Effects of histamine $H_1$-receptor blockade on respiratory and cardiac manifestation of systemic anaphylaxis

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Summary

In vivo anaphylaxis is associated with respiratory distress and cardiovascular failure. The present investigation was designed to further characterize respiratory and cardiac anaphylactic events. In guinea pigs, sensitization was produced by subcutaneous application of ovalbumin together with Freund’s adjuvant. Fourteen days after sensitization, the effects of an intravenous infusion of ovalbumin were tested in the anesthetized artificially ventilated guinea pigs. The renewed application of the antigen induced an initial increase of left ventricular pressure which was followed by a rapid decrease 5 min after antigenic challenge. Enddiastolic left ventricular pressure increased within 3 min, thus indicating left ventricular pump failure. In the same time range, ECG recordings uniformly showed signs of acute myocardial ischemia. In addition, heart rate steadily decreased. All animals died within 15 min. Simultaneously with cardiac anaphylactic malfunction, severe arterial hypoxia and carbon dioxide retention occurred, revealing respiratory distress.

Histamine is known as a potent bronchoconstrictor via histamine $H_1$-receptor stimulation. Administration of $H_1$-receptor antagonists to improve respiration may therefore provide further information on the contribution of pulmonary malfunction to anaphylactic cardiovascular shock. Therefore, additional experiments were performed with sensitized guinea pigs pretreated with the histamine $H_1$-receptor blocker mepyramine. In these experiments the antigenic challenge induced a dissociation of cardiac and respiratory manifestation of anaphylaxis. Despite inhibition of hypoxia and carbon dioxide retention, left ventricular pump failure and occurrence of myocardial ischemia were delayed but not suppressed.

It is concluded that histamine is an important mediator of anaphylactic respiratory distress. However, vasoactive anaphylactic mediators other than histamine are primarily involved in anaphylactic cardiac malfunction occurring during the later phase of systemic anaphylaxis.

Introduction

Experimental studies have proven that anaphylactic reactions can be induced directly in the heart [1–4]. An anaphylactic reaction in the sensitized heart is characterized by sinus tachycardia and arrhythmias. Initially, contractility increases followed by a sustained impairment of the contractile parameters. In addition, coronary flow rates rapidly decline due to a marked coronary constriction [4]. The heart has been described previously as a target organ during anaphylactic reactions in vivo. In sensitized guinea pigs, intravenous application of an antigen is followed by cardiac malfunction [5]. Concurrently, severe dysrhythmias develop which are characterized by an impairment of atrioventricular
conduction and increased ventricular automaticity. Eventually, the blood pressure steadily declines. During systemic anaphylaxis in experimental animals, electrocardiographic signs of myocardial ischemia as well as myocardial lesions have been reported [6, 7]. Impaired respiration during anaphylaxis may also affect the performance of the heart. It may be therefore suggested that myocardial ischemia is primarily due to acute hypoxia. Hence, cardiac anaphylactic malfunction should be separated from changes in pulmonary function. Recently, we have shown that cardiac and respiratory manifestation of anaphylaxis can be distinguished in guinea pigs. In animals ventilated with room air, severe hypoxia coincided with cardiovascular collapse. However, in the case of ventilation with 100% oxygen, a dissociation between the onset of cardiac damage and hypoxia occurred. Despite initial normoxia, acute myocardial ischemia and severe left ventricular pump failure developed [8].

Various mediators are responsible for pulmonary and cardiac anaphylactic events. Clinical investigations have proven that excessive histamine release plays a central role in cardiovascular anaphylactic reactions in man [9, 10]. In addition, via H₁-receptor stimulation, histamine is known to induce bronchoconstriction leading to respiratory failure [11]. Administration of H₁-receptor antagonists may therefore provide further information on the contribution of cardiac and pulmonary malfunction to systemic hypersensitivity reactions. In the present study an attempt was made to characterize pulmonary and cardiac events during systemic anaphylaxis in untreated guinea pigs and in guinea pigs pretreated with an H₁-receptor antagonist. The respiratory function was monitored by arterial blood gas analysis, the cardiac performance was investigated by measuring the left ventricular contractile parameters and by electrocardiographic recording.

Materials and methods

Animals

Dunkin-Hartley guinea pigs of both sexes (500–600 g) were actively sensitized by a subcutaneous injection of 0.5 ml 0.9% NaCl solution containing ovalbumin (100 mg/kg) together with 0.5 ml complete Freund’s adjuvans. A second subcutaneous injection of ovalbumin (100 mg/kg) was performed the following day. The guinea pigs were used 14 days later.

In vivo model

The animals were anesthetized with carfentanilyl (4 μg/kg i.m.) and etomidat (20 mg/kg i.m.) as described elsewhere [11]. The trachea was cannulated and connected to a small animal respirator (Rhemata Respirator, model 071784, Hofheim, FRG). Artificial ventilation (stroke rate 45/min, tidal volume 9 ml/kg) was maintained throughout the experimental period. Standard four-limb ECG’s were recorded by an electrocardiograph (Marquette, model 4000 E, Marquette Electronics Inc., Milwaukee, USA). The right jugular vein and the right and the left carotid arteries were carefully isolated. For the application of fluids, a polyethylene catheter (0.5 x 1 mm) was inserted into the superior vena cava via the right jugular vein. A Micro Millar PR-249 catheter tip pressure transducer (sensor size 3 F, main catheter size 2 F, Millar Instruments, Houston, Texas, USA) was placed in the left ventricle via the right carotid artery. The pressure transducer was connected to a Sensormedics recorder, model R 611 (Sensormedics, Witten, FRG). Left ventricular pressure was electronically differentiated to yield left ventricular peak positive dP/dt and left ventricular peak negative dP/dt. Continuous registrations included heart rate, left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), peak positive left ventricular dP/dt (+LVdP/dt_max) and peak negative left ventricular dP/dt (−LVdP/dt_max). To ascertain respiratory function, blood samples were drawn from a polyethylene catheter (0.5 x 1 mm) which was inserted into the left carotid artery and subjected to blood gas analyses (Corning bloodgas analyzer, model 178, Ciba Corning, Fernwald FRG).

Drugs

Ovalbumin and Freund’s adjuvants were obtained from Sigma (Munich, FRG). Carfentanilyl and etomidat were obtained from Janssen Pharmaceutica.