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ORIGINAL PAPER

Central and Peripheral Cytokines Mediate Immune-Brain Connectivity

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Abstract The immune system is a homeostatic system that contributes to maintain the constancy of the molecular and cellular components of the organism. Immune cells can detect the intrusion of foreign antigens or alteration of self-components and send information to the central nervous system (CNS) about this kind of perturbations, acting as a receptor sensorial organ. The brain can respond to such signals by emitting neuro/endocrine signals capable of affecting immune reactivity. Thus, the immune system, as other physiologic systems, is under brain control. Under disease conditions, when priorities for survival change, the immune system can, within defined limits, reset brain-integrated neuro-endocrine mechanisms in order to favour immune processes at the expenses of other physiologic systems. In addition, some cytokines initially conceived as immune products, such as IL-1 and IL-6, are also produced in the "healthy" brain by glial cells and even by some neurons. These and other cytokines have the capacity to affect synaptic plasticity acting as mediators of interactions between astrocytes and pre- and post-synaptic neurons that constitute what is actually defined as a tripartite synapse. Since the production of cytokines in the brain is affected by peripheral immune and central neural signals, it is conceivable that tripartite synapses can, in turn, serve as a relay system in immune-CNS communication.

Keywords Cytokines · IL-1 · IL-6 · Synaptic plasticity · Memory · Learning · Glucose homeostasis · Tripartite synapse

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It is now widely accepted that activation of peripheral immune cells results in changes of brain functions, an effect that is also expressed in the absence of overt disease. Conversely, activation of certain brain neurons results in immunoregulatory neuro-endocrine responses. More recent evidence indicates that brain-borne cytokines, such as IL-1 and IL-6, mediate to large extent such reciprocal effects. This evidence is based on data showing that the production of these cytokines by neural cells in a "healthy" brain can be induced by both peripheral immune signals and by central neuronal signals. Furthermore, as in the case of "classical" peripheral effects of cytokines on immunity, also the production of these mediators during increased neuronal activity affects, either in a paracrine or autocrine fashion, brain functions, for example memory consolidation. In the following, we concentrate on neurophysiologic aspects of brain-borne IL-1 and IL-6, and their relevance for immune-nervous system communication. Finally, we propose that the tripartite synapse provides the cellular and molecular basis for such communication.

The Brain Detects Peripheral Immune Signals that Induce Neuro-Endocrine Responses and Cytokine Production by Neural Cells

Early evidence on brain effects on immunity derives from experiments based either on neuronal destruction or depletion, thus inducing changes of brain neuronal activity,

or by interfering at central and peripheral levels with neuroendocrine and autonomic nerve functions integrated at CNS levels. However, it has to be considered that immune and inflammatory responses are phenomena that develop with a given kinetics and follow defined sequential stages that involve well-programmed, stepwise expression of genes, activation of different cell types, and generation of modulatory and effector molecules. Thus, the emission of centrally integrated immuno-regulatory signals necessarily requires that the brain receives information of what is going on at the level of the activated immune system. There is evidence that neurons from defined brain areas detect peripheral immune processes, even during conditions in which immune responses are elicited by innocuous antigens (for review [1]). Thus, immune signalling to the brain is dissociable from cognitive symptoms and organ and tissue damage during diseases in which the immune system is activated. There is a broad consensus that cytokines provide afferent information to the brain about the activity of the immune system, and elicit neuro-endocrine responses, although only in few cases the sequence of interactions during different types of immune responses have been elucidated. There are several neural and humoral pathways by which immune signals can reach the brain, but we shall not discuss this aspect here (for review see [2]). There is also evidence that peripheral cytokines released during activation of immune cells can induce cytokine production in the brain (for references see [2]). In turn, it is now well-established that cytokines, derived either from the periphery or from the brain, can elicit neuro-endocrine responses capable of regulating immune cell activity. Furthermore, as we shall discuss below, these mediators cause a resetting of glucose homeostasis, a condition that assures an adequate fuel supply during an immune response. The expression of IL-1 and IL-6 in the hypothalamus does not only occur, for example, during stimulation of Toll-like receptors, but also during adaptive immune responses, as we have recently reported [3]. Thus, the fact that activation of immune and neuronal cells results in IL-1 and IL-6 production indicates that not only peripheral but also brain cytokines are main mediators of immune-central nervous system connectivity.

