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The evolution of the molecular response to stress and its relevance to trauma and stressor-related disorders

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Abstract

The experience of “stress”, in its broadest meaning, is an inevitable part of life. All living creatures have evolved multiple mechanisms to deal with such threats and challenges and to avoid damage to the organism that may be incurred from these stress responses. Trauma and stressor-related disorders are psychiatric conditions that are caused specifically by the experience of stress, though depression, anxiety and

some other disorders may also be unleashed by stress. Stress, however, is not a mandatory criterion of these diagnoses. This article focuses on the evolution of the neurochemicals involved in the response to stress and the systems in which they function. This includes the skin and gut, and the immune system.

Evidence suggests that responses to stress are evolutionarily highly conserved, have wider involvement than the hypothalamic pituitary adrenal stress axis alone, and that excessive stress responses can produce stressor-related disorders in both humans and animals.

Key words: Stress and stressor-related disorders; molecular evolution; skin and gut responses to stress; immunology and stress physiology.

Introduction

"Stress" is a ubiquitous phenomenon and has become an umbrella term for all kinds of adverse and challenging experiences involving excessive physical or mental demands. A definition of stress is difficult, but the original one introduced by Selye (1936) may still be the best we have. Accordingly, stress is "the non-specific response of the body to any demand for change". Stress therefore is not necessarily a pathological condition. Stressors can be defined as events or circumstances that promote stress.

The Diagnostic and Statistical Manual DSM-5 identifies trauma and stressor-related disorders that may develop following excessive stress. This category comprises reactive attachment disorder, disinhibited social engagement disorder, posttraumatic stress disorder (PTSD), acute stress disorder and adjustment disorders. A recognisable

precipitating stressor is a mandatory requirement for these diagnoses (APA, 2013). Other psychiatric conditions such as depression and anxiety may also occur following the experience of significant stressors, but their relationship with stress is not mandatory and they can develop without the involvement of a recognised stressor. This review focuses on the molecular evolution of stress response mechanisms. Specifically, we argue that trauma and stressor-related disorders are associated with well conserved stress responses including predictable immunological responses and gastric and skin responses. This involves a wide range of evolutionarily highly conserved molecules involved in the response to stressors that is not specific to humans, but can be found in other animals. Accordingly, we start by indicating the stress response molecules that have been shown to be dysregulated in PTSD, the most serious and most studied of the stressor-related disorders.

We then describe the regulation of the stress response via the hypothalamic pituitary adrenal system (HPA) and its relationship to allostasis. We detail the relevance of the innate and adaptive immune systems as well as the relevance of the skin and the gut. In addition, we will specifically make the case for stressor-related disorders in nonhuman animals and the value of animal studies in stress research. Finally we will argue that stressor-related disorders represent the phylogenetically oldest pathologies to challenge life and need to be understood at a fundamental level before there can be a real understanding of a range of psychiatric conditions.

Stress response molecules and PTSD

In addition to the experiences that are necessary to consider a diagnosis of PTSD (criterion A), DSM-5 includes four clusters of symptoms in the diagnosis: (B)

intrusion symptoms; (C) persistent avoidance of stimuli associated with the trauma; (D) negative alterations in cognitions and mood that are associated with the traumatic event and (E) alterations in arousal and reactivity that are also associated with the traumatic event (APA, 2013). As in previous editions of the DSM, some of the symptoms are objective and some subjective and they cross many disciplines, particularly biology and psychology (Burges Watson, 1995). Some symptoms in all four groups are relevant but symptoms in groups D and E are perhaps most relevant to this article.

Early studies of the neurotransmitters immediately involved in the function of the HPA and dysregulated in PTSD were seen to be similar to those of other psychiatric disorders and the methodology was often doubtful (Mason et al., 1988, Hoffman et al., 1989; Pitman and Orr, 1990; Yehuda et al., 1990, 1992).

Mason et al. (1988) reported on an alteration in the norepinephrine/cortisol ratio that distinguished PTSD from other psychiatric disorders, and Yehuda et al. (1990) found low urinary free-cortisol levels in PTSD. Following a study by Pitman and Orr (1990) reporting on twenty-four hour urinary cortisol and catecholamine excretion in combat-related PTSD, Yehuda et al. (1992) found significantly higher 24-hour urinary excretion of dopamine, norepinephrine, and epinephrine in inpatients with PTSD compared with both outpatients with PTSD and normal controls.

At that time epinephrine and cortisol were still considered the ‘stress hormones par excellence’ and cortisol and the catecholamines continued to remain of central interest. From an empirical point of view, Kimble and Kaufman (2004) pointed to the dramatic increase in the study of PTSD after 1992, which coincided with the public recognition of this dramatic increase. They suggested that in contrast to other

disorders such as schizophrenia there was a dearth in understanding the biological vulnerability to PTSD.

Progress in discovering such biological factors, however, has been slow. Videlock et al. (2008) found that civilian trauma survivors with and without PTSD at five months post trauma had similar levels of plasma NE, urinary NE excretion, and NE: cortisol ratio at the time of their original admission and concluded that simplified biological models might not properly capture the complex aetiology of PTSD. More recently, Wingenfeld et al. (2015) indicate that findings regarding sympathetic nervous system and HPA activity in PTSD are 'heterogeneous'. Given the long evolution of the response to life's challenges this should not be a surprise.

The most common findings, nevertheless, remain that decreased cortisol and increased norepinephrine secretion are found in PTSD, corresponding to the symptoms of avoidance and arousal (McFarlane et al., 2011; Wingenfeld et al., 2015). A recent study seeking to find a biomarker that would assist in providing early treatment to combat veterans found that lower blood NE levels obtained from such servicemen, within two months after return from deployment, were associated with lower combat-related PTSD symptoms three months later (Highland et al., 2016). Despite the only partially successful search for biomarkers for PTSD a number of other stress response molecules, which are dysregulated in PTSD, have been identified.

