Distinctive Implication of Emotional Factors in Various Types of Stress-Induced Analgesia

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Abstract—Diazepam, an antianxietic agent, antagonized the stress-induced analgesia (SIA) distinctively depending on the characteristics of the stress. Psychological (PSY, using communication box)-SIA was completely blocked by 1 or 2 mg/kg of diazepam in the tail pinch (TP) method, but not antagonized by 1 mg/kg of the drug in the tail flick test. Swimming-SIA was resistant to diazepam in both methods, and footshock-SIA was only suppressed slightly by 2 mg/kg in the TP method. Thus, emotional factors play an essential role in the production of PSY-SIA, although the participation of the factors in the other SIAs cannot be excluded.

Anxiety or fear is one of the emotional responses induced when individuals are confronted with threatening stimuli or a disadvantageous environment, and it must be a signal of alertness, usually accompanied by an analgesic effect which might be elicited by activation of intrinsic pain-inhibitory systems (1). Actually, psychologically evoked stress (2) has been reported to produce analgesia. Besides, it has been also well recognized in man (3, 4), rats (5–8) and mice (2, 9, 10) with various stressful stimuli such as inescapable footshock (2–6, 10), forced swimming in cold water (2, 8), immobilization (7), immobilization-water immersion (10) and fighting (9) that the analgesic effect was induced. All these stress-induced analgesias (SIAs) may imply that emotional factors are involved in their production mechanisms to some extent.

Benzodiazepines are known as the primary medicine for anxiety and various psychosomatic complaints. In this context, studies have been carried out to determine how the analgesic effect produced by various stresses would be affected by the treatment with diazepam.

Male dd strain mice weighing 18–20 g were purchased, and they were housed in groups of 10 animals each in plastic cages with free access to food and water. They were kept in an ambient room temperature of 22±1°C; and after reaching 23–26 g, they were employed for the experiments.

Diazepam (Yoshitomi Pharm. Co.) was used. The drug was dissolved in 25% polyethylene glycol and injected i.p. 60 min before the exposure to each stress in a volume of 0.1 ml/10 g of body weight.

Details of the exposure to footshock (FS), swimming (SW) and psychological (PSY) stress have been described elsewhere (2, 10). Briefly, mice were exposed to FS (2 mA, 0.2 Hz, 1 sec duration for 30 min), SW (water at 20°C for 3 min) or PSY (communication box for 5 min), followed by the immediate assessment of analgesia. The analgesic effect was measured by two different methods, tail pinch (TP, a cut-off time of 6 sec) and tail flick (TF, maximal response time of 10 sec), every 5 min from immediately after the termination of stress exposure, because these different methods sometimes produce different results in the assessment of the analgesic effect (11).

Significance of the difference was determined by Student’s t-test.

In accordance with our earlier reports (2, 10), exposure to PSY-, FS- and SW-stress produced short-lasting analgesia. The analgesic effect induced by PSY-stress was completely antagonized by 60 min pretreat-
ment with 1 and 2 mg/kg of diazepam in the TP methods, but the treatment with 1 mg/kg of the drug failed to block the effect in the TF test. Each dose of diazepam was without effect on the SW-SIA in the TP and TF methods. FS-SIA was also not affected by 1 mg/kg of diazepam in both tests; however, at the dose of 2 mg/kg, a slight but not significant suppression was observed only in the TP test (Fig. 1).

Complete suppression of PSY-SIA by diazepam in the TP test may suggest that the analgesic effect is mainly induced by emotional factors. This is probably the case since both experimentally and clinically, diazepam possesses an antianxietic effect. However, in this experiment, neither SW-SIA nor FS-SIA was suppressed by a low dose of diazepam, and the production of SW-SIA was not affected even by higher dose of the drug. The explanation that the differences in diazepam antagonism are attributed to the quantitative differences in the intensities of analgesia induced by these stresses may not be adequate, since PSY-SIA was completely antagonized by even 0.5 mg/kg of diazepam (data not shown), although it is less potent than the other SIAs. Thus, the degree of the participation of the emotional factors in the production of each SIA may be qualitatively different. Stress using the communication box may consist of pure psychological factors such as anxiety, fear and unpleasantness of the situation, but in FS- and SW-SIAs, in addition to the physical stress, the involvement of the psychological factors cannot be neglected.

We have reported the participation of the opioid or non-opioid mechanism in the productions of these SIAs and concluded that FS-, PSY- and SW-SIA would be induced through the mediation of opioid μ-receptor, κ-receptor, and a non-opioid mechanism, respectively (2). SW-SIA was not affected by any doses of diazepam, and it was completely different from the other SIAs, and its pro-

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**Fig. 1.** Various types of stress induced analgesia and their diazepam antagonism. Mice were exposed to psychological (PSY), forced swimming (SW) or footshock (FS) stress. Analgesic effects (Response time) were measured by the tail pinch (TP) and tail flick (TF) methods, every 5 min from immediately after the termination of the stress exposure. Diazepam, 1 mg/kg or 2 mg/kg, or vehicle was injected intraperitoneally 60 min before exposure to the stress. Control (vehicle, ○), 1 mg/kg diazepam (△) or 2 mg/kg diazepam (×) mg/kg. Each point is the mean±S.E. of 8-18 animals. Dotted area indicates the mean±S.E. response time before exposure to stress. *P<0.05, compared with the respective vehicle pretreated group.
duction may be linked closely with the activation of non-opioid pain inhibitory mechanisms.

PSY-SIA was antagonized by diazepam in the TP test but not in the TF test. In our former experiment, a similar discrepancy was obtained in the naloxone antagonism of PSY-SIA (2). This may suggest that diazepam may have some properties in common with naloxone. In support of the possibility, the antagonism of morphine analgesia by diazepam has been reported (12). On the other hand, the involvement of an opioid-like mechanism in the effect of diazepam may be implicated. Actually, naloxone has been reported to reverse the sedative and anti-conflict effects of benzodiazepines (13), inhibit diazepam-induced feeding (14) and also antagonize acute diazepam intoxication (15). It is recognized that the analgesic effect mediated by κ-opioid receptor, compared with μ-opioid receptor, is rather resistant to naloxone antagonism (16, 17). In this context, it may be possible that benzodiazepines partly antagonize PSY-SIA through an opioid κ-receptor mechanism in addition to the participation of the emotional factors in the underlying mechanisms.

In conclusion, the emotional factors such as anxiety, fear and unpleasantness play an essential role in the production of PSY-SIA since pure emotional factors are possibly induced by the exposure to PSY-stress, although the participation of the emotional factors could not be excluded in the production of physical SIAs.

References