Increased Neuronal Activity Results in Il-1 and Il-6 Expression in the Hypothalamus

In the following, we discuss evidence showing that increased neuronal activity results in the production of cytokines, such as IL-1 and IL-6, in the hippocampus. Long term potentiation (LTP) of synaptic activity in the hippocampus, a process characterized by a sustained enhancement in synaptic transmission and post-synaptic neuronal activity following a high frequency stimulation of afferent fibres, has served as model to approach this issue. LTP induction allows to explore whether a long-lasting increase in the activity of a defined population of neurons affects the production of a given cytokine, and whether, in turn, this cytokine can affect the activity of these neurons. A clear increase in IL-1β gene expression, triggered by glutaminergic neurons via NMDA receptors, was observed in hippocampal slices and in freely-moving rats during the course of LTP [4]. Further, we have observed that the IL-6 gene is also over expressed during in vivo and in vitro LTP [5, 6]. Other laboratories have confirmed these results [7]. More recently, we have detected that IL-1 receptor antagonist (IL-1ra) but not TNFα, is induced during LTP in freely moving rats (manuscript submitted). These data constitute the first evidence that cytokine gene expression in the brain can be triggered by a pre-synaptic induced increase in the activity of a discrete population of neurons.

Complex mechanisms such as thermoregulation, sleep, food intake, pain, and stress are integrated at brain levels but are also modulated by endocrine and autonomic mediators linked to such mechanisms and by cytokines produced at peripheral levels. This is not expected to occur during LTP, which is initiated in the brain. Therefore, we and others have studied to what extent cytokines produced in the brain during LTP can affect synaptic plasticity and performance. It is necessary to distinguish between studies based on exogenous administration of cytokines and those that focus on the effects of cytokines endogenously produced by brain cells. There is a vast literature showing that exogenous in vivo and in vitro administration of cytokines can affect LTP induction and synaptic plasticity. Administration of IL-1 [8, 9], IL-2 [10], Interferon α and γ [10–13], TNFα [14, 15], IL-6 [16], and IL-18 [17] inhibits LTP. These studies, although important from the pharmacological point of view, cannot reliably reveal the effect of cytokines produced in the brain under natural conditions. In fact, LTP is a complex phenomenon that involves a number of receptors and mediators that influence its induction, establishment, and maintenance in different ways. In particular, the maintenance of LTP is protein synthesis-dependent and involves the activation of genes in a given sequence and the release of their products in certain quantity. It is almost impossible to mimick these conditions by the exogenous application of cytokines. For example, as it is discussed below, lL-1, a cytokine that inhibits LTP when it is exogenously administered, contributes to the consolidation and maintenance of this process when it is produced endogenously.

Using the specific IL-1 receptor antagonist (IL-1ra), we found that both in vivo and in hippocampal slices, blockade of IL-1 receptors results in the inhibition of LTP maintenance [4]. This effect is reversible and occurs only when the antagonist is administered after LTP is triggered, that is

at a time when, according to the studies mentioned above, increased IL-1 levels are expected. Studies in Type 1 IL-1 receptor knock-out mice are in line with this finding [18]. These mice exhibit enhanced paired-pulse inhibition in response to perforant path stimulation and no LTP in the dentate gyrus. Furthermore, paired-pulse inhibition and complete absence of LTP were observed in the CA1 region of hippocampal slices obtained from Type 1 IL-1 receptor knock out mice [19].

We have also found that, in contrast to the supportive effect of IL-1, IL-6 contributes to the extinction of a well-consolidated LTP [6]. Collectively, these results strongly suggest that IL-1β and IL-6 control the maintenance of LTP in the brain, a process that is assigned a role in memory formation and in certain types of learning. Furthermore, these studies provide evidence for a physiologic, neuromodulatory role of cytokines originally described as immune mediators.

