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COMMENTARY

The immune system as a sensorial system that can modulate brain functions and reset homeostasis

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Evidence indicates that activated immune cells release products, typically cytokines, that can convey information to the brain about the type of ongoing peripheral immune responses. This evidence led colleagues and me to categorize the immune system as another sensorial system that, upon receiving this information, can emit neuroendocrine signals with immunoregulatory functions that can also reset homeostatic mechanisms. Here, I discuss evidence and clues indicating (1) possible mechanisms by which cytokines, such as those of the interleukin 1 (IL-1) family, can reset energy homeostasis to balance the high fuel requirement of the immune system and the brain; and (2) the possibility that the tripartite synapse, which includes astrocytes as a third component, processes and integrates immune signals at brain levels with other sensorial signals that the central nervous system permanently receives.

Keywords: cytokines; neuroendocrine system; immunoregulation; resetting homeostasis; tripartite synapse

Introduction

Following a long history based on pragmatic interventions and conceptions, the science of immunology emerged because of the sagacity of the pioneers such as Louis Pasteur, Robert Koch, Elie Metchnikoff, Emil von Bohering, and Paul Ehrlich. With almost no resources but with an acute sense of observation, they proved and established the existence of the immune system as part of adaptive mechanisms. Following their initial discoveries, the focus was to understand the molecular, genetic, and cellular bases of immune responses since it was necessary first to know the immune system from within. This need would explain why at this early time it was almost inconceivable (somehow even heretical) to propose that, besides its high degree of autonomy, the immune system is subjected to neuroendocrine regulation and brain control, as are all physiological systems. However, even during this period, some evidence of this "control from without" was already available. It was already known that most types of immune cells express receptors for some hormones, neurotransmitters, and neuropeptides, and that most of these mediators can influence immunity. For example, glucocorticoids were already broadly used in medical practice due to their anti-inflammatory and immunosuppressive effect. Even before the T cell receptor was identified, there was evidence that the immune response itself can bring about some immunoregulatory neuroendocrine responses. It was also essential to prove this last point because regulatory mechanisms are based on a flow of information between the variable under regulation (in this case, immune responses) and regulatory agents under the brain's control. Today, many immune cell products, particularly cytokines, have been identified as relevant messengers between immune and brain integrated systems. Two early reviews that cover initial contributions[1,2] and another one published very recently that additionally documents more recent progress in the field[3] are used as examples. These articles provide ample historical perspective on the progress in this field.

The different immune–neuroendocrine agents involved in this communication led colleagues and me to conceive that, rather than being based

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on compartmentalized systems, such exchange of information constitutes a network of interactions between the systems involved. Coauthors and I previously defined the immune system as a sensorial system due to its capacity to perceive alterations in nonself or modified self-components and danger signals, to react to these alterations with different types of immune responses, and to inform the brain about such responses via afferent neural and humoral signals.[4]

I shall briefly mention below how the immune system communicates with the brain and elicits neuroendocrine responses, and then focus on two, in my view crucial, issues that are related to each other: (1) how energy is balanced and distributed to support highly demanding systems, such as the immune and nervous systems, and (2) how signals derived from the immune system are integrated and simultaneously processed with other sensorial signals that the central nervous system (CNS) permanently receives. I shall discuss different aspects of these issues (that were formulated previously[5]) and provide some clues that may serve to address them.

The sensing capacity of the immune system

The phylogenetically ancient mechanisms of natural immunity in mammals are based on cells that express germline-encoded pattern recognition receptors (PRRs) (see Refs. 6 and 7). Some of them, such as Toll-like receptors (TLR), detect certain components expressed by pathogens (i.e., pathogen-associated molecular patterns). Other PPRs do not necessarily sense pathogens but other products that are threatening to self; receptors such as these include certain cytosolic PRRs such as retinoic acid-inducible gene-I (RIG-I)-like receptors and nucleotide-binding oligomerization domain (NOD)-like receptors. Natural immune reactivity was followed in evolution by the more sophisticated adaptive immune system based on a huge repertoire of receptors that allows immune recognition and responses that are not inherited but mostly the result of random gene rearrangements. This was a clever way to increase the probability of successfully coping with newly emerging and dangerous infectious agents that are in continuous variation. Thus, both natural and specific immune recognition in an interlinked fashion allow the immune system to sense modifications of self-components independent of those caused by the intrusion of external challenges.

