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Immune-Neuroendocrine Interactions: Evolution, Ecology, and Susceptibility to Illness

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The integration between immune and neuroendocrine systems is crucial for maintaining homeostasis from invertebrates to humans. In the first, the phagocytic cell, *i.e.,* the immunocyte, is the main actor, while in the latter, the principle player is the lymphocyte. Immunocytes are characterized by the presence of pro-opiomelanocortin (POMC) peptides, CRH, and other molecules that display a significant similarity to their mammalian counterparts regarding their functions, as both are mainly involved in fundamental functions such as immune (chemotaxis, phagocytosis, cytotoxicity, etc.) and neuroendocrine (stress) responses. Furthermore, the immune-neuroendocrine system provides vital answers to ecological and immunological demands in terms of economy and efficiency. Finally, susceptibility to disease emerges as the result of a continuous dynamic interaction between the world within and the world outside. New fields such as ecological immunology study the susceptibility to pathogens in an evolutionary perspective while the field of neuro-endocrine-immunology studies the susceptibility from a more immediate perspective.

MeSH Keywords: Immune System • Invertebrates • Neuroendocrinology

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Background

Cells communicate with each other through highly specific chemical signals. The organisms that developed this form of communication during evolution seem to have greater opportunities for survival and thus the transmission of the new trait to their offspring. A conceivable reason underlying the appearance of this complex type of communication could have been driven by the presence of many synaptic molecules and hormones that promote intercellular communication.

The immune system and the central nervous system (CNS) "talk to each other" in order to maintain bodily homeostasis [1]. Different studies in mammals have demonstrated a bidirectional communication between these two systems [2,3].

In the course of evolution, the complexity of neuro-endocrine immune communication has increased reaching its highest degree of sophistication in mammals. However, the individual aspects of this dialogue must be traced back to the defense mechanisms of invertebrates. In this view, the innate response of the vertebrate appears to be a composed of a mosaic of various invertebrate immune mechanisms aimed to deal with pathogens [4].

In this review we summarize the three main emergent aspects in an evolutionary context, immunity, stress, and their relation to inflammation. First, a common pool of molecules exists that mediates these phenomena. Second, these molecules seem to have been highly conserved, suggesting that the immune and neuroendocrine systems have a common origin [3,4]. Third, a unique cell type endowed with phagocytic activity, called immunocytes, emerges above all others as the cell type best able to sustain immune responses, stress, and inflammation [5].

The Neuroendocrine Role of Vertebrate Lymphocytes and Invertebrate Immunocytes

The role of lymphocytes in the regulation of neuroendocrine functions in vertebrates is well-documented. Neuroendocrine hormones such as adrenocorticotropic hormone (ACTH) and endorphins are expressed by human lymphocytes [6]. The lymphocytes from different species (e.g., anuran amphibian, reptiles, birds, and mice) express ACTH [7-9]. ACTH and endorphins are generated by cleavage of the product of the pro-opiomelanocortin (POMC) gene [10,11]. Different cell types express and post-translationally process POMC protein into distinct sets of peptide products [12]. In mammals, the POMC gene consists of 3 exons, which in the pituitary gland are entirely transcribed to form the POMC mRNA. However, in extrapituitary sites cells express shorter transcripts of the POMC gene [13,14]. The biological activity of POMC-derived peptides is regulated by additional post-translational mechanisms including glycosylation, phosphorylation, amidation, sulfation, and acetylation [12,15–20]. More importantly, ACTH and endorphins produced in lymphocytes are almost indistinguishable from those produced by the pituitary [21]. Furthermore, lymphocytes display different peptidic hormones such as corticotropin-releasing hormone (CRH), thyrotropin hormone (TSH), growth hormone (GH), vasoactive intestinal peptide (VIP), somatostatin, vasopressin, and oxytocin [3]. Moreover, human peripheral blood lymphocytes, monocytes, and lymphoid cell lines express receptors for ACTH, β-endorphin, VIP, and GH [2,3,22]. Lastly, the major mediators of immune system activity, the cytokines, play a special role in interactions between the immune and neuroendocrine systems [23].