As in the case of LTP, the effects of cytokine administration on learning, memory, and behaviour in general have been extensively investigated [20, 21]. Again, these pharmacological studies, although of undoubtable clinical relevance, may not reflect the effect of cytokines in the "normal" brain, which is the main scope of this article. Thus, only possible physiologic effects of endogenous cytokines on memory and learning are discussed below. As mentioned above, a transient blockade of endogenous IL-1 in hippocampal slices and in the brain of freely moving rats results in inhibition of LTP maintenance. Considering that it is currently accepted that LTP underlies certain forms of memory, it was predicted that this process would be inhibited in animals in which IL-1 effects cannot be manifested. This is the case of IL-1 receptor type I knockout mice. Several paradigms of memory function and hippocampal plasticity have been studied in these animals [18, 22]. Compared to wild-type controls, type 1 IL-1 receptor knock out mice display significantly longer latency to reach a hidden platform in the spatial version of the water maze test. Furthermore, type 1 IL-1 receptor knock out mice exhibit diminished contextual fear conditioning, but behave similarly to control animals in hippocampal-independent memory tasks, i.e. their performance in the visually guided task of the water maze and the auditory-cued fear conditioning is normal. Blockade of IL-1 receptors in the brain of normal animals with IL-1ra administered in the brain and following a learning task (Morris water maze), causes hippocampal-dependent memory impairment, but does not influence the hippocampal-independent, non-spatial version of this test. IL-1ra causes memory impairment in the passive avoidance response, which also depends on hippocampal functions. Similar results were observed in transgenic mice overexpressing IL-1ra in the brain [23, 24]. These results suggest that IL-1 signalling in the hippocampus plays a critical role in learning and memory processes [18, 19]. The same authors have recently reported that enrichment can reverse the alterations in LTP and memory in mice with defective IL-1 signalling, indicating that genetically manipulated animals develop mechanisms that compensate to a certain extent the absence of effects of this cytokine [23].

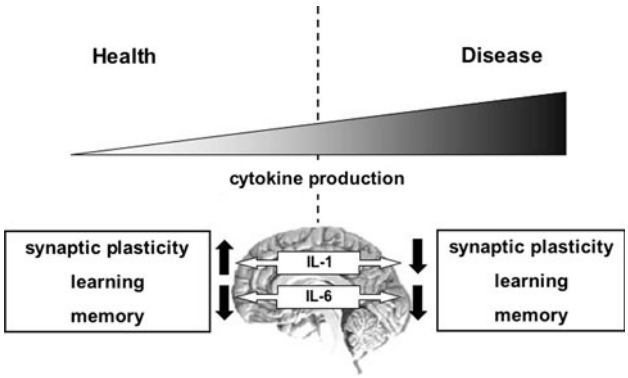

Fig. 1 Effect of IL-1 and IL-6 on synaptic plasticity, learning and memory. During healthy conditions, IL-1β supports LTP maintenance, learning acquisition, and consolidation of hippocampal-dependent memory, while IL-6 exerts opposite effects. When the concentration of IL-1 and IL-6 in the brain is increased during peripheral and central diseases, both cytokines tend to inhibit these processes

The role of IL-6 endogenously produced in the brain has also been studied. As discussed above, IL-6 is produced during LTP. Neutralization of the cytokine after tetanization results in a clear prolongation of LTP [6]. In agreement with these results, blockade of endogenous IL-6 after hippocampus-dependent spatial alternation learning results in significant improvement of long-term memory [6]. Furthermore, IL-6 KO mice exhibit a facilitation of radial maze learning over 30 days, in terms of lower number of working memory errors when compared to wild type mice [25].

