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Review article

The stress response and immune system share, borrow, and reconfigure their physiological network elements: Evidence from the insects

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ABSTRACT

The classic biomedical view is that stress hormone effects on the immune system are largely pathological, especially if the stress is chronic. However, more recent interpretations have focused on the potential adaptive function of these effects. This paper examines stress response-immune system interactions from a physiological network perspective, using insects because of their simpler physiology. For example, stress hormones can reduce disease resistance, yet activating an immune response results in the release of stress hormones in both vertebrates and invertebrates. From a network perspective, this phenomenon is consistent with the 'sharing' of the energy-releasing ability of stress hormones by both the stress response and the immune system. Stress-induced immunosuppression is consistent with the stress response 'borrowing' molecular components from the immune system to increase the capacity of stress-relevant physiological processes (i.e. a trade off). The insect stress hormones octopamine and adipokinetic hormone can also 'reconfigure' the immune system to help compensate for the loss of some of the immune system's molecular resources (e.g. apolipophorin III). This view helps explain seemingly maladaptive interactions between the stress response and immune system. The adaptiveness of stress hormone effects on individual immune components may be apparent only from the perspective of the whole organism. These broad principles will apply to both vertebrates and invertebrates.

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1. Introduction

Most animals live in environments in which food is limited, but competitors, predators and pathogens are abundant. Stress responses allow animals to reconfigure their physiological networks, resulting in increased survival under challenging conditions (Nation, 2008; Adamo, 2012a, b). For example, stress responses boost an animal's physical performance, increasing its ability to escape from predators (Adamo et al., 2013). However, this state is typically costly for animals to maintain (Hawlena and Schmitz, 2010). Similarly, the activated immune system also reconfigures physiological networks (e.g. Clark et al., 2013; Bajgar et al., 2015). Resources are redirected to the immune system, resulting in greater disease resistance (Bajgar et al., 2015). However, like the stress response, an immune response requires a costly investment of

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resources (e.g. Ardia et al., 2012). There is evidence that these physiological systems conflict with each other. Stress responses can inhibit immune function (Adamo et al., 2008), and activating an immune response reduces the ability to escape predators (Otti et al., 2012).

The traditional biomedical interpretation of stress-immune interactions was that the immunosuppressive effects of the stress response were an example of the harmful, pathological impacts of stress on the body (Webster Marketon and Glaser, 2008). More recently, the interpretation of these effects has shifted. Some stress hormone effects are now interpreted as an adaptive redistribution of immune resources (Dhabhar, 2014). For example, stress hormones help reconfigure immune resources to enhance protection against wound infections during fight-or-flight behaviour (Dhabhar et al., 2012; Dhabhar, 2014). However, this explanation does not fully account for the often contradictory effects of stress hormones on immune function (Sapolsky et al., 2000), especially at the cellular level (Webster et al., 2002).

Recently, stress response-immune system interactions have been interpreted from a comparative perspective (e.g. Adamo, 2012c; Boonstra, 2013). This perspective recognizes that many animals have evolved under a chronic threat of predation. In some, but not all, species this leads to the sustained elevation in the levels of stress hormones (Dickens and Romero, 2013). However, these elevated levels do not appear to reduce disease resistance in all species (e.g. snowshoe hares (*Lepus americanus*), Boonstra, 2013). In tree lizards (*Urosaurus ornatus*), chronic exposure to elevated levels of stress hormones (e.g. corticosterone) do not suppress wound healing unless females are energetically compromised (e.g. by actively producing eggs or from food shortage, French et al., 2007). These results demonstrate that even the chronic effects of stress hormones are context-dependent; immunosuppression is not necessarily the outcome (Boonstra, 2013). Some animals, such as the Arctic ground squirrel (*Spermophilus parryii plesius*), do experience the more 'typical' pattern, with males that experience elevated stress hormone levels becoming more susceptible to disease (Boonstra, 2005). However, in this ground squirrel, stress hormones shift resources from immunity to reproduction, enhancing reproductive success (i.e. fitness) in this species, even if it reduces lifespan (also known as terminal reproductive investment, Clutton-Brock, 1984). Therefore, immunosuppression can enhance fitness, despite the reduction in disease resistance.

