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VISIONS AND PERSPECTIVES

Around the word stress: its biological and evolutive implications

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Abstract

Stress is a general adaptive reaction crucial for survival and basically positive that involves the neuroendocrine and the immune systems. In all bilaterian metazoans, the molecular mediators of the stress response, i.e., corticotrophin-releasing hormone, corticotrophin, catecholamines and glucocorticoids, have been preserved during evolution, even if the increased complexity of animals have corresponded to a more articulated stress response that, following the eco-immunology perspective, we speculate to be hierarchically organized along three levels.

Kew Words: stressors; stress response; vertebrates; invertebrates; evolution

Eustress and distress, not simply “stress”

Among the general public, the word stress evokes a concept of negativity, which is maintained even among those that have, or should have, knowledge of biology. This situation becomes even more embarrassing when considering that the scientific concept of stress has had the good fortune to become very popular, but at the same time the misfortune to be insufficiently understood. Moreover, the use of the term stress in the field of advertising has certainly not clarified its meaning.

The present paper aims to provide a correct interpretation of the concept of stress, and especially to emphasize the importance of its positivity, i.e., the role played by stress response in the survival of all animal species on the Earth and maintained during evolution.

The phenomenon of stress was identified and conceptualized by Hans Selye who in 1936 published a paper, entitled: "A syndrome produced by different nocuous agents ".

Before describing the mechanisms of this phenomenon, we should underline some semantic details. Stress is fundamentally characterized by two moments and aspects, i.e., the “stimulus” and the “response”. The word stress can indicate both, so creating a possible semantic ambiguity. Selye (1978) suggested the word “stressors” (stressogenic agent) to indicate the causal agent, while keeping the word “stress” and “stress response” (response to stress) to indicate the final outcome. Moreover, according to Selye (1978), the word “stress” has meaning only if related to specific biological situations.

Regarding the mechanisms of the response to stress, in mammals different organs belonging to the nervous and endocrine systems, such as the hypothalamus, the pituitary and adrenal glands, are involved (Selye, 1978). The response triggers physiological processes that operate along two routes. The first is the nervous pathway involving the autonomic nervous system and the medullar portion of adrenal glands leading to the release of catecholamines (CA) (epinephrine and norepinephrine). These molecules provoke a very rapid response, inducing physiological changes, such as the degradation of glycogen to glucose and its increase in the blood, so improving the quality of the life. This situation is further improved with activation of the second track, the endocrine pathway, in which the cortex portion of adrenal glands is involved. Schematically, the different stimuli that cause stress induce the release of the corticotrophin-releasing hormone (CRH) by the hypothalamus. In turn, the CRH provokes corticotrophin (ACTH) release from the pituitary. This hormone enters the bloodstream and binds specific receptors for ACTH present on the cells of the cortical portion of the adrenal glands and results in the release of steroid hormones such as glucorticoids (GC). These hormones (cortisol in humans and corticosterone in mice) have different

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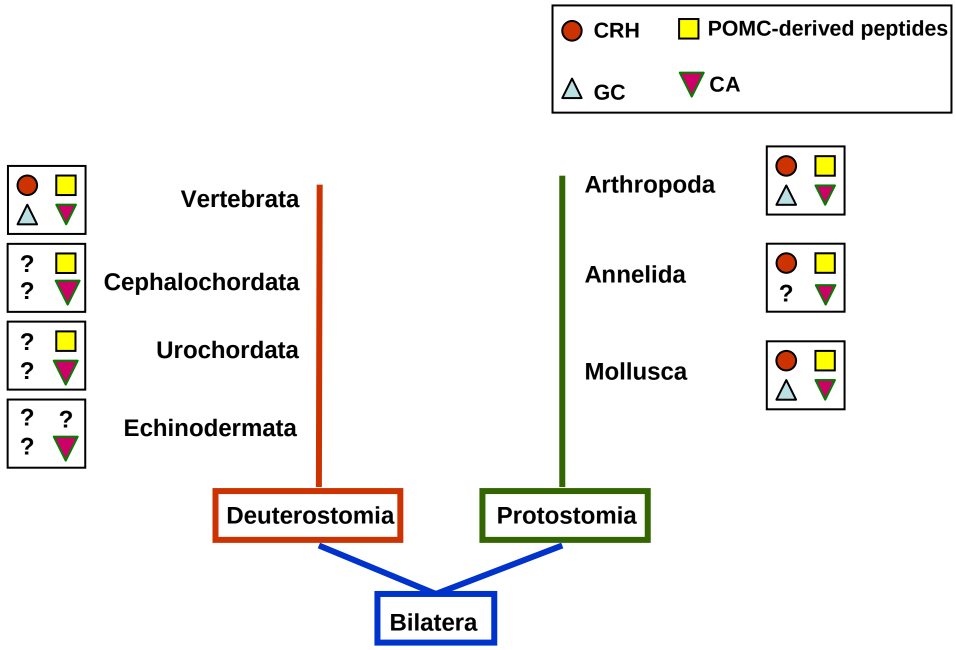