The immune system as another neurosensorial system

The capacity of immune cells to sense very diverse stimuli explains the large degree of autonomy that the immune system has to process information received and to generate efferent responses to different types of insults. However, from a physiological point of view, it seems essential that the information about ongoing processes devoted to eliminate factors that threaten the stability of the organism are detected by the brain so that it can coordinate necessary homeostatic adjustments. This is particularly relevant for the immune system due to its adaptive function in changeable environments, the high energetic and metabolic cost of immunity, and the fact that neuroendocrine agents produced under brain control can affect the activity of immune cells. Following this view, colleagues and I have studied the possibility that immune responses generated in the periphery bring about changes in the neuronal activity of the brain. To explore this possibility, innocuous antigens, that is, antigens that do not cause any disease were used; the results summarized in Ref. 8 showed that such changes occur and affect different brain areas depending on the type of the elicited immune response.

The evidence that immune responses elicited at peripheral levels can send messages to the brain brought us to propose long ago[4,9] that the immune system is another sensorial system capable of receiving, processing, and sending information to the brain about ongoing immune responses to external and internal stimuli. However, a difference should be highlighted. The information sent to the brain by classical senses can in most cases become cognitive when several filtering mechanisms and thresholds are surpassed. In the case of the immune system, the information that it sends to the brain is noncognitive *per se* but is anyhow perceived by the brain via the neuroendocrine responses elicited (see below). It is, however, difficult to conceive that the immune system could send to the brain specific information about the myriad of immunogenic stimuli received but not about the type of responses that are put in motion to neutralize them. Indeed, different types of stimuli elicit

different types of innate and adaptive immune responses, which can reflect the type of the ligands that immune cell receptors recognize. Immune information needs to be transduced into appropriate signals before it can be sent to defined brain centers via humoral or neural routes. The abundant literature showing that immune cell products such as interleukins, interferons, and chemokines can affect the brain and associated neuroendocrine mechanisms will not be reviewed here (see Refs. 8, 10–13).

The immune system needs to process peripheral information before sending it to the brain. This is similar to other sensorial systems, for example, the visual and auditory systems. The brain does not "see" light or "hear" sounds unless the information is transformed into electrochemical signals that can be centrally detected. Furthermore, there are physiological responses originating in the eye and the internal ear for refining and focusing the orientation of the stimuli that is received, such as ocular and acoustic reflexes. The fact that immune cells are not concentrated in one organ is also not an exception, considering the diffuse distribution of tactile and pain sensing receptors. Furthermore, information derived from immune cells present in mucosal and epithelial tissues and other innervated tissue may be "fused" with the information supplied by stimulation of tactile receptors, pain afferent nerve fibers, and other interoceptors, providing an anatomical representation of this combination of signals in the brain.

In summary, in my view there is enough evidence to consider the immune system as another sensorial system since it detects and reacts to components of the external and internal world and informs the brain about the type of the ongoing immune process.

Potential brain responses to immune signals

Immune information received by the brain, as other type of information, may or may not generate a response, and it is expected that immune responses would elicit neuroendocrine responses only when a given intensity is reached.[4,5]

It is known since a long time ago that there are neuroendocrine changes during infections and other diseases that involve the participation of the immune system. The initial view was that these alterations were the consequence of the stress of being and feeling sick and/or of the disease itself. However, this conclusion has been revised, since there is at present clear evidence that products released by immune cells mediate most of the effects detected. Probably the first indication in this context was fever during infections, which is mediated by endogenous pyrogens (see Ref. 14).