In invertebrates, molluscs, and leeches, the presence of POMC-products, cytokines, biologically active peptides [24–30], glucocorticoids [24,31–33], and biogenic amines [34] has been demonstrated using different technical approaches (e.g., radioimmunoassay (RIA), immunocytochemistry, flow cytometry, and *in situ* hybridization).

Immune-Neuroendocrine Response in Vertebrates and Invertebrates

All organisms, in order to survive, must activate defenses both at the molecular as well as the genetic level. Furthermore, they must cope with the environment in which they live, in addition to a multitude of diseases. Thus, they must be able to provide answers to all the stressors with which they come in contact in order to preserve bodily homeostasis.

In this context, previous studies have shown that in invertebrates and vertebrates, the same or similar "defense molecules" are present [21,35]. In these higher forms of life, the function of these molecules remains fundamentally alike. Nevertheless, nature has apparently made new uses of these old molecules, while at the same time evolving towards more complicated and centralized functions and organs.

With respect to immune function, cell shape changes, chemotaxis, and phagocytosis play a central role and are therefore of particular importance.

Cell shape changes and chemotaxis

The incubation of the hemolymph of the bivalve mollusc *Mytilus galloprovincialis* with ACTH (1-24) induced changes in the cell shape (expression of cell motility) of immunocytes via the cAMP pathway, as well as by protein kinase C activity [36]. Such conformational cell modifications were detected using computer-assisted microscopy image analysis and were evaluated as a shape factor that represents the degree of deviation of the cell

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from round (inactive state) to ameboid (active state). This value was determined by measurements of the cellular area and its perimeter and is mathematically expressed using the shape factor formula of the American Innovision Analysis System [37].

Also, opioid neuropeptides are involved in adherence and chemotaxis in invertebrates (the mollusc *M. edulis* and the insect *Leucophaea maderae*) and in human immunocytes [38,39]. Moreover, cytokines such as PDGF-AB, TGF-β1, and IL-8 provoke cell motility. These molecules trigger the cells by using different transduction signaling pathways. PDGF-AB and TGF-β1 transduce extracellular signals along the phosphoinositide signaling pathway. The action of PDGF-AB, extracellularly, is Ca^{2+}-independent, while that of TGFβ1 is Ca^{2+}-dependent [40,41]. IL-8 induces cell motility via protein kinase A and C pathways [42].

The complete ACTH molecule (1-39) and its fragments (1-24), (1-4), (4-0), (1-13), (11-24), CRH [43], and the entire endorphin molecule (1-31) all exert a chemotactic action on the molluscan immunocyte [44], stressing the fact that chemotaxis is the expression of non-random cell locomotion [45]. Similar behavior was observed for cytokines such as IL-1α, TNF-α, IL-8, PDGF-AB, and TGF-β1 [29].

Phagocytosis

This phenomenon is the first and vital defense mechanism of all living organisms. It was observed for the first time in the larvae of starfish by Metchnikoff in 1882 [46]. Experiments performed on molluscan immunocytes in the presence of ACTH fragments, CRH and cytokines, revealed a significant increase in the phagocytic activity of bacteria in controls, while no effect was observed in the presence of β-endorphin [47]. More importantly, the phagocytic action of ACTH (1-24) has been maintained as humans transitioned from lower vertebrates such as urodelan amphibians [9].

From these studies on chemotaxis and phagocytosis in invertebrates emerges the general assumption that these 2 phenomena are correlated, but this is not true [48].

Stress response

The phenomenon of stress was identified and conceptualized by the physiologist Hans Selye around the 1930s. Indeed, in 1936, he published the paper entitled: "A syndrome produced by diverse nocuous agents", in the journal Nature. Subsequently, Selye defined his concept of stress more articulately as "a non-specific reaction exhibited by the body when it is faced with a need or adapt to a new situation". This, then, suggests that all living beings must be equipped appropriately in order to survive.

The majority of studies in this area concern vertebrates, particularly mammals, and only since the 1990s have researchers focussed their attention on invertebrates.

