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BRIEF COMMUNICATION

Opiate Antagonists Reverse the Hypoactivity Associated with Systemic Anaphylaxis in Mice

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AMIR, S. *Opiate antagonists reverse the hypoactivity associated with systemic anaphylaxis in mice.* PHARMACOL BIOCHEM BEHAV **20**(3) 483–485, 1984.— Systemic anaphylaxis in the mouse is associated with marked hypoactivity. This effect is reversed by treatment with the opiate antagonists, naloxone (5–10 mg/kg) or naltrexone (1 mg/kg). Administration of naltrexone methyl bromide (1 mg/kg), a selective peripherally acting opiate antagonist, is ineffective in reversing the hypoactivity induced by anaphylaxis. These results suggest a role for central nervous system opiate mechanisms in the hypoactivity induced by anaphylaxis. They support the hypothesis that endogenous opiates contribute to the pathophysiologic consequences of anaphylactic shock.

Hypoactivity Opiate antagonist Anaphylaxis

SYSTEMIC anaphylaxis in the mouse is a complex phenomenon involving at least two classes of antibodies [11] and characterized by vascular collapse, respiratory depression and profound motor retardation [13]. The reaction is mediated by histamine and 5-hydroxytryptamine released from sensitized mast cells, and other substances such as bradykinin and slow reacting substance on anaphylaxis (SRS-A) presumed to be of mast cell origin [10,17]. Recently, we have demonstrated that blockade of opiate receptors by the opiate antagonist naloxone significantly improves survival in mouse anaphylaxis, suggesting the involvement of endogenous opiates (endorphins) in the pathophysiologic consequences of anaphylactic shock [1, 2, 3]. This study further investigated this hypothesis by evaluating the effect of blockade of opiate receptors on the diminished motor reactivity which follows induction of anaphylactic shock.

METHOD

Male ICR mice (28–30 g body weight) were immunized intraperitoneally (IP) with 2 mg bovine serum albumin (BSA) in 0.2 ml aluminium hydroxide gel. Anaphylactic shock was induced by challenging the mice intravenously (IV) with 5 μg BSA in 0.2 ml saline 10 days after immunization. This dose of BSA was found in preliminary experiments to cause respiratory depression and motor retardation but not to induce fatal shock.

Motor activity was evaluated by placing the shocked mice in a transparent Plexiglas chamber (10×13×20 cm) and counting the number of rearing responses displayed over 15 min. Testing started 5 min after induction of shock.

Naloxone (Endo Laboratories) was administered IV at 5 or 10 mg/kg together with the challenge dose of BSA. Naltrexone (Endo Laboratories) or naltrexone methyl bromide (MRZ 2663-BR), a quaternary analog of naltrexone which is impermeable to the blood brain barrier [16] were administered subcutaneously (SC) at 1 mg/kg 30 min before induction of shock.

The data were analyzed by student's t-tests; the p-valve was adjusted for multiple t-testing.

RESULTS AND DISCUSSION

Non immunized mice challenged IV with 5 μg BSA (controls) exhibited a high frequency of rearing over the 15 min testing period (Fig. 1). In immunized mice, motor activity was markedly depressed following IV challenge with 5 μg BSA ($p<0.05$ from non-shocked controls). Administration of naloxone, 5 or 10 mg/kg, together with the challenge dose of BSA significantly ($p<0.05$) increased motor responding in the shocked mice. To investigate the role of central versus peripheral opiate receptors, mice were pretreated with the opiate antagonist naltrexone (1 mg/kg) or the selective peripherally acting antagonist naltrexone methyl bromide (1 mg/kg) before induction of shock. As shown in Fig. 1, treatment with naltrexone significantly reversed the hypoactivity associated with anaphylaxis ($p<0.05$) whereas administration of naltrexone methyl bromide was ineffective.

