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Review

The immunomodulatory role of the hypothalamus-pituitary-gonad axis: Proximate mechanism for reproduction-immune trade offs?

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ABSTRACT

The present review discusses the communication between the hypothalamic-pituitary-gonad (HPG) axis and the immune system of vertebrates, attempting to situate the HPG-immune interaction into the context of life history trade-offs between reproductive and immune functions. More specifically, (i) we review molecular and cellular interactions between hormones of the HPG axis, and, as far as known, the involved mechanisms on immune functions, (ii) we evaluate whether the HPG-immune crosstalk serves as proximate mechanism mediating reproductive-immune trade-offs, and (iii) we ask whether the nature of the HPG-immune interaction is conserved throughout vertebrate evolution, despite the changes in immune functions, reproductive modes, and life histories. In all vertebrate classes studied so far, HPG hormones have immunomodulatory functions, and indications exist that they contribute to reproduction-immunity resource trade-offs, although the very limited information available for most non-mammalian vertebrates makes it difficult to judge how comparable or different the interactions are. There is good evidence that the HPG-immune crosstalk is part of the proximate mechanisms underlying the reproductive-immune trade-offs of vertebrates, but it is only one factor in a complex network of factors and processes. The fact that the HPG-immune interaction is flexible and can adapt to the functional and physiological requirements of specific life histories. Moreover, the assumption of a relatively fixed pattern of HPG influence on immune functions, with, for example, androgens always leading to immunosuppression and estrogens always being immunoprotective, is probably oversimplified, but the HPG-immune interaction can vary depending on the physiological and envoironmental context. Finally, the HPG-immune interaction is not only driven by resource trade-offs, but additional factors such as, for instance, the evolution of viviparity shape this neuroendocrine-immune relationship.

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1. Introduction

The physiological systems of organisms communicate among each other in order to maintain the internal homeostasis, to coordinate the appropriate allocation of the energy and nutrient resources, and to re-adjust the internal milieu under the challenge of internal and external stimuli. Particularly for the neuroendocrine and immune systems, functional interactions are widely established. The communication between these systems is possible because they share a common set of signaling molecules and receptors. In fact, molecules classified as either cytokines or hormones may belong to the same family of structurally related proteins as it is the case, for example, with the type-1 cytokine family which contains growth factors, neurotropins and prolactin (Huising et al., 2006; Ottaviani et al., 2007; Verburg-van Kemenade et al., 2009; 2011). Cytokines and hormones differ in several aspects, for instance, cytokines show primarily auto- and paracrine rather than endocrine actions, or hormones show high evolutionary conservation, in contrast to cytokines. However, the two groups of molecules also share a number of properties such as the activation of their target cells through – partly common – signaling pathways, or their transfer to the target cells via blood (Verburg-van Kemenade et al., 2009; 2016). Further evidence for the close linkage between the neuroendocrine and immune systems comes from the fact that immune cells can synthesize neuroendocrine hormones and have hormone receptors, as well as neuroendocrine cells possess receptrors for immune mediators and are capable of producing cytokines (Petrovsky, 2001).

Reproductive effort and immunocompetence are of crucial importance for the evolutionary fitness of organisms as they ensure survival of the individual and continuity of the species (Rauw, 2012; Downs and Stewart, 2014). At the same time, however, both reproduction and immunity are costly in terms of energy and nutrient usage. Therefore, organisms have to allocate their constrained resources between these competing activities probably leading to trade-offs (Sheldon and Verhulst, 1996). The question is which proximate mechanisms underly such life history decisions. Bidirectional communication between the physiological systems regulating reproductive and immune functions has been suggested as a key mediator of such trade-offs (Ricklefs and Wikelski, 2002; Hau, 2007; Cohen et al., 2012).

The physiological regulation of vertebrate reproduction occurs through the hypothalamic-pituitary-gonadal (HPG) axis. The neuroendocrine HPG axis integrates information from extrinsic and intrinsic cues in order to allocate energy and nutrient resources to reproduction as well as to synchronize reproduction-related life history events such as sexual differentiation or time to maturation. The immune system changes from the resting to the active stage after immune challenge, for example, by a pathogen. Physiologically, this is orchestrated by a complex network of immune mediators and cellular interactions which enable the organism to effectively mount a defense response against the foreign agents. While the reproductive system undergoes regular, predictable changes, the immune system is activated by stochastic events such as the presence of pathogens (Prall and Muehlenbein, 2014).

In the evolution of vertebrates, there occur major changes in the modes of reproduction and the functioning of the immune system (Angelini and Ghiara, 1984; Zeh and Zeh, 2000; Origgi, 2007; Zimmerman et al., 2010; Boehm et al., 2012). Examples of variation in reproductive modes include external versus internal fertilization or oviparity versus viviparity. A major driver behind these changes is the transition from aquatic to terrestrial environments. Also on the immune side, important differences exist between the vertebrate classes, for instance, the reptilian thymus undergoes seasonal involution, in contrast to the age-related thymus involution of mammals (Finger and Gogal, 2013). Another example is the absence of lymph nodes in lower vertebrates which in mammals are sites of certain HPG-sensitive processes such as B cell maturation. Moreover, in fish the efficacy of the adaptive immune system is lower than in birds or mammals. This difference probably relates to the ectothermic-endothermic transition among the vertebrates, as the lower metabolic rates of the ectothermic vertebrates is a limiting factor for the proliferation of T and B cells, the production of antibodies, and the kinetics of the antibody-antigen interaction (Malagoli and Ottaviani, 2010; Sandmeier and Tracy, 2014). Similarly, while endothermic mammals increase their body temperature during infection ("fever"), ectothermic fish and amphibia respond to infection by altered behavioural patterns ("behavioural fever") (Reynolds et al., 1976; Parris et al., 2004; Boltan et al., 2013). Such evolutionary changes in the properties of the reproductive and immune systems may have consequences for their resource needs and the hierarchical resource allocation between the systems, and this, in turn, may shape the proximate mechanisms underlying the HPG-immune communication. Here, the HPG-immune interaction may differ from the interaction between the hypothalamus-pituitary-adrenal axis and the immune system: while the principal processes of the stress responses are fairly similar among the vertebrate classes, the properties and processes of the reproductive systems of vertebrates display pronounced evolutionary variation.

To address the question of phylogenetic conservation of the HPG-immune interaction, we initially performed a comparative literature analysis of reported molecular and physiological interactions between the HPG axis and the immune system in the various vertebrate classes. In a next step we then considered the HPG-immune interactions in the context of the diverse life histories of vertebrates. While the interactions between the HPG axis and the immune system are indeed bidirectional, the focus of this review will be on the immunomodulating actions of the HPG hormones rather than on the neuroendocrine actions of the immune factors.

2. Hormones of the hypothalamus-pituitary-gonad (HPG) axis modulate the immune system of vertebrates

In the following we will review reports on immunomodulatory actions of the hormones of the HPG axis, tyring to evaluate – as much as possible on the basis of the available literature – how conserved or diverse the effects are across the vertebrate taxa. The activity of the HPG axis follows circadian and circannual rhythms which are accompanied by fluctuations in hormone and hormone receptor levels, what has consequences for the immunological effects. While the regular changes allow animals to respond to predictable environmental change, unpredictable challenges may superimpose the normal rhythms of hormone secretion and immune reactivity. Importantly, the communication between the HPG axis and the immune system is bidirectional and involves both