Described first by Ritossa (1962) in *Drosophila* heat shock proteins (HSPs) are the most highly conserved cellular stress response and are found in all animals, plants and bacteria. They are involved as an essential defence mechanism in humans (Kampinga et al., 2009) for the protection of cells from a wide range of stressors and serve as modulating signals for immune and inflammatory responses, as well as perhaps

having a role in the production of cytokines (Kim et al., 2006; Fink, 2010; Naviauk, 2014). Sriram et al. (2012) report alterations of the HSP90-chaperone network across a range of psychiatric conditions including PTSD, and Matic et al. (2014) have studied HSPs specifically in relation to PTSD in war trauma-exposed men. Moreover, Sunderland et al. (2003) and Gill et al. (2009) report on the multiplicity of cytokines (with multiple functions) and the high level of inflammatory cytokines associated with chronic PTSD. It has long been recognized, but not widely accepted, that PTSD may be associated with some physical conditions, including autoimmune diseases (Boscarino, 1997, 2004; Boscarino et al., 2010). Recent studies are more definitive. For example, Canetti et al. (2014) report that individuals exposed to terrorism are at dual risk for PTSD/depression and inflammation. More specifically, combat-exposed men with PTSD exhibit an aberrant profile of NK cells, a key component of the innate immune system (Bersani et al., 2016). Moreover, Nielsen et al. (2016) describe the involvement of cytokines in the function of NK cells and these two studies, as well as the extensive involvement of cytokines in the immune system provide evidence of a clear association of PTSD and the immune system.

Circulating levels of Substance P (SP) become elevated in stressful situations and monocytes stimulated by SP produce and release cytokines (O'Connor et al., 2004). Geracioti et al. (2006) conclude that the release of SP is implicated in the mechanism of acute PTSD symptoms. It is also involved in the pathogenesis, among other things, of nausea, pain, mood disorders, stress and anxiety.

Spitzer et al. (2010) found an almost twofold higher odds for elevated C-reactive protein (CRP) levels in subjects with PTSD, again suggesting that low-grade inflammation might be a pathway from PTSD to poor physical health. Similarly, Eraly et al. (2014) suggest that CRP, a marker of peripheral inflammation, may be

prospectively associated with PTSD symptom emergence, and that individuals with lesser inflammatory activity may be relatively resilient while those with greater inflammatory activity may be more vulnerable to developing PTSD symptoms. Both CRP and SP are also associated with immune function (Tegeler et al., 2016; Garcia-Recio and Gascón, 2015).

The neuropeptides arginine-vasopressin and oxytocin have been shown to have a conditioned response, respectively enhancing and inhibiting effects on memory retrieval (Pitman et al., 1993), suggesting involvement in arousal and avoidance. Southwick et al. (1999) enumerate the evidence of catecholamine dysregulation in PTSD and some studies have linked resilience with high levels of neuropeptide Y, through continued release of noradrenalin (Ahmed, 2007; Sabban et al., 2015). Meyer et al. (2013) suggest that ghrelin and growth hormone, together in the amygdala, have fear-enhancing effects. Beta-endorphin was studied by Hoffman et al. (1989) in relation to PTSD. It is associated with other products of proopiomelanocortin and is synthesised in several peripheral tissues, including the gastrointestinal and reproductive tracts, the placenta and cells of the immune system as well as the anterior and intermediate lobes of the pituitary gland. As well as having an effect on pituitary function and its well known association with stress induced anaesthesia (Van der Kolk et al., 1985) and PTSD (Savic et al., 2015), it and other opioid peptides may also be involved in a wide range of systems including the cardiovascular, gastric, reproductive and immune systems (Lee and Wardlaw, 2010).

Among a range of other substances that may be involved in the response to stress and/or stress-related disorders, gonadal hormones stand out although their roles, as far as they are currently understood, are contradictory and uncertain. All that can be said with certainty is that they act differently in males and females (Cahill, 2006; Young

and Korszun, 2010; Ressler et al., 2011; Bale and Epperson, 2015; Frijling et al., 2015).

The molecules involved in the stress response are also involved in a wide range of bodily functions. Accordingly, it is not surprising that PTSD is associated with cardiovascular disease (Wingenfeld et al., 2005, Kibler et al., 2014) and several other chronic illnesses affecting the skin and gut (Burges Watson et al., 1992; Schnurr et al., 1999, 2000) and immune system disorders (Bam et al., 2016; Bersani et al., 2016).

Many other neurochemicals are involved in the highly complex control and 'downstream' effects of the immediate stress response which putatively may lead to stressor-related disorders. Other such molecules include urocortins, neuropeptide S, nociceptin/orphanin and neurokinins. Their roles are discussed by Schank et al. (2012) in the section on stress associated with animal studies of toxicity and addictive behaviours.

No entirely satisfactory biomarker has been discovered for PTSD despite intensive study and it is clear, as a molecular evolutionary approach would suggest, that there is wide variability in individual responses.

Beyond the molecular engagement in the stressor-related disorders, genetic and epigenetic studies will clearly be important in understanding the mechanics of the response to stress and the determination of the relationships of the multiplicity of molecules involved in the response to stress is what is required.

The mathematical modelling employed in some recent studies may move in this direction (Savic et al., 2015; Sriram et al., 2012; Kim et al., 2016). The study of Kim et al. (2016), for instance, considers a number of distinctive physiological features of the HPA axis and a more complete picture of the dynamics of stress disorders that have not been considered in previous models. Neuronally, a recent study

demonstrated poor structural connectivity in the anterior cingulate cortex (ACC) and poor hippocampus-ACC connectivity in PTSD (Fani et al., 2016).

The neurochemical response to stress

In all vertebrates the neurochemical responses to stress centre around the HPA axis and the immediate neuroendocrine cascade (Salpolsky et al., 2000; Charney, 2004; McEwen and Gianos, 2011; Soares et al., 2012; Boonstra, 2013a). The extended hypothalamic pituitary peripheral gland (H-P-PG) system has operated with only minor modifications for some 250 million years. In most fishes, for example, the stress response consists of an almost identical physiological cascade of events to that in humans (Wendelaar Bonga, 1997).

