EFFECTS OF SEVERAL ANALGESICS ON THE NUMBER OF VOCALIZATION DISCHARGES OF THE RABBIT

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Vocalization (squeal, cry) has been used as a signal of pain in animals by a number of investigators (1, 2). Nevertheless, previous workers have raised the question of whether or not vocalization in rabbits can be regarded as a reliable index of pain for evaluating analgesic actions of drugs.

Kaneko et al. (3) and Graeff et al. (4) found that in rabbits, bradykinin-induced vocalization was not abolished by the administration of an analgesic dosage of morphine. Doi et al. (5) pointed out that in rabbits, vocalization was not regularly obtained with the administration of bradykinin. Since we found that vocalization could be securely evoked in anesthetized rabbits by electrical stimulation of the sciatic nerve and that this vocalization was characterized by the relative stability of the number of vocalization discharges (6), the present study was undertaken to clarify whether the change in the number of vocaliza-
tion discharges in rabbits could be utilized for evaluating the analgesic action of analgesics.

Female rabbits (2-3 kg) were anesthetized with urethane (1 g/kg s.c.) and vocalization was elicited by afferent stimulation of the sciatic nerve cut off, using square pulses of 30 V and 0.1 msec at a frequency of 10 Hz for 10 sec delivered through bipolar platinum wire electrodes. The number of vocalization discharges produced by this stimulation at 10 min intervals was almost constant for at least four hours. Vocalization was recorded on an ink-writing recorder (Nihon Kohden, WI-260) through integral circuits (7) mounted with a biophysical amplifier (Nihon Kohden, RB-2). According to the view of Carroll and Lim (8) and Hoffmeister (9), vocalization was classified into the following two parameters; vocalization during the stimulation (Vd) and vocalization continuing after the stimulus had ceased (Va), and in each rabbit the number of Vd and Va was counted, respectively. Results were expressed as the percent of the change to the values of the control, as shown in Fig. 1. Morphine, pentazocine, sodium salicylate, aminopyrine and levallorphan were dissolved in 0.9% NaCl solution and were injected into the marginal vein. Acetylsalicylic acid and mefenamic acid were suspended in 5% solution of gum arabic and were administered orally.

Among six analgesics tested, morphine and pentazocine caused decreases in the number of vocalization discharges. Morphine at doses of 1.25, 2.5 and 5 mg/kg decreased solely the number of Va, and at a dose of 10 mg/kg decreased not only the number of Va but also

![Fig. 1](image-url)  
**Fig. 1.** Effects of morphine and pentazocine on the number of vocalization discharges in urethanized rabbits. Each point was obtained from the mean of the percent of the change to the values of the control. Vd; vocalization during the stimulation, Va; vocalization continuing after the stimulus had ceased, n; number of rabbits.
the number of Vd. The decrease of the number of Va produced by morphine was dose-dependent. In two out of five rabbits, morphine at a dose of 10 mg/kg completely stopped vocalization for 20–30 min. Effects of pentazocine at doses of 1, 2 and 4 mg/kg on the number of Vd and Va were similar to those produced by morphine. The decrease of the number of Va produced by pentazocine was dose dependent, while the decrease of that of Vd was not produced until the dosage of pentazocine was increased up to 4 mg/kg. In three out of five rabbits, pentazocine at a dose of 4 mg/kg completely stopped vocalization for 20 min. Acetylsalicylic acid at a dose of 500 mg/kg (n=5), sodium salicylate at a dose of 200 mg/kg (n=4), mefenamic acid at a dose of 200 mg/kg (n=4) and aminopyrine at a dose of 50 mg/kg (n=5) produced little change in the number of Vd and Va.

In the present study, the number of vocalization discharges was decreased only by morphine and pentazocine which have been classified as centrally-acting analgesics (10, 11) but not by the remaining analgesics which have been pointed out to be peripherally-acting analgesics (10, 12). The result that the latter was ineffective on the number of vocalization discharges may have resulted from the experimental procedure in which vocalization was evoked by directly stimulating the sciatic nerve and sites of action of the peripheral analgesic action of drugs are eliminated. Thus the present method using the number of vocalization discharges in rabbits may be useful for the evaluation of the central analgesic action of drugs.

At a dose of 1.25 mg/kg, morphine produced changes of the number of vocalization discharges. Nevertheless, morphine, even when 10 mg/kg was injected, did not always stop vocalization. This result resembles that obtained previously by Kaneko et al. (3) and Graeff et al. (4), who found that in rabbits, bradykinin-induced vocalization was not interrupted by 10 mg/kg of morphine. On the other hand, Hoffmeister (9) described that several other pain responses obtained in rabbits, such as licking or chewing movement evoked by electrical stimulation of the dental pulp, was clearly inhibited by morphine at doses below 5 mg/kg. Therefore, it is suggested that at least in rabbits, mere "cessation of vocalization" as the standard of judgement is not a suitable one for evaluating the analgesic action of drugs.

From the difference between the pathway related with Vd and Va (8, 9) in the central nervous system, Hoffmeister (9) claimed that it was possible to postulate that Va is an index of an emotional component of pain in animals. As evidence to support this postulation, Hoffmeister (9) showed that in rats, the most typical effect of morphine at low dosage and psychotropic drugs, such as chlorpromazine or diazepam, was to increase solely the threshold of Va evoked by electrical stimulation of the tail. This finding is similar to that obtained in the present experiments with morphine at doses ranging from 1.25 to 5 mg/kg, which decreased solely the number of Va in rabbits. This similarity suggests the possibility that Va in rabbits is also an emotional parameter associated with pain, as claimed by Hoffmeister (9) in rats.

REFERENCES

**COMPARISON BETWEEN FLUORIMETRIC AND RADIOCHEMICAL ASSAYS OF IONTOPHORETICALLY RELEASED NORADRENALINE FROM A SEVEN-BARRELED MICROPIPETTE**

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Microiontophoretic methods enable the study of actions of putative chemical transmitters and central acting drugs on neuronal activity in the central nervous system. Before attempting such neuropharmacological experiments, however, the definite amount of the chemical substance released from a micropipette has to be accurately determined. In the present work, we determined the amount of noradrenaline (NA) released from a seven-barreled micropipette, using a fluorimetric method, and compared the findings with those seen in radiochemical assays.

Aqueous solution containing DL-NA-1-14C with specific activity of 30 Ci/m mole