Animal Behaviour 83 (2012) 1303–1312

Contents lists available at SciVerse ScienceDirect

Animal Behaviour

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

Review

Physiological mechanisms mediating costs of immune responses: what can we learn from studies of birds?

Dennis Hasselquist*, Jan-Åke Nilsson

Department of Biology, Lund University, Lund, Sweden

ARTICLE INFO

Article history:
Received 23 June 2011
Initial acceptance 29 July 2011
Final acceptance 9 March 2012
Available online 26 April 2012
MS. number: 11-00507R

Keywords:
antioxidant
autoimmunity
cost of immune response
energy requirement
immunopathology
life history trade-off
oxidative stress
stress-induced immunosuppression

Activating the immune system has associated fitness costs, both immediate costs in the form of reduced current reproduction and long-term costs in the form of reduced life span and future reproduction. This indicates that immune system activation can be an important agent in life history trade-offs. In this review, we evaluate the importance of four currencies generally considered as potential mediators of the costs of immune responses in ecological studies: (1) energetic costs, (2) nutrient costs, (3) autoimmunity and (4) oxidative stress, which may be responsible for these trade-offs. A meta-analysis revealed significant elevation of energy consumption during an immune response; however, the magnitude of this energetic cost was only 5–15%. In a direct comparison using similar immune system activation in tits, energetic savings in terms of lowered feeding rate was seven times higher than energetic costs of mounting an immune response. These results do not support the hypothesis that energy is the key proximate currency mediating the costs of immunity. Nutrient savings from immunosuppression seem to be even less beneficial as this constitutes only a minor part of the daily nutrient turnover in the body. In our view, there are some indications that oxidative stress can be an important currency that could mediate both short-term and long-term costs of immune system activation, although direct evidence is so far limited. The importance of autoimmune responses is at this point hard to evaluate owing to limited empirical studies in wild animals.

The vertebrate immune system is an induced defence that has evolved to destroy and remove particles of foreign origin, such as viruses, bacteria and other parasites, from the body. The fact that the immune system is fully activated only when needed implies that an immune response is connected to costs. In line with this notion, experimental activation of the immune system has resulted in fitness costs. Immediate costs in the form of reduced current reproductive success have been demonstrated experimentally by immunizing parents during breeding, resulting in a prolonged incubation period, reduced feeding effort and/or reduced fledging success (Table 1). A substantial long-term cost associated with immune system activation has been found in terms of considerably reduced between-year return rate in eiders, *Somateria mollissima*. Incubating and hence fasting females that mounted antibody responses to two antigens simultaneously apparently suffered from impaired survival (Hanssen et al. 2004). Furthermore, induced immune responses commonly reduce growth rate in chicks (Fair et al. 1999; Soler et al. 2003; Brommer 2004; Grindstaff 2008), impair postfledging survival (Eraud et al. 2009) and reduce testosterone levels in adults (Boonekamp et al. 2008).

In addition, studies manipulating workload to measure effects on immune responses can indirectly provide data of importance for interpreting fitness costs associated with immune system activation. A meta-analysis of experiments increasing/decreasing clutch/brood size to alter parental effort found a significant negative relationship between parental effort and immune responses (Knowles et al. 2009). For other demanding tasks that can be experimentally manipulated, such as mating and incubation effort, flight cost and thermoregulation, negative associations with the strength of an immune response have also been found (Table 2). Thus, a trade-off between workload and immunocompetence seems to be common in free-living birds during physiologically demanding activities such as breeding.

One indirect method to study the potential fitness effects of immune system activation is to measure selection on artificially induced immune responses or natural parasite resistance. Survival until the breeding season of blue tits, *Cyanistes caeruleus*, injected with nonpathogenic antigens in winter revealed stabilizing selection on the diphtheria toxoid response (Råberg & Stjernman 2003). Blood parasite resistance among infected blue tits was also subjected to stabilizing selection (Stjernman et al. 2008), suggesting that individuals with the strongest and weakest immune responses disappeared before the breeding season. However, both these studies are correlational and causality is therefore unclear.

---

* Correspondence: D. Hasselquist, Department of Biology, Lund University, Ecology Building, 223 62 Lund, Sweden.
E-mail address: dennis.hasselquist@biol.lu.se (D. Hasselquist).

0003-3472/$38.00 © 2012 The Association for the Study of Animal Behaviour. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.anbehav.2012.03.025

Table 1
Effects of experimental immune system activation on fitness-related traits during breeding in studies of birds

