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EXPERIMENTAL PAPER

β-Adrenergic blockade during systemic inflammation: Impact on cellular immune functions and survival in a murine model of sepsis☆

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Summary
Aim of the study: Adrenergic immuno-modulation mediated by β-adrenergic receptors has been demonstrated. Pharmacological blockade of β-adrenergic receptors is a therapeutic intervention frequently used in critically ill patients. The effect of β-adrenergic blockade on cellular immune functions in a critical illness, such as polymicrobial sepsis, has not been investigated.
Methods: Male NMRI-mice were subjected to sham operation or to sepsis (caecal ligation and puncture, CLP) following administration of either the non-selective β-adrenergic antagonist propranolol (0.5 mg/kg s.c. every 12 h in 1 ml vehicle) or saline 0.9% (1 ml s.c. every 12 h). Mice were kept in metabolic cages and were sacrificed 48 h after induction of sepsis. Survival rate, clinical situation (body weight and temperature, fluid and food intake, urine output), and immunological variables (splenocyte proliferation, apoptosis, and IFN-γ and IL-6 release) were determined.
Results: Administration of propranolol in septic mice increased the splenocyte apoptosis rate, reduced the proliferative capacity of splenocytes, and modulated cellular cytokine release (IL-6, IFN-γ). This was paralleled by a higher loss of body weight and temperature, and a decreased urine output. Furthermore, treatment with propranolol increased the sepsis-induced lethality from 47% up to 68%, respectively.
Conclusion: β-Adrenergic blockade was accompanied by alterations of cellular immune functions, a deterioration in the clinical situation and a reduced survival in a

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murine model of sepsis. These data demonstrate the potential immuno-modulatory effects of β-adrenergic antagonists.

Introduction

Pharmacological blockade of β-adrenergic receptors is a frequent therapeutic intervention in critically ill patients.[1–3] Examples are the long-term treatment with β-adrenergic antagonists due to chronic cardiovascular disease and the use of β-adrenergic blocking agents in the treatment of acute cardiac arrhythmias and hypertension.[1] Furthermore, a pharmacologic blockade of β-adrenergic receptors is used to prevent the catecholamine-mediated hypermetabolism in critically ill patients suffering from severe trauma or burn injury. In this group of patients a reduction in cardiac work, resting energy expenditure, and muscle-protein catabolism was recorded after pharmacological β-adrenergic blockade.[2–4]

In addition to these effects it has been demonstrated that the adrenergic system modulated cellular immune functions through activation of β-adrenergic receptors.[5–9] The potential immunological side effects of a β-adrenergic blockade have not been investigated although infectious complications are the leading cause of death in critically ill patients after trauma or burn injury.[10–12]

In line with this, several reports demonstrate an adrenergic modulation of cellular immune functions that is at least partly mediated via activation or inhibition of β-adrenergic receptors.[5–9]

Accordingly, it was reported that non-selective β-adrenergic blockade following administration of the non-selective β-adrenergic antagonist propranolol in healthy human volunteers induced a reduction in the numbers of circulating CD8+-lymphocytes and natural killer (NK)-cells. Furthermore, this effect was accompanied by inhibition of the antibody-dependent cellular cytotoxicity and the cytotoxic activity of NK-cells.[5,6,13] Moreover, administration of the non-selective β-adrenergic antagonist propranolol or of the β_1-selective adrenergic antagonist metoprolol in a clinically relevant murine haemorrhagic shock model revealed that administration of either β-adrenergic antagonist abolished the haemorrhage-induced increase of circulating CD8+-lymphoyctes and NK-cells and modulated splenocyte apoptosis.[14] However, the effect of a β-adrenergic blockade on cellular immune functions during systemic inflammation and its impact on the clinical cause of this disease remains to be established.

We therefore investigated the effect of a non-selective β-adrenergic blockade on the clinical course and cellular immune functions during polymicrobial sepsis in mice.

Materials and methods

Animals and animal care

Male NMRI-mice (Charles River Laboratories, Wilmington, MA), 8—9 weeks old with a body weight between 30 and 34 g were used in this study. Mice were kept with a 12 h dark/light cycle and received water and food *ad libitum*. The experiments were performed in adherence to the guidelines for the Care and Use of Laboratory Animals of the National Institute of Health. The experimental protocol was approved by the local legislative committee.

Drug administration

Propranolol (PROP; 0.5 mg/kg) (Dociton, AstraZeneca, Germany) was administered subcutaneously in control mice, in sham-operated mice and in mice subjected to polymicrobial sepsis by CLP. Mice in the septic and the sham-operated groups received PROP at baseline, and 12, 24, 36 and 48 h after laparotomy or CLP with the baseline dosage being given 20 min prior to laparotomy or CLP. Mice in the control group received a single dose of PROP to determine the baseline effects of the β-adrenergic antagonist. Referring to the literature the dose of propranolol used in our experiment is the lowest dose that is be effective in blocking β-adrenergic activity.[15–17]

Experimental groups

Mice were randomly assigned to one of the following experimental groups. Groups 1—2 ($n = 8$/group) served as untreated controls (UNT). Group 1 received 0.9% saline (UNT/saline, 0.2 ml) and group 2 received a single dose of propranolol (UNT/PROP; 0.5 mg/kg s.c.). Groups 3—4 underwent a sham operation (laparotomy: 1 cm midline incision without caecal ligation and puncture, SHAM, $n = 16$/group) without (SHAM/saline, 0.2 ml s.c.) or with administration of propranolol (SHAM/PROP; 0.5 mg/kg/12 h s.c.). Groups 5—6 were subjected