Blockade of the Development of Analgesic Tolerance to Morphine by Psychological Stress through Benzodiazepine Receptor Mediated Mechanism

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Abstract—β-Carboline-3-carboxylic acid ethyl ester (β-CCE) dose-dependently potentiated psychological-stress induced analgesia (PSY-SIA), and the effect was reversed by diazepam. Concurrent exposure to PSY stress or concomitant treatment with β-CCE blocked the development of analgesic tolerance to morphine; the effect of PSY stress was antagonized by diazepam, and that of β-CCE was reversed by Ro 15-1788. These results suggest that psychological factors which are mediated through benzodiazepine receptors are involved in the mechanism for blocking the development of analgesic tolerance to morphine by PSY stress.

We have demonstrated that concurrent treatment with psychological (PSY) stress completely suppressed the development of analgesic tolerance to morphine (1). Furthermore, based on the fact that the analgesic effect induced by PSY stress was antagonized by diazepam, an anti-anxiety agent, we have reported the implication of emotional factors in the production of this type of stress induced analgesia (SIA) (2). The present study was aimed to clarify the involvement of the psychological factors in the suppressive effect of PSY stress on the development of analgesic tolerance to morphine.

Male mice of the ddY strain weighing 23 to 28 g were employed for the experiments. Using the communication box, the animals were exposed to PSY stress for 5 min. Briefly, the mice were placed individually into the 9 compartments and electric footshock was delivered through the floor grids. Animals placed in the compartments in which the floor is covered with a plastic plate are prevented from receiving the shock, but they were exposed to PSY stress by watching and hearing the struggle, jumping and vocalization of the shocked animals. Details of the exposure to PSY stress have been described elsewhere (3). The analgesic effect was measured by the tail pinch method. β-Carboline-3-carboxylic acid ethyl ester (β-CCE, an inverse agonist for benzodiazepine receptors; Research Biochemicals, Inc.) potentiated the PSY-SIA in a dose-dependent manner, although β-CCE itself did not produce any analgesic effect, and the effect was reversed by 0.1 mg/kg of diazepam that did not affect the PSY-SIA (Fig. 1a, 1b and 1c). On the other hand, Ro 15-1788 (a benzodiazepine antagonist, Roche), 2 mg/kg, i.p., neither possessed an analgesic effect nor potentiated PSY-SIA, but completely suppressed the enhancing effect of β-CCE on the PSY-SIA. As was expected, Ro 15-1788 antagonized the suppressive effect of diazepam on PSY-SIA (Fig. 1c and 1d).

These results may suggest that exposure to the PSY stress induces a state sensitive to the drugs, agonists for benzodiazepine receptors such as diazepam and β-CCE; and accordingly, the PSY-SIA was antagonized by diazepam (2) and potentiated by β-CCE. The evidence obtained in the experiments with Ro 15-1788 also supports the hypothesis. By itself, Ro 15-1788, like diazepam and β-CCE, lacked the analgesic or algesic effect, but completely nullified the effects of diazepam and β-CCE on PSY-SIA.

In the present experiment, we could confirm our previous finding that concurrent ex-
Fig. 1. Effect of β-CCE and Ro 15-1788 on PSY-SIA. Analgesic effect (response time, a cut off time of 6 sec) was measured 4 times by the tail pinch test, every 5 min from immediately after the termination (0 min) of stress exposure. β-CCE was given i.p. 30 min before exposure to the stress. DZP or Ro 15-1788 was injected i.p. 60 min before exposure to the stress. The control group was treated with vehicle, propyleneglycol, instead of the drug at the corresponding time. (a) Control (●○●): β-CCE, 0.1 (○—○), 0.5 (□—□) or 2 (△—△) mg/kg; β-CCE, 2 mg/kg alone, without stress (▲—▲). (b) Control (●○●): DZP, 0.1 (▽—▽), 0.5 (×—×) or 1 (○—○) mg/kg; DZP, 1 mg/kg alone (●—●). (c) Control (●○●): β-CCE, 2 mg/kg (△—△); β-CCE, 2 mg/kg+DZP, 0.1 mg/kg (▽—▽); β-CCE, 2 mg/kg+Ro 15-1788, 2 mg/kg (○—○); Ro 15-1788, 2 mg/kg alone (●—●). (d) Control (○—○): DZP, 1 mg/kg (○—○); Ro 15-1788, 2 mg/kg (○—○); DZP, 1 mg/kg+Ro 15-1788, 2 mg/kg (○—○). Each group consisted of 5–15 animals, and each point represents the mean±S.E. (vertical bar). The dotted area indicates the mean±S.E. of the response time before exposure to stress. The statistical significance of differences between the control and each group was determined using repeated measures analysis of variance followed by Scheffe's test. *P<0.05, **P<0.01, compared with the control group (Scheffe's test). For abbreviations, refer to the text.

Exposure to PSY stress completely blocked the development of analgesic tolerance to morphine (1). Similarly, β-CCE completely suppressed the development of tolerance to morphine without affecting morphine analgesia (Fig. 2b). The blocking effect of PSY stress on morphine tolerance was antagonized by diazepam and that of β-CCE by Ro 15-1788, respectively (Fig. 2a and 2b). These facts suggest the involvement of psychological factors which is mediated through the activation of benzodiazepine receptors in the mechanisms for blocking the development of analgesic tolerance to morphine by PSY stress and β-CCE.

We have suggested that the production of PSY-SIA may be mediated by κ-opioid receptors (3). In support of our earlier suggestion, Yamamoto et al. recently reported that the development of analgesic tolerance to morphine is blocked by the concomitant treatment with U-50,488H, a κ-receptor agonist (4). Thus, the results obtained in the present study, in addition to the confirmation of the role of a κ-receptor mediated mechanism in blocking the development of analgesic
Fig. 2. Blockade of the development of analgesic tolerance to morphine by PSY stress and β-CCE and reversal of the effect by diazepam (DZP) and Ro 15-1788. Animals were exposed for 5 min to a PSY stress 15 min after 10 mg/kg morphine, i.p. (a) or were pretreated 15 min with 1 mg/kg β-CCE, i.p. (b). DZP, 1 mg/kg or Ro 15-1788, 2 mg/kg, i.p., was injected 45 min before morphine injection. Daily changes of the analgesic effect of morphine was expressed as the area under the curve (AUC) by plotting the increase in response time (sec) on the ordinate and the time intervals (min) on the abscissa. (a) Morphine alone (●●●●), morphine+PSY (△—△), morphine+DZP (□——□), morphine+DZP+PSY (○——○). (b) Morphine alone (●●●●), morphine+β-CCE (△—△), morphine+Ro 15-1788 (□——□), morphine+β-CCE+Ro 15-1788 (○——○). Each group consisted of 7–14 animals, and each point is the mean±S.E. *P<0.05, **P<0.01, compared with the group treated with morphine alone (Scheffe’s test). For abbreviations and other details, refer to the text and the legend for Fig. 1.

tolerance to morphine, suggest the close interaction between actions mediated by κ-opioid and benzodiazepine receptors.

References