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REVIEW

Norepinephrine and octopamine: linking stress and immune function across phyla

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Abstract

In species from three widely divergent phyla (Arthropoda, Mollusca and Chordata) tyrosine derivatives (norepinephrine or octopamine) mediate a response to acute stress. Part of this response is a change in immune function that results in a decrease in resistance to pathogens. This decrease in disease resistance appears maladaptive. However, if the connections between norepinephrine/octopamine and immune function were maladaptive, they should have been selected against. None of the four commonly proposed adaptive explanations for acute stress-induced changes in immune function fit the available data for species from all three phyla. However, this result is probably due to the lack of information about acute stress-induced immunosuppression in invertebrates and a lack of ecologically valid studies in vertebrates. Understanding why immune function and disease resistance changes during acute stress will require greater comparative study.

Key words: immunocompetence; immunosuppression; insect; mollusc; vertebrate; adaptive benefits

Introduction

When responding to danger, animals from across the animal kingdom alter their physiology in order to optimize it for the performance of flight-or-fight behaviours (Wingfield, 2003). This reaction is called the acute stress response. Species from at least three diverse phyla (Chordata, Mollusca and Arthropoda) coordinate their acute stress response using chemically similar derivatives of the amino acid tyrosine (Ottaviani and Franceschi, 1996). Vertebrates (Cooper *et al*., 2003) and molluscs (Lacoste *et al*. 2001a) release norepinephrine (NE) during acute stress, while insects release norepinephrine's chemical cousin, octopamine (O) (Orchard *et al*., 1993). In both vertebrates (Charmandari *et al*., 2005) and invertebrates (Roeder, 2005) NE and OA mediate a range of stress related responses. Most of these responses prepare the animal for extreme physical exertion (Charmandari *et al*., 2005; Roeder, 2005). However, the acute stress response also has complex, but largely immunosuppressive effects in a wide range of animals (Adamo and Parsons, 2006). The acute stress response can influence immune function because immune cells in vertebrates (e.g. Webster *et al*., 2002; Madden, 2003), molluscs (Lacoste *et al*., 2001b) and insects (Gole *et al*., 1982; Orr *et al*., 1985) have receptors for NE or OA. The consistent connection between acute stress, NE (vertebrates and molluscs) or OA (insects) and immune function suggests that modulating immune function during acute stress serves an important adaptive function. In this paper, I use a comparative approach to examine four adaptive explanations for the existence of acute stress-induced immunosuppression.

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Two tyrosine derivatives: norepinephrine and octopamine

OA and NE are both derived from the amino acid tyrosine, although via different pathways (Cooper *et al*., 2003). OA is synthesized from tyramine, while NE is synthesized from dopamine (Fig. 1). OA and NE are identical in structure, except for the number of hydroxyl groups on the benzene ring (Fig. 1).

Molluscs use both NE and OA as a signaling molecule (e.g. NE: Sloley *et al*., 1990, Lacoste *et al*., 2001a, b; OA Vehovszky *et al*., 2005). Insects, on the other hand, use OA, but not NE as a signaling molecule (Roeder, 1999). Vertebrates make extensive use of NE and its metabolite, epinephrine as signaling molecules (Cooper *et al*.,