In brief, the stress response in humans is initiated by perception of a stressor (conscious or not) and communicated to the body via the central nervous system (CNS) acting both neuronally and hormonally (Pecoraro and Dallman, 2010). Primary hormones include the catecholamines and those of the HPA axis. The increase in circulating levels of hormones results in changes in secondary physiological responses involving most organ systems.

Apart from modifications in anticipation, and action initiated by the frontal lobes, the molecular ‘cascade’ that follows the recognition of a stressful situation is essentially the same in all vertebrates including humans. The first wave (Salpolsky et al., 2000), occurring within seconds, involves among other things, enhanced secretion of catecholamines (epinephrine and norepinephrine) from the sympathetic nervous system (SNS); hypothalamic release of CRH into the portal circulation and, a few seconds later, pituitary secretion of ACTH. There is also decreased hypothalamic

release of gonadotropin-releasing hormone and, shortly thereafter, decreased secretion of pituitary gonadotropins, a pituitary secretion of prolactin and (in primates) growth hormone, and pansecretion of glucagon to raise the level of glucose in the bloodstream.

A second, slower wave involves the steroid hormones. Over the course of minutes, glucocorticoid (GC) secretion is stimulated and gonadal steroid secretion generally declines. The molecular evolution of GC and proopiomelanocortin (POMC) are central features of the evolution of the endocrine system and the expression of corticosteroids (CS) and POMC in the skin and gut will underline the particular relevance of molecular evolution to a more complete understanding of the stress response.

Evolutionary pathways of the neurochemical stress cascade

To achieve survival and reproduction, coping with a range of stressors and challenges whilst maintaining homeostasis has always been an important task for all organisms. In the earliest single cell forms of life heat shock proteins (HSPs) are the most conserved stress response molecules. Billions of years later, primitive invertebrate animals**,** such as ascidians, appeared lacking a complete H-P-PG system. However, while none of the major pituitary hormones appear to be present, they do possess a very complex collection of molecular orthologs/homologs and their receptors. These include some of the vertebrate hypothalamic gonadotropin releasing hormone (GnRH), and peripheral gland insulin-like peptide and iodotyrosine ligand-receptor systems regulating growth and metabolism in vertebrates (Campbell et al., 2004).

Corticotrophin-releasing hormone (CRH) and cortisol-like molecules are present in the haemocytes of some invertebrates (e.g. molluscan species) as well as POMC-derived peptides, such as adrenocorticotropic hormone (ACTH) (Ottaviani et al., 1998). From an evolutionary point of view, it is likely that these systems evolved in marine animals originally as an excretory mechanism to eliminate the excess sodium load absorbed from salt water environments, whereas the renal system evolved later enabling sodium retention in the body (Perlman, 2013).

In addition, similar multi-functional signalling molecules have been found in the immune systems of invertebrates and vertebrates, including the neuropeptides derived from POMC, that provide bidirectional communications between the endocrine and immune systems. Among the 40 neuropeptides isolated in annelids (invertebrate segmented worms) all, with the exception of some species-specific peptides, have also been identified in vertebrates. These findings seem to confirm the existence of a primitive neuroendocrine system in the annelids even though annelid neural tissues do not contain anatomical correlates of hypothalamus or pituitary (Ottaviani, 2011). Thus precursors of the major stress response molecules are found scattered among the invertebrates.

Taken together, the prototype stress response in some invertebrates seems to be concentrated in a single cell, the haemocyte. Over evolutionary time, this conserved stress response became concentrated locally within a single organ, the thymus (in which all the main mediators of this biological response, such as CRH, ACTH and glucocorticoids (GC), are present) before becoming centred in the brain and HPA.

Glucocorticoids

In addition to their critical role in the stress response, GCs are important hormones that have a number of actions, with mediating effects in some cases, and suppressive or preparative effects in others (Sapolsky et al., 2000; Herman, 2010). They regulate metabolism, development, and the immune system and are produced continuously; maximal levels being reached following stress-related stimuli. Likewise, all the neurochemicals involved in the response to stress have multiple functions leading to a wide range of possible functional disorders (Olff et al., 2006); thus a major problem with the study of stress response molecules is their ubiquitous involvement in all aspects of vertebrate life.

Classically, GC suppresses the stress response, preventing it from being pathologically over-activated. Cortisol, as a representative GC, serves to mobilize and replenish energy stores. It has important regulatory effects on the hippocampus, amygdala, and prefrontal cortex. It contributes to increased arousal, vigilance, focused attention, and memory formation; inhibition of growth and the reproductive system, and containment of the immune response (Sapolsky et al., 2000; Yehuda and LeDoux, 2007; Herman, 2010; Pecoraro and Dallman, 2010). The H-P-PG system completes the coordination of growth, metabolism, reproduction and the response to stress. Despite the organisation around the HPA, and the similarity of the response to stress in all vertebrates, there is considerable individual and species variation. The ‘corticosterone-fitness hypothesis’ (Angelier et al., 2010) suggests that elevated baseline corticosterone levels should be found in individuals that have difficulty coping with their environment. The maintenance of elevated baseline levels over a prolonged period can have deleterious effects on immunity, cognition and metabolism. Elevated corticosterone levels disrupt the HPA and reduce reproductive effort (Wingfield and Sapolsky, 2003; Angelier et al., 2010). For instance baseline

corticosterone and cortisol levels have been measured in birds under extreme stress, revealing a typical but variable stress response that includes a decrease in reproductive behaviours (Schmidt and Soma 2008; Dickens et al., 2009; Hau et al., 2010; Angelier et al., 2010).

Here, the concept of allostasis (McEwen and Wingfield, 2003; Doom and Gunnar, 2013) is important for the understanding of individual differences in stress responsivity and the development of stressor-related disorders. Allostasis is defined as the adaptive process for actively maintaining stability (homeostasis) through change. A feature of allostasis is the ability to mount a fast and strong response after the experience of specific stressors. Thus, maintaining stability through change is a fundamental process through which all organisms actively adjust to both predictable and unpredictable events (McEwen and Wingfield, 2003; Korte et al., 2005). The mediators of allostasis, adrenal hormones, neurotransmitters, and cytokines, produce effects that are adaptive in the short term but can be damaging if the mediators are not shut off. Korte et al. (2005) describe four types of allostatic states leading to such damage (allostatic load): (a) repeated challenges; (b) failure to habituate with repeated challenges; (c) failure to shut off the response after the challenge is over; and (d) failure to mount an adequate response. In all types, secretion of GC and activity of other mediators of allostasis such as the autonomic nervous system (ANS), CNS neurotransmitters, and inflammatory cytokines, wax and wane with allostatic load. If allostatic load is chronically high, pathologies develop, including (though not exclusively) trauma and stressor-related disorders (McEwen and Wingfield, 2003).

