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Abstract to be send to humanphysiologie-ws@dlr.de

Influence of acute normobaric and hypobaric hypoxia on hemodynamics, cognitive function, cerebral near-infrared spectroscopy and gene expression

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Introduction: Acute hypoxia in both high altitude and under normobaric conditions is associated with symptoms of acute mountain sickness (AMS) and cognitive dysfunction in humans. However, global or molecular predictors for the development of AMS are missing. Thus, the aim of this study was to investigate in non-acclimatized subjects associations between AMS and 1) hemodynamic changes, cerebral oxygen saturation and cognitive function, as well as 2) leukocyte mRNA expression of inflammatory molecules under acute hypobaric and normobaric hypoxia, respectively.

Methods: Eleven healthy subjects were examined in hypobaric hypoxia under resting and exercise conditions at 3883 m above sea level. Pulse oximetric oxygen saturation (SpO_2), cerebral near-infrared spectroscopy (NIRS) and advanced hemodynamic parameters (cardiac output (CO), cardiac index (CI), stroke volume (SV), index of contractility (ICON), thoracic fluid content (TFC), left-ventricular ejection time (LVET) and pre-ejection period (PEP)) were measured non-invasively. AMS (assessed with Lake Louise Score (LLS)) and cognitive function (Trail making test and two newly developed cognitive function tests) were assessed. Additionally, 7 out of 11 individuals were tested under normobaric conditions in a hypoxic chamber simulating a similar situation to compare these results with hypobaric environment (520m above sea level, 13.1% inspired oxygen). PAXgene blood samples of subjects were used to analyse changes in leukocyte mRNA expression of IL-1β, CXCR4 and CCR2 in normobaric and hypobaric hypoxia compared to normoxic baseline using real-time PCR (qPCR). To reappraise molecular results from normobaric and hypobaric experiments and to distinguish between hypoxic and exercise effects, we isolated peripheral blood mononuclear cells (PBMCs). PBMCs were incubated for 24 hours under normoxia, 10% and 5% hypoxia or stimulated with CD3/CD28. mRNA expression of aforementioned variables was again performed using qPCR.

Results: Under hypoxia SpO_2 (data not shown) and NIRS highly decreased (Baseline vs. normobaric hypoxia: 73.4%±8.3 vs. 62%±5.6; $p<0.05$; Baseline vs. hypobaric hypoxia: 73.4%±8.3 vs. 56.3%±11.0, $p<0.001$) and volunteers developed AMS. Heart rate, cardiac output and LLS increased, whereas LVET and SV decreased under normobaric and hypobaric conditions, especially following exercise. Hemodynamic changes did not correlate with cognitive function tests or AMS. LLS after 24h correlated with NIRS after exerciseunder hypobaric conditions ($p<0.01$). After 24 h on the mountain, LLS scores, indicating AMS, correlated with IL-1β ($p=0.03$; $r=0.735$) and CXCR4 ($p=0.01$; $r=0.796$) mRNA expression. In detail, CXCR4 mRNA expression highly increased immediately after exercise under hypobaric hypoxia and remained elevated after 24 h ($p<0.01$), whereas IL-1β increased after 24 h on the mountain ($p=0.04$). CCR2 increased both under normobaric and hypobaric hypoxia after exercise ($p<0.05$) and further increased until 24 h on the mountain ($p=0.01$). In contrast, in vitro CXCR4 mRNA expression remained unaltered when applying hypoxic (10% and 5%) or stimulatory conditions (CD3/CD28), suggesting that in vivo CXCR4 increase was due to a combination of both hypoxia and exercise. IL-1β strongly increased following CD3/CD28 stimulation ($p=0.006$) and 5% hypoxia ($p=0.004$) in vitro. CCR2 did not increase following CD3/CD28, but after hypoxia in vitro ($p=0.005$).

Conclusions: Acute normobaric and hypobaric hypoxia alters hemodynamic and cerebral oximetry and leads to AMS. Cognitive function tests were unaltered and did not correlate with systemic or cerebral oximetry readings and thus were insensitive to detect cerebral dysfunction under acute normobaric or hypobaric hypoxia. Additionally, non-invasive hemodynamic variablesand cognitive function tests did not correlate with the development of AMS whereas NIRS after exercise in normobaric and hypobaric hypoxia showed a correlation with LLS after 24h. Also induction of molecular markers was correlated with LLS: IL-1β, CXCR4 and CCR2 gene expression revealed as regulated by hypoxia or inflammatory stimuli in vitro. Further studies are needed to analyse whether NIRS and these molecular markers may be a promising tool to identify people at risk for AMS.