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Catecholamine and Hypoxic Tolerance in Mice

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ABSTRACT

The effect of intraperitoneal administration (i.p.) of certain catecholaminergic drugs on altitude convulsion threshold (ACT) was studied in conscious mice. It was observed that administration of reserpine (3.0-7.0 mg/kg body weight) or α-methyl-p-tyrosine (α-MT, 800 mg/kg) to deplete stores of catecholamine, produced a significant increase in the ACT of mice. In addition, blockade of adrenergic α-receptor with phentolamine (2.5-10.0 mg/kg), adrenergic β-receptor with propranolol (1.0-2.0 mg/kg) or dopaminergic receptor with haloperidol (2.0-4.0 mg/kg), also caused a significant increase in the ACT. Besides, administration of pargyline (50-200 mg/kg), L-dopa (50-400 mg/kg), or Pargyline (50 mg/kg) combined with L-dopa (200 mg/kg) did not affect the ACT. However, mice treated with pargyline (50 mg/kg) combined with L-dopa (200 mg/kg) could be induced a marked prevention in the increase of the ACT induced by treatment of reserpine or α-MT. The present results suggest that catecholaminergic mechanisms are involved in the regulation of hypoxic tolerance.

Evidence suggests that catecholaminergic mechanisms are involved in the experimental convulsions, i.e., drug-induced convulsion, electroshock convulsion and audiogenic seizure[1-5]. But, little information is available about the catecholaminergic mechanisms on the altitude convulsion. It is known tht convulsion at altitude indicates the critical phase of the body's reaction to severe hypoxia. Some animals, such as mice, always show marked altitude convulsion, whereas guinea pigs and rats may frequently exceed the lethal threshold without having altitude convuslion. In the present study, the mice are thus selected for investigating the possible role of endogenous catecholamine in altitude convulsion.

MATERIALS AND METHODS

Male ICR mice, weighing between 18 and 22 g, were used throughout these studies. The mice were housed for at least five days before using. They were kept in groups of five per cage and had free access to food and water at all times. The room temperature was maintained within 22-24℃. On the day of experiment, the mice

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were placed in a decompression chamber and subjected to severe hypoxia at the rate of ascent of 1600 ft/min. The altitude convulsion threshold in mmHg, i.e., the chamber pressure at which the convulsion was brought about, was determined by using the method described previously[6].

The drugs used in this study were obtained from the following sources: α-MT, reserpine, L-dopa and pargyline (Sigma Chemical Co. St. Louis, MO); phentolamine and propranolol (Ciba-Geigy, Switzerland) and haloperidol (Janssen Pharmaceutica,Belgica). Reserpine was dissolved in a few drops of glacial acetic acid and then diluted with 0.3 M sucrose. Other drugs were dissolved in normal saline. All drugs were freshly prepared on the day of testing and injected intraperitoneally in a volume of 0.1 ml/10 g of body weight. Appropriate vehicle (saline or reserpine-vehicle) was administered to controls. The results were statistically evaluated by Fisher's t-test.

RESULTS

Catecholamine-depleted mice were induced in this experiment by pretreating the mice with reserpine or α-MT. Reserpine was administered six hours prior to measurement of convulsion. α-MT was given 30 minutes before the experiment. After administration of reserpine, it caused a significant increase in the ACT as compared to the vehicle-treated control mice. In addition, with the dosing of α-MT, above 800 mg/kg, it also increase the ACT of mice (Fig. 1.).

Either phentolamine, propranolol or haloperidol was administered 30 minutes prior to measurement of convulsion. Fig. 2. showed the effects of adrenergic α-receptor antagonist (phentolamine), β-receptor antagonist (propranolol), and dopaminergic receptor antagonist (haloperidol) on the ACT. After administration of

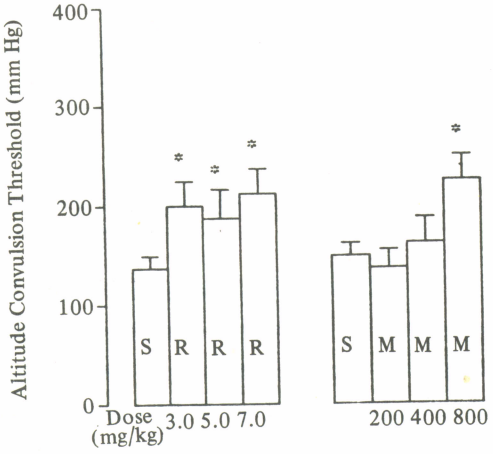

Fig. 1. Effects of catecholamine-depletion on the altitude convulsion threshold. Each column indicates the mean ± S.E. of 10 mice. S: saline/vehicle-treated; R: reserpine-treated; M: α-MT-treated. *: $p < 0.05$, as compared with the corresponding saline/vehicle-treated group.

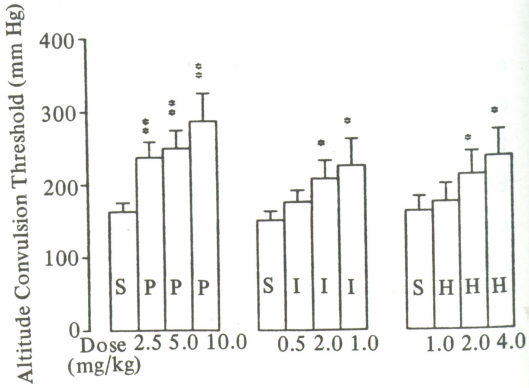

Fig. 2. Effect of pretreatment of mice with catecholaminergic receptor antagonists on the altitude convulsion threshold. Each column indicates the mean ± S.E. of 10 mice. S: saline-treated; P: phentolamine-treated; I: propranolol; H: haloperidol-treated. *: $p < 0.05$, **: $p < 0.01$, as compared with the corresponding saline-treated group.

