Developmental and Comparative Immunology xxx (2016) 1–22

Contents lists available at ScienceDirect

Developmental and Comparative Immunology

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

Neuroendocrine-immune interaction: Evolutionarily conserved mechanisms that maintain allostasis in an ever-changing environment

B.M. Lidy Verburg-van Kemenade [a], [*], Nicholas Cohen [b], Magdalena Chadzinska [c]

[a] Cell Biology and Immunology Group, Dept. of Animal Sciences, Wageningen University, P.O. Box 338, 6700 AH Wageningen, The Netherlands
[b] Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY 14620, USA
[c] Department of Evolutionary Immunology, Institute of Zoology, Jagiellonian University, Gronostajowa 9, PL30-387 Krakow, Poland

ARTICLE INFO

Article history:
Received 29 April 2016
Received in revised form
23 May 2016
Accepted 23 May 2016
Available online xxx

Keywords:
Neuroendocrine-immune interaction
Psychoneuroimmunology
Homeostasis
Receptor interaction
Blood brain barrier
Stress axis
Leukocytes

ABSTRACT

It has now become accepted that the immune system and neuroendocrine system form an integrated part of our physiology. Immunological defense mechanisms act in concert with physiological processes like growth and reproduction, energy intake and metabolism, as well as neuronal development. Not only are psychological and environmental stressors communicated to the immune system, but also, *vice versa*, the immune response and adaptation to a current pathogen challenge are communicated to the entire body, including the brain, to evoke adaptive responses (e.g., fever, sickness behavior) that ensure allocation of energy to fight the pathogen. This phenomenon is evolutionarily conserved. Hence it is both interesting and important to consider the evolutionary history of this bi-directional neuroendocrine-immune communication to reveal phylogenetically ancient or relatively recently acquired mechanisms. Indeed, such considerations have already disclosed an extensive "common vocabulary" of information pathways as well as molecules and their receptors used by both the neuroendocrine and immune systems. This review focuses on the principal mechanisms of bi-directional communication and the evidence for evolutionary conservation of the important physiological pathways involved.

1. Introduction

Prior to Ader and Cohen's publications in the 1970s and 1980s (Ader and Cohen, 1975, 1982; Cohen et al., 1979; Bovbjerg et al., 1982) demonstrating that immune responses can be behaviorally (classically) conditioned, the neuroendocrine and immune systems were generally considered separate and isolated systems. Since classical or Pavlovian conditioning involves learning, and learning involves the central nervous system (CNS), the inescapable conclusion from these studies is that there must be cross-talk between the brain and the immune system. These studies of conditioned immunomodulation, together with subsequent but also early studies that disclosed direct sympathetic innervation of lymphoid tissues (Williams et al., 1981; Felten et al., 1987), neuroendocrine activation in response to antigen administration (Besedovsky et al., 1979), and the presence of receptors for hormones and neuropeptides on/in immune cells (Blalock and Smith, 1985), revealed machinery that enables bi-directional interactions between the immune and neuroendocrine systems and initiated the research field now known as psychoneuroimmunology (Ader, 1980; Kusnecov and Anisman, 2014). This early history of psychoneuroimmunology has been elegantly detailed by Ader (2000). In 2016, thanks to data generated during the past 40 years by an ever-increasing number of investigators, it has finally become accepted that the immune system and neuroendocrine system form an integrated part of our physiology. In other words, immunological defense mechanisms act in concert with physiological processes like growth and reproduction, energy intake and metabolism, as well as neuronal development (Sipe et al., 2016).

Not only are psychological and environmental stressors communicated to the immune system, but also, the immune response and adaptation to a current pathogen challenge are communicated to the entire body, including the brain, to evoke, if needed, adaptive responses like e.g. fever, or sickness behavior that ensures allocation of energy to fight the pathogen. A continuous allostatic response, the "active process of maintaining or re-establishing homeostasis" (McEwen and Wingfield, 2010) demands activity of the autonomic nervous system, hormones and

---

[*] Corresponding author. Cell Biology & Immunology, Dept. of Animal Sciences, Wageningen University, De Elst 1 P.O. Box 338, 6700 AH Wageningen, The Netherlands.
E-mail address: Lidy.vankemenade@wur.nl (B.M.L. Verburg-van Kemenade).

http://dx.doi.org/10.1016/j.dci.2016.05.015
0145-305X/© 2016 Published by Elsevier Ltd.

Please cite this article in press as: Verburg-van Kemenade, B.M.L., et al., Neuroendocrine-immune interaction: Evolutionarily conserved mechanisms that maintain allostasis in an ever-changing environment, Developmental and Comparative Immunology (2016), http://dx.doi.org/10.1016/j.dci.2016.05.015

cytokines. This is nicely illustrated by network analyses. For instance, Frankenstein et al. (2006) showed that there is a rich connection of leukocytes and body cells in inherently integrated and hierarchical collectives. The global network of cytokine interactions shows a close and complicated network between 14 immune cell types and at least 15 non-immune body cells types with many mutual and one-way connections. Within the brain and in the pituitary, immune cells with pathogen recognition receptors may be in close proximity to the neural and endocrine cells (Glennon et al., 2015). It is important to realize that there may be a large variation in individual responses (coping styles), and in situations when environmental situations are "abnormal" this allostatic state may alter the regulatory capacity of the individual. Thus, physiological and behavioral set points may be modified to allow the individual to most efficiently cope with the actual situation. Already early in vertebrate evolution it is evident that different coping styles may exist as illustrated by the classical experiments of Faisal et al. (1989) showing clearly different changes in immune response between dominant and submissive fish (*Tilapia*).

