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Interleukin-6: A Cytokine with a Pleiotropic Role in the Neuroimmunoendocrine Network

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Abstract: Interleukin 6 (IL-6) is a typical pleiotropic cytokine that modulates a variety of physiological events in vertebrates, including cell proliferation, differentiation, survival, and apoptosis, among other functions. IL-6 plays roles in the immune, the endocrine, the nervous, and the hematopoietic systems, in bone metabolism, regulation of blood pressure and inflammation. IL-6 exerts its effects on different tissues and organ systems. Many cell types are reported to produce IL-6: T cells, B cells, polymorphonuclear cells, eosinophils, monocyte/macrophages, mast cells, dendritic cells, chondrocytes, osteoblasts, endothelial cells, skeletal and smooth muscle cells, islet cells, thyroid cells, fibroblasts, mesangial cells, keratinocytes, microglial cells, astrocytes, oligodendrocytes, adipose tissue and certain tumor cells. Here, we review the participation of the IL-6 in the neuroimmunoendocrine network. The specific targeting of the IL-6 pathway can be a promising new approach for the treatment and prevention of neurodegenerative disorders in humans as well as improving the autoinflammatory process both systemically and locally.

Keywords: IL-6, immunoendocrine, neuroimmune, parasitic diseases, cytokine, network.

INTRODUCTION

The immune and neuroendocrine systems are integrated by a network in which hormones and neuropeptides modulate immune function and immune responses triggered by neuroendocrine changes. These systems function together to maintain homeostasis [1]. Two of the main components of this network are the hypothalamic-pituitary-adrenocortical (HPA) axis [2] and the hypothalamic-pituitary-gonadal axis (HPG) [3].

Interactions between the immune system and both HPA and HPG axes are characterized by their activation and initiation of the stress response, which, in turn, has immunomodulating activities [4, 5] that are important in preventing excessive immune responses. Furthermore, the function of both axes is implicated in adaptation and maintenance of homeostasis during critical illness and viral, bacterial, parasitic and autoimmune diseases [6-8].

In this complex network, interleukin-6 (IL-6) plays key roles in modulating the HPA-HPG axes response at central and peripheral levels. An important aspect of cell communication that has emerged as a result of studying neuroendocrine-immune interactions is the redundancy of the use of some chemical messengers. As an example, neurotrophins are chemical messengers first identified and characterized in the nervous system. Members of this family protein are also expressed and secreted by immune and endocrine cells, having immunological and endocrinological functions [9-11].

Thus, the lack of exclusivity of the use of some cellular messengers by specific organic systems might be a rule, rather than an exception. Although strong evidence supports that 1) neurons, endocrine and immune cells produce hormones and 2) neural, endocrine and immune cells synthesize and secrete neuroactive messengers. It remains somewhat controversial whether IL-6 can indeed be produced by neural cell lineages and modulate neural functioning locally. Hence, in the following paragraphs, we will review and discuss some of the information available on 1) IL-6 production, sensitivity and signal transduction in neural cell lineages, 2) IL-6 morphological and physiological actions during neural development, regeneration, communication, aging and behavior, 3) IL-6 participation during neuroinflammation and neurodegeneration and 4) IL-6 role in endocrine cells.

IL-6 STRUCTURE AND IMMUNE FUNCTION

IL-6 is a typical pleiotropic cytokine that modulates a variety of physiological events in vertebrates, such as cell proliferation, differentiation, survival, and apoptosis. IL-6 plays roles in the immune, the endocrine, the nervous and the hematopoietic systems, and on bone metabolism [12-15]. Many immune cell types are reported to produce IL-6 including T cells, B cells, polymorphonuclear cells, eosinophils, monocyte/macrophages, mast cells and dendritic cells. Other cell types known to produce IL-6 are chondrocytes, osteoblasts, endothelial cells, skeletal and smooth muscle cells, islet cells, thyroid cells, fibroblasts, mesangial cells, keratinocytes, certain tumour cells, adipose tissue cells, microglial cells and astrocytes. IL-6 has been implicated in the pathology of different diseases including multiple myeloma, rheu-

