Diversity of Underlying Mechanisms in the Production of Analgesic and Pentobarbital-Hypnosis Prolonging Effects of Various Analgesic Drugs and Stresses

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Abstract—Stressful stimuli, electric footshock (FS), immobilized-water immersion (IW), and cold-water swimming (CWS), produced analgesia and prolonged the pentobarbital hypnosis as well as morphine and clonidine. Naloxone completely antagonized the analgesic effects of morphine and FS and partially that of IW; however, that of clonidine and CWS were not reversed by naloxone. Naloxone eliminated the hypnosis prolonging effect of morphine and FS, but failed to reverse the effect of clonidine, IW and CWS. Differences in the analgesic and hypnosis prolonging effects and also the respective naloxone sensitivity of each drug and stress suggest the diversity of the underlying mechanisms.

Data have been accumulated that various kinds of stressful stimuli induce analgesia (1-5) and changes in sensitivity to barbiturates (6-8). As the underlying mechanisms for the production of these effects, the involvement of endogenous opioid system has been suggested (1, 2, 5-7). However, our previous report indicates that different mechanisms, opioid and non-opioid forms, are involved in each stress-induced analgesia (SIA) and the catecholaminergic system also plays a role in the mechanisms (9). The purpose of the present study is to compare the participation of different mechanisms in the production of analgesia and the hypnosis potentiating effect of morphine, clonidine and three different kinds of stresses.

Male mice of the dd-strain weighing 23 to 26 g were used. They were kept in a temperature controlled room at 22±1°C and given a normal laboratory diet and tap water ad libitum. The following drugs were used: morphine-HCl, naloxone-HCl, clonidine-HCl and pentobarbital-Na. The drugs were dissolved in saline and administered in a volume of 0.1 ml/10 g of body weight. The dose was expressed in terms of the respective salt. The conditions for the stresses were as follows: 1) footshock (FS), inescapable and unsigned footshock (2 mA, 1 sec duration, 0.2 Hz) were delivered by a scramble electric shock generator (Biomedica Co., Ltd.) through the grid floor of the chamber (10(D) x10(W)x30(H) cm) for 30 min. 2) immobilized-water immersion (IW), each of the animals was confined in a plastic box (4 x 4 x 10 cm) and immersed except for the head in water (25°C) for 30 min. 3) cold-water swimming (CWS), each mouse was forced to swim in a water bath (30 x 30 x 20 cm) of 15 cm depth, at 20°C, for 3 min. The analgesic effect was assessed by the modified Haffner's method (10) every 5 min from immediately after the termination of stress exposure for 15 min or every 15 min after the injection of analgesic drugs for 90 min. The effect was calculated by plotting the increase of response time (sec) against time (min) and expressed as the area under the curve (AUC). The hypnotic effect was assessed by measuring the sleeping time which elapsed from the loss to regain of the righting reflex. The analgesic effect induced by morphine, 10 mg/kg, s.c., and FS was completely antagonized by 2 mg/kg, i.p., naloxone. Naloxone had a partial antagonistic effect on...
IW-SIA, and it failed to reverse the analgesia induced by clonidine, 5 mg/kg, s.c., and CWS. Morphine, clonidine and all stresses significantly potentiated the hypnotic effect of pentobarbital. In particular, the effect of clonidine was marked and even a sub-analgesic dose, 0.1 mg/kg, prolonged the hypnosis about 3.5 times. The intensities of SIAs were almost maximal under the conditions employed; however, they were short-lasting and much less than that of morphine or clonidine. No significant difference was obtained between each stress in the degree of the analgesic effect; however, IW had a more remarkable effect on pentobarbital hypnosis than morphine, FS and CWS treatment. Naloxone, 2 mg/kg, completely nullified the hypnosis prolonging effect of morphine and FS, but it could not modify the effect of clonidine, IW and CWS (Figs. 1 and 2).

As evidenced by naloxone sensitivity, direct or possible involvement of opioid receptors or the endogenous opioid system is suggested for the production of the analgesic effect of morphine, FS and IW and the hypnosis prolonging effect of morphine and FS. These results are consistent with previous reports (1, 2, 5–7, 9). However, the intensity of the analgesic effect induced by each treatment was not directly proportional to the hypnosis prolonging effect, and the antagonistic effect of naloxone was also not parallel against both effects as in the case of IW. Thus, the differences in the analgesic and hypnosis prolonging effects and also the different naloxone sensitivities of the treatments may suggest the diversity of the underlying mechanisms.

**Fig. 1.** Analgesia and effect of naloxone. Mor: morphine (10 mg/kg), Clo: clonidine (5 mg/kg) FS: footshock, IW: immobilized-water immersion, CWS: cold-water swimming. : control, drug or stress alone. : pretreated with naloxone (2 mg/kg, 5 min before drug administration or stress exposure). : number of animals. Values are the mean and vertical bars indicate the S.E. Significantly different from the respective control, **P<0.001.

**Fig. 2.** Prolongation of pentobarbital hypnosis and effect of naloxone. Pentobarbital (40 mg/kg, i.p.) was injected 30 min after drug administration or immediately after stress exposure. For code and other details, refer to the footnote of Fig. 1. Range of sleeping time of saline pretreated animals. : control, pretreated with drug or stress. : pretreated with naloxone plus drug or stress. Significantly different from saline groups, **P<0.001. Significantly different from the respective control, *P<0.05, **P<0.001.

References