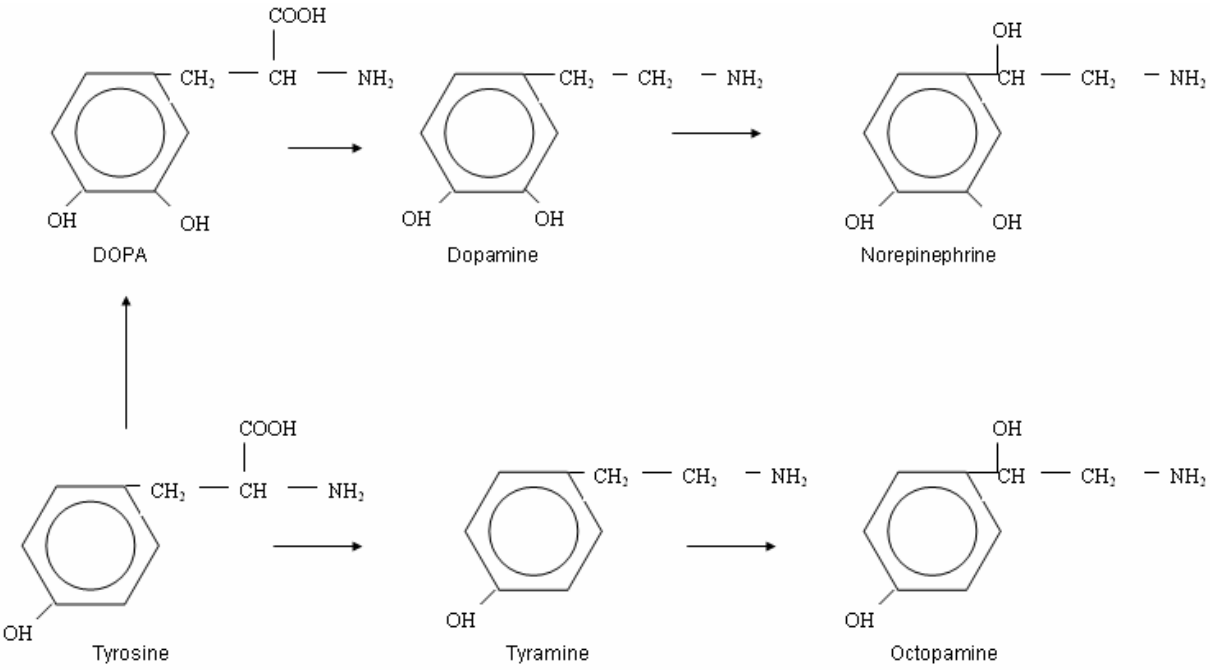

Fig. 1. Biosynthetic pathways for norepinephrine and octopamine. Adapted from Cooper *et al*. (2003).

2003), but make little, if any, use of OA (Roeder, 1999; Pflüger and Stevenson, 2005; Farooqui, 2007).

Most invertebrate OA receptors have substantial sequence homology with vertebrate adrenergic (e.g. NE) receptors (Evans and Maqueira, 2005; Roeder, 2005). Also, OA receptors in invertebrates have similar pharmacological profiles to vertebrate adrenergic receptors (e.g. Farooqui, 2007; Evans and Maqueira, 2005). Moreover, pharmcological studies of invertebrate OA receptors demonstrate that they show some affinity for NE (Evans and Maqueira, 2005). For example, in the aquatic snail *Lymnaea stagnalis* the cloned OA receptor has high affinity for OA, but also exhibits some affinity for NE (Gerhardt *et al*., 1997). Similarly, human alpha-adrenergic receptors (subtypes 2a, b, c) have high affinity for NE, but they also show some affinity for OA (Gerhardt *et al*., 1997). The similarity between OA and NE receptors suggests that both had a common origin millions of years ago (Pflüger and Stevenson, 2005).

OA and NE transporters also seem to have had a common origin (Caveney *et al*., 2006). Interestingly, molluscs appear to lack both an OA and an NE transporter, even though they contain both compounds. Some insects also lack an OA transporter (e.g. *Drosophila*) and must deactivate OA enzymatically (Caveney *et al*., 2006).

The chemical similarity between OA and NE, the similarity in the enzymes involved in their synthesis, and the similarities in the sequences of their receptor and transporter molecules support the argument that OA and NE pathways arose from the same ancestral pathway (Caveney *et al*., 2006). Both OA and NE play a role in stress adaptation, suggesting that this is an ancient conserved function for these compounds (Gerhardt *et al*., 1997; Roeder, 1999).

