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The Antinociceptive Effect of Vaginal Stimulation in the Rat Is Reduced by Naloxone

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HILL, R. G. AND S. J. AYLIFFE. *The antinociceptive effect of vaginal stimulation in the rat is reduced by naloxone.* PHARMAC. BIOCHEM. BEHAV. **14**(5) 631–632, 1981.—Mechanical stimulation of the vagina produces a powerful antinociceptive effect against a variety of noxious stimuli. In rats tested in either the radiant heat tail flick or the warm water tail immersion test the antinociceptive effect of vaginal stimulation was found to be significantly reduced, but not abolished, following the administration of 10 mg/kg of naloxone. These results are in contrast to those of an earlier study in which naloxone was ineffective against the antinociceptive action of vaginal stimulation in a tailshock vocalization paradigm. It therefore appears that the nature of the noxious stimulus used may influence the type of antinociceptive mechanism triggered by vaginal stimulation.

Naloxone antagonism Antinociception Vaginal stimulation Rats

MECHANICAL stimulation of the vagina of the rat with a blunt probe has a strong antinociceptive effect against a variety of noxious stimuli such as foot pinch, pressure on an inflamed paw and tail heating [6], and this procedure has been found to produce stronger analgesia than 2 mg/kg of morphine given intraperitoneally [6]. It has now been established that a number of other peripheral stimuli that produce behavioural antinociception are reduced in effectiveness following the administration of the opiate antagonist naloxone [4] suggesting the involvement of endogenous opioids in these effects but the effects of vaginal stimulation have been reported to be naloxone resistant [2]. Recently, we established that vaginal stimulation was one of the stimuli that would produce a naloxone reversible inhibition of the firing of reticular formation neurones in the caudal medulla of the anaesthetized rat [3] and it therefore seemed worthwhile to re-investigate the action of naloxone on the behavioural antinociception produced by vaginal stimulation.

METHOD

Experiments were performed on adult rats of the MRC Porton strain (195–270 g). Nociception reaction times to tail heating were assessed using either a radiant heat lamp or the warm water tail immersion technique [5] the endpoint in each case being the withdrawal of the tail from the vicinity of the stimulus. The water was maintained at 55°C and a cutoff time of 15 sec was used in both tests to avoid tissue damage. To compensate for variations in control reaction time results were expressed in the form of an index of antinociception, computed for each rat, using the formula:

$$\text{Index of antinociception (IA)} = \frac{\text{Reaction time} - \text{control reaction time}}{\text{Cut off time} - \text{control reaction time}}$$

A maximum antinociceptive effect (i.e., equal to or beyond the cutoff time) was therefore given a value of one and each animal's control reaction time was defined as zero. Vaginal stimulation was performed by pressing against the vaginal cervix with the soft silicone rubber piston of a 1 ml plastic tuberculin syringe, and stimulation was applied for 30 sec prior to and during the testing of nociception reaction time. Animals were restrained in a cardboard tube during testing and were held in a lateral position so that the vaginal probe did not impede movement of the tail. Immediately before each experiment vaginal smears were taken and the state of oestrus of each animal was determined histologically. Naloxone, in a dose of 10 mg/kg of the hydrochloride salt was administered intraperitoneally 30 min prior to testing.

RESULTS AND DISCUSSION

Three separate experiments were conducted on groups of 25 rats, one using radiant heat and the other two with warm water tail immersion. Of the total of 75 rats, only 3 did not respond to vaginal stimulation with an increase in nociception reaction time and antinociception was seen regardless of the state of oestrus. Control reaction times in the radiant heat tail flick test were in the range 3 to 5 sec and were extended to between 12 and 15 sec by vaginal stimulation whereas in the tail immersion test control values were shorter at 1 to 3 sec and were extended by vaginal stimula-

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TABLE 1

EFFECT OF NALOXONE PRE-TREATMENT ON THE ANTINOCICEPTIVE EFFECT OF VAGINAL STIMULATION

	Vaginal stimulation alone	Vaginal stimulation after naloxone
Radiant heat, (n=24)	0.79 ± 0.07	0.62 ± 0.09*
Hot water, group 1 (n=24)	0.50 ± 0.07	0.28 ± 0.07*
group 2 (n=24)	0.40 ± 0.07	0.12 ± 0.04*

All values are mean IA ± SEM (see text). Naloxone was administered at a dose of 10 mg/kg IP, 30 minutes before testing its effects on the response to vaginal stimulation.

*=$p<0.01$, Mann-Whitney U-test. One rat in each group failed to respond with an increase in reaction time following vaginal stimulation and these animals were therefore excluded from the naloxone study. The two hot water groups represent separate experiments performed with an interval of two weeks between them.

tion to between 7 and 12 sec. Naloxone (10 mg/kg) did not significantly alter the baseline reaction time (IA = −0.02 ± 0.06, n=24) but, in each of the three experiments, clearly reduced the antinociceptive effect of vaginal stimulation (Table 1).

It therefore appears, that under our experimental conditions, the antinociception produced by mechanical distention of the vagina in the rat may be, in part, attributable to the action of endogenous opioids. As antagonism by naloxone was not complete, in spite of the high dose of naloxone used [4] it is likely that other mechanisms, for example, those involving noradrenaline may also be important [1]. The failure of other workers to show naloxone reversibility may be attributable to the use of a different nociception test which measured vocalization in response to electrical stimulation [2] and it is noteworthy that in the present experiments naloxone was least effective in the radiant heat test where vaginal stimulation had its greatest antinociceptive effect.

It is now increasingly apparent that all tests of nociception are not equivalent and, for example, it has been possible to show that opiate agonists acting at the K receptor are much more effective against mechanical noxious stimuli than they are against thermal noxious stimuli [7]. It is possible that the antinociceptive effect of distention of the vagina may act through endogenous opioid systems against thermal noxious stimuli but through an alternative pathway against noxious electrical stimulation.

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