Undeniable Neuroimmunology

Abstract

The effective therapy for illnesses associated to the excess, or lack, of immunological response depends on the advances in knowledge about the effects of neurotransmitters on the leukocytes activity. The HPA axis and the autonomous nervous system control inflammation, while certain substances secreted locally by peripheral nervous system tend to enhance the inflammatory response. In this last case, possibly as a support mechanism to the elimination of an infectious agent. Data available on the literature are still scarce, but they already emphasize the Neuroimmunology as a promising field of investigation and, above all, necessary.

Keywords: Neuroimmunology; VIP; Inflammation; IS; Immune System; CRH; Leukocytes; HPA axis

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Abbreviations: IS: Immune System; NS: Nervous System; HPA: Hypothalamus-Hypophysis-Adrenal Axis; CRH: Corticotrophin Releasing Hormone; ACTH: Adreno Cortico Tropic Hormone; VIP: Vasoactive Intestinal Peptide

Introduction

The functional imbalance of the Immune System (IS) can express itself, basically, in two different and conflicting ways: through the lack or over response. The commitment of the IS protective capacity causes susceptibility to infections and neoplasms; while the exacerbated reactivity to its own components or to innocuous substances justifies the incidence of autoimmune diseases and allergies.

It's not a surprise that the regulation and the recovery of the homeostasis of the IS are the most pursued objectives by researchers who work in the Immunology area. However, despite the benefits originated from some immuno modulation strategies, the majority of the immunologic reactivity control medical practices is still done with antigen non-specific immuno suppresses [1-2]. And, in the case of hyper activity, the treatments are based on the combat to the consequences of the pathology, in such a way that opportunist infections are treated with microbicides [3], and tumor cells are removed through chemical or surgical procedures [4-6].

It's possible that the major progresses in the capacity of manipulation of the immune response depend on the set of therapeutic agents that fulfill the integration of the immune system with other systems, particularly with the Nervous System (NS).

In this article, a survey is done on some of the main information generated in the researches on neuroimmunomodulation, as well as a brief discussion regarding the physiologic implications that result from the conservation of receptors and connectors between distinct cellular types.

History of the mind- immune system link

The first empirical evidences about the existence of interactions between the NS and the IS date back to 200 C.E. and come from observations, made by the Greek doctor Galeno, that melancholic women were more susceptible to the development of breast cancer.

Long after, other studies revealed that newly widowed women with a criterion to depressive syndromes had a reduction in the functional capacity of the lymphocytes; and researches done with experimental animals, under social stress, unveiled some of the impacts which psychic disturbance may cause on cells and organs of the immune system [7-8].

Currently, the available data on the "neuroimmune axis" already enable some authors argue inflammation as a risk factor for the development of mood disorder [9-11].

Molecular bases of the communication between the NS and the IS

The identification of the receptors and the connector's common to leukocytes and to neurons [12-17] has clarified which are the molecules that allow the inter-systems communication. Indeed, it's already known that the bidirectional transmission of messages between the IS and the NS it's done by molecules classically known as neurotransmitters, neuropeptides, cytokines and chemokines. Therefore, leukocytes were discovered to be a source of corticotrophin releasing hormone [12], endorphins [13] and neuropeptides [14]. Besides, expressing cholinergic receptors, adrenergic and serotonergic [15-17]. Mutually, it's already known the fact that neurons synthesize several types of cytokines and chemokines, and express their respective receptors [18].

Leukocytes & Hypothalamus & HPA axis

One of the better known "immune-neuro-immune" signaling

circuits manifests itself, clinically, as fever. The rising of the body temperature it's provoked by the direct or indirect action of certain cytokines, such as TNF-α, IL1-β, IL-6 e IFN. These endogenous pyrogens induce to the synthesis of prostaglandin E2 that, on the other hand, act on the hypothalamic thermoregulatory centers causing effects that culminate in thermo genesis [19].