It was later shown that immune mediators released during infections are responsible for neuroendocrine responses that can have immunoregulatory consequences and for the course of a disease independent of pyrogenic actions. This is the case of the stimulation of the hypothalamus–pituitary–adrenal (HPA) axis.[15,16] I have shown that the stimulation of this axis following the inoculation of New Castle Disease virus into mice is mediated by endogenous IL-1.[16,17] This effect is not associated with disease since this virus is innocuous for mice and humans, although it is lethal for chickens. A comparable immune-mediated activation of the HPA axis was later detected during several other viral infections, including murine cytomegalovirus, lymphocytic choriomeningitis virus, influenza, herpes simplex virus type 1, and human immunodeficiency virus (see Ref. 18). It was also shown that the response of the HPA axis to low amounts of lipopolysaccharide (LPS) from Gram-negative bacteria is mediated by IL-1,[19] and that when this endotoxin is given at subpyrogenic doses the response is mediated by activated macrophages, an effect that today can be interpreted as dependent on TLR4 activation.[20]

To study the possibility that the adaptive branch of the immune system can elicit neuroendocrine responses, it was also necessary to deal with the confounding factor that, under natural conditions, immune responses are frequently associated with tissue damage and altered organ functions, and that the illness *per se* can elicit neuroendocrine responses linked to the stress of being sick. The approach to circumvent this problem was to immunize animals with innocuous antigens that can elicit a strong adaptive immune response without causing any disease. One of the antigens used was sheep red blood cells, a model of immunization that permits to have as a control the animals that receive the same number of syngeneic red blood cells. Following this approach, an increase in glucocorticoid blood levels and a decrease in thyroid hormones[21]

starting before the peak of the immune response was detected. At brain levels, an increase in the rate of firing of neurons, predominantly in the ventromedial hypothalamic nucleus,[22] and changes in the concentration of hypothalamic noradrenergic neurotransmitters were observed during the immune response to this and other innocuous antigens.[4] I have also shown that products released during an *in vitro*–induced mixed human lymphocyte immune response can mediate the activation of this axis.[23] Later, I showed that the immune response elicited by inoculation of allogeneic cells evokes changes in neuronal activity in brain regions different from those elicited by other types of T cell–dependent immune responses.[24]

The type of cells and mediators involved in immune responses to different antigenic stimuli, as well as their kinetics, makes it difficult to make a strict evaluation of the immunoregulatory relevance of the neuroendocrine responses that occur at different times. However, there are some models of immune response in which neuroendocrine responses have been studied at critical steps, such as induction, expansion, generation of effector molecules and cells, and extinction. I have recently reviewed these aspects, particularly those referring to the immunoregulatory relevance of brain responses to the HPA axis and the sympathetic nervous system during natural and adaptive immune responses in health and disease.[5]

The immune system can mediate an adaptive resetting of homeostasis

The question that arises is whether, and if so how, the brain uses information derived from the immune system to adjust basic mechanisms that control the distribution of energy between different tissues and processes, such as thermal and cardiovascular/respiratory regulation. I believe that such adjustments are a necessary function of the immune system since it is not only directed at fighting infective and dangerous agents but also at reducing the cost of these fights in order to reestablish health. We are currently far from understanding how the immune system performs this function. However, a minimal but essential requirement is already fulfilled: some immune products have the capacity to affect homeostatic mechanisms at the brain level. My intention is, therefore, to provide some clues that may contribute to answer the question of whether the immune system has the potential capacity to mediate a resetting of homeostasis as an adaptive process.

Although I am aware that other mediators may participate, I shall mainly discuss the capacity of IL-1 to reset glucose homeostasis, an important fact when it is considered that provision of glucose-derived energy is essential for the maintenance of immune reactivity and brain functions. Another reason why I have chosen to concentrate in IL-1 is its capacity to activate a cytokine network that includes anti- and proinflammatory products, and to act as an adjuvant and a costimulatory agent that links innate and adaptive immunity. These multiple effects of IL-1, together with the evidence that the activity-dependent production of IL-1 in the brain supports synaptic plasticity and several brain processes (see below), and with its capacity to mediate immunoregulatory neuroendocrine and metabolic processes, place this cytokine at the center of basic immunological and physiological processes. However, as expected from a mediator, which has multiple immune and brain functions, deregulation of IL-1 production at peripheral and brain levels can also cause pathology. Also, the ectopic production of IL-1 in tissues, such as adipose cells, leads to inflammasome activation and to the development of the metabolic syndrome.[25]

Immune responses are frequently prolonged and require high energetic support for their maintenance.[26] It is therefore conceivable that many homeostatic systems need to be adjusted during the course of immune responses. Under these circumstances, physiological systems need to be remodeled not only to provide energy to support inflammatory cell turnover and lymphocyte clonal expansion, but also for the mobilization of immune cells so that they can reach the tissues and organs where, for example, they can eliminate infectious agents. As a whole, it has been estimated that activated immune cells use more than 20% of the glucose-derived energy available in the body (for more information, see Ref. 27).