These studies demonstrated that the stress response occurs in vertebrates and invertebrates using the same molecules, following the same order and pattern, *such as* CRH> ACTH> biogenic amines [49]. However, they substantially differ in the location where such molecules are produced. In vertebrates, the areas of production are the hypothalamus, pituitary, and adrenal glands, which are organs that do not exist in invertebrates. In the latter, the above-mentioned molecules are secreted by the immunocytes. It is important to appreciate that in this invertebrate scenario the same actors are involved in a different and simpler scenario.

Eco-Immune-Neuroendocrinology

From an ecological point of view, the immune response should provide the optimal response with minimum cost [50]. The activation of a common pathway involving immune and neuroendocrine components is a classic example used by living organisms to cope with a series of endogenous and exogenous molecules and to combat dangers that may alter their body homeostasis. Indeed, as previously reported, these 2 systems share a whole series of mediators or defensive molecules from lower to higher organisms.

Bow ties, a theoretical framework [51,52], may be considered another example in favor of ecological requirements. The proposed model consists of a large ''fan in'' (many inputs) and a relatively small ''knot'', composed of a small number of elements, for processes of control and elaboration, and a large ''fan out'' of products that may exert a feedback type of control. The "knot" is able to integrate a wide variety of stimuli. In this way, the immune system can be considered as a network of bow ties working at different levels of immune response.

In vertebrates, the thymus and bursa of Fabricius (in chicken) are crucial in acquired immunity and are responsible for B and T lymphocyte maturation. These 2 organs represent another example that emphasizes an evolutionary strategy of re-using pre-existing material [53]. Both organs display involution and remodeling of the cellular microenvironment and the presence of POMC-derived peptides and cytokines [54–56], involved in thymic education and positive selection [57,58].

On the whole, an increased number of POMC-products emerge, together with a decline in the area of lymphoid tissue observed during aging of the 2 organs, suggest a survival role of these molecules in the maintenance of the thymus and bursa of Fabricius.

Finally, epigenetic mechanisms influence the immune-neuroendocrine responses regulating gene expression [59]. LPS injection in the apple snail, *Pomacea canaliculata,* provokes the

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induction of phospho-acetylation of histone H3 in the ganglia within 3 h after immune challenge, whereas 6 h later the values were close to those of control snails. Moreover, these findings were correlated with an increase in c-Fos protein levels.

Susceptibility to Illness

To conclude, a proper dialogue between immune and neuroendocrine functions plays a fundamental part in the balance of living organisms [3,60,61]. Occasional unbalances in 1 of the 2 systems are absorbed by the compensatory actions of the other. To date, it is very difficult to give priority to 1 of the 2 systems in regulating health or illness. Indeed, it is much more useful and probably more appropriate to talk about equilibrium and continuous dialogue.

Numerous data in the literature show that functional alterations in the activity of the immune system can cause profound alteration in both the nervous and endocrine systems [61–65]. Similarly, changes in the neuroendocrine system profoundly modify the activities and functionality of the immune system [66–68].

From this emerges that these 2 systems, historically studied and considered separate, affect each other, and this reciprocal influence has fundamental repercussions regarding health or disease. Consequently, the relative certainty that separate systems act by using independent mechanisms and mediators belonging to different parts of the organism has been replaced by now firmly rooted knowledge that emphasizes that the major mediators of immune system activity, the cytokines, play a special role in the functioning of the neuroendocrine system [68–73]. In humans and rodents, the activation of immune responses by the administration of LPS induces massive immune activation that culminates in a complex molecular, systemic, and behavioral response called sickness behavior [73–77]. This complex framework is induced and maintained mainly by cytokines (e.g., IL-1, IL-6, and IL-18) [73]. Many cytokines, especially the pro-inflammatory ones, are produced by CNS cells and released under the influence of specific stimuli [73]. These molecules are capable of binding their receptors to distinct central cellular populations, including neurons and microglia cells, by activating highly specific signaling pathways [75–78]. The levels of these cytokines and the activity of the associated signal transduction systems modify extremely complex functions such as, mood, psychosis, anxiety, and the control of food intake [79]. In rodents, the ablation of the gene coding for the pro-inflammatory cytokine IL-18 produces an obese phenotype, while the direct application of the recombinant cytokine to the bed nucleus of the stria terminalis (BST) has a potent anorexigenic effect. This led us to propose that the immune mediator IL-18 directly contributes to the loss of appetite observed during sickness [80].