Norepinephrine, octopamine and acute stress

Molluscs (bivalves) react to stressful stimuli by contracting the large muscles that hold the shell closed (Moore, 2006). This is the bivalve equivalent of flight-or-fight behaviour. It also results in an increase in NE in the hemolymph (Lacoste *et al*., 2001a). NE is released by chromaffin-like cells in the oyster heart (Lacoste *et al*., 2001a).

In vertebrates, the sympathetic nervous system (SNS) is activated in response to flight-or-fight situations and releases NE into immune organs (Nance and Sanders, 2007). All primary and secondary immune organs receive noradrenergic innervation, as do all body surfaces that are potential sites of microbial invasion (e.g. skin, gut or oral mucosa) (Nance and Sanders, 2007). NE also increases in concentration in the plasma (Sachser, 1987; Matt *et al*., 1997). Therefore NE can reach the entire vertebrate immune system.

In insects, OA is released as a neurohormone during flight-or-fight behaviours (Orchard *et al*., 1997; Pflüger and Stevenson, 2005; Roeder, 2005). OA is released into the periphery by dorsal unpaired medial cells (DUM cells) (Roeder, 2005). DUM cells are considered to be the insect equivalent of the vertebrate SNS based on their anatomy and pattern of innervation (Evans and Maqueira, 2005; Roeder, 2005).

Therefore NE, or its chemical cousin OA, is released by a wide range of animals in response to acute stress. These compounds are widely disseminated allowing NE (Charmandari *et al*., 2005) and OA (Orchard *et al*, 1993; Roeder, 2005)

to affect the immune system as well as mediating other stress responses.

Norepinephrine, octopamine and immune function

Immune cells release NE and it appears to have a paracrine-like function in both molluscs (Ottaviani *et al*., 1993; Ottaviani and Franceschi, 1996; Lacoste *et al*., 2001b) and vertebrates (Flierl *et al*., 2007). Therefore, the role of NE as an immunoregulator may be very ancient (Ottaviani and Franceschi, 1996).

In molluscs, acute stress transiently suppresses immune function and increases susceptibility to bacterial infection (Table 1). This increased susceptibility to disease is caused, at least in part, by the release of NE during acute stress. Molluscan hemocytes contain receptors for NE (Lacoste 2001b), and NE has negative effects on hemocyte function (Table 1). Injections of NE result in decreased bacterial clearance and increased mortality in oysters challenged with a bacterial pathogen (Lacoste *et al*., 2001c).

Acute stress results in a transient decline in resistance to bacterial infection in insects as well (crickets, Adamo and Parsons, 2006). Some of this decrease in disease resistance may be mediated by OA. Injections of OA prior to a bacterial challenge results in increased mortality (Adamo and Parson, 2006). However, OA also has immunoenhancing effects (Brey, 1994; Table 2). It can even increase resistance to infection when the pathogen is co-incubated with OA (Baines *et al*., 1992; Baines and Downer, 1992).

As in insects, acute stress in vertebrates results in a mix of immunosuppressive and immunoenhancing effects (Dhabhar, 2002; Ortega, 2003; Gleeson *et al*., 2004; Glaser and Kiecolt-Glaser, 2005; Nance and Sanders, 2007; Ortega *et al*., 2007). Despite this complex mix of positive and negative effects, acute stress increases susceptibility to pathogens (e.g. Cao and Lawrence, 2002). One bout of intense exercise in mice (e.g. Davis *et al*., 1997) or humans (Gleeson *et al*., 2004) leads to an increased risk of disease and/or mortality in response to a pathogen challenge. NE appears to be causally involved in the increase in disease susceptibility after acute stress (e.g. Kohut *et al*., 1998; Cao et al., 2003; Emeny *et al*., 2007).