Evolutionary aspects of immune function

Aside from the neuroendocrine system, the immune system is foremost and equally relevant in the understanding of the evolution of defence systems, including stress responses and the development of stressor-related disorders. After all, infection as a consequence of invasion by bacteria and/or viruses, has always been a potentially life threatening challenge. An association with psychiatric disorders, particularly in relation to allergy, has been recognised for the best part of a hundred years, but, more recently, a more developmental relationship has attracted attention. For example, Wang et al. (2015) have recently reported on the overlap between psychiatric disorders and immune disorders, although they say that the molecular development of PTSD remains poorly understood. Breen et al. (2015) suggest differences in cytokine production and natural killer cell cytotoxicity in immune responses between males and females, and Bam et al. (2016) indicate that while PTSD is associated with dysregulated immune function, the elevated expression of pro-inflammatory cytokines might be regulated by multiple epigenetic mechanisms and micro-RNAs.

In essence, the evolutionary trail of the immune systems can be divided into the periods before and after the arrival of vertebrates: innate immunity and the later development of the adaptive immune system.

For billions of years innate immunity and its elaboration was the most readily recognizable defence system in all living things (Medzhitov and Janeway, 1997) and it can be traced back, more or less continuously, to those earliest forms of life (Ji et al., 1997). Recognition of foreign and noxious substances has been an important issue for the hunted and the hunters from life's earliest manifestation in the bacterial jungle (Damasio, 2010). Furthermore the earliest organisms had to find ways to adjust to dramatic changes in pH and changing gas concentrations and other noxious and sometimes beneficial changes in their environmental medium.

The innate immune system operates at the site of attack – commonly the skin and the gut/mucosal system, which are topographically and functionally 'external surfaces'.

The adaptive immune system, not found in any invertebrate, is present in all vertebrates (Pancer and Cooper, 2006), although Wiedenheft et al. (2012) suggest a primitive adaptive system as well as an RNA-guided genetic silencing system in bacteria and archaea as the functional equivalent of an innate immune system.

As seen in invertebrates, the first line of host responses to pathogen invasion in vertebrates relies on innate immunity. In addition, the jawed vertebrates have evolved an adaptive immunity mediated primarily by lymphocytes. Vertebrates alone generate a lymphocyte receptor repertoire of sufficient diversity to recognize the antigenic component of any potential pathogen or toxin (Pancer and Cooper, 2006).

Phagocytic cells formed the cellular arm of innate immune defences and a new type of circulatory cell appeared near the beginning of vertebrate radiation in the form of the long-lived lymphocyte. On the other hand there is evidence for bona fide lymphocytes in lamprey and hagfish (Pancer and Cooper, 2006; Herrin and Cooper, 2010) and evidence for lymphocyte antigen receptor diversification appearing at the dawn of vertebrate evolution some 500 million years ago. This strongly points to the enormous fitness value of adaptive/anticipatory immunity (Pancer and Cooper, 2006).

Based on the high percentage of echinoderms (starfish, sea urchins etc.) that coexist with endosymbiotic microbes and the need of mammals to maintain their gut flora, Pancer and Cooper (2006) argue that highly elaborate immune mechanisms and active cross talk between the microflora and the host mucosal immune system was necessary.

The immune system underwent radical changes with the early vertebrates. In jawed vertebrates, T and B lymphocytes are the acknowledged cellular pillars of adaptive

immunity. T lymphocytes are primarily responsible for cell-mediated immunity, and B lymphocytes are responsible for humoral immunity.

In vertebrates, immune cells are found scattered throughout the body in blood, lymph and a variety of tissues including spleen, skin and gut, bone marrow, lymph nodes, thymus, brain (Adamson et al., 2002).

The complement system is part of the innate and the adaptive systems and its basic functions are enhancing phagocytosis of antigens by attracting macrophages and neutrophils, rupturing membranes of foreign cells, and clumping of antigen-bearing agents. The C3 complement appears to be central in the elaboration of the history of all three complement pathways. Complement C3 and factor B (Bf) have been identified from echinoderms, ascidians and cyclostomes, indicating a very ancient origin for this system (Nonaka, 2001). The recent accumulation of genomic information from some mammals, chicken, clawed frog, a few bony fish, sea squirt, fruit fly, nematoda and sea anemone indicate that bony fish and higher vertebrates share practically the same set of complement genes (Janssen et al., 2005). Thus most of the genetic changes that played an essential role in establishing the mammalian complement system had occurred by the time of the teleost/mammalian divergence around 500 million years ago and the origin of the central part of the complement system now appears to have been established 700 to 1,000 million years ago (Nonaka, 2001; Janssen et al., 2005; Nonaka and Kimura, 2006).

Gastric and skin defences

Cnidaria (e.g. jellyfish and corals) represent one of the earliest branches in the animal tree of life. They have no specific immune cells and to defend against microbial

pathogens have had to rely on their capacity of self/non-self discrimination to detect such cells as foreign, and to eliminate them (Augustin and Bosch, 2010). Some cnidarians are colonized by complex bacterial communities and, in many cases, are home to symbiotic algae. Thus a capacity to distinguish between beneficial symbionts and pathogenic intruders has also been necessary. These animals consist of only two cell layers, the epidermis and invaginated gastrodermis and a middle layer the mesoglea. These epithelial cells are able to mediate all innate immune responses. Augustin and Bosch (2010) hypothesized that the establishment of epithelial barriers, more than 600 million years ago, represents an important step in evolution of host defence in eumetazoan animals. The origins of such allogenic, as well as xenogenic (from a different species), immune-type recognition can be traced to the earliest metazoans (Dishaw and Litman, 2009). Various reports have shown that more sophisticated invertebrate haemocytes are responsive to mammalian neuropeptides and cytokines. This suggests significant complexity of intercellular signalling within the immune systems in relatively primitive animals. It also suggests that auto-neuroimmunoregulatory activities in mammals must have had an earlier beginning than previously believed (Dishaw and Litman, 2009).

