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FROM THE BLOOD- BRAIN BARRIER TO BEHAVIOR

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SUMMARY

Research in the field of neuropsychimmunology has enabled the researchers to show that cytokines target the brain to organize a "sickness response," which is fever, activation of hypothalamus-pituitary – adrenal axis and behavioural alterations that develop in sick individuals. Perypheral cytokines do not act directly on the brain; they trigger the production of cytokines in the brain parenchima itself, with a possible relay at the interface between internal milieeu and the brain, which are endothelial cells and circumventricular organs.

The affective and behavioural changes that develop during influenza are the product of a transient brain inflammatory response induced by the same proinflammatory cytokines that are produced in the bronchial tree. The cytokine pattern is distal to this phenomenon while the receptor molecules that decipher the molecular nature of microbial pathogens (pathogens associated molecular patterns PAMPs) at the membrane level of cells is a proximal factor. PAMPs are recognized by specialized receptors on innate immune cells that belong to the TOLL/IL-1 like receptor family. These receptors are phylogenetically old. the brain uses these receptors to defend itself against something different (several forms of brain injury that have nothing to do with infectious pathogens) from infectious pathogens. Assuming that the factors that activate these receptors involve endogenous substances derived by cell death (cell death by-products) is the concept at the origin of the danger theory.

Evidence in favor of a cytokines role in mediating mood disorders and cognitive disturbances in patients receiving cytokine immunotherapy is fast growing (capuron e dantzer 2003). Several items of data support the role for cytokines in mediating a variety of non-specific symptoms that develop in patients suffering from diseases with an inflammatory component (cad, immunorheumatolic, neuropathologies). These non-specific neurovegetative and psychiatric symptoms represent just another facet of the inflammatory process and they are not necessarily derived from a direct cause-effect chain.

Key words: neuropsychimmunology, perypheral cytokines, behavioural changes

NEUROPSYCHOIMMUNOLOGY

Accumulating evidences have shown that the Central Nervous System (CNS) and the Immune System (IS) mutually interact within a triangular network, with the aim to maintain the whole- body homeostasis; this network also includes the Endocrine System, and represents the basis of neuropsychimmunology. On the one hand, CNS is not considered immunologically isolated anymore and is able to activate an innate immune response to infectious agents; on the other hand, immune cells express several receptors for neuromodulators and induce an immunological sensitivity at the site of CNS, by secreting specific cytokines which activate a brain immune response. In the same vein, both immune cells and CNS produce hormones with immunomodulatory properties that can reduce or inhibit the inflammatory response [1].

For instance, lymphocytes secrete growth hormone (GH), macrophages produce epinephrine and norepinephrine, monocytes produce a brain-derived neurotrophic factor (BDNF), whose expression is upregulated by TNF α and IL-6 [2]. Moreover, hormones with immunomodulatory properties include IGF-1, which inhibits TNF α , or Vitamin D, which influences the proliferation of antigen presenting cells (APCs), monocytes, macrophages and B and T lymphocytes, and stimulates self- tolerance by acting on TGF β [3].

The discovery that blood brain barrier (BBB) grants passage to certain molecules due to its configuration in some areas of the brain, gave the hint for further research in this field; other areas, presenting different configuration of BBB, are better shielded [4].

The advancing knowledge in neuropsychimmunology enabled the researchers to show that peripheral cytokines do not act directly on the brain; they trigger the production of cytokines in the brain parenchyma itself, with a possible relay at the interface between internal milieu and the brain, which is represented by endothelial cells and circumventricular organs (CVOs) [5]. Up to the 1990s, the deceptive conception of BBB led to a large scale misunderstanding about the immune profile of CNS and, consequently, about the effects of cytokines on the brain.

BLOOD BRAIN BARRIER

The cellular interface between blood and the central nervous system (CNS) is represented by the vascular endothelium of the brain, which is characterized by tight junctions between endothelial cells, forming an uninterrupted layer and representing the main cellular component of the so- called blood- brain barrier (BBB). This is known as a strictly selective feature of the vascular wall at this site, so that it is either permeable or not to a range of small molecules and cells. The first description of this feature was made, by Ehrlich, in 1900. He observed that some of the dyes, following injections into veins or arteries, strongly stained various organs but stained the brain weakly or not at all. Then, Lewandowski summarized the experiments of Ehrlich concluding that the brain capillary “must hold back certain molecules” [6-7]. The subsequent metaphor of a barrier gained

wide acceptance, even being deceptive, especially extending its meaning within the context of leucocyte recruitment at this site. As explained below, it consequently led to such a misconception as to the immunological profile of the CNS [8]. Actually, BBB limits the entry of immune cells and mediators into the CNS; however, the knowledge about cell and molecule recruitment and trafficking through BBB has significantly changed over the last ten years.