The complexity of the effects of NE on vertebrate immune function has prevented a clear adaptive explanation for these changes (Sternberg, 2006). Madden (2003), Maestroni (2005), and Kin and Sanders (2006) suggest that these complex effects are a result of NE playing a role in maintaining immune function homeostasis. NE and OA may play a similar role in invertebrates. In molluscs and insects, NE or OA are present in the hemolymph of resting animals. Although this could be because it is difficult to take blood from animals without stressing them, it may also indicate that OA and NE are chronically present in the hemolymph. OA has a half-life of 15 min or less in insect hemolymph (Goosey and Candy, 1982), and, therefore it should not be detectable unless it is constantly being released. A background level of OA or NE in non-stressed animals would be consistent with the hypothesis that these compounds help maintain normal immune function in invertebrates. However, if OA or NE helps maintain immune homeostasis in a variety of animals, why do the levels of OA and NE increase dramatically during acute stress? In other words, how does pushing the 'immune thermostat' towards an extreme end benefit animals during acute stress?

Adaptive function of NE and OA effects on immune function during acute stress

In molluscs, insects and vertebrates, the acute stress response results in a brief period during which the animal's ability to fight off infection is reduced (Fig. 2, however see below). NE or OA appear to mediate some of this immunosuppression (Fig. 2). This effect of NE or OA on the immune system appears to be maladaptive. Increasing susceptibility to disease seems likely to reduce survival and reproductive success, and such a response should be selected against. As Dhabhar (2002) has pointed out, during fighting or fleeing, animals run a real risk of injury and, therefore, exposure to pathogens. Although it might make good adaptive sense to delay copulation, digestion, and egg laying until the predator has passed, the immune response may not be dispensable during flight-or-fight behaviours because of the increased risk of injury (Dhabhar, 2002). Nevertheless, the fact that animals from three different phyla exhibit the same apparently maladaptive response suggests that, despite the costs, it provides some benefit. Below I review some of the suggestions as to why animals display acute stress-induced immunosuppression. These hypotheses are not mutually exclusive. In particular I explore whether there are any explanations that might fit the evidence from animals across all three phyla.

Table 1 Effects of norepinephrine on molluscan immune functions

Immune functions	Effects	References
Susceptibility to bacterial infection	↑	Lacoste *et al*., 2001c
Phagocytosis at physiological concentrations	↓	Lacoste *et al.*, 2002a
Production of reactive oxygen species induced by interleukin-1	↓	Lacoste *et al.*, 2001d
Apoptosis	↑	Lacoste *et al*., 2002b

I focus on evidence obtained from whole animal studies. Immune values taken *in vitro* are often different when measured *in vivo* (Nance and Sanders, 2007). More importantly, as Kohut *et al*. (2005) comments, there is often a lack of association between declines in various immune functions and actual disease resistance (also see Adamo, 2004). From an evolutionary perspective, it is the change in disease resistance that is important.

1. The 'energy crisis' hypothesis. One common hypothesis for the existence of acute stress-induced immunosuppression is that it allows animals to channel more energy into flight-or-fight behaviour (e.g. see Råberg *et al*., 1998; Segerstrom, 2007). However, it is unclear whether immunosuppression would save energy. For example, some mechanisms of immunosuppression, such as apoptosis, require an increase in energy expenditure (Dhabhar, 2002).

At present there is little direct evidence supporting the 'energy-crisis' hypothesis (Adamo and Parsons, 2006).

2. The 'resource crunch' hypothesis. Animals make a number of physiological changes in order to make flight-or-fight possible (Wingfield, 2003; Charmandari *et al*., 2005). The 'resource crunch' hypothesis suggests that some of these changes will result in resources being shifted away from the immune system in order to optimize the flight-or-fight response. This hypothesis differs from the 'energy-crisis' hypothesis because it is not energy *per se* that is limiting, but specific molecules that are required for both immunity and some other physiological function.