More importantly, such effects are generated by high levels of cytokines produced by cerebral cells or cytokines formed by immune cells that pass the blood-brain barrier [35]. This constitutes one of the most convincing demonstrations of a tight link between these systems in support of the existence of a single, highly intertwined, and interdependent immune-neuroendocrine system. Because this is now firmly accepted and demonstrated, the role of the nervous and endocrine system in controlling immune function was next questioned. The resulting studies are now historical and form the cornerstone of the stress response literature [3]. Currently, the clearest and best-studied example accepted in support of a single intricate system is the activity, functionality, and pathophysiological role of the hypothalamus-pituitary-adrenal axis. This system is considered to be one of the main controllers of mammalian activity [81,82], especially as it relates to stress and the stress response in relation to susceptibility to disease. Its activation or shutdown is under strict control of limbic areas [81]. Changes in the activity of areas of the limbic system, caused by endogenous or exogenous stimuli, are crucial in determining complex functions such as fight or flight reactions and thus the survival of individuals. In addition, the end-product of HPA axis activity, cortisol in humans or corticosterone in other species, profoundly regulates the functionality and efficiency of the immune response. Chronic high levels of circulating steroid hormones cause a state of widespread inflammation and powerful immunosuppression. Under these conditions, the immune system loses its ability to respond properly to pathogens or to exercise appropriate immunosurveillance [69]. In humans, major depression, which is the most prominent psychiatric illness, is associated with the deregulation of HPA axis feedback mechanisms that are major contributors to the clinical picture of the disease. The therapeutic response is often mediated by normalization of HPA axis activity. These data have been confirmed by studies in animal models, where genetic alterations in the genes that control HPA axis function generate a pathophysiological condition very similar to the neuroendocrine dysfunctions associated with major depression observed in patients [83]. In this regard, it is essential that we relinquish the erroneous idea that different systems play functionally and spatially separate roles, and consider these systems as a single highly integrated system in which, depending on contexts and situations, one system controls the other or vice versa. Moreover, this determines that, depending on the place or situation a system find its self in, it can adapt by performing actions normally not attributed to it.

Currently, immunology is used to study disease susceptibility and the neural and neuroendocrine structural and functional architecture that mediate these intrinsic as well as extrinsic factors, among which are the role of parasites and pathogens in sickness behavior and the susceptibility to somatic and well as mental disease [81].

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The more we learn about the interaction among the nervous, endocrine, and immune systems, the more we see that the susceptibility to disease and illness is controlled or influenced by biological as well as behavioral characteristics of the organism, which are characteristics that go both ways. On the one hand, we need to understand the relevance of the environmental context, made up by factors [4,68,81,82] such as temperature, altitude, and photoperiod, but also crowding, urbanization, the presence of parasites and pathogens, drought, and famine. On the other hand, we should consider intrinsic or innate factors such as changes in hormonal and neurotransmitter communication, network formation, and the direct or indirect interference with the neurons and brain regions that mediate behavioral expression. These factors, in combination with the genetic predisposition to stress and the physiological and the behavioral response to stress, eventually determine who is healthy and who is not [81].

Conclusions

Consequently, we need an interdisciplinary approach that examines interactions among host physiology and disease susceptibility in an ample set of environmentally relevant contexts, studying the appropriate animals or animal systems from the simpler ones to the most complex, while combining different methods and approaches that include fields as evolution, ecology, and life history theory with endocrinology, neuroscience, molecular biology, and, ultimately, behavior.