Species	Immune challenge	Fitness-related trait	Effect on trait	Source
Blue tit, *Cyanistes caeruleus*	DT	Nestling feeding	Reduction	Råberg et al. 2000
Pied flycatcher, *Ficedula hypoleuca*	DT	Nestling mass	Reduction	Ilmonen et al. 2000
		Fledging success	Reduction	
Tawny owl, *Strix aluco*	Tetravac	Nestling size	Reduction	Gasparini et al. 2009
		Recruitment	Reduction	
Collared flycatcher, *Ficedula albicollis*	SRBC	Song rate[*]	Reduction	Garamszegi et al. 2004
		Testosterone level[†]	Reduction	
		Body mass	Reduction	
Blackbird, *Turdus merula*	SRBC	Bill coloration[*]	Reduction	Faivre et al. 2003
Great tit, *Parus major*	RRBC+DT	Plumage coloration[*]	Reduction	Fitze et al. 2007
House martin, *Delichon urbica*	NDV	Relaying interval	Prolonged	Marzal et al. 2007
		Fledging success	Reduction	
House sparrow, *Passer domesticus*	LPS	Nestling feeding	Reduction	Bonneaud et al. 2003
		Fledging success	Reduction	
		Relaying interval	No effect	
Blue-footed booby, *Sula nebouxii*	LPS	Foot coloration[*]	Reduction	Torres & Velando 2007
Zebra finch, *Taeniopygia guttata*	LPS	Bill coloration[*]	Reduction	Alonso-Alvarez et al. 2004a
Common eider, *Somateria mollissima*	SRBC+DT	Between-year return rate/survival	Reduction	Hanssen et al. 2004
Common eider, *Somateria mollissima*	SRBC	Length of incubation period	Prolonged	Hanssen 2006
Mallard, *Anas platyrhynchos*	SRBC	Bill UV-reflectance[*]	Reduction	Peters et al. 2004
		Testosterone level[†]	Reduction	
Zebra finch, *Taeniopygia guttata*	SRBC	Nestling growth rate	No effect	Verhulst et al. 2005
		Time to second clutch	No effect	
Starling, *Sturnus vulgaris*	SRBC	Relaying interval	No effect	Williams et al. 1999

Injections were with the following antigens: DT = diphtheria toxoid and tetanus toxoid vaccine, Tetravac = blend of diphtheria toxoid, tetanus toxoid, pertussis toxoid, filamentous haemagglutinin, D antigen of the poliovirus type 1, 2 and 3, SRBC = sheep red blood cells, NDV = Newcastle disease virus vaccine, LPS = lipopolysaccharide, RRBC = rabbit red blood cells.

[*] Male secondary sexual ornament of importance for mating success.

[†] Hormone important for male mating success.

Thus, a negative relationship between demanding activities and the strength of immune responses is commonly observed in birds, implying that immune responses can induce significant ultimate costs. However, empirical evidence for the proximate nature of such costs, that is, the currencies mediating the conversion of immune response costs into fitness costs, is much scarcer. The most frequently suggested currencies in ecological studies are (1) energetic costs, (2) nutrient costs, (3) autoimmunity and (4) oxidative stress. The energetic costs hypothesis is based on 'the principle of allocation' and involves direct trade-offs for energy between the immune system and other demanding tasks (Sheldon & Verhulst 1996). This implies a cost of rather short duration, at least in physiologically nonexhausted individuals; that is, when the strenuous activities cease, immune responses should be restored within days or weeks (Verhulst et al. 2005). The same logic is plausible for nutrient costs related to synthesis and proliferation of immune cells (e.g. leucocytes, antibodies, cytokines), in particular for macronutrients (e.g. protein). In contrast, costs induced by oxidative stress or autoimmunity may be long lasting, acting over months or years (Råberg et al. 1998; von Schantz et al. 1999). We stress that this partitioning into short- and long-term costs is not clear-cut; still, we think it is a useful concept because it delineates different physiological mechanisms. Generally speaking, the short-term costs are more transient and can be (at least partly) compensated for after the end of the immune challenge, whereas the harmful effects of long-term costs accumulate and become more severe over time.

The main aim of the present review is to evaluate empirical evidence to elucidate the importance of different proximate mechanisms (currencies) proposed to mediate the cost of immune responses affecting fitness traits. Hence, we are mainly interested in natural systems under selection and because the majority of these studies have been conducted on birds, we focus our review on bird studies. Our choice of natural systems under selection puts the emphasis of this review on the ecological/evolutionary literature. The complementary, more mechanistic approach in studies of model organisms taken by immunologists is also important but will not be explicitly dealt with in this review. We first compile the

Table 2
Experimental manipulation of work rate, except manipulations of parental effort, and its effects on immunity in studies of birds

Species	Manipulated work rate	Immune measure	Effect on immunity	Source
Pied flycatcher, *Ficedula hypoleuca*	Mating effort	DT-H	Negative	Kilpimaa et al. 2004
Tree swallow, *Tachycineta bicolor*	Cost of flying	KLH-H	Negative	Hasselquist et al. 2001
Zebra finch, *Taeniopygia guttata*	General activity	PHA-C	Negative	Ewenson et al. 2003
Blue tit, *Cyanistes caeruleus*	Thermoregulation	DT-H	Negative	Svensson et al. 1998
Red knot, *Calidris canutus*	Flight endurance	PHA-C DT-H	No effect No effect	Hasselquist et al. 2007

Abbreviations of immune measures are: PHA-C = phytohaemagglutinin-induced (unspecific) cell-mediated immunity, DT-H = humoral immunity induced by injection with diphtheria toxoid and tetanus toxoid vaccine, KLH-H = humoral immunity induced by injection with keyhole limpet haemocyanin (KLH).