In summary, cytokines are induced during increased neuronal activity and affect synaptic strength. The data reported constitute the first evidence that cytokines such as IL-1 and IL-6 are involved in this basic aspect of brain physiology. However, an uncontrolled over-expression of these cytokines during brain diseases results in cognitive deficits that include disturbances in synaptic strength and memory formation (Fig. 1).

Similarities Between Modulatory Effects of Cytokines on Immune and Neural Cells: Effects of Il-1 on Glucose Supply as an Example

Besides the well-known effects of IL-1 on immune and neuro-endocrine mechanisms, this cytokine stimulates

glucose transport in all cell types so far studied, including immune and neural cells, and induces a prolong hypoglycemia in normal and in insulin-resistant diabetic animals [26, 27]. IL-1 stimulates glucose uptake via glucose transporters, such as GLUT1, which predominates in immune cells [28] and astrocytes [29], and GLUT3 in neurons [30]. As discussed above, IL-1 production can be induced in the brain both following stimulation of peripheral immune cells and neuronal activation. Due to the effect of IL-1 on glucose homeostasis, it is reasonable to propose that a physiologic role of this cytokine is to enhance fuel supply to both immune and neural cells during conditions in which there is a sustained increase in their activity.

IL-1 is released by antigen presenting cells, particularly dendritic cells, and it can induce glucose uptake by lymphoid and accessory cells. Glucose is the main fuel for immune cells and the immune response is a process highly demanding in terms of energy [31]. Glucose uptake increases in macrophage-rich tissues, mainly mediated by GLUT1 [28, 32], and is insulin-independent [33, 34], indicating a deviation of glucose supply towards immune cells. This effect can be facilitated by the capacity of IL-1 and TNF to induce insulin resistance, thus preferentially affecting tissues such as skeletal muscle and fat, in which glucose uptake is mediated by the insulin-dependent glucose transporter GLUT4 [34].

Besides its pro-inflammatory actions and its capacity to active a cytokine network, IL-1 acts as a co-stimulatory molecule for T cells, either directly or through interaction with other co-stimulatory molecules, such as B7/CD28 [35–37]. Its capacity to induce glucose uptake indicates that IL-1 is a major candidate to mediate glucose supply, the main fuel that immune cells use, for essential processes such as phagocytosis, increased cell turnover, clonal expansion and generation of effector mediators and cells. The effect of IL-1 is largely independent of that of insulin [26], which, as mentioned, mediates its effects via GLUT4. However, without a change in the set-point of glucose homeostasis, which is tightly controlled by complex neuroendocrine mechanisms integrated at brain levels, a re-distribution of glucose supply during disease in favor of immune cells [34] would not be sustained because signals derived from non-immune tissue would tend to keep the *status quo*. We have recently shown that IL-1, produced and acting in the brain, changes the set-point of glucose homeostasis during activation of peripheral immune cells, by interfering with centrally integrated neuro-endocrine counter-regulatory mechanisms [38]. Once again, this evidence illustrates the relevance of this cytokine for immunoregulatory processes based on exchange of information between the immune and the central nerve systems.

Increased neuronal activity implies a big energetic cost and the main source of fuel derives from glycolysis. Thus, a supportive role of IL-1, similar to that played in the immune system, can be conceived during prolonged increases in neuronal activity. IL-1 can stimulate glucose uptake using predominately GLUT1 in astrocytes and GLUT3 in neurons. Since, as discussed above, IL-1 and IL-6 production is induced during LTP, we propose that IL-1 enhances fuel supply to both astrocytes and neurons during a sustained increase in activity. IL-1 activates astrocytes and stimulates their glucose metabolism [39, 40] acting either in an autocrine or paracrine way, and these cells are also activated during LTP [41, 42]. Thus, IL-1 produced during LTP is expected to favour glucose incorporation into these cells [43]. Since astrocytes are considered the main suppliers of energy during increased neuronal activity, acting directly or following the astrocyte-neuron lactate shuttle [44], the stimulation of these cells by IL-1 would support the metabolic demands of the increased activity of the neurons that they contact.

