INvolvement of Different Mechanisms, Opioid and Non-Opioid Forms, in the Analgesia Induced by Footshock (FS) and Immobilized-Water Immersion (IW) Stress

Reiko Izumi, Masakatsu Takahashi and Hiroshi Kaneto
Department of Pharmacology, Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki 852, Japan
Accepted July 7, 1983

It has been recognized that various stressful procedures such as foot shock (1-3), environmental heat (4), immobilization (4, 5) and fighting (6) produce an analgesic effect in experimental animals. Akil et al. (1) and Chesher and Chan (7) showed that the analgesic effect induced by foot shock stress is antagonized by naloxone, a potent opioid receptor blocker, and suggested the involvement of the endogenous opioid system in the underlying mechanisms of stress-induced analgesia (SIA). On the other hand, Lal et al. (8) described a lack of the antagonistic effect of naloxone on the analgesia induced by forced swimming stress. Thus, the difference and the characteristic nature of various SIA has not been definitely clarified and comparative studies were made on the underlying mechanisms in the production of the analgesia induced by morphine and stresses.

Male ddN mice (23-26 g) were used throughout. Foot shock (FS), 90V, 1 sec duration, 0.2 Hz, was applied through the grid floor for 30 min. As the immobilized-water immersion (IW) stress, animals were confined in a plastic box and immersed in water, 25°C, for 30 min. Analgesic effect was assessed by the modified Haffner's method (9). Morphine-HCl and naloxone-HCl were dissolved in saline and administered intraperitoneally in a volume of 0.1 ml/10 g of body weight.

Both FS- and IW-stress produced short-lasting analgesia as shown in Fig. 1. The intensity of the analgesia was maximal immediately after the termination of stress exposure and was nearly equipotent to the analgesic effect of 5 to 10 mg/kg of morphine. The analgesic effect was antagonized by 2 mg/kg i.p. of naloxone, completely in FS-

Fig. 1. Stress induced analgesia (SIA) and its naloxone antagonism. Mice were exposed to foot shock (FS, 90V, 1 sec duration, 0.2 Hz) or immobilized-water immersion (IW, immobilized in a plastic box and immersed in water, 25°C) stress for 30 min. Analgesic effect (response threshold, a cut-off time of 6 sec) was measured by the modified Haffner's method, every 5 min from immediately after the termination of stress exposure. Naloxone, 2 mg/kg, or saline was injected intraperitoneally 10 min before exposure to each stress. Left: FS-SIA, saline + FS (--; n=8); naloxone + FS (---, n=8). Right: IW-SIA, saline + IW (--; n=16); naloxone + IW (---, n=16). Broken line indicates the mean response threshold before exposure to stress. **P<0.01, ***P<0.001, compared with the respective saline pretreated group.
SIA and partially in IW-SIA, suggesting the participation of the endogenous opioid system in the production of their effects and also the discrepancies between FS- and IW-SIA. Two mg/kg of naloxone is sufficient to antagonize the effect of 10 mg/kg of morphine, and the fact that this dose of naloxone could not completely antagonize the analgesic effect induced by IW-SIA may imply the involvement of a non-opioid mechanism in IW-SIA. The short durations of both SIA as compared with morphine analgesia may be due to the rapid in vivo degradation of endogenous opioid peptides by peptidases (10).

Daily exposure to stress developed tolerance to SIA, and on the 3rd day, the same stress failed to produce appreciable analgesia. Animals tolerant to SIA were also tolerant to morphine analgesia, and vice versa. Thus, as Chesher and Chan (7) have described, cross-tolerance was demonstrated between morphine and each SIA. On the other hand, IW-SIA was markedly potentiated in FS-SIA-tolerant mice, and FS-SIA was enhanced (not significant) in the animals tolerant to IW-SIA. (Fig. 2) These results also suggest the discrepancies of the underlying mechanisms between FS- and IW-SIA. The potentiation of alternative SIA may be explained by the following: the development of tolerance to either one of the SIA resulted in the acceleration of the other mechanism as Martin has proposed in his redundant theory of tolerance to and dependence on narcotic analgesics (11).

In addition to the important role of endogenous opioid peptides in the production of analgesia and the development of tolerance/dependence, the role of neurotransmitters could not be excluded. It is also emphasized that stressful stimuli affect neurotransmitters, and the effect depends on the characteristics of the stimuli. Actually, an opposite effect has been reported in the turnover of brain amines after exposure to FS- and immobilization-stress (12, 13). Thus, the discrepancies observed in this experiment between FS- and IW-SIA may be partly explained from this point of view. It is revealed from the present study that the endogenous opioid system is more closely associated with the mechanism of FS-SIA than with IW-SIA; on the other hand, the non-opioid mechanism is more closely concerned in IW-SIA than in FS-SIA.

References

1) Akil, H., Madden, J., IV, Patrick, R.L. and Barchas, J.D.: Stress-induced increase in