The 'resource crunch' hypothesis explains, at least in part, acute stress-induced immunosuppression in insects. In crickets, conflicts between immune function and lipid transport can lead to acute stress-induced immunosuppression (Adamo *et al*., 2008). Crickets release OA during flight-or-fight behaviours (Adamo *et al*., 1995). For about an hour after flying or fighting, crickets become more susceptible to bacterial infection (Adamo and Parsons, 2006). OA, either directly and/or indirectly, induces the mobilization of lipid from the fat body in order to fuel flight-or-fight behaviours (Orchard *et al*., 1993). As lipid levels in the hemolymph increase, the protein apolipophorin III (apoLpIII) changes its confirmation, and combines with high density lipophorin (HDLp) to form low density lipophorin (LDLp) which has an increased lipid carrying capacity (see Weers and Ryan, 2006, for review). However, in the unlipidated form, apoLpIII acts as an immune surveillance molecule (Weers and Ryan, 2006). Once apoLpIII becomes part of LDLp, it appears to loose that ability, resulting in a decline in immune surveillance. The decline in immune surveillance probably explains the increase in disease susceptibility after flying and fighting (Adamo *et al*., 2008). Therefore, in crickets, intense activity leads to transient immunosuppression because apoLpIII is co-opted into lipid transport and becomes unavailable as an immune surveillance molecule. Therefore, crickets become immunosuppressed during flight-or-fight even if they have abundant energy stores (Adamo *et al*., 2008).

The ability of OA to mobilize lipid explains why OA can produce immunosuppression when injected into crickets. Injecting OA results in the release of lipid (Woodring *et al*., 1989), which leads to a decline in the immune surveillance molecule apoLpIII as it combines with HDLp to form LDLp (Weers and Ryan, 2006). But why does OA also have immunoenhancing effects (Table 2)? I hypothesize that OA also works to maintain immune system function as some of the components of the immune system are being siphoned off into lipid transport. In other words, OA helps liberate lipid stores (needed to fuel flight-or-fight behaviour) while simultaneously reconfiguring the immune system to maintain maximal function under the new physiological conditions. I predict that without the effects of OA on immune function, disease resistance would decline even more precipitously during flying or fighting in crickets. This hypothesis explains why OA can have both immunosuppressive and immunoenhancing effects.

Why do crickets not make enough apoLpIII to support both immune surveillance and increased lipid transport? First, it would be energetically expensive to do so. ApoLpIII is already a very abundant protein in the hemolymph of many adult insects (Weers and Ryan, 2006). To produce more of this protein would decrease the energy available for reproduction and other activities. Furthermore, as apoLpIII concentrations increase, apoLpIII may begin to bind to the animal's own molecules, initiating an inappropriate immune response. Such autoimmunity could be costly (e.g. Sadd and Siva-Jothy, 2006). Therefore, shuttling apoLpIII between immune surveillance and lipid transport may be the most adaptive response, even though it results in transient immunosuppression during flying or fighting.

Table 2 Effects of octopamine on insect immune functions

Immune functions	Effects	References
Susceptibility to bacterial infection	↑	Adamo and Parsons, 2006
Phagocytosis	↑	Baines *et al.*, 1992
Nodule formation (insect immune response)	↑	Baines *et al.*, 1992
Hemocyte locomotion	↑	Dielh-Jones *et al.*, 1996
Hemocyte number at low (physiological) doses	↓	Dunphy and Downer, 1994
Hemocyte number at higher (pharmacological) doses	↑	Dunphy and Downer, 1994

