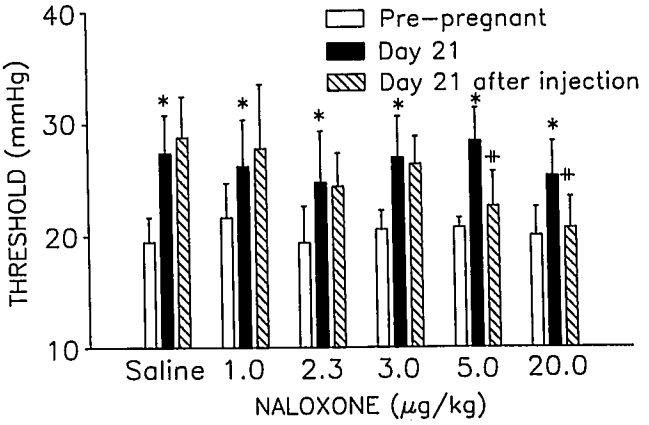

FIG. 5. Effects of intravenous administration of low doses of naloxone or saline on colorectal distention thresholds in pregnant rats (n = 44). On day 21 of gestation, significantly elevated thresholds as compared to prepregnant threshold values were demonstrated. Doses of naloxone are indicated below each of the hatched bars. However, no significant change after administration of low-dose naloxone 1.0 (n = 5), 2.3 (n = 10) and 3.0 (n = 9) μg/kg or the same volume of saline was observed. Naloxone 5.0 (n = 5) and 20.0 (n = 7) μg/kg significantly reduced the increase in the threshold observed on day 21 of gestation. Vertical bars indicate the mean ± SD. *$P < 0.05$ compared to prepregnant values. ††$P < 0.05$ compared with values on day 21 of gestation.

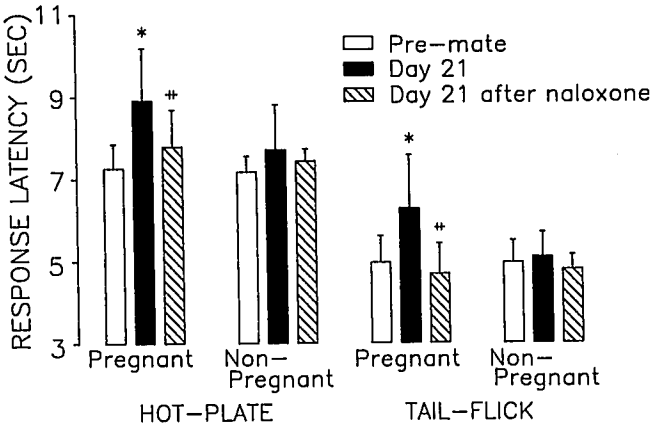

FIG. 4. Effects of 1.0 mg/kg naloxone on tail-flick and hot-plate latencies in pregnant rats and in nonpregnant animals. On day 21 of gestation, elevated tail-flick (n = 22) and hot-plate (n = 17) latencies were significantly decreased after naloxone, whereas no significant change in the two tests was observed after naloxone administration in the nonpregnant animals. Vertical bars indicate the mean ± SD. *$P < 0.05$ compared to prepregnant baseline values in pregnant rats. ††$P < 0.05$ compared to values on day 21 of gestation in pregnant rats.

§ Collins JG, Ren K: Unpublished observations.

¶ Sinatra R, Marando R, Ngeow JYF, Collins JG: Visceral pain tolerance in pregnant rats following intrathecal administration of fentanyl (abstract). ANESTHESIOLOGY 65:A370, 1986.

** Marando R, Sinatra R, Fu ES, Collins JG: Failure of intrathecally administrated nalbuphine to suppress visceral pain in pregnant rats (abstract). ANESTHESIOLOGY 67:A447, 1987.

those investigations (22.4 ± 0.9 mmHg). It would appear that this stimulus is also appropriate for the study of pregnancy-induced analgesia in rats.

Activation of endogenous opiate systems is believed to mediate increases in pain threshold observed during the late stage of pregnancy in rats.[3,22] However, additional possibilities exist. Decreased minimum alveolar concentration (MAC) levels of inhaled anesthetic agents during pregnancy have been associated with increased plasma progesterone concentration in rabbits, although hormonal influences do not appear to be as effective in rats.[23]

The current results obtained from pregnant rats support the possible role of an endogenous opiate system in modulating animal responses to pain associated with pregnancy. Kayser *et al.*[17] have shown that in rats with chronic arthritis, intravenously administered naloxone, at very low doses, produces a paradoxical analgesic effect that peaks at 3 μg/kg. Little is known about the mechanism of the paradoxical analgesic action of naloxone, but it is generally accepted that at least a part of its effect is due to an interaction with opiate receptors, since cross-tolerance between low-dose naloxone and morphine analgesia has been reported in experimental arthritic animals.[15,17] The lack of paradoxical naloxone analgesia in normal rats suggests that it may be seen only when endogenous opiate systems have been modified.

We speculated that conditions causing low-dose naloxone analgesia in the chronic inflammatory model may be present in pregnancy-induced analgesia. The naloxone reversibility of the pregnancy-induced analgesia suggests that the endogenous opiate systems have been modified. However, similar doses of low-dose naloxone that produced analgesia in arthritic rats did not significantly increase the level of pregnancy-induced analgesia to visceral stimulation in pregnant animals. There are a number of methodologic, analytical, and conceptual differences that may have contributed to low-dose naloxone's lack of effect on pregnancy-induced analgesia. Kayser *et al.* observed neither the antinociceptive nor the hyperalgesic effect of naloxone[24] 8 weeks after the induction of arthritis, although they did see these effects 3–4 weeks after the induction of arthritis. Furthermore, Ueda *et al.* have reported that in both writhing and tail-flick tests in mice the range of optimal naloxone dose for the enhancement of analgesia was very narrow, whereas naloxone produced biphasic effects.[25] The results of the current study suggest that the use of low-dose naloxone to avoid side effects of perispinal opiates in a parturient is not likely to add to an existing pregnancy-induced analgesia.

Our results not only demonstrated the utility of colorectal distention in pregnant rats, but also confirmed the existence, in rats, of naloxone-reversible, pregnancy-induced analgesia, an analgesia that influences both somatic and visceral stimuli. Naloxone reversibility suggests the possible role of endogenous opiates on pregnancy-induced analgesia. Although low-dose naloxone has been demonstrated to produce paradoxical analgesia in animals with inflammatory pain, this study indicates that low-dose naloxone does not produce an additional analgesia beyond that seen as a result of pregnancy in rats. These observations suggest that conditions causing naloxone analgesia in the chronic inflammatory model may not be present in pregnancy-induced analgesia.

Of particular interest, pregnancy-induced analgesia suggests a mechanism by which animals enhance their tolerance of pain. Further research using colorectal distention may clarify the pharmacology of pregnancy-induced analgesia, a pharmacology that may someday be applied to the treatment of human chronic pain.

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