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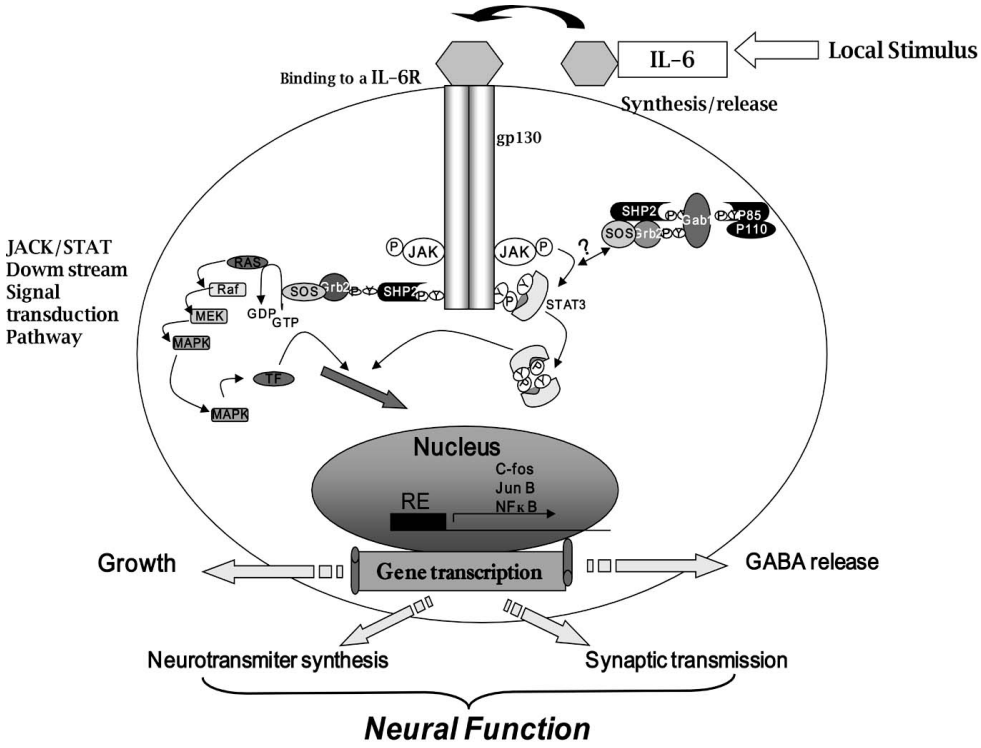

Fig. (1). Structural model of signaling of the IL-6-IL-6 receptor complex in the central nervous system.

Upon binding, IL-6-IL-6R complex activates the JAK/STAT3 pathway and the MAPK cascade, which induces specific gene expression, resulting in a specific neuronal function. The structures for vIL-6/gp130, gp80, STAT3 and SHP2 are represented, as well as the molecular models of a JAK2 kinase domain and SOCS1.

matoid arthritis, Castleman disease, AIDS, mesangial proliferative glomerulonephritis, psoriasis, Kaposi`s sarcoma, sepsis and osteoporosis [16-27].

The IL-6 gene is located at chromosome 7p21 [28] and 5 [29] in the human and mouse genomes, respectively. The genes for human, mouse and rat IL-6 have been cloned and sequenced, and all contain four introns and five exons [30-32]. The deduced amino acid sequence of human IL-6 (hIL-6) consists of 212 amino acids with 27 of them as a signal peptide, and two sites of potential N-glycosylation. Its molecular weight ranges from 21 to 30 kDa with isoelectric point at 5.4 [33]. hIL-6 tridimensional structure shows a four-helix bundle: two pairs of antiparallel-helices with up-up-down-down orientation [34] whose folding is conserved among cytokine family members. The mouse IL-6 protein is a refolded 185 amino acid polypeptide, 42% homologous to the human form and contains several potential O- glycosylation sites instead of the N- glycosylation site [35].