Fig. 1 Presence of the molecules involved in the stress response in the most representative taxa of Bilatera.

effects; in particular they are involved in regulating the biosynthesis and release of CA.

Altogether, it emerges that the stress pathway involves molecules in the following order: CRH, ACTH and CA.

This complex mechanism that improves the quality of life by means of the release of CA, hormones and steroids is called "eustress" that means beneficial, positive stress. However, stress response must be of short duration. Indeed, prolonged exposure to stressors leads to a sustained release of CA and cortisol associated with psychological, functional and pathological symptoms (including bleeding and ulcers) described by Selye (1978). This overrun of the stress response is better defined as "distress" that means negative stress.

The relationship between neuroendocrine and immune systems

Stressor and stress response, by one side, and antigens and immune response, on the other, have always been considered as two distinct phenomena, having been discovered and studied separately and, consequently, having become the topics of specific disciplines. However, this division is inconsistent with reality, and the distinction between stressor and antigen or stress and immune response, is to be considered only quantitative and semantic. This dualism was first overcome in experiments undertaken by Hugo Besedovsky and colleagues (1987). They showed that interleukin (IL)-1, a classic mediator of the immune system, is able to activate the hypothalamus-pituitary-adrenal axis. This observation indicates that stressors that induce an immune response (bacteria, viruses, etc.) must also be inserted in the list of the stressogenic agents, suggesting that there is a deep correlation between the immune system and response to stress. Edwin Blalock and Eric Smith demonstrated that cells from the immune system, such as lymphocytes and macrophages may play a central role in the induction of stress (Blalock and Smith, 1985; Blalock *et al.*, 1985; Blalock, 1989). Indeed, lymphocytes and macrophages, well-known producers of cytokines, have also to be considered as neuroendocrine cells being able to synthesize a variety of hormones (i.e., classical molecules produced by the endocrine system) and neuropeptides (i.e., classical molecules produced by the nervous system). Furthermore, lymphocytes and macrophages may, in turn, respond to hormones and neuropeptides produced by cells from the neuroendocrine system (Blalock and Smith, 1985; Blalock *et al.*, 1985; Blalock, 1989).

In summary, various levels of integration between the immune and neuroendocrine systems can be traced:

- classical products from the immune system, i.e., cytokines, can act on cells from the neuroendocrine system, modifying the latter's functions;
- immune stimuli and hypothalamic releasing factors induce immune cells to synthesize neuropeptides which, in turn, may influence the activity of the neuroendocrine system;
- classical hormones and neurotransmitters bind to specific receptors on immune cells and modulate their activity;
- cytokines and cytokine-like peptides that are potentially able to modulate immune cell activity are produced by cells from the nervous system.

These observations suggest that the three systems (immune, endocrine and nervous) should be considered as anatomically distinct components of a single integrated immuno-neuro-endocrine system involved in the maintenance of the body homeostasis, justifying the conclusion that the response to stress is essential for survival. Accordingly, It should be underlined that this interplay between the immune and neuroendocrine systems is not restricted to mammals or other vertebrates, but can be retrieved also in invertebrates (Ottaviani and Franceschi, 1996), where the molecular cascade of stress response described in the previous paragraph has been observed in immune-competent cells.