The concept of homeostasis as defined by Claude Bernard and Walter Cannon derived largely from studies on glucoregulation, as evidenced by the stability of glycemia, which quickly returns to a defined basal level after eating or fasting. It was accepted long ago that while many hormones can induce hyperglycemia, insulin was considered to have the

monopoly on being the agent that reduces glycemia. By decreasing glucose blood levels, insulin elicits brain integrated counter-regulatory responses mediated by hormones and neurotransmitters that tend to return glycemia to preset levels. Without such responses, life threatening hypoglycemic shock would follow. However, this seems not to be the case for IL-1, a hypoglycemic mediator that is produced following immune stimulation and during increased synaptic activity. IL-1 is the only cytokine that at endogenous levels can induce an acute reduction in blood glucose under physiological conditions and in diabetic animals.[27] Acting at brain levels, fibroblast growth factor 1 (FGF1) also reduces glycemia in diabetic mice,[28] but at doses 1000-fold higher than IL-1. It is intriguing that the primary receptor-binding site of the FGF family members is structurally related to the IL-1β receptor-binding site, opening the possibility that the effects reported could be mediated by IL-1.

Low doses of IL-1 induce a profound reduction of glucose blood levels in mice that, as compared with the effect of an acute administration of natural insulin, is long lasting (more than 12 hours). The effect of IL-1 is insulin-independent and, importantly, is not paralleled by overt neurological symptoms. This is a unique property of an immune-derived product that is endogenously released following the activation of, for example, TLR4. Colleagues and I have shown that IL-1 changes the set point of glucoregulation at a lower level, as shown during glucose tolerance studies.[29] Glucose administration either simultaneously or 4 h after IL-1 results in less hyperglycemia, and the hypoglycemia that follows is maintained for many hours. In fact, after a glucose tolerance test, glycemia is clearly reduced in IL-1–treated mice and maintained for a long time at values around 50% of that in control mice. This effect is inhibited by administration of the natural IL-1 receptor antagonist (IL-1RA). A similar resetting of glucose homeostasis is observed during a glucose tolerance test when IL-1 is injected into the lateral ventricle of the brain at doses that induce only marginal hypoglycemia when given peripherally.[29] IL-1RA, acting at central levels, inhibits hypoglycemia induced by peripheral administration of IL-1.[30] Furthermore, the decrease in glucose blood levels induced by IL-1 does not go beyond a limit even when the minimal dose that induces hypoglycemia is increased more than 20 times, and no hypoglycemic shock is observed. All these effects of IL-1 are clearly different from those of insulin. It is possible that the capacity of IL-1 to reset glucose homeostasis is directed at redistributing resources needed to supply fuel to highly demanding immune cells. In mice, IL-1–induced hypoglycemia is neither paralleled by a prolonged counter-regulation mediated by hormones, such as glucocorticoids, glucagon, and catecholamines, nor by a compensatory increase in food intake. In other species, such as the rat, IL-1 induces only a 10–15% decrease in the concentration of blood glucose, but this is paralleled by a decrease in insulin levels and somewhat compensated by adrenal hormones, since administration of the cytokine to adrenalectomized rats leads to profound hypoglycemia (for more information, see Ref. 27). Also, insulin-independent hypoglycemia caused by products from immune cells is observed in rats during sepsis induced by cecal ligation. At a late phase of sepsis there is a tendency for hyperglycemia due to IL-1– and tumor necrosis factor (TNF)-α–mediated insulin resistance; in contrast, there is increased glucose uptake in macrophage-rich tissues that are insensitive to this hormone[31] (for more information, see Ref. 27). In humans, LPS administration at low doses induces hypoglycemia, an effect that is paralleled by a reduction in insulin levels.[32] It was also observed in humans that LPS-induced hypoglycemia causes an increase in counter-regulatory hormones that only moderates its effects, since the reduction in glucose levels is accentuated after blockade of glucocorticoid receptors. Furthermore, hypoglycemia induced in humans by LPS is dissociable from proinflammatory effects of the endotoxin, since it is even more profound following the administration of inflammatory blockers.[32]