The morphological similarities between the way in which dendritic cells contact lymphocytes, and astrocytes contact neurons is outstanding. Both, dendritic cells and astrocytes, wrap the corresponding partner, and are thus well positioned to sense increases in immune and neuronal activity, and to satisfy enhanced fuel demands. In addition, astrocytes have specialized processes that cover the surface of intraparenchymal capillaries, and dendritic cells can take advantage of the increased blood flow and vessel permeability in the inflamed/infected tissue. Both conditions facilitate glucose uptake from the blood. Thus, due to its capacity to stimulate glucose uptake and metabolism in an auto/paracrine fashion, IL-1, released as consequence of interactions between dendritic cells and lymphocytes, and between astrocytes and neurons, would serve to support immune and neural cells functions, respectively. Although the type of cells affected by IL-1 are quite distinct, it is also remarkable that, as discussed above, brain-borne IL-1 is relevant for memory formation, and recent data indicate that the same cytokine is mandatory for the development of immune memory [45, 46].

The Tripartite Synapse as a "Relay System" that Mediates Immune-Brain Communication

The concept of a tripartite synapse is at present well-established [47–49]. A tripartite synapse is based on interactions between neurons and surrender astrocytes that do not only influence neuronal metabolism but also affect synaptic strength and, thus several brain functions such as memory consolidation. The facts that IL-1 and IL-6 are induced in the brain during increased neuronal activity and that these cytokines can influence both neurons and astrocytes strongly suggest that they function as mediators of

the tripartite synapse. Since, as mentioned, the production of IL-1, IL-6 and other cytokines can also be induced in the brain upon activation of peripheral immune cells, tripartite synapses would constitute an interface between the immune system and the central nervous system. The fact that astrocyte processes are part of the blood–brain barrier and can be affected by peripheral signals also contributes to the establishment of such interface. Furthermore, afferent nerve fibres also convey information from the immune system to the brain and, by acting on defined neurons, they can also have an input on tripartite synapses.

Under basal conditions, the release of low amounts of cytokines by brain cells could be one of the various inputs that modulate the activity of neurons involved in the regulation of adaptive functions integrated at hypothalamic and limbic system levels. Under conditions during which the activity of the immune system changes, peripheral cytokines and other mediators would trigger the initial steps of neuro-endocrine responses that occur as consequence of immune cell stimulation. The quick neuro-endocrine response observed when certain cytokines are administered peripherally may indicate that this initial step does not involve the *de novo* synthesis of cytokines in the brain. However, peripheral immune mediators and neurons and glial cells activated during this initial step would trigger increased expression of cytokines in the brain. This confluence of signals may contribute to determine a defined pattern of central cytokine expression during an immune response. This pattern may differ in relation to the type of immune response that it is elicited.

As we have shown during LTP, these cytokines are expected to feed-back on the neurons that were originally affected. In this way, de novo produced cytokines would influence the neural or endocrine mechanisms controlled by the neurons that triggered their production. If these neurons are those that are activated during the immune response, they will in turn elicit a neuro-endocrine immunoregulatory response. If increased cytokine production is triggered following activation of neurons that receive other sensorial inputs, e.g. stress, the tripartite synapse will mediate the corresponding neuro-endocrine responses. However, the response to different types of stress also involves different combinations of hormones and neurotransmitters that can affect immune processes. In addition, both the CNS and the immune system are permanently active, and the brain receives neuro/sensorial and immune signals that can elicit different responses during different life events linked to health and disease. Thus, to be adaptive, neuro-endocrine responses must be coordinated and integrated at brain levels. We postulate that tripartite synapses posses the cellular and molecular components to function as a "relay system" capable of receiving and integrating peripheral immune signals with central neural signals. Considering that these signals can induce either synergistic or antagonist effects, the integration of their effects would result in neuro-endocrine and behavioural responses with different outcomes. Thus, the proposed integrative relay system is expected to be relevant in determining to what extent neuro-endocrine and metabolic mechanisms under brain control can contribute to maintain health, and also influence the course and consequences of a disease.

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