Thus the skin and gut were the primary stress defence systems in the invertebrates, the skin alone being the essential organ in early multicellular organisms. In the process of evolution the gut went on to develop the mucosal immune system including the respiratory tract and the urogenital tract. These provide a critical line of defence against infectious diseases, as the majority of infections are initiated at mucosal sites (McGhee and Fujihashi, 2012; Azizi et al., 2010). The mucosal surfaces of the respiratory, the gastrointestinal and the urogenital tract, are the largest areas within the body in contact with the external environment and the major sites of antigen exposure

(Wiedermann, 2003). Consistent with this observation, the lymphoid system of mucosal membranes contains a larger number of B and T lymphocytes as well as plasma cells, than any other tissue (Mestecky, 1987).

This mucosal immune system has generated two layers of defence: immune exclusion to modulate or inhibit surface colonization of microorganisms and dampen penetration of potentially dangerous antigens; and suppressive mechanisms, 'oral tolerance' when induced via the gut, to avoid local and peripheral hypersensitivity to innocuous antigens, particularly food proteins and components of commensal bacteria (Wiedermann, 2003; Brandtzaeg, 2010). Most interest in the mucosal immune system stems from the importance of its potential use in vaccination but its dysfunction is seen increasingly as having a role in the pathogenesis of irritable bowel syndrome and other inflammatory bowel conditions (Chadwick et al., 2002, Stengel and Taché, 2010, Larauche et al., 2012, Buckley et al., 2014, Keightley et al., 2015).

The skin is also an active immunological micro-environment quite different from the mucosal immune system. Slominski (2007) proposed that during evolution the fundamental mechanism of the stress response, the HPA axis, developed first in the integument to promote species survival and was then adapted and perfected by the CNS and endocrine system. This primordial HPA in the integument was composed of CRH, POMC, and steroid signalling pathways that act in concert with the innate immune system to create the optimal response against pathogens and other stressors, and protect internal homeostasis (Slominski, 2007; Slominski et al., 2013). Even now it is sometimes referred to as the "skin immune system" and exact immunophenotypes of lymphocyte subpopulations with their localizations in normal human skin were determined quantitatively (Bos et al., 1987). The skin has an unusual set of immunologic requirements. Apart from pathogenic organisms, it is confronted by

environmental challenges/agents that represent a spectrum of antigenic threats. It is subjected to physicochemical stresses such as irradiation with ultraviolet light that alter dramatically its immunologic properties. It is a highly complex organ provided with a unique collection of lymphoid cells, reticular cells, and organized lymphoid organs to deal with these special demands (Streilein, 1983; Heath and Carbone, 2013). Slominski (2007) indicated that the human skin expresses peptides of the HPA axis, including CRH and POMC as well as the processing machinery that generates ACTH, β-endorphin, and melanocyte-stimulating hormone. Communication with the brain is again two-way and there are costly functional consequences when psychological stress-mediated activation of central HPA axis signalling negatively affects protective and antimicrobial skin barrier function in mice (Aberg et al., 2007). Two-way communication between the gut and brain (Galland, 2014) has also been clearly established in studies with mice that show a substantial contribution of the host microbiota to microglial homeostasis and microglial defects leading to impaired CNS innate immune responses (Erny et al., 2015).

Studies of the skin and gut again confirm the wide distribution of stress response molecules and their evolution strongly suggests that stressor related disorders were the earliest of life's pathologies.Table 1 summarizes the evolutionary trajectories of some of the most relevant molecules in the stress response.

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Stress responses in animals

Animals can suffer a range of diseases similar to humans (Natterson-Horowitz and Bowers, 2012) and pathophysiological and behavioural changes can be elicited in laboratory animals by exposure to 'unnatural' stressors to which no adaptation has evolved. Many experiments have been reported, using swim tests, tail suspension and other means that produce stress in animals that exceed what these species normally experience during their lifetime (e.g., Krystal, 1990; Dohrenwend and Dohrenwend, 1974; Friedman et al., 1996; LeDoux, 1998; Schank et al., 2012; Everds et al., 2013). In recent years, concern for animal welfare has led to wide reporting of severe trauma and stressor-related symptoms in a range of animals used in research and other captive roles, especially great apes, and including bears (Vickery and Mason, 2005; Bekoff, 2009), horses (Bradshaw et al., 2008; Muller-Paisner and Bradshaw, 2010) parrots and other birds (Bradshaw et al., 2009). Post-traumatic behavioural abnormalities, physical ill health and even death have been reported in captive cetaceans (Rose, 2011). Rats and mice have been extensively studied in circumstances mirroring extreme stress in humans (Cameron, 2005; Cohen et al., 2006; Siegmund and Wotjak, 2006, 2007). Bradshaw (2009) has also provided convincing evidence of elephants suffering a condition that is similar to human PTSD and an interesting mouse model of PTSD has been suggested, using two strains of mice, allowing distinction between vulnerable and resilient individuals (Siegmund and Wotjak, 2007).

Recently the possibility that some species may develop PTSD, particularly those in captivity for our amusement or medical research, has been seriously considered. The symptoms that are reported in captive primates (often undergoing extensive and invasive study) include stereotypies, such as swaying and rocking, bar biting, hair picking, coprophagy, regurgitation, infanticide, lethargy, self injury, affect

dysregulation, incessant screaming, hyper-vigilance and hyper-aggression, all of which contribute to a profound failure to form and maintain social relationships, including failure to copulate and breed (Brüne et al., 2006; Bradshaw, 2008; Ferdowsian et al., 2011).