There is evidence of other resetting effects of IL-1, for example, of the baroreceptor reflex, which controls cardiovascular functions,[33] and during fever, which is defined as a change in the set point of thermoregulation.[14] IL-1, by mediating leptin actions, can also affect the set point for the regulation of food intake.[34]

Thus, the conclusion is that immune responses can contribute to reset homeostasis by releasing cytokines and other products that, besides their intrinsic immune functions, can also induce immunoregulatory neuroendocrine responses.

The role of the tripartite synapse in the processing and integration of immune information by the brain

The fact that the immune system can send sensorial information to the brain opens questions such as how this information is processed at central levels and is integrated with other sensorial and intrinsic inputs to the CNS, and which brain areas are involved in such integration. In the following, some clues that may serve as an attempt at answering these questions are discussed.

Humoral and neural pathways have been proposed as a way to convey immune information to the brain.[35] However, the production of immune mediators, such as cytokines, in the brain could be part of this communication system. Cytokine production in the brain is triggered following peripheral immune stimulation. For example, peripheral administration of LPS induces the production of several cytokines in the CNS.[36] Also, intraperitoneal administration of IL-1β induces the expression of its own gene in the brain,[29] and cytokines such as IL-1 and IL-6 are produced in the hypothalamus during peripheral specific immune responses.[37] On the other hand, increased expression of cytokines such as IL-1β, IL-6, IL-18, and IL-1RA is also observed during increased neuronal activity, as during long-term potentiation (LTP) *in vivo* and in hippocampal slices.[36,38]

The cytokines induced in this way are relevant for synaptic plasticity, as IL-1 is necessary to support LTP maintenance,[39,40] while IL-6 affects this process in an opposite way.[41] In line with these results are the findings that IL-1 also supports, while IL-6 inhibits, learning and memory consolidation.[36,38,41–44]

Furthermore, colleagues and I have recently shown that the expression of these cytokines is increased after learning a hippocampal-dependent task,[38] an effect that is dissociable from the stress of the learning paradigm. These results indicate that the production of immunoregulatory cytokines in the brain is a physiological process crucial for brain functions based on synaptic plasticity, functions such as learning and memory.

It has also been reported that IL-4 and IFN-γ produced by T cells located in the meninges are necessary for the maturation of brain functions, and these cytokines have been linked to learning.[45] However, there is no evidence for direct connections and feedback interactions between neural cells involved in learning acquisition and meningeal T cells. Also, the effect could be the result of immune cell redistribution caused, for example, by the stress of learning a task. In any case, even if there were not via such direct effects, IL-4 produced by T cells and released in the meningeal space or in the periphery could reach the brain parenchyma via the cerebrospinal fluid. In this way, these mediators can influence the production or action of cytokines such as IL-1, IL-1RA, IL-6, and IL-18, which, as mentioned above, are produced by neural cells during learning a task and during other processes linked to synaptic plasticity such as LTP.

In my view, the physiological effects of brain-borne cytokines produced following peripheral immune or central neuronal signals on brain functions should be considered in the context of the present widely accepted concept of the tripartite synapse, which includes astrocytes[46] as the third party.

For a long time, it has been considered that astrocytes, a large (probably the largest) neural cell type in the brain, exert only a supportive role for neuronal activity. Today, it is known that due to extended distribution and close contact with neurons, these cells are the main components of the neuronal environment and the microarchitecture of the brain parenchyma. In this way, astrocytes can store and provide energetic substrate for neural cell development, synaptogenesis, and synaptic activity. Importantly, due to their immune functions, astrocytes are also part of the intrinsic defense system of the brain.[47,48] Thus, because of their dual neural and immune functions, astrocytes can be categorized as neuroimmune cells. These functions include the production of a variety of transmitters with immune and neural effects, such as IL-1, IL-6, and TNF-α.[30,49,50]

I have previously proposed that the tripartite synapse plays a central role in processing immune signals in the brain and in their integration with neurosensorial signals.[36] More recent data support this proposal. Coauthors and I have reported that the stimulation of glucose transport by IL-1 produced either by astrocytes or neurons can be transferred from one cell type to another,[30] suggesting that the main role of this cytokine in the tripartite synapse is the mediation of a reciprocal control of energy supply between neural cells.