IL-6 is involved in the regulation of both type-1 and type 2 helper T-cell responses (Th1/Th2 responses), and acts on B cells to promote immunoglobulin (Ig) production [15]. IL-6 has the ability to stimulate B-cell differentiation, activate thymocytes and T-cells for differentiation, activate macrophages, stimulate hepatocytes to produce acute-phase proteins, and activate natural killer (NK) cells [36-41]. IL-6 also possesses anti-inflammatory properties [42]. Mouse IL-6 also acts on B cells activated with anti-Ig or dextran sulfate [43]. In T cells IL-6 confers significant effects on proliferation, survival, and Th1/Th2 responses. IL-6 also affects the differentiation of professional antigen-presenting cells such as macrophages and dendritic cells [44, 45].

LOCAL AVAILABILITY OF IL-6 IN THE NERVOUS SYSTEM: CELL SOURCES AND TARGETS

a). IL-6 Cell Sources

For many years astrocytes were considered to provide structural support to neuronal networks and to constitute part of the cellular elements that induce and form the blood-brain barrier. Only recently, we have realized that astrocytes play a variety of different roles in the developing and mature brain. As an example, it is now known that they express different voltage- and ligand-gated ion channels [46], as well as metabotropic receptors [47], which opens the possibility that astrocytes might also participate in neural information processing. In addition to their neural-related functions, astrocytes play an immunological role as antigen-presenting cells [48]. They, in fact, help in orchestrating brain immunological responses. In doing so, astrocytes produce cytokines and chemokines that attract different types of immunological cells and promote/facilitate their crossing of the blood-brain barrier during inflammatory responses [49]. What it is more remarkable though, is that astrocytes have the ability to produce and secrete cytokines constitutively, suggesting that these messengers may modulate normal neural functioning. Accordingly, primary astrocyte cultures obtained from mice synthesize IL-6 when exposed to tumor necrosis factor alpha (TNF-α), IL-1β, and interferon-gamma (IFN-γ), but they do so more importantly after incubation with neuromodulators such as substance P, vasoactive intestinal polypeptide and

histamine [50, 51]. It has also been shown that IL-6 regulates its own expression in cultured astrocytes, likely through autocrine mechanisms [52].

The idea that neurons may produce IL-6 has only been accepted very recently. The resistance to this idea probably reflected the dominance of the long-held view that brain is a privileged site in which immunological surveillance is greatly restricted because of the difficulty of immune cells to enter the nervous system. It was believed that, if immune cells gained access to the brain, they would produce irreversible damage to neuronal connections. Recent experimental evidence has proved both concepts wrong. Hence, studies conducted *in vitro* documented that cultured neurons from sympathetic and sensory ganglia express IL-6 mRNA and synthesize IL-6 [53-56]. Neuronal production of IL-6 is increased following N-methyl-D-aspartate (NMDA)-mediated glutamatergic depolarization. This effect is abolished after selectively blocking L-type voltage-dependent Ca2+ channels, and by inhibiting calmodulin and/or Ca2+/calmoduline protein kinases [57].

b). Neural IL-6 Targets

To sustain that cytokines constitutively produced by neural cell lineages indeed play important roles in modulating neuronal functions, it is required not only to show their production within the brain itself, but to demonstrate the presence of receptors at proper targets. In accordance, IL-6 and IL-1 receptors have been detected in various neuronal populations along the peripheral and central nervous system (CNS) structures [58, 59]. Although IL-6 exerts its function mainly through its binding to its specific membrane receptor, it has been recently described that it is able to function as an agonist to cells lacking the membrane receptor but instead expressing the membrane bound subunit gp130. In this case, IL-6 binds to a soluble form of its receptor (sIL-6R) and this complex (IL-6/sIL-6R) associates to gp130 leading to intracellular signaling, a process named trans-signaling [60].