References:

1. Elenkov, IJ, Wilder RL, Chrousos GP et al: The sympathetic nerve – an integrative interface between two supersystems: The brain and the immune system. Pharmacol Rev, 2000; 52: 595–638
2. Weigent DA, Blalock JE: Interactions between the neuroendocrine and immune systems: Common hormones and receptors. Immunol Rev, 1987; 100: 79–108
3. Besedovsky H, del Rey A: Immune-neuro-endocrine interactions: Facts and hypotheses. Endocr Rev, 2013; 17: 64–102
4. Malagoli D, Ottaviani E: Eco-immunology, evolutive aspects and future perspectives. Dordrecht 2014; The Netherlands: Springer. Eds Springer
5. Ottaviani E: Immunocyte: The invertebrate counterpart of the vertebrate macrophage. Inv Surv J, 2011; 8: 1–4
6. Smith EM, Blalock JE: Human lymphocyte production of corticotropin and endorphin-like substances: Association with leukocyte interferon. Proc Natl Acad Sci USA, 1981; 78: 7530–34
7. Siegel HS, Gould NR, Latimer JW: Splenic leukocytes from chickens injected with *Salmonella pullorum* antigen stimulate production of corticosteroids by isolated adrenal cells. Proc Soc Exp Biol Med, 1985; 178: 523–30
8. Harbour DV, Galin FS, Hughes TK et al: Role of leukocyte-derived pro-opiomelanocortin peptides in endotoxic shock. Circ Shock, 1991; 35: 181–91
9. Ottaviani E, Trevisan P, Pederzoli A: Immunocytochemical evidence for ACTH- and β-endorphin-like molecules in phagocytic blood cells of urodelan amphibians. Peptides, 1992; 13: 227–31
10. Mains RE, Eipper BA, Ling N: Common precursor to corticotropins and endorphins. Proc Natl Acad Sci USA, 1977; 74: 3014–18
11. Roberts JL, Herbert E: Characterization of a common precursor to corticotropin and beta-lipotropin: Identification of beta-lipotropin peptides and their arrangement relative to corticotropin in the precursor synthesized in a cell-free system. Proc Natl Acad Sci USA, 1977; 74: 5300–4
12. Eberle AN: The melanotropins. Chemistry, physiology and mechanisms of action, Karger, New York, NY, 1988
13. Notake M, Tobimatsu T, Watanabe Y et al: Isolation and characterization of the mouse corticotropin-beta-lipotropin precursor gene and a related pseudogene. FEBS Lett, 1982; 156: 67–71
14. Uhler M, Herbert E, D'Eustachio P et al: 1983. The mouse genome contains two nonallelic pro-opiomelanocortin genes. J Biol Chem, 1983; 258: 9444–53
15. O'Donohue TL, Handelmann GE, Chaconas T et al: Evidence that N-acetylation regulates the behavioral activity of alpha-MSH in the rat and human central nervous system. Peptides, 1981; 2: 333–44
16. O'Donohye TL, Handelmann GE, Miller RL, Jacobowitz DM: N-acetylation regulates the behavioral activity of alpha-melanotropin in a multineurotransmitter neuron. Science, 1982: 215: 1125–27
17. O'Donohue TL, Dorsa DM: The opiomelanotropinergic neuronal and endocrine systems. Peptides, 1982; 3: 353–95
18. Farah JM, Millington WR, O'Donohue TL: In central action of ACTH and related peptides, De Wied D, Ferrari W (eds.), Liviana Press, Springer Verlag, Padua, Berlin, 1986; 33–52