The final effect of cytokines produced during activation of the tripartite synapse on brain mechanisms and on neuroendocrine immunoregulation will depend on how, when, and where in the brain such stimulation occurs, and on the type of synapsis affected. As discussed, when the increased production of IL-1 and other cytokines would be initially triggered by psychosensorial signals, their effects on tripartite synapses located in brain areas such as the hippocampus and the frontal cortex would be to modulate physiological brain functions such as learning and memory. When their production in the brain is immunologically triggered, their effect would predominate in brain areas, such as the hypothalamus and the brain stem, where these mediators can reset homeostasis and exert immunoregulatory actions by eliciting neuroendocrine responses.

Overview

Here, I have provided some examples showing that the response of the brain to sensorial information from the immune system is relevant for immunoregulation in health and disease. I have also formulated two questions about how the immune system can adjust homeostasis when it is activated beyond a certain threshold, and how the brain processes and integrates immune information. These questions are complex, and we have at present only some clues that may serve to provide successive approximations to their answer.

Homeostasis as a concept remains the only way to conceive of how high evolved organisms can survive in free life. However, if homeostasis is considered as a way to maintain essential variables constant under all circumstances, its adaptive role is questionable. Thus, the concept of allostasis emerged to denominate a process addressed to achieve stability through physiological or behavioral changes. This concept indicates the need of homeostatic adjustments in a highly variable environment.[51] However, when allostatic adjustments are maintained for a long period of time, it has a functional cost (allostatic load) and can favor the expression of chronic diseases.[52]

An adaptive allostatic change can be transient because of a rapid need to cope with a sudden event, but if this change is prolonged, a conflict with the preset regulatory homeostatic mechanism emerges. This is the case when allostasis is linked to the immune system that tends to maintain the constancy of molecular and cellular constituents of the body. Allostatic adjustments during prolonged immune responses would be very costly if every time these responses are elicited it is necessary to violate homeostatic rules and pre-established setups that tend to maintain the *status quo*. This cost could be minimized to some extent if the set point for the regulation of the variables that mediate an allostatic change can be adjusted, thus avoiding counter-regulation.

The example discussed above about the capacity of endogenous IL-1 to reset glucose homeostasis illustrates a mechanism that does not have the cost of glucose counter-regulation. However, immune-mediated resetting of homeostasis cannot persist for a long time because it can imbalance other physiological mechanisms. It has to be considered that the immune system operates at the interface between health and disease, and that the immune response can be protective and adaptive, in particular during acute or short-lasting pathologies. If the immune system is hyperactive over a long time, because it cannot cope, for example, with an infective agent, it can trigger metabolic disruptions as seen during sepsis.[53] These neuroendocrine-mediated disruptions constitute the most common pathway leading to death during several infections and are therefore nonadaptive. Indeed, sepsis is presently defined as "a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs."[54] Besides autoimmune diseases, deleterious immune-mediated effects can now be extended to infections that do not lead to sepsis and to noninfectious pathologies with inflammatory components.[55,56]

In my view, resetting of homeostasis by the immune system is intimately linked to the processing of immune information by the brain. Indeed, the brain can orchestrate the adequate resetting of neuroendocrine mechanisms that assure the distribution of energy during immune processes with restricted effects on brain functions based only on this information. Even the mentioned effects of brain-borne cytokines on processes underlying synaptic plasticity, such as LTP, can be viewed as an adaptive resetting of the synaptic strength. The proposed link between resetting homeostasis and processing immune information at brain levels is schematically depicted in Figure 1.