In another function involving the hypothalamus, on the hypothalamus-hypophysis-adrenal axis (HPA), which is responsible for the response to different internal and external stimuli, there is also regulation by cytokines. The activity of the HPA axis is measured by the hormones and controlled by negative feedback. The Corticotrophin Releasing Hormone (CRH)-secreted by the hypothalamus as a response to stress- stimulates the pituitary gland to release the adreno cortico tropic hormone (ACTH), which acts on cortex of the adrenal glands inducing them to secrete a powerful glucocorticoid immunosuppressive, the cortisone. The interleukin-1 (IL-1), for instance, can interfere on the HPA axis by the stimulus to the releasing of CRH by the hypothalamus or via direct stimulus on the adrenals.

Furthermore, as it was suggested by some authors, since the leukocytes also produce ACTH, CRH and endorphins, it's plausible that the operation of the HPA axis can also get under the influence of this hormonal source. As there is also the possibility of leukocytes constituting an alternative axis to the HPA axis. Nevertheless, it's not clear yet if the leukocyte originated hormones are able to have endocrine action, if its actions are strictly autocrine and paracrine or, still, if the high mobility of the leukocytes can compensate the quantitative limits on the production of hormones by these white cells [20].

Autonomous Nervous System & Leukocytes

The regulation of the leukocytes activity by cholinergic and adrenergic fibers it's a still partially comprehended function. In any way, there are several studies indicating the importance of this control via.

The autonomous nervous system seems to negatively regulate the inflammation. Both the sympathetic nervous system and the parasympathetic nervous system, after being stimulated by pro-inflammatory innate immune constituents, exert anti-inflammatory actions on the cells of the IS. The sympathetic nervous system can act in a more local way, through the intervention of lymphoid organs, or in a systemic manner by the stimulation of the adrenal medulla to release adrenaline in the blood. There are reports in the literature showing that this catecholamine inhibits the leukocyte synthesis of cytokines such as the IL-1, IL-6, IL-12 and TNF [21], at the same time that it stimulates the production of the anti-inflammatory cytokine IL-10 [22].

The parasympathetic nervous system, conversely, has also showed anti-inflammatory actions over the leukocytes. Tracey demonstrated that the secretion of TNF-α by macrophages can be inhibited by the acetylcholine, having already denominated this effect as the "cholinergic anti-inflammatory pathway"[23].

Peripheral Nervous System & Leukocytes

The majority of the substances released by the peripheral nervous system seems to have a pro-inflammatory effect on the cells of the IS. Moreover, the CRH-that in the HPA axis contributes to the stimulation of anti-inflammatory mediators-when released by nerve endings, shows pro-inflammatory effect on macrophages and lymphocytes [24].

Similarly, the P substance released by the peripheral nerves induces to the production of pro-inflammatory cytokines by macrophages and eosinophils [25-26]. On the other hand, the vasoactive intestinal peptide (VIP) appears to be an exception. The VIP causes inhibition of the synthesis of the pro-inflammatory cytokines by mononuclear cells [27], reduces the expression of receptors similar to Toll (TLRs) over epithelial cells [28], besides stimulating the production of the anti-inflammatory cytokine IL-10 by macrophages [29].

Serotonin & Leukocytes

The serotonin (5HT) is one monoamine which can have different effects depending on its concentration and depending on the receptor that it is linked to. In the brain, the serotonin acts as a neurotransmitter capable of interfering in behavioral and cognitive functions [30].

The cells of the immune system possess all the components of the serotonergic system, having the necessary machinery to not only be sensitive to serotonin, but also to produce and catabolize this amine [31]. Despite of attending to "molecular prerequisites", the action of the serotonin on the modulation of the immune response is still underexplored. What it's known is that it can induce to changes in the profile of the leukocyte secreted cytokines [31]. Besides, some studies suggest the existence of a complex cross-communication mechanism between the signaling triggered by 5-HT receptors and the signaling induced by molecular pattern recognition receptors [32]. In this sense, it was demonstrated that the signaling via Toll type receptors can regulate the action of the serotonin on the smooth muscle by modifying the expression of receptors to the substance [33]. Conversely, in another study, it was verified that the treatment of murine with Paliperidone, an antagonist drug of the 5-HT2 receptor, it's capable of preventing the activation path of TLR-4 [34].

Conclusion

The results of studies on the interactions and existing molecular coincidences between IS and the NS denounce the size of our negligence when analyzing these systems as independent entities. At the same time, they show that there is an emergent investigation field that promises the development of new therapeutic modalities.

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