Circulatory depression and ventricular arrhythmias induced by compound 48/80 in anaesthetized rats

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Abstract

The effects of graded doses of compound 48/80 on various cardiovascular and respiratory parameters were studied in pentobarbitone-anaesthetized rats. Following intravenous injections, this compound significantly depressed the mean blood pressure (MBP), left ventricular pressure (LVP) and $d_{LVP}/dt_{max}$, and caused ventricular tachycardia (VT) or fibrillation (VF) and death. Heart rate (HR) response were variable, and there were no marked changes in airway resistance or blood gases. Pretreatment of the animals with either cimetidine or diphenhydramine significantly prolonged the time of onset of VT/VF but failed to alter the changes in other circulatory variables. A combination of cimetidine and diphenhydramine significantly alleviated the decreases in MBP and LVP and prevented the occurrence of VT/VF. It is suggested that the circulatory depression and the occurrence of ventricular arrhythmias following the administration of compound 48/80 result from activation of H_1- and H_2-receptors by elevated blood histamine levels due to release of the amine from tissues.

Introduction

Histamine is known to be highly arrhythmogenic in mammalian hearts [1]. However, rat hearts are generally believed to be less responsive to this amine [2]; it has even been suggested by Levi et al. [2] that there are no histamine receptors in the rat heart. On the contrary, recent studies have pointed to a possibility that histamine released from the ischaemic myocardium may contribute to the genesis of ventricular arrhythmias during acute myocardial ischaemia in rats [3–6]. Administration of histamine alone is unable to elicit ventricular arrhythmias in isolated rat hearts. However, it significantly accelerates the occurrence of hypoxia-induced ventricular arrhythmias [7]. These findings suggest that histamine is able to cause, or to facilitate the occurrence of, ventricular arrhythmias in the rat under certain circumstances. However, direct evidence in intact animals is still lacking. A preliminary study has been carried out in intact rats and found that intravenous injections of histamine, even in large doses, do not produce severe ventricular arrhythmias other than few extrasystoles (unpublished data). However, it still cannot exclude the possibility that a persistently high circulating histamine level, induced by administration of a potent histamine liberator, may trigger the occurrence of ventricular arrhythmias.

Compound 48/80 is a synthetic polyamine produced by the acid-catalysed condensation of p-methoxy-
N-methylphenethylamine and formaldehyde, and is often regarded as a classical mast cell degranulating agent. Administration of the compound leads to degranulation of mast cells in situ, a corresponding depletion of tissue histamine, and an elevation in the plasma level of the amine [8]. However, its action exhibits a high degree of species and tissue specificity. Rats have been shown to be sensitive to the actions of compound 48/80. Intravenous injection of this compound induces a very fast and pronounced increase in blood histamine concentrations [9]. It has also been reported to produce a severe anaphylactoid reaction in rat [10], but the changes in circulatory function and in cardiac rhythm induced by this compound have not been described in detail.

The present investigation examines the responses of various cardiovascular and respiratory parameters, including cardiac rhythm, to intravenous injections of graded doses of compound 48/80 in anaesthetized rats. In order to evaluate the roles of histamine H₁- and H₂-receptors in these circulatory reactions, the effects of pretreatment with selective histamine H₁- and H₂-receptor antagonists, diphenhydramine and cimetidine respectively, or with their combination, were also studied.

Materials and methods

General

Male Sprague-Dawley rats, weighing 400–460 g, were used. They were housed in a temperature (23 ± 1 °C)- and humidity (65 ± 5%)-controlled room, and were exposed to a 12-h day-night cycle. They were allowed free access to a standard laboratory diet of pellets (Ralston Purina, USA) and tap water.

Cardiovascular and respiratory responses to compound 47/80

Under general anaesthesia with pentobarbitone sodium (Abbott) 60 mg/kg intraperitoneally, the trachea, left femoral vein, and right femoral artery were cannulated; a polyethylene tube was introduced into the left ventricle via the right common carotid artery. Arterial blood pressure and left ventricular pressure (LVP) were measured using Statham P23ID pressure transducers, and dLVP/dt max was triggered from LVP by a differentiator coupler (Narco Bio-Systems). The electrocardiogram (ECG) was monitored via standard limb lead II by using an Universal coupler (Narco Bio-Systems), and the heart rate (HR) was triggered from the ECG waveforms by a biotachometer (Narco Bio-Systems). The rats were ventilated by a respirator (Palmer, England) with room air, using a stroke volume of 1 ml/100 g at a rate of 102 strokes/min. The airway resistance of the animals was continuously assessed by monitoring the pressure in the side arm of the tracheal tube, using a Statham PM-5 air pressure transducer; this technique provides only a qualitative measurement, and the pressure elevation in the side arm indicates increased airway resistance. All variables were displayed on a physiograph (E & M Instrument Co., Inc.). The rats were kept warm with a heating lamp throughout the whole experimental period. Experiments were started at 15 min after the cannulation procedure was completed. The rats were injected intravenously through the cannulated left femoral vein with compound 48/80 (Sigma) 0.125, 0.25, 0.5 or 1.0 mg/kg, or with equivalent volumes (1 mg/kg) of 0.9% NaCl w/v (saline) given to the controls. The cardiovascular parameters and airway resistance were continuously observed for 2 h or until the animals died. The time of onset of ventricular tachycardia (VT) or ventricular fibrillation (VF) was recorded. Compound 48/80 was freshly prepared before use and was dissolved in saline. It was given by slow intravenous injection over a 30-sec period.

Samples of femoral arterial blood were collected in some rats before, and at 15 and 30 min after, injection of compound 48/80. They were used for the determination of blood gases/pH using a Ciba-Corning 278 Blood Gas System.

Pretreatments

In order to study the role of H₁- and H₂-receptor activation in the effects of compound 48/80, separate groups of rats which received compound 48/80 0.25 mg/kg were pretreated with cimetidine (SK & F) 12.5 or 25 mg/kg, diphenhydramine HCl (Parke Davis & Co.) 6.25 or 12.5 mg/kg, or a combination of cimetidine 12.5 mg/kg and diphenhydramine 6.25 mg/kg. These drugs were injected intravenously 15 min before the administration of compound 48/80. They were freshly prepared before use by dissolving them in saline. All drug