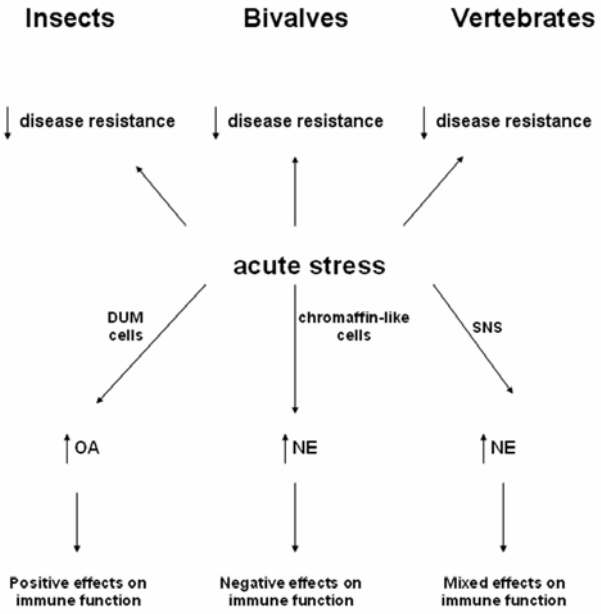

Fig. 2. Schematic outline of the connections between NE, OA, acute stress and immune function in different phyla. DUM cells, dorsal unpaired median cells; NE, norepinephrine; OA, octopamine; SNS, sympathetic nervous system. See text for references

It is unclear whether a similar scenario can explain acute-stress induced immunosuppression in molluscs. In molluscs, the known effects of NE are all negative (Table 1). However, there have been few studies on acute stress-induced immunosuppression in molluscs. More data are needed to assess whether molluscs suffer from a 'resource crunch' during acute stress.

In vertebrates a number of molecules are shared between the immune system and other physiological systems. For example, lipid metabolism and immune function are also intertwined in vertebrates (e.g. van Elzen *et al*., 2005). Mammalian lipoproteins transport lipid (e.g. cholesterol), but they also participate in innate immunity (Khovidhunkit *et al*., 2004). Lipid carriers such as very low density lipoprotein (VLDL) bind to and neutralize viruses and other pathogen products (Khovidhunkit *et al*., 2004). During infection, VLDL levels increase (Khovidhunkit *et al*., 2004). However, after a single bout of intense exercise, the total concentration of VLDL particles in the blood declines by 38 % in humans (Børsheim *et al*., 1999). Whether changes in mammalian lipoprotein concentrations during intense activity results in acute stress-induced immunosuppression remains unknown.

Some studies in mammals indirectly support the 'resource crunch' hypothesis. For example, despite the immunosuppressive effects of NE, mice that were stressed by minor surgery, and then exposed to infectious agents, were more likely to die from infection if they received ß-adrenoreceptor blockers (Schmitz *et al*., 2007). In another study, mice given ß-adrenoreceptor blockers prior to intense exercise were more likely to die after a viral challenge compared with controls (Kohut *et al*., 2005). These studies suggest that the effects of NE on immune function result in increased disease resistance when they occur within the context of an acute stress response. These results are consistent with the hypothesis that NE works to reconfigure the immune system in order to maintain immune function during a 'resource crunch'. However, other studies have found that blocking ß1-adrenergic receptors decreased acute stress-induced immunosuppression (Cao *et al.*, 2003). Emeny *et al*. (2007) found that mice lacking adrenoreceptors on their immune cells cleared a bacterial infection (*Listeria monocytogenes*) more quickly after acute stress than mice with immune cells capable of responding to NE. However, the relationship between the speed with which an animal can clear bacteria from liver and spleen and its ability to survive an infection was not stated in these studies (Cao and Lawrence, 2002; Cao *et al*., 2003; Emeny *et al*., 2007). When determining the effects of various drugs on disease resistance, Keil *et al.* (2001) used an LD_{10} dose of *L. monocytogenes* and measured the effect on mortality, not on bacterial clearance. In *Drosophila melanogaster*, the ability to clear bacteria from the hemocoel does not correlate with the ability to survive an infection (Corby-Harris *et al*., 2007).

3. The 'over excitation' hypothesis. Acute stress-induced immunosuppression may be beneficial because it prevents the immune system from becoming too active and harming the animal. During intense exercise, tissues such as muscle suffer minor damage, increasing the risk of inflammation and an autoimmune reaction (Råberg *et al*., 1998). Therefore, the immune system shifts towards a less inflammatory state, (i.e. a shift from Th1 to Th2 responses, Elenkov and Chrousos, 2006). This shift leads to a decrease in inflammation, but also an increased susceptibility to bacterial and viral pathogens. The cost of the increased risk of infection is thought to be less than an autoimmune reaction or damage from an overactive immune response. However, this key assumption remains untested.