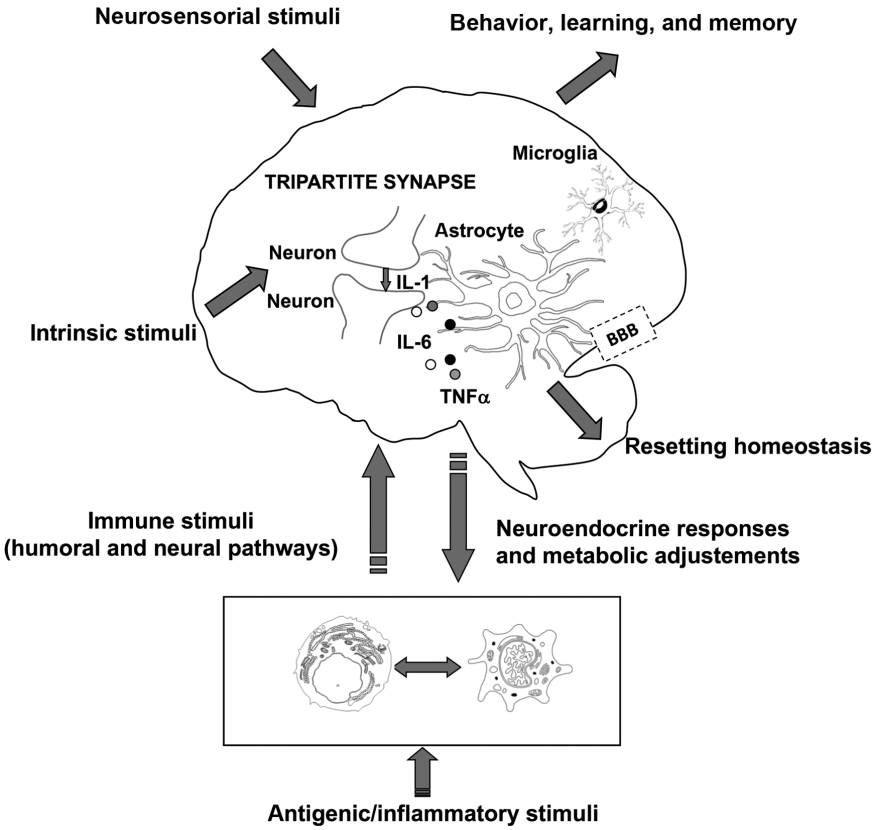

Figure 1. The role of the tripartite synapse in the integration of immune and neuro/sensorial signals. It is proposed that the tripartite synapse provides the molecular and cellular bases for the integration of these multiple signals, since, as its third party, it includes astrocytes, a neuroimmune cell that also forms part of the blood–brain barrier (BBB). The outcome of this integration will depend on the relative impact of the different signals and the areas where they are received by tripartite synapses. It is likely that, during the immune response, this integration would predominantly occur in the hypothalamus, which controls the emission of immunoregulatory neuroendocrine signals, and where the resetting of homeostatic mechanisms necessary to support an increased immune cell activity can be mediated. On the other hand, when neurosensorial and brain intrinsic signals predominate, it would be expected that the activity of tripartite synapses in the hippocampus, for example, would modulate processes linked to synaptic plasticity, such as LTP, learning, and memory. The production of IL-1 and IL-6 by neural cells is triggered during these processes, reaching levels that can, respectively, support or inhibit their consolidation.

As clues for understanding how immune information is processed at central levels, I have also discussed the evidence that cytokines can be induced in the brain under conditions of increased immune and neural activity and then affect brain functions. This admittedly rudimentary knowledge is certainly not enough to allow definitive conclusions regarding how immune and neural signals are integrated during diverse life events. Indeed, the outcome of multiple possible combinations of immune and neural stimuli, which may involve different types of neural cells and brain areas, has to be analyzed during each particular condition. However, even with our present limited knowledge, I would like to propose that adequate processing of immune and neurosensorial information occurs at the level of the tripartite synapse that is ubiquitously distributed in the CNS. This actual view of synaptic transmission provides the molecular and cellular bases for immune–brain interactions. In my view, astrocytes, as the third component of this synaptic complex, interacting with neurons and eventually also with microglia cells, would serve as the sensors of immune information. However, it should also be considered that deregulation of the activity of the tripartite synapse—because of neuroinflammatory processes, leading, for example, to altered cytokine production—could be maladaptive and contribute to brain and systemic pathology.

Competing interests

The author declares no competing interests.

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