Other classic studies on the effects of social stress have been carried out on the tree shrew, regarded as an intermediate between insectivores and primates (Von Holst, 1972, 1986). However, even in natural environments, many animals suffer sickness and even death as a consequence of extreme stress. In some species (e.g. marsupial mouse and salmon males during the reproductive effort) this is part of their normal life cycle (Bradley, 2003).

The evidence for a stress response in birds and mammals, similar to humans, is thus compelling, and animals have been used extensively in medical research involving measurement of neurochemicals putatively central to the human response to stress.

Stress associated with animal studies of toxicity and addictive behaviours

A large body of studies have discussed important issues involving the complexity of the response to stress in animal models. Everds et al. (2013) describe the downstream effects of the immediate response to stress, which may include decreased total body weights or body weight gain; food consumption and activity; altered organ weights (e.g., thymus, spleen, adrenal); lymphocyte depletion in thymus and spleen; altered circulating leukocyte counts (e.g., increased neutrophils with decreased lymphocytes and eosinophils); and altered reproductive functions. They indicate that seemingly minor events can have a dramatic impact on an individual animal while eliciting no detectable responses in others. An identical stressor can have different effects

depending on a range of factors including the species/strain and the age of the test subject and prenatal stress can program and influence stress responses in postnatal life (Everds et al., 2013).

Most of the work focuses on rodents, due to the number used in pathophysiological research, but involves many other species. Perhaps the most relevant message from these animal studies is the wide variation in the response to different stressors despite the similarity of the key stress response molecules.

The Schank et al. (2012) review includes a focus on the role of stress-related neuropeptides. The authors indicate that reward and stress-related neural processes are frequently considered in isolation from each other but they suggest that a conceptualization informed by an evolutionary perspective could highlight their intricate interrelationship (Schank et al., 2012). CRF, the first member of the CRF/Ucn family to be isolated, is a prototypical neuropeptide that predominantly promotes withdrawal/avoidance, while neuropeptide Y (NPY) has the opposite profile. The urocortins (Uncs), neurokinins (NK), nociceptin/orphanin (N/OFQ) and its receptor NOPR, and neuropeptide S (NPS) have similar activity profiles but also differ in being more complex. It is suggested that Substance P (SP), a neuropeptide, acting as a neurotransmitter and as a neuromodulator, and the neurokinin receptor (NK1R) are involved in the regulation of stress and anxiety-related behaviours mediated through post-synaptic actions, and modulation of other transmitter systems. NK1R has a bidirectional effect on SP release (Singewald et al., 2008; Schank et al., 2012). Its activation suppresses SP release within the amygdala but stimulates it during acute stress exposure. Consistent with its role in stress responses, the SP/NK1R system also contributes to the regulation of the HPA axis.

NPS and its receptor (NPSR) in these studies are reported to have potent anxiolytic-like actions and appear to reduce expression of the conditioned fear response and facilitate fear extinction.

The studies in both reviews used rodents as subjects, but the similarity with humans is clear and once again the findings point to the involvement of the many stress response molecules in a wide range of life functions consistent with their long evolution.

Oxytocin

Oxytocin (OT), a nonapeptide hormone with a wide range of functions, has been studied in many different animals and is attracting increasing interest (Chini et al., 2014; Alves et al., 2015). It has been proposed to underlie social bonding behaviour and social support in reducing stress responsivity (Olff et al., 2014), including grooming (Eguibar et al., 2015); non-ingestive behaviours in rats, humans, rhesus monkeys and mice (Blevins et al., 2015; Iwasaki et al., 2015); induced oviposition in hawksbill turtles (Kawazu et al., 2014); lactation and general health in Nili Ravi buffaloes (Iqbal et al., 2015); learning and memory processes (Hou et al., 2015); male and female sexual behaviour (Veening et al., 2014) as well as early life, birth and lactation (Alves et al., 2015). With vasopressin (AVP), OT has been investigated for its therapeutic potential in several psychiatric disorders (Ramos et al., 2014; Brüne et al., 2015).

The evolution of OT has been studied in invertebrates and vertebrates (Beets et al., 2013; Knobloch et al., 2014). The recent identification of vasopressin/oxytocin-related signalling in *C. elegans* reveals that this peptidergic system is widespread among nematodes. Genetic analysis of the *C. elegans* nematocin system denotes

vasopressin/oxytocin-like peptides as ancient neuromodulators of neuronal circuits involved in reproductive behaviour and associative learning, whereas earlier invertebrate studies, on Echinoidea (sea urchins), *Octopus vulgaris* and *Tribolium castaneum* (red flour beetle), focused on conserved peripheral actions of this peptide family. Nematocin provides neuromodulatory input into the gustatory plasticity circuit as well as into distinct male mating circuits to generate a coherent mating behaviour. Molecular interactions are comparable to those underlying vasopressin- and oxytocin-mediated effects in the mammalian brain (Beets et al., 2013). They suggest that understanding how the vasopressin/oxytocin family fine-tunes neuronal circuits for social behaviour, learning and memory poses ‘a major challenge’. Functional conservation of these effects in nematodes, and most likely in other invertebrates, enables the development of future models to help answer this question.

During evolution OT-like genes and peptides remained highly conserved but, despite the gene conservation, neurons expressing OT-like peptides underwent tremendous evolutionary transformations (Knobloch and Grinevich, 2014) and the development of the OT- system in vertebrates, compared with invertebrates, is more fully researched. In primitive vertebrates (including agnathans, fish and amphibians), magnocellular neurosecretory neurons produce homologs of OT and vasopressin that reside in the wall of the third ventricle of the hypothalamus composing a single hypothalamic structure, the preoptic nucleus. This nucleus further diverged in advanced vertebrates (including reptiles, birds, and mammals) into the paraventricular and supraoptic nuclei with accessory nuclei between them. Due to microanatomical and cytological changes, the ancient release modes of OT into the cerebrospinal fluid were largely replaced by vascular release and a feature of the progressive transformations of the oxytocin system has been the expansion of OT axonal projections to forebrain

regions. OT neurons in advanced vertebrates acquired a voluminous dendritic tree and bifurcating/branching axons in addition to the preserved early features (Knobloch and Grinevich, 2014). Finally, in their review, they summarize the effects of OT and its homologs on pro-social reproductive behaviours in representatives of the phylogenetic tree and propose anatomically plausible pathways of OT release contributing to these behaviours in both ancient and more advanced vertebrates. Despite its many functions its role specifically in PTSD is still uncertain (Frijling et al., 2015) although it is being studied for its potential in treatment (Koch et al., 2016).

