Brain, Behavior, and Immunity 52 (2016) 11–17

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Psychological distress and salivary secretory immunity

C.G. Engeland [a,b,c,*,1], F.N. Hugo [d,1], J.B. Hilgert [d], G.G. Nascimento [e], R. Junges [d,f], H.-J. Lim [g], P.T. Marucha [c,h], J.A. Bosch [i,j,*]

[a] Department of Biobehavioral Health, The Pennsylvania State University, University Park, PA, USA
[b] College of Nursing, The Pennsylvania State University, University Park, PA, USA
[c] Center for Wound Healing and Tissue Regeneration, University of Illinois at Chicago, Chicago, IL, USA
[d] Department of Social and Preventive Dentistry, College of Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil
[e] Post-graduate Program in Dentistry, Federal University of Pelotas, Pelotas, RS, Brazil
[f] Institute of Oral Biology, Faculty of Dentistry, University of Oslo, Oslo, Norway
[g] Department of Orthodontics, School of Dentistry, Chonnam National University, Dental Science Research Institute, Gwangju, South Korea
[h] School of Dentistry, Oregon Health and Science University, Portland, OR, USA
[i] Department of Clinical Psychology, University of Amsterdam, Amsterdam, The Netherlands
[j] Mannheim Institute of Public Health, Social and Preventive Medicine, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

ARTICLE INFO

Article history:
Received 8 June 2015
Received in revised form 14 August 2015
Accepted 22 August 2015
Available online 28 August 2015

Keywords:
Immunoglobulin A
Stress
Depression
Loneliness
Saliva
Secretory Component
Immunoglobulin subclass
IgA1
IgA2

ABSTRACT

Stress-induced impairments of mucosal immunity may increase susceptibility to infectious diseases. The present study investigated the association of perceived stress, depressive symptoms, and loneliness with salivary levels of secretory immunoglobulin A (S-IgA), the subclasses S-IgA1, S-IgA2, and their transporter molecule Secretory Component (SC). S-IgA/SC, IgA1/SC and IgA2/SC ratios were calculated to assess the differential effects of stress on immunoglobulin transport versus availability.

This study involved 113 university students, in part selected on high scores on the UCLA Loneliness Scale and/or the Beck Depression Inventory. Stress levels were assessed using the Perceived Stress Scale. Unstimulated saliva was collected and analysed for total S-IgA and its subclasses, as well as SC and total salivary protein. Multiple linear regression analyses, adjusted for gender, age, health behaviours, and concentration effects (total protein) revealed that higher perceived stress was associated with lower levels of IgA1 but not IgA2. Perceived stress, loneliness and depressive symptoms were all associated with lower IgA1/SC ratios. Surprisingly, higher SC levels were associated with loneliness and depressive symptoms, indicative of enhanced transport activity, which explained a lower IgA1/SC ratio (loneliness and depression) and IgA2/SC ratio (depression).

This is the first study to investigate the effects of protracted psychological stress across S-IgA subclasses and its transporter SC. Psychological stress was negatively associated with secretory immunity, specifically IgA1. The lower immunoglobulin/transporter ratio that was associated with higher loneliness and depression suggested a relative immunoglobulin depletion, whereby availability was not keeping up with enhanced transport demand.

1. Introduction

Human and animal studies have provided convincing evidence that psychological stress may increase susceptibility to infection and infectious diseases (Engeland and Marucha, 2009; Moreira et al., 2008; Ojard et al., 2015; Pedersen et al., 2010). Approximately 95% of all infections start at mucosal surfaces such as the lining of the mouth, the respiratory and gastro-intestinal tracts, and the eyes (Bosch et al., 2002; Castro-Sanchez and Martin-Villa, 2013; Mayer and Walker, 2005; Sato and Kiyono, 2012). These vulnerable soft tissues are protected by various antimicrobial proteins secreted by local exocrine glands, which constitute a first line of immunological defense (Mayer and Walker, 2005). A key immunological component in these secretions is secretory immunoglobulin A (S-IgA) (Macpherson et al., 2008; Mantis and Forbes, 2010; Mantis et al., 2011). Studies

* Corresponding authors at: Department of Biobehavioral Health, 229 Biobehavioral Health Building, The Pennsylvania State University, University Park, PA 16802, USA (C.G. Engeland). Mannheim Institute of Public Health, Social and Preventive Medicine, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; Department of Clinical Psychology, University of Amsterdam, Amsterdam, The Netherlands (J.A. Bosch).

E-mail addresses: cge2@psu.edu (C.G. Engeland), j.a.bosch@uva.nl (J.A. Bosch).

[1] Both authors contributed equally.

http://dx.doi.org/10.1016/j.bbi.2015.08.017
0889-1591/

have shown that S-IgA concentrations predict susceptibility to respiratory, oral, and aural infections (Lee et al., 2010; Nakamura et al., 2006; Tiollier et al., 2005). Hence, total S-IgA is considered an immunologically meaningful measure of mucosal host resistance (Macpherson et al., 2008).

The release of S-IgA is under strong neuroendocrine control, and acute stress studies have shown robust effects on S-IgA whereby its concentration typically increases (Bosch et al., 2002; Takatsuji et al., 2008; Trueba et al., 2012). This likely occurs due to increased release of antibody from B-lymphocytes and/or increased transport of IgA across the epithelium into saliva (Bosch et al., 2002). Evidence from chronic stress studies is less robust, although the balance of evidence indicates that protracted stress (e.g., caregiving) is associated with decreased levels of S-IgA (Bosch et al., 2002, 2004; Teeuw et al., 2004). For example, a study conducted by Phillips and colleagues involving two cohorts (total $N = 1282$), found that the experience of major stressful life events was associated with lower salivary IgA levels (Phillips et al., 2006).

