EFFECTS OF NARCOTIC AND NON-NARCOTIC ANALGESICS ON THE ABDOMINAL OR TAIL STIMULATION-INDUCED STRUGGLING IN RATS

Katsuo KAMATA, Kunihiko OGAWA and Tsutomu KAMEYAMA
Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences, Meijo University, Nagoya 468, Japan
Accepted January 10, 1981

Abstract—As a model, we used struggling induced by a repetitive stimulation of the tail or abdomen and two types of pseudoaffective responses were evoked in rats. The effects of narcotic and non-narcotic analgesics on these responses were alternately assessed. Narcotics were markedly effective in inhibiting struggling elicited by tail stimulation and slightly less effective in suppressing the abdominal stimulation-induced struggling. These effects on two types of struggling differed quantitatively but not qualitatively. On the other hand, non-narcotics such as aspirin (200 mg/kg, i.p.), aminopyrine (160 mg/kg, i.p.) and indomethacin (20 mg/kg, i.p.) had an inhibitory action on the struggling elicited by the tail stimulation but showed equivocal and far less inhibition on the abdominal stimulation-induced response. These two effects were quantitatively and qualitatively different because the slope of the dose-response curves were not in parallel. The action of baclofen appears to be ambiguous since it had distinctive inhibitory actions on both types of struggling. However, baclofen can be classified into the latter group in that it exerted an inhibitory action on two types of struggling, in a quantitatively different manner. These results suggest that two types of struggling in rats provide a convenient means to assess the potency of analgesics.

Guzman et al. (1-2), Lim et al. (3), Potter et al. (4) and Taira et al. (5-6) reported that an intra-arterial administration of bradykinin induces vocalization of animals, such being one of the indicators of visceral pain response. Collins et al. (7) suggested that vocalization, as an indicator of visceral pain elicited by electrical stimulation of the rectum can be used to evaluate the potency of analgesics.

We previously reported that struggling in response to repetitive stimulation of the tail was useful for the evaluation of analgesics and also that when the struggling and flexor reflex arc assessed simultaneously, an analgesic-like action of the drug resulting from muscle relaxation could be detected separately from the analgesic action itself (8). In an attempt to reproduce two types of pseudoaffective responses in the rat, we have studied the nature of struggling elicited by a repetitive electrical stimulation of the abdomen (peritoneal cavity) and tail. Effects of narcotic and non-narcotic analgesics on two types of pseudoaffective responses were also examined, using a modified method.

MATERIALS AND METHODS
All experiments were carried out on male Wistar rats weighing approximately 150 g.
These rats were anesthetized with α-chloralose (50 mg/kg, s.c.) and urethane (500 mg/kg, s.c.). The experimental arrangement is schematically illustrated in Fig. 1.

The effects of analgesics were determined on the basis of inhibitory actions on the struggling induced by the electrical stimulation of the abdomen and tail. When the abdomen or tail was repeatedly stimulated, the rat struggled violently. Movements of the head significantly increased and in parallel with struggling. Movement of the head was recorded as the indicator of struggling, by means of a force displacement transducer (Nihon-Kohden, SB1T). Repetitive stimulation was given at 30 min intervals following drug administration until the extent of struggling returned to the pre-medication level. The stimulation of the abdomen or tail was performed for 5 sec per stimulation. Rectangular wave pulses were applied through a pair of stainless steel electrodes placed on the root of the tail and in the peritoneal cavity, as shown in Fig. 1, at a frequency of 50 Hz. The intensity and duration of the pulse were 5–15 V and 2.5 msec, respectively. Stimulation of the tail was given immediately after the termination of that of the abdomen, and measurement of each struggling was alternately performed. Recordings were begun 90 min after the start of anesthesia (control response) and the drugs were administered 100 min later. All drugs were given i.p. through an implanted cannula.

The drugs used were morphine hydrochloride (Shionogi), pethidine hydrochloride (Tanabe), codeine phosphate (Shionogi), pentazocine (Sankyo), aspirin, aminopyrine, indomethacin (Milan) and baclofen (CIBA-Geigy).

RESULTS

Examination of frequency of stimulation and depth of anesthesia: Since the rats were not artificially ventilated and intensive stimulation was given to animals to reproduce visceral pain, somewhat higher doses of α-chloralose and urethane were used, in comparison with previous study (8). As previously reported, 50 mg/kg, s.c. of α-chloralose and 500 mg/kg, s.c. of urethane exerted no appreciable influence on the response to electrical stimulation of the tail. As shown in Fig. 2, when 50 mg/kg of α-chloralose and 500 mg/kg of urethane were administered, reproducible responses to electrical stimulation of the tail or abdomen were obtained for at least 5 hr.

In preliminary experiments, the inhibitory
patterns seen on the electroencephalogram following administration of the aforementioned doses of α-chloralose and urethane took the form of arousal responses when the tail or abdomen was stimulated at 5 V for 10 sec, indicating that the rats responded to pain, even during the state of anesthesia.