CRH and ACTH

CRH has been isolated and characterized by hypothalamic extracts of sheep by Vale's group (1981). Later searches showed the presence of CRH also in not nervous tissue (Seasholtz *et al.*, 2002). A similar picture has been detected in cartilaginous and bony fish as well as in tetrapods, i.e., in all vertebrates (Fig. 1) (Sato and George, 1973; Petrusz *et al.,* 1983; Waugh *et al*., 1985; Panzica *et al.,* 1986; Roubos, 1997; Lovejoy and Balment, 1999; Summers, 2001; Engelsma *et al.*, 2002; Seasholtz *et al.*, 2002; Malagoli *et al.*, 2004; Huising *et al.*, 2005). CRH-like molecules were also found in the nervous system of different invertebrate taxa, such as molluscs (Sonetti *et al.*, 1986), annelids (Rèmy *et al.*, 1982) and insects (Verhaert *et al.*, 1984; Malagoli *et al.*, 2002), as well as in the immunocytes and hemolymph of molluscs (Ottaviani *et al.*, 1990). Unfortunately, no data are at present available for echinoderms, urochordates and cephalochordates, that represent the most important invertebrate taxa sharing the deuterostomian lineage with vertebrates (Fig. 1).

ACTH is a small peptide enclosed within the pro-opiomelanocortin (POMC) precursor that was initially found in the human pituitary gland (Phifer *et al.*, 1974; Eberle, 1988). Subsequently, ACTH was also detected in mammalian extra-pituitary areas (Ottaviani *et al.*, 1997). As noted above for CRH, ACTH-like molecules were also found in intra- and extra-pituitary areas in other vertebrate taxa, namely fish, amphibians, reptiles and birds (Fig. 1) (Ottaviani *et al.*, 1997; Roubos, 1997; Engelsma *et al.*, 2002). Also different invertebrate taxa (molluscs, annelids, insects, urochordates and cephalochordates) contain immunoreactive ACTH molecules (Ottaviani *et al.*, 1997). No data are available for echinoderms (Fig. 1).

GC, CA and cytokines

In 1985, David Norris identified the source of GC, in particular, of cortisol and corticosterone, in the cells of the adrenal cortex of mammals. Non-mammalian vertebrates also produce GC (Fig. 1) (Summers, 2001; Engelsma *et al.*, 2002; Wada, 2008), but the typical adrenal glands found in mammals are not present in these animals. Fish present a group of cells homologue to adrenocortical and chromaffin mammalian tissue, and these two tissues are joined in various ways in tetrapods. The presence of GC-like molecules has also been detected in invertebrates, even if few studies are reported in literature. Cortisol immunoreactive molecules were detected in immunocytes from molluscs using an immunocytochemical method (Ottaviani *et al.*, 1998), and cortisol and corticosterone have been recorded in the insect *Calliphora vicina* by autoradiography (Bidmon and Stumpf, 1991). No further data are available for other invertebrate taxa.

As far as the presence of CA is concerned, these molecules were detected in all vertebrates (Leboulenger *et al.*, 1984; Korte *et al.*, 1997; Reid *et al.*, 1998; Summers, 2001; Tsigos and Chrousos, 2002). In invertebrates CA were found in molluscs (Ottaviani and Franceschi, 1996; Lacoste *et al.*, 2001; Hooper *et al.*, 2007; Adamo, 2008), annelids (Díaz-Miranda *et al.*, 1982; Fleming, 1993), arthropods (Murdock, 1971; Klemm, 1983; Adamo, 2008), echinoderms (Huet and Franquinet, 1981), urochordates (Kimura *et al.*, 2003) and cephalochordates (Moret *et al.*, 2004).