19. Vaudry H, Jenks BG, Verburg-Van Kemenade L, Tonon MC: Effect of tunicamycin on biosynthesis, processing and release of proopiomelanocortin-derived peptides in the intermediate lobe of the frog *Rana ridibunda*. Peptides, 1986; 7: 163–69
20. Burbach JPH, Wiegant WM: In Neuropeptides: Basic and perspectives, De Wied D (ed.), Elsevier, Amsterdam, 1980; 45–103
21. Blalock JE, Smith EM: Human leukocyte interferon: Structural and biological relatedness to adrenocorticotropic hormone and endorphins. Proc Natl Acad Sci USA, 1980; 77: 5972–74
22. Kiess W, Butenandt O: Specific growth hormone receptors on human peripheral mononuclear cells: Reexpression, identification, and characterization. J Clin Endocrinol Metab, 1985; 60: 740–46
23. Hughes TK Jr., Chin R: Interactions of neuropeptides and cytokines, In Scharrer B, Smith EM, Stefano GB (eds.), Neuropeptides and immunoregulation, Springer-Verlag, Berlin; 1994; 101–9
24. Ottaviani E, Petraglia F, Montagnani G et al: Presence of ACTH and beta-endorphin immunoreactive molecules in the freshwater snail *Planorbarius corneus* (L.) (Gastropoda, Pulmonata) and their possible role in phagocytosis. Regul Pept, 1990; 27: 1–9
25. Ottaviani E, Capriglione T, Franceschi C: Invertebrate and vertebrate immune cells express pro-opiomelanocortin (POMC) mRNA. Brain Behav Immun, 1995; 9: 1–8
26. Salzet M, Salzet-Raveillon B, Cocquerelle C et al: Leech immunocytes contain proopiomelanocortin: Nitric oxide mediates hemolymph proopiomelanocortin processing. J Immunol, 1997; 159: 5400–11
27. Grimaldi A, Girardello R, Malagoli D et al: Amyloid/Melanin distinctive mark in invertebrate immunity. Inv Surv J, 2012; 9: 140–62
28. Grimaldi A, Tettamanti G, Girardello R et al: 2014. Functional amyloid formation in LPS activated cells from invertebrates to vertebrates. Inv Surv J, 2014; 11: 286–97
29. Ottaviani E, Malagoli D, Franchini A: Invertebrate humoral factors: Cytokines as mediators of cell survival. Prog Mol Subcell Biol, 2004; 34: 1–25
30. Tascedda F, Ottaviani E: Biologically active peptides in molluscs. Inv Surv J, 2016; 13: 186–90
31. Chapman JC, Lockley WJ, Rees HH et al: Stereochemistry of olefinic bond formation in defensive steroids of αcilius sulcatus (Dytiscidae). Eur J Biochem, 1977; 81: 293–98
32. Bidmon HJ, Stumpf WE: Uptake, distribution and binding of vertebrate and invertebrate steroid hormones and time-dependence of ponasterone A binding in *Calliphora vicina*. Comparisons among cholesterol, corticosterone, cortisol, dexamethasone, 5 alpha-dihydrotestosterone, 1,25-dihydroxyvitamin D3, ecdysone, estradiol-17 beta, ponasterone A, progesterone, and testosterone. Histochemistry, 1991; 96: 419–34
33. Ottaviani E, Franchini A, Franceschi C: Presence of immunoreactive molecules to CRH and cortisol in invertebrate haemocytes and lower and higher vertebrate thymus. Histochem J, 1998; 30: 61–67

