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Review article

Linking stress and immunity: Immunoglobulin A as a non-invasive physiological biomarker in animal welfare studies

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ABSTRACT

As the animal welfare community strives to empirically assess how care and management practices can help maintain or even enhance welfare, the development of tools for non-invasively measuring physiological biomarkers is essential. Of the suite of physiological biomarkers, Immunoglobulin A (IgA), particularly the secretory form (Secretory IgA or SIgA), is at the forefront because of its crucial role in mucosal immunity and links to physical health, stress, and overall psychological well-being. While interpretation of changes in SIgA concentrations on short time scales is complex, long-term SIgA patterns are consistent: conditions that create chronic stress lead to suppression of SIgA. In contrast, when welfare is enhanced, SIgA is predicted to stabilize at higher concentrations. In this review, we examine how SIgA concentrations are reflective of both physiological stress and immune function. We then review the literature associating SIgA concentrations with various metrics of animal welfare and provide detailed methodological considerations for SIgA monitoring. Overall, our aim is to provide an in-depth discussion regarding the value of SIgA as physiological biomarker to studies aiming to understand the links between stress and immunity.

1. Introduction

Animal welfare is a multifaceted concept that refers to an animal's collective physical, mental, and emotional states and is measured on a continuum from very poor to very good (AZA; WAZA). Welfare is enhanced when an individual is provided an environment that is free of chronic stressors, nurtures positive affective states, and facilitates the expression of natural behaviors and instincts such as exploration (digging, smelling, rubbing, swimming, etc.), healthy social interactions, and play (Green and Mellor, 2011; McMillan, 2005; Mellor, 2012; Mendl et al., 2010; Yeates and Main, 2008). On the other hand, welfare is reduced if an animal's ability to survive or reproduce is decreased, health problems exist, and/or it experiences an unpleasant emotional state (e.g., fear, anxiety, boredom, frustration) (Barnett and Hemsworth, 1990; Broom, 1991; Dawkins, 1980, 1990; Duncan and Petherick, 1989; Sandøe and Simonsen, 1992). For animals under professionally managed care, it is not only our ethical responsibility, but also our scientific imperative, to continue to advance animal welfare science and improve best management practices (APA; AVMA; AZA; FAWC, 2009; WAZA). To meet this goal, multiple behavioral, physiological, and psychological dimensions should be regularly monitored to provide empirical assessments of welfare (Clark et al., 1997a, 1997b).

Of growing interest to both the animal welfare and broader scientific community is the measurement of non-invasive physiological biomarkers to assess how the spectrum of poor to excellent welfare influences physical and psychological health (Barak, 2006; Dillon et al., 1986; Dockray and Steptoe, 2010; Hucklebridge et al., 2000; Lamb et al., 2017). Historically, such studies have predominantly targeted biomarkers that reflect activity of the hypothalamic-pituitary-adrenal (HPA) axis (i.e., glucocorticoids). However, this approach requires cautious interpretation since HPA axis activity reflects arousal but not valence; that is, whether a stimulus is intrinsically positive or negative. Consequently, HPA axis activity alone cannot be used to infer an animal's affective, or emotional, state (i.e., an educated judgement regarding the subjective emotional experience of the subject, as observed in their behavior or measured in their physiology) (McEwen et al., 2016; McEwen and Seeman, 1999; Mendl et al., 2010; Moberg and Mench, 2000). Thus, the field is moving towards implementing additional biomarkers, first applied in human research, that may enable more robust welfare assessments by facilitating discrimination between arousal that is associated with a positive valence (i.e., pleasure) from arousal associated with a negative valence (i.e., displeasure). These biomarkers include but are not limited to molecules associated with the sympathetic branch of the autonomic nervous system (e.g. alpha-amylase, chromogranin-a), stress-related inflammatory markers (e.g.

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cytokines, C-reactive protein), neuroprotective androgens (dehydroepiandrosterone (DHEA) and DHEA-sulfate), and proteins whose synthesis or secretion is influenced by stress-immune interactions (e.g. Immunoglobulin A, cytokines) (Hänsel et al., 2010; Maninger et al., 2009; Nakane et al., 1998; Nater and Rohleder, 2009). While promising, such novel physiological biomarkers must first be validated for use within each target species and critically evaluated with respect to biologically relevant parameters to ensure accurate interpretation of results.

In this review, we focus on the measurement and validation of the antibody isotype Immunoglobulin A (IgA), and more specifically its secretory form (Secretory IgA or SIgA), as a non-invasive biomarker for evaluating the interplay between the stress and immune systems. IgA is secreted at all mucosal surfaces and thought to reflect the functional status of the mucosal immune system (Corthesy, 2013; Mantis et al., 2011). In addition to its fundamental role in frontline disease prevention, IgA concentrations can be influenced by both physical and psychosocial stress (Bishop and Gleeson, 2009; Tsujita and Morimoto, 1999). Understanding how interactions between the stress response and immune systems influence IgA concentrations, therefore, may help elucidate the mechanisms that drive the well-documented negative consequences of chronic stress on physical health and disease (Ganster and Rosen, 2013; Pacella et al., 2013; Salovey et al., 2000). In the context of animal welfare, IgA has primarily been applied in assessments of biomedical, agricultural, and companion animals. Interest in IgA continues to grow, in part, because IgA can be effectively sampled using minimally- or non-invasive methods such as saliva or fecal collections (for e.g., see (Eriksson et al., 2004; Escribano et al., 2015; Estes, 2010; Gourkow et al., 2014b; Peters et al., 2004; Schatz and Palme, 2001)). Our intention is to expand the discussion surrounding IgA to the broader scientific community, both in the context of optimizing animal care practices and enhancing assessments of how poor versus good welfare impact immune function.