Integration of the neuroendocrine and immune systems

From an evolutionary and ecological perspective the immune and neuroendocrine systems have mostly been studied as two separate entities. However, there is increasing evidence of a two-way communication between the immune system and the neuroendocrine response to stress (Stengel and Taché, 2010; Ottaviani, 2011; Verbrugghe et al., 2012; Calvo et al., 2013). This poses the question of their coordination during evolution. Ottaviani (2011) suggests that immunity and the neuroendocrine systems might have evolved separately or, alternatively, the two systems may have developed together from a common origin thus explaining their continual bilateral integration, whereby the data seem to support the latter possibility (Ottaviani, 2011). The immunity, stress responses, and to some extent inflammation, seem to be mediated by a common pool of molecules: CRH, POMC products, catecholamines, corticosteroid hormones, cytokines and nitric oxide. All these molecules have been highly conserved across evolution, suggesting that the immune and neuroendocrine systems evolved from a common root: the functional similarities

between invertebrate immunocytes and vertebrate macrophages point toward the existence of an ancestral cell able to support an immune response, stress and inflammation. The three phenomena can be seen as an integrated network that plays a fundamental role in survival (Ottaviani, 2011). Reproduction could be added and indeed the close interdependence and conservation of the range of biological systems, despite massive diversification suggests, as is often alluded to, the danger of a similar range of disciplines pursuing their studies in relative isolation (Donovan, 1985). Both the skin and the gut, now and in the distant past, are directly involved as a part of the response to threat, and dermatologists are aware that stress plays a part in skin disease (Hunter et al., 2015). Likewise gastroenterologists are aware of the relationship between stress and bowel pathology (Buckley et al., 2014). A wider involvement in a range of pathologies has long been recognised (Rampton, 2011; Millar and Murrell, 2012) particularly by interested psychiatrists (Boscarino, 2004) but the skin, surprisingly, has excited little interest. Both skin and gastric problems have been reported in patients with PTSD (Burges Watson et al., 1992; Schnurr and Jankowski, 1999). However, it is not generally acknowledged that this should be expected, even though studies in the early 1950s reported episodes of urticaria and eczema in response to psychological stress (Koblezer, 1987). In a later study Schnurr et al. (2000) found a significant relationship with arterial, gastric, dermatologic and musculoskeletal disorders in older veterans presenting with combat-related PTSD. The possibility that this may be related to allostatic overload was not considered and, indeed, they appear to have dismissed the possibility of a direct relationship with PTSD.

The relationship between stress and pathology however is not straightforward and while chronic and excessive stress can have pathological effects, acute and moderate

stress can have immunoenhancing effects (Dhabhar, 2013). Clearly considerably more study is still needed to clarify these relationships.

Discussion

General remarks

Apart from infections, there are no human conditions with a more inclusive molecular evolutionary history than the trauma and stressor-related disorders, of which PTSD is clearly the most serious. It is the argument of this review that the nature of these disorders, and PTSD in particular, has, in part, been skewed through a tendency to focus on a psychological perspective, while not paying enough attention to the essentially physical features of the trauma and stressor-related disorders – a top down, psychological, rather than a bottom up, neuroscience approach (Panksepp, 2014).

Gitau et al. (2001) reported that the human foetus had a functional pituitary and adrenals, independent of the mother, by 20 weeks gestation. Subsequent papers report on the long term effects of stress during gestation (Lupien et al., 2009; Kertes et al., 2016) and even as a result of maternal undernutrition around conception (Zang et al., 2013). These matters might be described as preclinical bottom up studies.

Thus, with the Research Domain Criteria (RDoC) project (Insel and Cuthbert, 2015; Cuthbert, 2015) we favour two psychiatric classifications, a neuroscience based research classification and a clinical classification.

A neuroscience-based research will need to be roundly based in the context of evolution, as indeed does a comprehensive understanding of all life processes (Nesse, 2008). There is still a very long way to go to fully understand stress responses and the

disorders that can flow from their excess. Research will have to focus beyond the molecular to the atomic and it is therefore probable that the assistance of quantum biology will be required for an ultimate explanation of the physicochemistry of these reactions (Arndt et al., 2009; Li et al., 2016). Quantum biology has already proved helpful in tracking small animals (Ekvall et al., 2013) and explaining magnetoreception in the migration of birds and molecular mechanisms enabling the sense of smell (Brookes et al., 2012; McFadden and Al-Khalili, 2014).

PTSD remains a contentious diagnosis, in part because of the symptom overlap with other conditions, some of which are also clearly related to the experience of extremely stressful events. Adequate attention to the molecular management of these experiences would silence much of the argument.

Indeed, the molecules involved in the response to stress are so widely involved in the organization of the whole of life that a comprehensive understanding may well lead to a complete revision of what we understand about stress and most mental illness.

We have sought to address the evolution of the neuroendocrinological and immunological response to everyday, as well as extreme, stress and we argue that trauma and stressor-related disorders cannot be fully understood in all their facets without acknowledging the molecular evolution of stress physiology and the neurochemical mechanisms that are involved.

The increasing complexity of nervous systems caused by anagenesis or evolutionary "arms-race" (Krebs and Dawkins, 1984) renders the systems vulnerable to dysfunction. One would therefore expect that dysfunction of stress physiology can be elicited more easily in highly complex organisms, and this notion is supported by the presence of PTSD, or PTSD-like conditions, in many highly developed non-human mammals. These species depend on long periods of parental care and nurturing, and

have evolved a highly complex social-cognitive and emotional repertoire of responses to challenges from the social and physical environment (Dunbar, 2003; Panksepp, 2011).