The 'over-excitation' hypothesis does raise the question as to why the prevention of 'over-excitation' occurs to the point that animals are left susceptible to bacterial infections during acute stress. It would be more adaptive to prevent autoimmunity and over-inflammation while maintaining normal anti-microbial defenses, unless there is some physiological constraint that makes this impossible.

The 'over-excitation' hypothesis does fit the available data on molluscs (Table 1), but is not supported by the insect data (Table 2). In insects, immune cell activity appears to be up-regulated during acute stress (Table 2).

Animals run the risk of having an over-active immune system during both an acute stress response and during an immune challenge. In vertebrates, an immune challenge also activates the acute stress response (Elenkov and Chrousos, 2006). This indirectly supports the 'over-excitation' hypothesis. However, insects release OA during an

immune challenge too (Dunphy and Downer, 1994), although its source is uncertain (Adamo, 2005). Given that OA appears to increase immune cell activity (Table 2), these data do not support the 'over-excitation' hypothesis. Immunologists should be wary of putting too much confidence in this hypothesis without more supporting data.

4. The 'shift in focus' hypothesis. This hypothesis suggests that during flight-or-fight animals are not immunosuppressed *per se*, but that they have shifted the focus of their immune effort from protecting against systemic invaders, to protecting against opportunistic organisms that might gain entry during wounding (Dhabhar, 2002). Dhabhar (2002) has shown that acute stress can increase a delayed-type hypersensitivity in rodents and that catecholamines (e.g. NE and epinephrine) play a role in this enhancement. This change could result in increased protection from wound infection (Dhabhar, 2002). However, tests with real bacteria have mixed results. Restraint stress produced a decrease in wound healing and a decrease in the ability mice to clear bacteria introduced into a wound (Rojas *et al*., 2002). However, the duration of the stress (mice were restrained for 12 h at a time for 8 days) is more typical of a chronic than an acute stress. Campisi *et al*. (2002) found that after a series of tail shocks given over 2 h, acutely stressed rats recovered more quickly than unstressed rats from a subcutaneous injection of a relatively benign bacterium (there was no mortality) (Campisi *et al*., 2002). However, this experiment does not convincingly show that acutely stressed rats are less likely to develop infected wounds.

The 'shift in focus' hypothesis does not appear to apply to insects. Although OA enhances hemolymph clotting in some arthropods (e.g. Battelle and Kravitz, 1978), in insects, flight-or-fight behaviour results in an increase in infection after wounding (Adamo and Parsons, 2006). There is no evidence available from the molluscs.

Conclusions

The involvement of NE (or OA) in mediating stress-induced changes in immune function may be ancient (Ottaviani and Franceschi, 1996). Regardless of whether these connections have been conserved over millions of years or have evolved independently in multiple lineages, their existence in animals from different phyla suggests that there is strong selection pressure for a change in immune function in response to acute stress. None of the four suggested adaptive functions reviewed here explains acute stress-induced immunosuppression in all species. In part this is due to a lack of information about acute stress-induced immunosuppression in invertebrates. All of the information presented here rests on a handful of studies. But it is also because the key experiments are missing in vertebrate studies. For example, despite work on the 'shift in focus' hypothesis for more than a decade, whether acute stress actually decreases susceptibility to opportunistic wound infections under real world conditions remains unknown.

The lack of a real world test of the 'shift in focus' hypothesis highlights a general lack of ecological context in these studies. For example, acute stress is typically produced using highly artificial stimuli, such as restraint stress or tail shock. These stressors have an unknown connection to an ecologically relevant stressor (e.g. a predator). Nor is the duration or intensity of the artificial stressors correlated with data about what the animal would experience in the field. Studies using a more ecological perspective will be critical if we are to understand the adaptive significance of the changes in immune response that occur during acute stress.

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