Finally, as for CA, cytokines have been observed in all vertebrate lineages (Cohen and Haynes, 1991; Myers *et al.*, 1992; Abbas *et al.*, 1994; Scapigliati *et al.*, 2000; Engelsma *et al.*, 2002; Kaiser *et al.*, 2004) and in some invertebrate taxa. With regard the latter, either cytokines or cytokine-like molecules were found in molluscs (Ottaviani *et al.*, 2004; De Zoysa *et al.*, in press), annelids (Ottaviani *et al.*, 2004), arthropods (Morisato and Anderson, 1994; Agaisse *et al.*, 2003; Kauppila *et al.*, 2003; Söderhäll *et al.*, 2005; Ottaviani *et al.*, 2004; Lemaitre and Hoffmann, 2007; Malagoli *et al.*, 2007) and urochordates (Parrinello *et al.*, 2008; Zhang *et al.*, 2008).

A refined orchestra with the same players

All the actors that play a role in the stress response must have appeared quite early in animals, since they can be retrieved in different bilaterian lineages (Fig. 1). It should be underlined that the cascade of molecular events involved in the stress response is the same in all the bilaterians analyzed so far, i.e., CRH, ACTH and CA. However, since invertebrates lack the organs usually related to vertebrate stress-response, i.e., hypothalamus, pituitary and adrenal glands, it remains to be established how invertebrate stress response can occur in such a simplified scenario. Our experiments in molluscs let us to speculate that in less complex organisms the stress response involves the circulating and phagocytic immunocyte endowed with the same molecules that are released and act in the same order described above (Ottaviani *et al.*, 1997).

However, if the primitive organization of stress response was restricted to single cells, how it came that it has been split up in different organs in vertebrates? In experiments in the catfish *Ameiurus nebulosus* we have observed that fish exposed to lipopolysaccharide (LPS) for 15 and 120 min showed an increase in proCRH-like molecules in the brain after 15 min but not after 120 min, while the increase in proCRH levels in the peripheral organs such as the liver and head kidney persisted for the entire treatment. These findings suggest that stress response is hierarchically- and time-regulated (Malagoli *et al*., 2004). More precisely, the first and simpler level is the "cell" level by which circulating immunocytes and some cells in various organs, have maintained the capability to resume the stress response. The "cell" level can be taken to represent the persistence of the "ancestral" version of stress response in complex organisms. The second level is the "organ" level, representing a local stress response in which cells distributed within a whole organ are involved. In this case, other organs may not be interested by the stress response that is therefore managed by single components. Finally, the third level is the "body" levels, involving different organs connected in a functional net, coordinating the entire system, as it is for the hypothalamus-pituitary-adrenal gland axis (Ottaviani *et al.*, 1998). This level represent the most complex machinery in stress response, but not necessary its activity is overlapped to that of the other levels (Malagoli *et al.*, 2004). It may be surmized that during evolution of vertebrates, while circulating cells maintain their capability of promoting an immune-neuroendocrine response to stressor ("cell level"), some cells were specialized to respond to stressor within organs, thus constituting the "organ" level. The organization of a "system" or "body" level could derive form the constitution of a functional net between organs that were progressively specialized for the intertwined relations between increasingly complex nervous and endocrine systems. This concept of "hierarchy" is in agreement with the fundamental tenet of ecological immunology, i.e., to minimize the cost of biological responses (Lochmiller and Deerenberg, 2000). In this respect, the "organ" level described above represents a paradigmatic example. Fish challenged with LPS increased their expression of proCRH-like molecules in the brain after 15 min but not after 120 min, while after 120 min the increase in proCRH levels persisted in the liver and head kidney. In terms of energy expenditure, we can speculate that it is more convenient for the organism to face the stressor at first also with the "body" level, then, if the stressor does not change its intensity, the stress response is mainly transferred to the periphery and to the "organ" level, thus limiting the involvement of the central nervous system to just the first phase of the stress (Malagoli *et al.*, 2004; Ottaviani *et al.*, 2008).

Conclusions

In their response to agents that are potentially able to alter their homeostasis and threaten their survival, living organisms exploit a complex and integrated mechanism involving the immune-neuroendocrine system and molecules that have been preserved during evolution, though differently located as a consequence of the increasing complexity of the organisms.

Stress is a general, adaptive reaction that is crucial for survival and basically positive. Most of the negative effects reported in the literature derive from the general perception of stress and refer to extreme conditions of excessive stress. The most common stress of moderate magnitude must be considered physiological and, as Seyle (1978) reported, represents "the spice of life".

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