Inability to mount an adequate response to some stressors can lead to death, so it is not surprising that extreme stress can lead to dysfunction or death through illness arising from these responses. The molecules involved have such widespread functions in the human body that disturbances in their relationships with each other could well underlie other psychiatric diagnoses. Indeed there is currently a growing realisation of the need for much greater cross-talk between a range of disciplines (Zoladz and Diamond, 2013; Doom and Gunnar, 2013; Panksepp, 2014).

The growing interest in neuroplasticity (Li et al., 2015) and genetics and epigenetics (Pitman et al., 2012), despite their importance in the mechanics of evolution, are outside the scope of this review.

Future directions

Our emphasis on the molecular response invites consideration of some hitherto unanswered or unquestioned issues:

1. Epigenetic mechanisms are beginning to address the question of why so few people get PTSD despite the prevalence of traumatizing events. The complexity of the molecular response to stress and its long evolutionary history, with multiple and regular small mutations, would point to wide variations in susceptibility, although PTSD has also been demonstrated as dose dependent (Selley et al., 1997). On the other hand other factors may well explain the increased risk of PTSD with, for example, man-made rather than natural disasters, and sexual rather than physical

assault, and the differences in stress responses between the sexes across the lifespan (Bale and Epperson, 2015).

Thus differences in life history patterns present a challenge to both evolutionary psychology and molecular evolution (Boonstra, 2013b).

2. Evolution strongly suggests that gastric and skin conditions particularly, and other physical and psychiatric disorders, should be expected with PTSD – albeit unevenly distributed. Polymorphism must be expected. This has important clinical implications. Indeed the immune response, stress and inflammation can be seen as an integrated network that plays a fundamental role in survival and reproduction underlining the need for much closer interdisciplinary cooperation (Donovan, 1985; Boonstra, 2013b). Beyond this there appears to be a need to move away from a systems approach to pathology to a cellular and molecular (Naviaux, 2014) if not a quantum/atomic approach (Arndt et al., 2009).

3. A more balanced and better informed view of the reality of stressor-related disorders, and PTSD in particular, would help in the problem area of compensation. An in-depth understanding would help to limit the number of successful false claims and there is little doubt that they do exist. Nevertheless, it is relevant to remember that in the past, thousands of people with significant symptoms have had to suffer in silence and many others have managed, despite them, to live full and productive lives.

4. There are clear treatment implications arising from a comprehensive evolutionary perspective.

Current medications in use with PTSD include antidepressants, anxiolytics and antipsychotics – the full gamut of the psychiatric pharmacopoeia. A better and wider understanding of the molecular disturbances should lead to more specific drugs. Frank physical behaviours may also have a part to play. Nevertheless there is no reason to

suppose that psychological techniques will not retain a central part in the treatment of PTSD and likewise benefit from a more inclusive understanding of the condition. These issues underscore the argument that a single physical and or psychological explanation alone is inadequate and potentially misleading. Both are a necessary prerequisite for a current understanding and treatment of PTSD and other stressor-related disorders.

Conclusions

Describing the ailing performance of himself and others, at the end of 1915, after months in the WW I trenches, Robert Graves (1929) writes: “Dr W.H.R. Rivers told me later that the action of one of the ductless glands - I think the thyroid – caused this slow general decline in military usefulness, by failing at a certain point to pump its sedative chemical into the blood. Without its continued assistance the man went about his tasks in an apathetic and doped condition, cheated into further endurance. It has taken some ten years for my blood to recover”.

Only now, one hundred years later, are we beginning to understand the complexity of the molecular mechanisms that probably account for the changes that Graves recognised and Rivers tried to explain. It is only in the last forty years, since the discoveries of Hughes et al. (1975), that our knowledge of brain chemistry has increased dramatically. Recent articles (Sah et al., 2014; Mahan and Ressler, 2011; Pitman et al., 2012; Holmes and Singewald, 2013; Bersani et al., 2016) attest to the growing awareness of the biochemistry of PTSD and other trauma and stressor-related conditions.

Table legend

This table attempts to summarize, on a long evolutionary timescale, the absence, appearance or presence of selected groups of molecules that have been reported to be involved in the response of organisms to challenge enabling continuity of life. The presence of these molecules may be thought of as stress response biomarkers that may have survival value rather than merely being considered deleterious. Representative life forms are chosen to represent some critical stages of evolution.

Symbols used are: + = present; ++ = both present; * = some variant of the molecule is present (for example may represent a different peptide sequence and may act in a similar way); A = not found; Blank = not reported.

We have employed the terminology of 'biomarkers' (Roshchina, 2010) to include the very broad category of neurotransmitters. We have not included in the table a number of specific molecules that are associated with the stress response and for which levels have been reported to be altered in PTSD e.g., C-reactive protein, ghrelin, growth hormone, substance P, dehydroepiandrosterone (DHEA), thyroid hormones etc (see review of Michopoulos et al. (2015) for listing of recently implicated neuroendocrine and immune biomarkers for PTSD).). HPA = Hypothalamo-pituitary-adrenal; HPI=hypothalamo-pituitary-interrenal (also intrarenal). HPI is relevant to lower vertebrates where no discrete adrenal gland is present.

A number of molecules depicted in the table, known now to act at a system level during the stress response and rarely or never acting in isolation, can be seen to have an impressively long evolutionary history albeit in some cases undergoing subtle transformations in form.

Glossary to Table 1

ACC	Anterior cingulate cortex
CRH	Corticotropin releasing hormone
CRF	Corticotropin releasing factor
CRP	C-reactive protein
HSP	Heat shock protein
HPI	Hypothalamo-pituitary-interrenal (also intrarenal)
H-P-PG	Hypothalamic-pituitary-peripheral gland
HPA	Hypothalamic-pituitary-adrenal axis
NOPR	Nociceptin/orphanin FQ receptor
N/OFQ	Nociceptin/orphanin FQ
NPY	Neuropeptide Y
NK	Neurokinins
NK_1R	Neurokinin receptor
NK cells	Natural killer cells
OT	Oxytocin
POMC	Proopiomelanocortin
SP	Substance P
Uncs	Urocortins

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