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UP-REGULATION OF THE ADENOSINE-INDUCED INHIBITION OF H2O2 PRODUCTION IN EX VIVO STIMULATED GRANULOCYTES FOLLOWING PARABOLIC FLIGHT

Abstract

Background: Parabolic flights (PF) represent a standardized tool to train astronauts and to investigate the human adaption to gravitation changes. It has been shown that gravitational stress may alter functions of immune cells, e.g. granulocytes (PMN) as the key element of innate immunity. Previously, we observed in the course of parabolic flight significant changes of the cytotoxic capabilities of PMN to react when challenged in vitro to soluble stimuli (e.g. N-formyl-met-leu-phe [fMLP]/tumor necrosis factor-α [TNF-α]). Granulocytes increase their "alertness" to react upon stimuli ("priming") but not their activity per se; therefore, we hypothesize that endogenous immune-modulatory metabolites may control granulocyte functions and limit their activation. Among many hormones and hormone-like acting substances, the purine-nucleoside adenosine (ADO) is considered to mediate a "stop-signal" to control cells activation. This study investigated the ex vivo responsiveness of human PMN to ADO after PF. Study protocol: Fourteen healthy male volunteers (mean age 42 years, body mass index 24.4 kg*m-2) participated in PF campaigns in 2006 and 2007. Each flight day consisted of 30 subsequent parabolic manoeuvres of each 22-second periods of nearly weightlessness. Blood samples were drawn 24 h prior to take off, after 30 parabolas and 48 h post flight. For the determination of TNF-α/fMLP-induced production of hydrogen peroxide (H2O2), leukocytes were incubated with dihydrorhodamine 123 (1M) in 0.5 mL saline (without or with adenosine 10-10 to 10-5M) at 37C for 5 min until TNF-a (10 ng*mL-1) and fMLP (10-7M) were added. After 15 min H2O2 production of PMN was assessed by flow cytometry. The inhibitory concentration of ADO to reduce the H2O2 production by 50% (IC50) was calculated. In addition, the blood concentrations of adenosine were quantified by dual column switching HPLC. Results: After 30 parabolas the IC50 of ADO did not change (IC50 pre-flight=21.6 nmol*L-1; IC50 30 parabolas=23.7 nmol*L-1). However, 48 h after flight the IC50 was remarkably lower (IC50 48h=7.5 nmol*L-1) which was paralleled by a significant increase ($p<0.04$, paired T-test, n=6) of the adenosine plasma concentrations. Conclusions: Our results of a concomitant increase in adenosine plasma concentrations and in the capability of adenosine to limit receptor-dependent H2O2 production by PMN after parabolic flights suggest a redundant endogenous mechanism to control and limit innate immune functions after acute gravitational stress. Acknowledgements: Supported by the German National Space Program supported by the German

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