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34. Ottaviani E, Caselgrandi E, Petraglia F et al: Stress response in the freshwater snail *Planorbarius corneus* (L.) (Gastropoda, Pulmonata): Interaction between CRF, ACTH and biogenic amines. Gen Comp Endocrinol, 1992; 87: 354–60
35. Malagoli D, Mandrioli M, Tascedda F: Circulating phagocytes: The ancient and conserved interface between immune and neuroendocrine function. Biol Rev, 2017; 92: 369–77
36. Sassi D, Kletsas D, Ottaviani E: Interactions of signaling pathways in ACTH (1-24)-induced cell shape changes in invertebrate immunocytes. Peptides, 1998; 19: 1105–10
37. Schön JP, Torre-Bueno J, Stefano JB: Microscopic computer-analysis of conformational state: Reference to neuroimmunology. Adv Neuroimmunol, 1991; 1: 252–59
38. Stefano GB, Cadet P, Scharrer B: Stimulatory effects of opioid neuropeptides on locomotory activity and conformational changes in invertebrate and human immunocytes: Evidence for a subtype of delta receptor. Proc Natl Acad Sci USA, 1989; 86: 6307–11
39. Stefano GB, Leung MK, Zhao XH et al: Evidence for the involvement of opioid neuropeptides in the adherence and migration of immunocompetent invertebrate hemocytes. Proc Natl Acad Sci USA, 1989; 86: 626–30
40. Ottaviani E, Sassi D, Kletsas D: PDGF- and TGF-beta-induced changes in cell shape of invertebrate immunocytes: Effect of calcium entry blockers. Eur J Cell Biol, 1997; 74: 336–41
41. Kletsas D, Sassi D, Franchini A et al: PDGF and TGF-beta induce cell shape changes in invertebrate immunocytes via specific cell surface receptors. Eur J Cell Biol, 1988; 75: 362–66
42. Ottaviani E, Franchini A, Malagoli D et al: Immunomodulation by recombinant human interleukin-8 and its signal transduction pathways in invertebrate hemocytes. Cell Mol Life Sci, 2000; 57: 506–13
43. Genedani, S, Bernardi M, Ottaviani E et al: Differential modulation of invertebrate hemocyte motility by CRF, ACTH, and its fragments. Peptides, 1994; 15: 203–6
44. Genedani, S, Bernardi M, Ottaviani E et al: Influence of endorphins on the migration of molluscan hemocytes. Comp Biochem Physiol, 1994; 107C: 79–81
45. Manske M, Bade EG: Growth factor-induced cell migration: Biology and methods of analysis. Int Rev Cytol, 1994; 155: 49–96
46. Tan SY, Dee MK: Elie Metchnikoff (1845–1916): Discoverer of phagocytosis. Singapore Med J, 2009; 50: 456–57
47. Ottaviani E, Franchini A, Franceschi C: Pro-opiomelanocortin-derived peptides, cytokines and nitric oxide in immune responses and stress: An evolutionary approach. Int Rev Cytol, 1997; 170: 79–141
48. Malagoli D, Ottaviani E: Discrepant effects of mammalian factors on molluscan cell motility, chemotaxis and phagocytosis: Divergent evolution or finely tuned contingency? Cell Biol Int, 2010; 34: 1091–94
49. Ottaviani E, Franceschi C: The neuroimmunology of the stress response from invertebrates to man. Prog Neurobiol, 1996; 48: 421–40
50. Tauber AI: Immunity: The evolution of an idea. Oxford University Press New York, 2017; Chapter 5: Eco-immynology
51. Csete M, Doyle J: Bow ties, metabolism and disease. Trends Biotechnol, 2004; 22: 446–50
52. Ottaviani E, Malagoli D, Capri M et al: Ecoimmunology: Is there any room for the neuroendocrine system? BioEssays, 2008; 30: 868–74
53. Jacob F: Evolution and tinkering. Science, 1977; 196: 1161–66
54. Franchini A, Ottaviani E, Franceschi C: Presence of immunoreactive pro-opiomelanocortin-derived peptides and cytokines in the thymus of an anuran amphibian (Rana esculenta). Tissue Cell, 1995; 27: 263–67
55. Ottaviani E, Franchini A, Franceschi C: Evidence for the presence of immunoreactive pro-opiomelanocortin-derived peptides and cytokines in the thymus of the goldfish (Carassius c. auratus) Histochem. J 1995; 27: 597–601
56. Ottaviani E, Franchini A, Franceschi C: Evolution of neuroendocrine thymus: studies on POMC-derived peptides, cytokines and apoptosis in lower and higher vertebrates. J Neuroimmunol, 1997; 72: 67–74
57. Ezine S: The thymus: Colonization and ontogeny. Bull Inst Pasteur, 1989; 87: 171–203
58. Ritter MA, Crispe IN: The thymus, IRL Press at Oxford University Press; 1992