There are several ways in which knowledge about the effects of chronic stress on S-IgA can be enhanced. For example, it remains unresolved if stress-induced alterations in S-IgA concentrations are primarily determined by effects on immunoglobulin production (by B-lymphocytes), or by altered transport of immunoglobulin to mucosal surfaces. To clarify, S-IgA concentrations are determined through a 2-phase process. First, B lymphocytes, which are present in the glandular tissues, produce and release IgA. This IgA is then transported through the glandular cell, via the transporter molecule Secretory Component (SC), into fluids such as saliva. It is the IgA–SC complex that forms S-IgA (Mora and von Andrian, 2008; Norderhaug et al., 1999; Sun et al., 2004). The transporter SC can also be secreted into mucosal secretions unbound to IgA, and salivary S-IgA and SC are partially independent indicators of B-cell IgA production and glandular transport capacity, respectively. By separately measuring S-IgA and SC, as well as their ratio, it is therefore possible to determine if the effects of stress are due to lower availability of IgA (i.e., decreased release from B-lymphocytes) or due to reduced glandular transport capacity.

A further limitation of the literature is that chronic stress studies have assessed total S-IgA only; however, this is a summary measure of two distinct subclasses, denoted S-IgA1 and S-IgA2 (Woof and Russell, 2011). Differentiating between these subclasses may be relevant because decreased salivary S-IgA1 levels, but not S-IgA2 levels, are associated with an increased risk of upper respiratory tract infections (Gleeson et al., 1999; Moreira et al., 2008; Nakamura et al., 2006). Interestingly, both acute stress and exercise have been found to selectively increase the salivary concentrations of IgA1 but not IgA2 (Bosch et al., 2001; Gleeson et al., 1999). These findings suggest that the secretion of the two subclasses is under differential control, and might therefore be differentially affected by protracted forms of psychological stress.

In light of the preceding discussion, the aim of the current investigation was to determine via ELISAs the salivary levels of S-IgA, IgA1, IgA2, SC, and the S-IgA/SC, IgA1/SC and IgA2/SC ratios in a sufficiently powered cohort selected for high and low levels of depressive symptoms and loneliness (Bosch et al., 2007). It was hypothesised that being more lonely, depressed, or stressed would result in decreased levels of S-IgA in saliva. Further, on the basis of acute stress studies (Bosch et al., 2001; Gleeson et al., 1999) it was anticipated that these effects would be stronger for S-IgA1 than S-IgA2. Finally, we quantified the S-IgA/SC ratio to examine the differential effects of these psychosocial factors on IgA production versus transport.

2. Methods

2.1. Participants

This present study was based on a sub-sample of a larger cohort (Bosch et al., 2007), a portion of which were selected to have particularly high scores on depression or loneliness measures. The Beck Depression Inventory short form (BDI-sf) and the Revised UCLA Loneliness Scale (UCLA-R) were administered to 1630 undergraduate Ohio State University students. This was done to increase the range of depression and loneliness scores in our study sample. Participants who scored in the upper or lower quintile on one or both of these questionnaires were invited to participate. These cut-offs were determined a priori on the basis of previous research in a similar population (Hawkley et al., 2005). For the UCLA-R, the inclusion criterion was a score of $\leqslant 28$ or $\geqslant 46$; for the BDI-sf, the inclusion criterion was a score of $\leqslant 1$ or $\geqslant 8$ (for further details see Bosch et al., 2007).

Based on the above criteria and available saliva samples, 113 undergraduate volunteers were included in this study (61 male, 52 female, mean age 20.7 ± 2.9, range 17–33). Most participants were Caucasian ($N = 86$; 76%). Exclusion criteria included the use of prescribed oral medication, reporting medical problems (e.g., inflammatory, endocrine) that have known effects on immune or salivary gland function, oral health problems that required prompt treatment, and self-reported signs of infectious disease (e.g., cold) within 2 weeks before assessment. In addition, individuals receiving treatment/medication for systemic diseases, including diabetes, were excluded from our sample. Given the low age of participants (highest age 33 years) no periodontitis was observed in these individuals. Participants provided informed consent and received financial compensation for their time and effort. The study protocol was approved by the Institutional Review Board (IRB) of OSU where the study was conducted and by the IRB of the University of Illinois at Chicago (UIC) where samples were analysed.

2.2. Procedures

Participants were scheduled between 10:00 a.m. and 11:30 a.m. to minimise the influence of circadian variation. In preparation for the study, participants were instructed not to engage in strenuous physical exercise, and to refrain from using alcohol or non-prescription drugs 24 h before the experimental sessions. In addition, participants were instructed to abstain from caffeine the day of the experiment, to eat breakfast before 9:30 a.m., and to eat or drink nothing after that point (except for water).

Upon arrival at the School of Dentistry Research Clinic at OSU, participants filled out questionnaires to assess psychological traits and states, demographics, and health behaviours, and saliva was subsequently collected.

2.3. Questionnaires

2.3.1. Psychological measures

The Perceived Stress Scale (PSS) consists of 10-items on a 5-point Likert scale, with values ranging from 0 to 4; it assesses the degree in which situations in one's life over the past week are appraised as taxing and stressful. The questionnaire assesses thoughts and feelings about stressful events, control, overload, experienced stress, as well as how often the individual felt or thought in a stressful manner. The scale allows for the examination of stress pathology relationships and has been found to predict mental and physical health outcomes (Cohen et al., 1993). In this study, internal reliability for PSS was high (Cronbach's $\alpha = 0.85$).