These results demonstrate that blockade of central nervous system (CNS) opiate receptors can reverse the hypoactivity associated with analphylaxis in mice. Previously, we

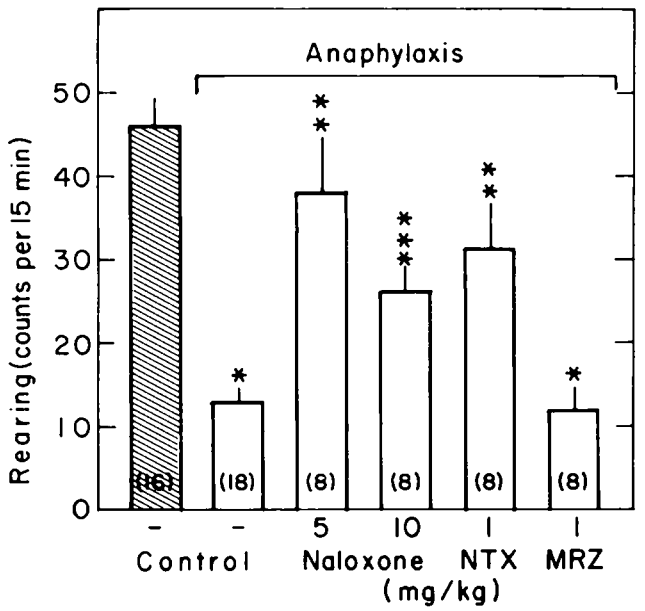

FIG. 1. The effect of naloxone, naltrexone (NTX) or naltrexone methyl bromide (MRZ) on motor reactivity (rearing responses) in anaphylactically-shocked mice. Naloxone was administered IV, together with the challenge dose of BSA (5 μg). Naltrexone or naltrexone methyl bromide were injected SC, 30 min before induction of shock. Testing started 5 min after induction of shock. The bars and vertical lines indicate means±SEM of rearing responses per 15 min. The numbers inside the bars indicate the number of animals in each group. The asterisks indicate: (*)-significant difference from non-shocked control group (hatched bar); (**)-significant difference from shocked control; (***)-significant difference from both non-shocked and shocked control groups ($p<0.05$ student's t-tests).

have shown that treatment with naloxone or naltrexone significantly improves survival in analphylactic shock [1,3] and suggested that this effect might be due to antagonism of the central cardiovascular depressive effects of endorphins (i.e., [8, 9, 12, 15]) which are released in response to circulatory trauma (e.g., [5,7]). Moreover, we have demonstrated that the antianaphylactic effect of naloxone is peripherally mediated through activation of the sympatho-adrenomedullary system, as treatments which disrupted the functional integrity of the adrenal medulla reversed the protective effect of naloxone [2,3]. We have now observed in preliminary experiments that the sympatho-adrenomedullary system also may be involved in the motor facilitatory effect of naloxone in anaphylactic shock. Specifically, we found that treatment with the ganglionic blocker chlorisondamine chloride (2.5 mg/kg, 1 hr before induction of shock), which diminishes peripheral sympathetic transmission, prevented the effect of 5 mg/kg naloxone to increase motor activity in shocked mice. Rearing responses (mean ±SEM) in chlorisondamine-pretreated non-shocked mice = 29.6±2.3 (n=8); chlorisondamine-pretreated shocked mice = 12.25±1.3 (n=8); chlorisondamine-pretreated, naloxone-treated shocked mice = 8.62±2.4 (n=8). Collectively, these results suggest that the effect of opiate antagonists to reverse the hypoactivity associated wtih anaphylactic shock may be due to increased sympathetic tone and a consequent improvement in circulatory functions, secondary to blockade of the central sympatho-inhibitory effects of endorphins (see [6,14]).

Anaphylaxis in the mouse is associated with rapid vasodilation and marked loss of intravascular fluid due to increased capillary permeability [4,13]. These effects might contribute to the progressive motor deterioration and incoordination observed in anaphylactic shock by diminishing tissue perfusion and consequently limiting oxygen supply to the brain. Treatment with opiate antagonists might restore oxygen supply by improving circulatory performance (i.e., [6,14]) and thus could reverse the motor deterioration associated with shock. Studies on the hemodynamic and metabolic consequences of naloxone administration in anaphylaxis and their relationship to changes in motor functions are currently under way in this laboratory.

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