An understanding of the evolutionary history of this bidirectional neuroendocrine-immune system communication has the potential to reveal mechanisms that are phylogenetically ancient or relatively recently acquired. Our knowledge of such interactions, therefore, will be greatly enhanced by a thorough exploration of the phylogeny of the relevant vertebrate and invertebrate molecules. We already know that the evolutionary origins of neuropeptides are ancient. Indeed several conserved peptide signaling pathways originated even before a nervous system developed (Taghert and Nitabach, 2012; Mirabeau and Joly, 2013; Veenstra, 2011). For example neuropeptide families have been identified in protostomes and deuterostomes. Very recently in echinoderms, which have a simple radial nervous system with a modified nerve net of interconnecting neurons with no central brain, at least forty conserved neuropeptide precursors have been identified. Also the evolutionary history of immune components can be traced from before the echinoderm phylum, which has a simplified complement system homologous to the alternative pathway, through the agnathans (hagfish and lamprey) and the elasmobranchs (sharks and rays) to the teleosts (bony fish) and tetrapods (Smith et al., 2001). Also many immune recognition receptors, for example, the Toll-like receptor family (TLR) are phylogenetically quite old (Bosch, 2014; Buckley and Rast, 2015; Kasamatsu, 2013; Langevin et al., 2013; Priyam et al., 2016; Valanne, 2014).

Indeed we now know that there is an extensive functional "common vocabulary" of information molecules and their receptors that is used by both the neuroendocrine and immune systems.

For example, hemocytes from several molluscan, annelid, and insect species exhibit immunoreactivity for, and functional responses to, a variety of vertebrate neuropeptides (reviewed by Kinney and Cohen (2009) and Song et al. (2015)). This not only argues for a long history of interaction between the two systems, but also supports a long-term adaptive significance for this crosstalk.

Teleost fish are the earliest vertebrates studied that have developed neural and endocrine pathways that resemble the mammalian classical pathways. They also developed a complex immune response with innate and adaptive responses that act and interact in similar ways as they do in mammals. Already in teleosts it is clear that communication is not uni-directional, and multiple studies on stress, growth, and reproduction have already shown clear patterns of bi-directional communication (reviewed by Weyts et al. (1999) and Verburg-Van Kemenade et al. (2009a)). This no doubt greatly contributed to their evolutionary success and adaptive radiation. Fish, moreover, offer interesting models. For example, in fish the head kidney comprises the interrenal tissue with cortisol-producing cells and the adrenaline producing chromaffin cells, as well as the major hematopoietic tissue and even certain thyroid follicles (Fig. 1). Local production of endocrine hormones and expression of their receptors in immune cells is already demonstrated at this level of phylogeny (reviewed by Verburg-van Kemenade et al., 2012, 2011). Thus, the head kidney of fish is an exemplary tissue where endocrine and paracrine interactions are feasible. For a number of fish species, multiple tools as well as annotated genomes are now available to address a wide range of psychoneuroimmunologic-specific questions.

It can be justifiably argued that the class, Amphibia, mirrors a potentially pivotal transition in terms of immune function. The colonization of land is, at least loosely, associated with a substantial reorganization of the immune system, most likely in response to altered immunological challenges and selective pressures. If neural-immune crosstalk is adaptive for immune function, it seems logical to examine amphibians for important phylogenetic transitions in the development of such crosstalk. Indeed there are several lines of evidence indicating that neuroendocrine immune system interactions are well developed and operational at least in the anuran amphibian *Xenopus laevis* (reviewed by Kinney and Cohen (2009)).

The long evolutionary history of neuroendocrine-immune communication also implies that immunology needs to be thought of in a much broader *organismal and even population context* to ultimately reveal the mechanisms and players that are of prime importance for the eventual final disease resistance of an individual or a total population to a pathogen.

Working at the crossroads of different research fields poses significant challenges to the researcher. The level of complication rises exponentially and expert knowledge of different fields is a prerequisite. A whole variety of potential neural-immune system pathways with multiple ligands and complicated receptor profiles have now been identified and their relative physiological impact awaits further identification.

2. Mechanisms and pathways for neuroendocrine – immune interaction

Unless otherwise stated, the information in each of the following sections comes from studies with mammals (primarily

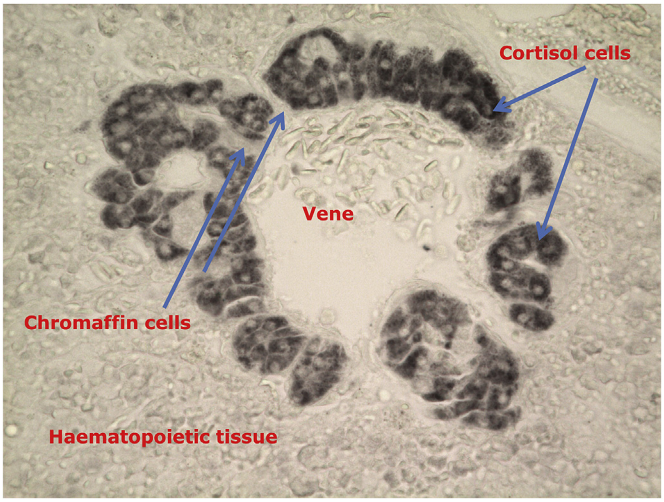

Fig. 1. Immunohistochemistry of the head kidney tissue of carp (*Cyprinus carpio* L.). (Courtesy: Dr. Juriaan Metz, Radboud University, Nijmegen, the Netherlands).