



## Effects of restraint stress on NALT structure and nasal IgA levels

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### ABSTRACT

The effects of stress on the mucosal immune responses in inflammatory disorders of the gut, as well as on salivary and intestinal IgA levels are well known. However, its effects on the structure and function of the NALT have not yet been reported, and are examined in the present study. Balb/c mice were submitted to restraint stress for 3 h per day during 4 or 8 d. The immunohistochemistry and flow cytometric analysis revealed that repeated restraint stress (4 and 8 d) decreased the percentage, compared to the control group, of CD3<sup>+</sup> and CD4<sup>+</sup> T cells, without affecting the percentage of CD8<sup>+</sup> T cells or B220<sup>+</sup> cells (B cells). The numbers of IELs (CD4<sup>+</sup> and CD8<sup>+</sup> T cells) were lower at 4 d of stress and higher at 8 d. IgA<sup>+</sup> cells in NALT and nasal IgA levels showed a similar pattern, being significantly lower at 4 d of stress and significantly higher at 8 d. In summary, repeated restraint stress altered the distribution and number of lymphocytes and IgA<sup>+</sup> cells in nasal mucosa, probably due to changes in norepinephrine and corticosterone levels.

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### 1. Introduction

The effects of stress on the mucosal immune responses have been widely analyzed in relation to inflammatory disorders of the gut and the secretion of IgA in saliva. The robust information available confirms that psychological stress plays a key role in the pathophysiology and clinical presentation of inflammatory bowel disease [1–5].

There are contradictory reports on the relationship between secretory IgA (S-IgA) levels in saliva and different conditions of stress, such as exercise, mood states and academic examinations. Whereas some studies found decreases in S-IgA, others detected increases or no change [6–11]. We recently reported that stress decreases intestinal IgA levels, and affects the population of intraepithelial lymphocytes in the duodenal mucosa of mice [12,13]. However, the effects of stress on the nasal immune system have not been explored in detail.

It has been documented that psychological stress alters susceptibility to several different strains of respiratory viruses [14], and numerous reports indicate that exercise stress can increase the risk for upper respiratory tract infection, particularly in highly trained and elite athletes [15–17]. Although some elite athletes and subjects under severe stress produce less IgA in saliva, it has not been established that this is the cause of the higher incidence of respiratory infections in these populations [17–20]. Other causative factors that have been proposed are the presence of infiltrated inflammatory cells in mucous membranes and the removal of one or more immune functions [15,16,21].

It is unknown whether chronic stress can alter the structure and/or function of the nasal-associated lymphoid tissue (NALT), and if so whether such change would contribute to the increased incidence of respiratory infections found among elite athletes. Studies on animals suggest that stress can affect the immune responses in the upper respiratory tract. In mice infected intranasally with influenza virus, restraint stress increases levels of IgM and IgG antibody-secreting cells, which are virus-specific responses in the superficial cervical lymph node, the latter being considered part of the NALT [22]. On the other hand, restraint stress inhibits the production of IgE, IgG1 and IgG2a, specific for an allergen inoculated intranasally [23]. Moreover, acute treadmill exercise of mice decreases the number of CD4<sup>+</sup> T cells in the submandibular lymph

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