We preliminarily examined the effects of various drugs on flexor reflex under conditions of the type of anesthesia used in the present work. The 50% inhibitory doses of various drugs to flexor reflex were as follows (mg/kg, i.p.): morphine, 7.93; pethidine, 37.87; codeine, 52.79; pentazocine, 15.70; aspirin, no effect; aminopyrine, no effect; indomethacin, no effect; baclofen, 8.15.

When the frequency of stimulation was changed from 10 to 100 Hz, the most intensive struggling was elicited at 50 Hz (Fig. 3). Five successive repetitive stimulations were given at intervals of 30 sec in each experiment, but there was no sign of adaptation.

Effects of drugs on two types of pseudo-affective responses: Figures 4 and 5 show effects of narcotic and non-narcotic analgesics on the struggling induced by a repetitive electrical stimulation of the tail or abdomen. Morphine and codeine were markedly effective in inhibiting the tail stimulation-induced struggling responses but were less effective in suppressing that induced by abdominal stimulation (Fig. 4). In contrast to morphine and codeine, aspirin and indomethacin exerted an inhibitory action on struggling induced by the tail stimulation but appreciably no effects on the abdominal stimulation-induced struggling, as shown in Fig. 5. The effects of these drugs were time-dependent and the time to peak effect of morphine, codeine, aspirin and indomethacin

![Fig. 2. Changes in abdominal and tail stimulation-induced struggling after anesthetization of the rat with α-chloralose and urethane. Each symbol represents mean value with S.E. of 8 determinations.](image)

![Fig. 3. Effects of frequency of stimulation of the abdomen and tail on struggling. Quantitative determinations of the struggling were made by measuring the area of struggling circumscribed by the base line. Each symbol represents mean value with S.E. of 7 determinations.](image)
was 30, 45, 90 and 60 min, respectively.

As shown in Fig. 6, the inhibitory actions of morphine, codeine, pethidine and pentazocine on both struggling induced by the tail or abdominal stimulation appeared in a dose-dependent manner, but higher doses of drugs were required for inhibition of the abdominal stimulation-induced struggling. Non-narcotic analgesics such as aspirin, aminopyrine and indomethacin induced struggling seen with tail stimulation whereas these drugs exerted only slight inhibitory actions on
the abdominal stimulation-induced struggling, as shown in Fig. 7. Baclofen was unique in that it exerted an inhibitory action on both types of struggling, but a higher dose of the drug was required for inhibition of the abdominal stimulation-induced struggling.

Table 1 summarizes ED50 (95% confidence limits) of all drugs used in the present experiment.
DISCUSSION

When a vocalization response of the dog to i.a. administration of bradykinin was used as an indicator of pain perception, the assessment of analgesics may be unreliable because of spontaneous diminution of or a marked tachyphylaxis in the vocalization response (2, 9). In case of the struggling as the indicator, however, it was shown in our previous study that such spontaneous diminution or tachyphylaxis rarely occurred. This was confirmed in the present work. It was reported that when measuring struggling and flexor reflex simultaneously, an analgesic-like action of the drug resulting from muscle relaxation could favorably be separated from an analgesic action itself (8). We used two types of pseudoaffective responses in an attempt to make a clear distinction between potent and mild analgesics, not only quantitatively but also qualitatively, and the results were rewarding.

The non-narcotic analgesics, aspirin, aminopyrine and indomethacin exerted inhibitory actions on the tail stimulation-induced struggling but only equivocal inhibitory action on the abdominal stimulation-induced response. On the other hand, narcotic analgesics, morphine, pethidine and codeine produced a suppression of both struggling responses. Thus, it may be assumed that when making simultaneous assessments of two types of struggling induced by electrical stimulation of the abdomen and tail, evaluation of the analgesic action of narcotics can be made separately from that of non-narcotic analgesics.

Conflicting evidence for this assumption was the suppression by baclofen of the
abdominal stimulation-induced struggling. Even though the analgesic potencies of baclofen and morphine are similar (10-11, present experiment), the mechanism of analgesia of baclofen appears to differ from that of morphine since baclofen-induced analgesia was not antagonized by naloxone and, moreover, cross-tolerance between morphine and baclofen did not occur (11). In an attempt to elucidate this discrepancy, experiments related to determination of the mechanism of the potent suppressive action of baclofen on the abdominal stimulation-induced struggling is under way.

With respect to the nature of abdominal stimulation-induced struggling, it is obscure whether the response represents a visceral pain as the result of excitation of the sensory nerves in the viscus, somatic pain resulting from excitation of free nerve terminals of the abdominal wall including the peritoneum, or a mixed type of pain. However, since mild analgesic drugs showed only equivocal effects on this struggling, this particular response is not indicative of slight pain. Furthermore, the slopes of dose-response relationships on two types of struggling were virtually in parallel for the narcotic analgesics but not for the non-narcotic analgesics. This clearly indicates that these two types of struggling are quite different in nature and that the abdominal stimulation-induced struggling response is effectively suppressed by only potent analgesics. Accordingly, the method used in the present study shows promise for application in evaluating potent and mild analgesic drugs, quantitatively and qualitatively.

REFERENCES