Recognizing the elements composing the whole BBB structure is fundamental to better understand the mechanisms involved in molecule transport and cellular element entry. Three main compartments can be distinguished at this site: the vascular wall, the perivascular space and the juxtavascular neuropil, which is the brain parenchyma. Different cell types are included in each of these compartments: the endothelium, along with basal lamina and astrocyte endfeet forms the horizontal element neurovascular unit (NVU) [9], being the vertical one represented by pericytes and neurons with their axons. NVU is more a conceptual construct than a physical barrier, on the side. At least one fundamental difference should be made between the capillary and post-capillary compartments of BBB. Indeed, it is remarkable to note that only solute passage is regulated at the capillary site, while cellular entry occurs at the post-capillary venules [10]. Among the various celltypes included in the whole structure, it is of some importance to note the role played by pericytes and microglia. Actually, pericytes play several roles, including blood vessel stabilization and blood flow regulation [11]; further, they have a multipotent differentiation potential, so that they have been considered a target in therapeutic approaches due to their involvement in tissue repair processes [12]. Also the “resting” (uninjured) microglia play a role that has been greatly underrated. These specialized cells act primarily as the first-line defense system in the normal brain and not after injury. Indeed, this cell type has been shown to have a morphological feature, that is, fine moving branches, providing a continuous surveillance of the cellular environment. It has been demonstrated that a rapid chemotactic response to tissue injury depends on these highly mobile branches.¹³

IMMUNOLOGICAL PRIVILEGE OF CNS

The concept of unique immunological characteristics in CNS, referred to as immune privilege, is a construct whose basis lies in the lack of lymphomonocyte trafficking in the brain [14]. As written above, an imprecise and rigid description of BBB permeability led to a serious misunderstanding of the immune system-brain crosstalk and the CNS immunological profile. For instance, cytokine and immune lineage cells may circulate in the CNS at sites where the BBB is absent, by a carrier-mediated transport mechanism or by generating central mediators altering the permeability of the BBB [9]. Several pieces of evidence show leucocyte trafficking occurs in the brain, and afferent and efferent roots in drainage have been described [15]. Under homeostatic conditions in non-disease states, leukocyte trafficking is low, but it increases considerably in inflammation and dis-

ease. Since immunological privilege can influence such a CNS neurological disease, including autoimmune and neuroinflammatory ones, redefining the concept of BBB and immunological privilege of CNS might be crucial to identify new therapeutic strategies. Advancing the knowledge in this field is essential to better define the gold standard in the therapeutic approach of autoimmune diseases, such as Multiple Sclerosis, cerebrovascular disease and neurodegenerative diseases [9].

CYTOKINES AND BEHAVIOR

Immune cytokines can influence complex mechanisms involving neuronal circuits such as thermoregulation, food intake and behavior [1]. The first discovery that cytokines target the brain to organize the sickness response, gave the impetus for further investigations in this field. The sickness response consists in behavioral alterations that develop in sick individuals, as a part of the whole complex of symptoms. Influenza typically represents an example of how the sick individual undergoes behavioral changes, due to the influenza itself. Actually, the affective and behavioral changes that develop during influenza are the product of a transient brain inflammatory response induced by the same proinflammatory cytokines that are produced in the bronchial tree [16]. The mainstream hypothesis about this phenomenon is that the receptor molecules at the membrane level of cells are the cause at the origin of sickness response, rather than the cytokines. These receptor molecules are able to decipher the molecular nature of microbial pathogens, named PAMPs (pathogens associated molecular patterns); PAMPs are recognized by specialized receptors on innate immune cells, that belong to the TOLL/IL-1 like receptor family. These receptors, which are phylogenetically old, are deemed to interact in the brain with endogenous substances derived by cell death, in aim to defend the brain itself, against several forms of brain injury not necessarily related to infectious pathogens. Indeed, according to the danger theory, recently revised as the damage theory [17], endogenous products secreted after cellular stress, cellular damage or inappropriate death interact with receptors for PAMPs, triggering non-specific neurovegetative and psychiatric symptoms. This phenomenon represents just another facet of the inflammatory process and is not derived from a direct cause-effect chain.

Apart from influenza, other pathologies with a basis of inflammation can be accompanied by the same behavioral effects. Evidence in favor of the role of cytokines in mediating mood disorders and cognitive disturbances in patients receiving cytokine immunotherapy is growing fast [18]. Several items of data support the relation between cytokine and non-specific symptoms that develop in patients suffering from diseases with an inflammatory component [19] (coronary artery disease, rheumatologic pathologies, neuropathologies). Moreover, manifold evidence indicates that patients receiving recombinant cytokines present an increased risk for developing depressive disorders; however, the activation of innate immune system in depressed patients still remains controversial [20].

A crucial question, still unanswered, is: could it be of some usefulness to treat inflammatory pathologies by using molecules that target cytokine production and action in the CNS?

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