In this paper I take a physiological (i.e. organismal) network perspective to interpret stress response effects on immune function. In this perspective, the stress response and the immune system are not viewed as independent entities, but as different parts of a larger defensive system. This defensive system is itself embedded within the web of the animal's total physiological network. As this paper demonstrates, some network pathways are shared between the stress and immune responses (Fig. 1, Table 1). This sharing can lead to both conflict and cross-tolerance. Under some conditions, network pathways are also borrowed between the two responses, and some pathways become reconfigured (Fig. 1). This perspective also helps clarify the vital role the stress response plays in optimizing immune function for the animal's present ecological context. To make these points more clearly, I use examples from the insects. Although their physiological networks are not as well known as that of mammals, they are simpler, making it easier to see the adaptive functions of some connections (Adamo, 2012a, b, c, 2016).

I will also focus on papers that use non-living immune challenges. Live pathogens add an additional layer of complexity because they have evolved to alter their host's physiology in order to survive, reproduce and find a new host. For example, in bees, pathogens such as *Nosema ceranae* can manipulate host intermediate metabolism, increasing the supply of energy to the pathogen (Mayack et al., 2015). These effects make it more difficult to interpret pathway interactions during active infections. In terms of stress, this paper focuses on the classic fight-or-flight responses, as these are of universal relevance. Moreover, these pathways are well studied from a behavioural and physiological perspective (e.g. Orchard et al., 1993).

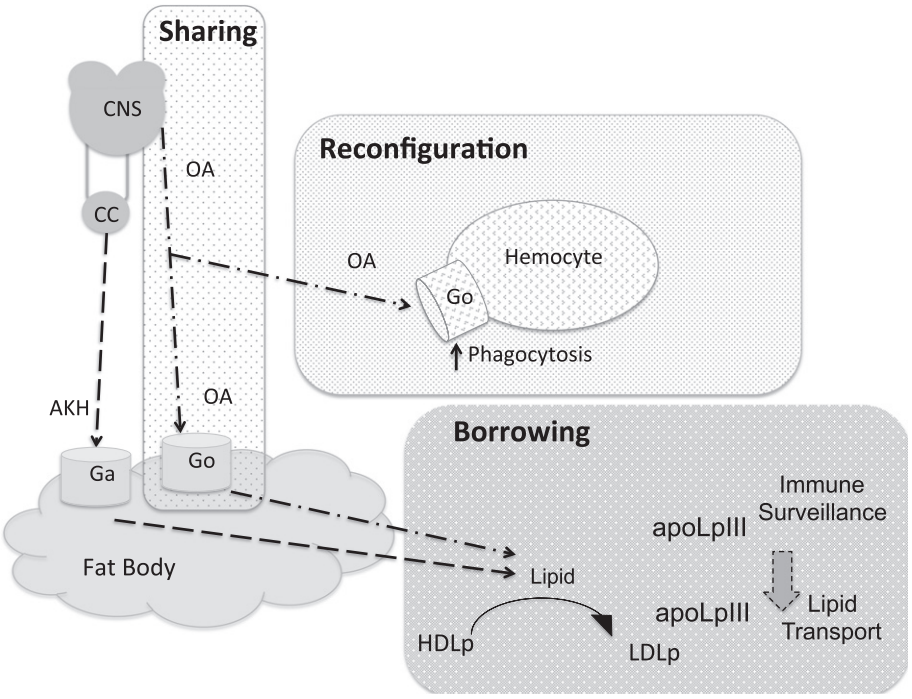

Fig. 1. Stress response and immune response networks interact. The two responses *share* some pathways; for example, both responses induce the release of OA. OA, acting through G-protein-coupled receptors, promote lipid release. OA also *reconfigures* the immune system by enhancing phagocytosis. The stress response induces the release of AKH from the CC that triggers a large release of lipid from the fat body. The stress response *borrows* apolipophorin III from the immune system to increase the transportation of lipid from the fat body to muscle. AKH – adipokinetic hormone, apoLpIII – apolipophorin III, CC – corpora cardicum, CNS – central nervous system, Ga – G-protein-coupled AKH receptors, Go – G-protein-coupled OA receptors, HDLp – high density lipophorin particle, LDLp – low density lipophorin particle, OA – octopamine. Dashed line – stress response pathway. Dashed and dotted line – combined stress and immune response pathway. References in text.