Effects of dietary salt levels on monocytic cells and immune responses in healthy human subjects: a longitudinal study

BUQING YI, JENS TITZE, MARINA RYKOVA, MATTHIAS FEUERECKER, GALINA VASSILIEVA, IGOR NICHIPORUK, GUSTAV SCHELLING, BORIS MORUKOV, and ALEXANDER CHOUKÈR

MUNICH AND ERLANGEN, GERMANY; NASHVILLE, TENNESSEE; AND MOSCOW, RUSSIAN FEDERATION

Increasing evidence indicated that excess salt consumption can impose risks on human health and a reduction in daily salt intake from the current average of approximately 12 g/d to 5–6 g/d was suggested by public health authorities. The studies on mice have revealed that sodium chloride plays a role in the modulation of the immune system and a high-salt diet can promote tissue inflammation and autoimmune disease. However, translational evidence of dietary salt on human immunity is scarce. We used an experimental approach of fixing salt intake of healthy human subjects at 12, 9, and 6 g/d for months and examined the relationship between salt-intake levels and changes in the immune system. Blood samples were taken from the end point of each salt intake period. Immune phenotype changes were monitored through peripheral leukocyte phenotype analysis. We assessed immune function changes through the characterization of cytokine profiles in response to mitogen stimulation. The results showed that subjects on the high-salt diet of 12 g/d displayed a significantly higher number of immune cell monocytes compared with the same subjects on a lower-salt diet, and correlation test revealed a strong positive association between salt-intake levels and monocyte numbers. The decrease in salt intake was accompanied by reduced production of proinflammatory cytokines interleukin (IL)-6 and IL-23, along with enhanced producing ability of anti-inflammatory cytokine IL-10. These results suggest that in healthy humans high-salt diet has a potential to bring about excessive immune response, which can be damaging to immune homeostasis, and a reduction in habitual dietary salt intake may induce potentially beneficial immune alterations. (Translational Research 2015;166:103–110)

Abbreviations: DMEM = Dulbecco's modified eagle medium; EDTA = ethylenediaminetetraacetic acid; HF = heart failure; IL = interleukin; PWM = pokeweed mitogen; TLR = toll-like-receptor; TNF-α = tumor necrosis factor α; VEGF-C = vascular endothelial growth factor C

From the Hospital of the University of Munich (LMU), Department of Anaesthesiology, Munich, Germany; Interdisciplinary Center for Clinical Research, Friedrich-Alexander-University, Erlangen, Germany; Department of Nephrology and Hypertension, Friedrich-Alexander-University, Erlangen, Germany; Division of Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; Institute for Biomedical Problems, Moscow, Russian Federation.

Submitted for publication August 13, 2014; revision submitted November 13, 2014; accepted for publication November 18, 2014.

Reprint requests: Alexander Choukèr, Hospital of the University of Munich (LMU), Department of Anaesthesiology, Research Group Stress & Immunology, Marchioninistrasse 15, 81377 Munich, Germany; e-mail: alexander.chouker@med.uni-muenchen.de.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2014.11.007

AT A GLANCE COMMENTARY

Yi B, et al.

Background

It has been revealed in the studies on mice that sodium chloride plays a role in the modulation of the immune system and a high-salt diet can promote tissue inflammation and autoimmune disease. However, translational evidence of dietary salt intake on human immunity is scarce.

Translational Significance

The results have revealed a positive association between dietary salt levels and the amount of immune cell monocytes and suggest that in healthy humans high-salt diet has a potential to trigger excessive immune responses. To our knowledge, these results provided the first translational evidence for the effects of salt-intake levels maintained for a prolonged period on immunity.

INTRODUCTION

Mounting evidence for the risks imposed on human health by excess salt consumption has attracted public attention in the past decades. Adult populations in many countries have average daily salt intake of about 12 g.[1-3] Most salt-related studies focused on the relation of salt intake with the risk of hypertension and cardiovascular disease.[4-9] It has been estimated on the basis of the results from previous studies that a population-wide reduction in habitual dietary salt intake could markedly decrease the incidence of cardiovascular disease.[10] The current public health recommendations in most countries are to reduce salt intake to 5–6 g/d.[1-3] However, it is largely unknown if this recommended dietary salt reduction from 12 to 6 g has an effect on other aspects of human health, such as the immune system and immune functions.

Studies on mice have shown that high-salt diet can promote tissue inflammation and autoimmune disease,[11-13] which raises the possibility that high salt intake might play an important role in driving the dramatically increased incidence of autoimmune diseases in the past half-century together with other environmental factors and genetic factors.[14] Validation of this hypothesis by a randomized controlled trial of the effects of long-term reduction in dietary salt on morbidity and mortality from inflammation or immune function–related disease would provide such confirmative proof. A study of this kind is not available at present and in fact, because of practical difficulties of the long duration and the related high costs it seems unlikely that it can be performed in the near future. And even preliminary translational evidence of dietary salt intake on human immunity is still scarce. Only one recent salt-control study performed in human subjects with a 7-day high-salt diet (≥15 g NaCl/d) followed by a 7-day low-salt diet (≤5 g NaCl/d) reported salt-related immune variation.[15] However, it was hard to predict to what extent the results from this study can reflect the influence of habitual dietary salt levels since no similar long-term salt-control study was performed.

On the basis of the current public health recommendations for a modest reduction in salt intake for a long duration, a 205-day salt balance study with stepwise change in dietary salt was performed in the frame of a controlled simulated spaceflight program termed Mars520, which provided a unique opportunity to investigate the effects of dietary salt intake on human immunity under metabolic ward conditions. During the simulation conducted in an enclosed habitat, daily salt intake was solely modified (12, 9, 6 g/d and back to 12 g/d NaCl; see Fig 1, *A*, Table I) for 30–60 days. We carried out a variety of immune analyses to investigate the effects of long-term modest salt-intake reduction on immune status, and at the same time monitored plasma angiogenic protein vascular endothelial growth factor C (VEGF-C) level at each salt stage to testify the potential role of macrophages in the regulation of salt homeostasis as suggested by animal studies.[16]

MATERIAL AND METHODS

Subjects and environmental conditions. This long-term salt-intake study with healthy human subjects was performed in the frame of a spaceflight simulation (Mars520) conducted at the Institute for Biomedical Problems in Moscow and approved by several ethical boards of European Space Agency authorities, the Russian Federation and the University of Munich. Six healthy male volunteers (mean age, 33 ± 6 years) were selected based on the modified astronaut selection criteria. They provided written informed consent after due approval to live in an enclosed habitat with well-controlled environmental factors and to perform this salt-intake study and relevant investigations. All participants underwent a thorough clinical examination before participation, and during the study period medical control of their health condition was regularly performed. All studies were done as outlined in the Declaration of Helsinki.

Salt-controlled diet. The salt-intake study took place during the first 205 days of the Mars520 mission.