59. Ottaviani E, Accorsi A, Rigillo G et al: Epigenetic modification in neurons of the mollusc *Pomacea canaliculata* after immune challenge. Brain Res, 2013; 1537: 18–26
60. Ashley NT, Demas GE: Neuroendocrine-immune circuits, phenotypes, and interactions. Horm Behav, 2017; 87: 25–34
61. Brestoff JR, Artis D: Immune regulation of metabolic homeostasis in health and disease. Cell, 2015; 161: 146–60
62. Benatti C, Alboni S, Capone G et al: Early neonatal inflammation affects adult pain reactivity and anxiety related traits in mice: Genetic background counts. Int J Dev Neurosci, 2009; 27: 661–68
63. Benatti C, Alboni S, Montanari C et al: Central effects of a local inflammation in three commonly used mouse strains with a different anxious phenotype. Behav Brain Res, 2011; 224: 23–34
64. Benatti C, Blom JMC, Rigillo G et al: Disease-induced neuroinflammation and depression. CNS Neurol. Disord. Drug Targets, 2016; 15: 414–33
65. Blom JMC, Benatti C, Alboni S et al: Early postnatal chronic inflammation produces long-term changes in pain behavior and N-methyl-D-aspartate receptor subtype gene expression in the central nervous system of adult mice. J Neurosci Res, 2006; 84, 1789–98
66. Blom JMC, Tamarkin L, Shiber JR et al: Learned Immunosuppression is associated with an increased risk of chemically-Induced tumors. Neuroimmunomodulation, 1995; 2: 92–99
67. Nelson RJ, Blom JMC: Photoperiodic effects on tumor development and immune function. J Biol Rhythms, 1994; 9: 233–49
68. Nelson RJ: Seasonal immune function and sickness responses. Trends Immunol, 2004; 25: 187–92
69. Weil ZM, Martin LB, Nelson RJ: Interactions among immune, endocrine, and behavioural response to infection. In: Morand S, Krasnov BR, Poulin R (eds.), Micromammals and Macroparasites. Springer, Tokyo, 2006
70. Pyter LM: The influence of cancer on endocrine, immune, and behavioral stress responses. Physiol Behav, 2016; 166: 4–13
71. Glaser R, Kiecolt-Glaser JK: Stress-induced immune dysfunction: Implications for health. Nat Rev Immunol, 2005; 5: 243–51
72. Nusslock R, Miller GE: Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis. Biol Psychiatry, 2016; 80; 23–32
73. Dantzer R, O'Connor JC, Freund GG et al: From inflammation to sickness and depression: When the immune system subjugates the brain. Nat Rev Neurosci, 2008; 9: 46–56
74. Verburg-van Kemenade BML, Cohen N, Chadzinska M: Neuroendocrine-immune interaction: Evolutionarily conserved mechanisms that maintain allostasis in an ever-changing environment. Dev Comp Immunol, 2017; 66: 2–23
75. Alboni S, Gibellini L, Montanari C et al: N-acetyl-cysteine prevents toxic oxidative effects induced by IFN-α in human neurons. Int J Neuropsychopharmacol, 2013; 16: 1849–65
76. Alboni S, Montanari C, Benatti C et al: Interleukin 18 activates MAPKs and STAT3 but not NF-κB in hippocampal HT-22 cells. Brain Behav Immun, 2014; 40: 85–94
77. Alboni S, Benatti C, Montanari C et al: Chronic antidepressant treatments resulted in altered expression of genes involved in inflammation in the rat hypothalamus. Eur J Pharmacol, 2013; 721: 158–67
78. Caraci F, Tascedda F, Merlo S et al: Fluoxetine prevents Aβ1-42-induced toxicity via a paracrine signaling mediated by transforming-growth-factor-β1. Front Pharmacol, 2016; 7: 389
79. Elenkov IJ: Neurohormonal-cytokine interactions: Implications for inflammation, common human diseases and well-being. Neurochem Int, 2008; 52: 40–51
80. Francesconi W, Sánchez-Alavez M, Berton F et al: The proinflammatory cytokine interleukin 18 regulates feeding by acting on the bed nucleus of the stria terminalis. J Neurosci, 2016; 36: 5170–80
81. Demas GE, Carlton ED: Ecoimmunology for psychoneuroimmunologists: Considering context in neuroendocrine-immune-behavior interactions. Brain Behav Immun, 2015; 44: 9–16
82. Hau M, Goymann W: Endocrine mechanisms, behavioral phenotypes and plasticity: Known relationships and open questions. Front Zool, 2015; 12: S7
83. Alboni S, Tascedda F, Corsini D et al: Stress induces altered CRE/CREB pathway activity and BDNF expression in the hippocampus of glucocorticoid receptor-impaired mice. Neuropharmacology, 2011; 60: 1337–46

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