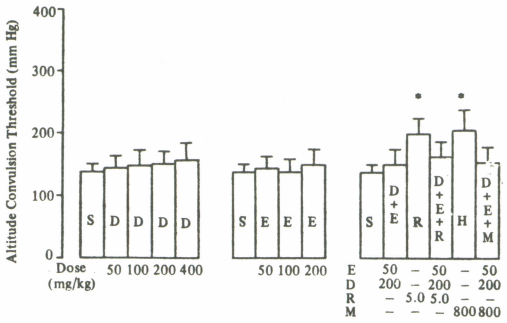

Fig. 3. Effects of L-dopa and pargyline on the altitude convulsion threshold. Each column indicates the mean ± S.E. of 10 mice. S: saline/vehicle-treated; D: L-dopa-treated; E: pargyline-trated; R: reserpine-trated; M: α-MT-treated. * : $p < 0.05$, as compared with the corresponding saline/vehicle-treted group.

phentolamine (2.5-10.0 mg/kg), propranolol (1.0-2.0 mg/kg) or haloperidol (2.0-4.0 mg/kg), each produced a significant increase in the ACT as compared to corresponding saline-treated group. Administration of L-dopa (50-400 mg/kg) 30 min before the experiment, pargyline (50-200 mg/kg) 60 min before the experiment, or L-dopa (200 mg/kg) combined with pargyline (50 mg/kg) could not significantly affect the ACT. However, the treatment of L-dopa (200 mg/kg) combined with pargyline (50 mg/kg) produced a marked prevention of the increase of the ACT induced by reserpine or α-MT (Fig. 3).

DISCUSSION

The severity of the altitude convulsion depends on the rate of ascent. Since it was observed that the convulsion was very severe when the ascending rate about 1600 feet per minute, such a rate was, therefore, used in the present study. It is known that there is a close relationship between the ACT and body weight. In our previous study[6], it was observed that obesity could cause a higher ACT and a decrease in the time to altitude convulsion. Our experimental animals which were nearly alike in weight were thus chosen for the study.

It is well know that the neuronal elements of the brain is unusual among the body organs in requiring a large blood flow and a constant supply of oxygen. Most of the oxygen is consumed in the metabolism of glucose to yield energy in the form of labile phosphate intermediates. The energy is utilized in the synthesis of structural elements and provides the fuel for neuronal function. A reduction in arterial oxygen content and tension, induced an increase in cerebrospinal fluid[7,8], and this hyperemia undoubtedly represents an important homeostatic mechanism, tending to maintain oxygen availability. Many investigators found that acute brain hypoxia was accompanied by a decrease in tissue high energy phosphates, glycogen and glucose and an increase in the lactate-pyruvate ratio with an accompanying decrease in tissue pH[9,10,11,12]. On the other hand, the metabolism of neurotransmitter substances were also affected by a decrease in arterial Po_2. Davis and Carlsson[13] and Siesjo[14] reported that exposure of rats to 8.5% O_2 (simulated altitude of 23000 ft) in a decompression chamber or to gas mixtures containing 8-10% O_2, both resulted in a drop in the levels of noradrenaline and dopamine, and also a decrease in the synthesis of both catecholamine and indoleamines. Furthermore, it was reported that ephedrine in the dose of 0.5 mg/kg increased the altitude convulsion threshold of mice[15]. In the present study, in order to evaluate the catecholamine on the hypoxic tolerance, the ACT, therefore, determined in saline/vehicle-treated and catecholaminergic drug-

treated mice. The results indicated that the ACT was significantly increased in mice pretreated with reserpine to deplete stores of catecholamine of adrenergic nerve ending in the brain as well as peripheral organs. In addition, blockade of adrenergic α-receptor with phentolamine, adrenergic β-receptor with propranolol or dopaminergic receptor with haloperidol, each produced a significant increase in the ACT as compared with the corresponding controls. In contrast, mice treated with pargyline combined with L-dopa could caused a marked prevention in the increase of the ACT induced by administration of reserpine or α-MT, although pargyline-, L-dopa- or pargyline combined L-dopa- treated mice did not show significantly different from controls. it is generally accepted that L-dopa, particularly after monoamine oxidase inhibitor (pargyline), may produce a marked increase in the catecholaminergic activity of mice[3]. The results reflect that catecholaminergic mechanisms are involved in the regulation of hypoxic tolerance, and some pathways which regulate catecholamine metabolism are affected at reduction in arterial Po_2.

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兒茶酚胺對小白鼠高空痙攣閾之影響

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本實驗乃研究腹腔注射某些兒茶酚胺類藥品，對清醒小白鼠高空痙攣閾之影響。投予 Reserpine (3.0-7.0 mg/kg)或 α-methyl-p-tyrosine (α-MT, 800 mg/kg)，以耗竭貯存之兒茶酚胺，會造成小白鼠高空痙攣閾有意義的增加，而以 Phentolamine (2.5-10.0 mg/kg)阻斷腎上腺素性 α-接受器，以 Propranolol (1.0-2.0 mg/kg)阻斷腎上腺素性 β-接受器，或以 Haloperidol (2.0-4.0 mg/kg)阻斷度巴明接受器，皆會導致高空痙攣閾有意義的增加。

又投予 Pargyline (50-200 mg/kg)或 L-dopa (50-400 mg/kg)或混合投予 Pargyline (50 mg/kg)及 L-dopa (200 mg/kg)，雖不影響小白鼠高空痙攣閾，但投予 L-dopa 加 Pargyline 則對因投予 Reserpine 或 α-MT 所引起的高空痙攣閾之增加有抑制作用。由實驗結果顯示，兒茶酚胺似乎參予小白鼠高空缺氧耐受力的調節機制。

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