First, we describe the physiological interactions between the immune and stress response systems, providing the biological context for how IgA is a sensitive measure of both. Secondly, we review the literature associating IgA with conditions that promote poor versus good welfare. Lastly, we detail methodological considerations for measuring IgA including sample type, sampling frequency, and assay considerations. Ultimately, our goal is to explore how incorporating IgA into animal welfare studies can help clarify the links between physiological stress responses, the valence of stimuli, and immune function.

2. Functional overview of Immunoglobulin A

Immunoglobulin A, or IgA, is the major antibody of the humoral mucosal immune system in mammals and birds. Homologous IgA genes have been discovered in some reptile lineages, specifically testudines and crocodiles, but are lacking in lizards and snakes examined to date (Deza et al., 2007; Magadan-Mompo et al., 2013). IgA genes have also been found in several amphibian species, although the functional significance of IgA in vertebrate taxa outside of birds and mammals remains undescribed (Estevez et al., 2016). Therefore, this section will provide an overview of IgA function and production in mammals and birds, with specific emphasis on the links between mucosal IgA concentrations and other physiological systems.

The main function of IgA is in immune exclusion of pathogens and commensals. In other words, IgA acts to neutralize viruses and toxins as well as prevent microorganisms from interacting with or penetrating the mucosal epithelium. Overall, this enhances nonspecific immune defenses at these surfaces and, within the gut, helps maintain a balanced microbiota (Corthesy, 2013; Mantis et al., 2011; Moor et al., 2017). While the majority of IgA produced recognizes redundant microbial antigens, high-affinity, pathogen-specific IgA can also be synthesized in response to infection (Kaetzel, 2014). Additionally, IgA is present at low concentrations in serum where it helps control inflammatory responses and can be passively transferred from mother to offspring via milk in mammals or the egg in birds, protecting offspring during growth and development (Bar-Shira et al., 2014; Curtis and Bourne, 1971; Fischer et al., 2016; Mackenzie et al., 1997; Van Egmond et al., 2001). This maternally derived IgA has been experimentally shown to influence the establishment of the gut microbiota and gut homeostasis in mammals, including expression of genes associated with intestinal inflammatory diseases (Rogier et al., 2014). Despite serving such crucial functions, the usefulness of IgA in studies examining interactions between the stress response and immune systems has been complicated by both a lack of congruence between different sample types and a need to improve our understanding of how IgA links to other physiological systems (Peters et al., 2004; Watt et al., 2016).

Physiological signals can influence IgA dynamics by affecting IgA production and secretion at the cellular level. IgA at mucosal surfaces is produced locally by resident IgA-secreting plasma cells (mature B cells); consequently, IgA concentrations at different surfaces are independent of circulating IgA concentrations and each other (Corthesy, 2013; Kurimoto et al., 2016). While IgA in circulation is typically monomeric, the secretory form of IgA (Secretory IgA or SIgA) predominates at mucosal surfaces. SIgA is characterized by the addition of the secretory component, which serves to stabilize SIgA and make it resistant to degradation by host and microbial proteases alike (Brandtzaeg, 2013; Corthesy, 2013; Rogier et al., 2014). The production and secretion of SIgA begins with the joining of IgA monomers through the Joining (J) chain protein to form polymeric (typically dimeric) IgA. The J chain is then selectively bound by the polymeric immunoglobulin receptor (pIgR) on the basal surface of the mucosal epithelium. Once bound, the polymeric IgA is transcytosed across the epithelium to the apical surface where pIgR is cleaved and SIgA, which now includes the extracellular domain of the pIgR (the secretory component), is released (Corthesy, 2013; Rogier et al., 2014). The production and secretion of SIgA can therefore be regulated at a number of steps, the dynamics of which are influenced by signaling molecules associated with immune activation (i.e., cytokines) and/or physiological stress responses (i.e., glucocorticoids and catecholamines) (Fig. 1).

SIgA regulation has been proposed to occur through a variety of cellular mechanisms including changes to the population of IgA-producing plasma cells at mucosal surfaces, altered IgA mRNA expression and/or synthesis, and controlling SIgA secretion rates via regulation of pIgR expression (Godinez-Victoria et al., 2012; Jarillo-Luna et al., 2007; Lara-Padilla et al., 2015; Oros-Pantoja et al., 2011; Reyna-Garfias et al., 2010) (Fig. 1B–C). Some studies examining acute stressors have found support for alteration of SIgA concentrations without change to the number of IgA-producing plasma cells while others have demonstrated changes in the numbers of IgA-producing plasma cells, but such changes are not always associated with a similar change in SIgA concentrations (Bianco et al., 2014; Jarillo-Luna et al., 2007; Jarillo-Luna et al., 2015; Oros-Pantoja et al., 2011). In contrast, the evidence supporting altered SIgA concentrations occurring via regulation of IgA expression, pIgR expression, or both is more robust (Godinez-Victoria et al., 2012; Jarillo-Luna et al., 2007; Lara-Padilla et al., 2015; Oros-Pantoja et al., 2011; Reyna-Garfias et al., 2010). The exact mechanisms employed, however, may depend on the underlying physiological pathway(s) activated and whether tissues are responsive to, or in other words express the receptors for, the associated signaling molecules (Fig. 1).

SIgA concentrations can be influenced by changes in the immune environment, the signals of which are mediated by small proteins (cytokines and chemokines) that have pleiotropic effects in regulating immune responses and inflammation. Cytokines and chemokines can be secreted by a variety of cell types throughout the body in response to microbe recognition. Cytokines can promote B cell development, proliferation, and isotype switching (i.e., TGF-β promotes class switching of B cells to produce IgA) while chemokines are predominantly