IL-6/IL-6 receptor complex has short-term effects on synaptic transmission and plasticity that are thought to be mediated by the activation of intracellular protein kinases. The effects of IL-6 on the expression of paired pulse facilitation (PPF), post-tetanic potentiation (PTP), and long-term potentiation (LTP) in the CA1 region of the hippocampus are mediated via the activation of the signal transducer and activator of transcription-3 (STAT3), the mitogen-activated protein kinase ERK (MAPK/ERK), and the stress-activated protein kinase/c-Jun NH(2)-terminal kinase (SAPK/JNK). Pheochromocytoma PC12 cells exposed to IL-6 develop neuritic processes and sodium inward currents following *c-fos* activation (Fig. **1**) [61]. Transgenic overexpression of IL-6 decreases the rate of proliferation of neuronal precursors in the dentate gyrus of young adult transgenic mice. These mice also showed a deficiency in the number of surviving and differentiated granule cells [62]. IL-6 family of proteins are powerful signals to induce neural stem cell differentiation [12] and improve the postnatal survival of cultured mesencephalic catecholaminergic and septal cholinergic neurons.

IL-6 and Neural Regeneration

Although the prevailing view is that cytokines, especially those considered as pro-inflammatory, promote the formation of glial scars, thus interfering with regenerative processes in the nervous system, important evidence supports that at least some of them are capable of facilitating regeneration of neural tissue [63, 64]. This last statement seems to be true for both the peripheral and central pathways. IL-6 and other structurally related cytokines such as IL-11, IL-17, leukaemia inhibitory factor (LIF) and cilliary neurotrophic factor (CNTF) have shown effects on haematopoietic and nervous systems. These neuropoeitic cytokines signal through the gp130 receptor. Their signaling has been associated to normal development and adult brain, as well as in the response to brain injury and disease [65]. Interleukin-6 plays an important role in peripheral nerve regeneration. This cytokine activates Janus kinase/STAT3 signaling in spinal microglia as a response to a peripheral injury, and this transduction pathway participates in development of pain associated with nerve alteration [66]. IL-6 activates STAT3 in Schwann cells. The IL-6/STAT3 signaling in primary Schwann cells induce the gene expression of glial fibrillary acidic protein (GFAP), which is known to be required for the proper regeneration of the injured nerves, while in IL-6-deficient mice GFAP induction in the sciatic nerves after injury is significantly delayed [67]. IL-6 upregulates several genes involved in both neural differentiation and regeneration in the peripheral glia [68, 69] which could be the mechanism by which it participates in regeneration.

It is interesting to mention that mice deficient in IL-6 show impaired somatosensory function and delayed regeneration of peripheral sensory nerves. However, the effects of chronic IL-6 exposure on neuronal function in the CNS are largely unknown, but could include the loss of cerebellar Purkinje neurons [70]. For instance, extracellular recordings from cerebellar slices revealed that the mean firing rate of spontaneously active Purkinje neurons is significantly reduced in slices from IL-6 transgenic mice compared to control mice. In addition, a significantly greater proportion of Purkinje neurons from transgenic IL-6 mice slices exhibited an oscillatory pattern of spontaneous firing than Purkinje neurons in control slices. However, the inhibitory period following the complex spike (climbing fiber pause) was significantly longer in slices from transgenic mice. Purkinje neurons also express high levels of both the IL-6 receptor and its intracellular signaling subunit, gp130, indicating that IL-6 could act directly on Purkinje neurons to alter their physiological properties [70]. This cytokine also exerts trophic action on various neuronal populations in the CNS. The *in vitro* trophic effects of IL-6 have been studied in two well-characterized populations of cranial sensory neurons throughout embryonic development. Cutaneous sensory neurons of the trigeminal ganglion, showed an early, transient survival response to IL-6 in the late fetal period. This evidence indicates that populations of sensory neurons display different developmental patterns of cytokine responsiveness, and show that embryonic trigeminal neurons pass through several phases of differing neurotrophic factor survival requirements [63]. Furthermore, by using intracellular recording and calcium imaging techniques, it has been shown that chronic IL-6 exposure affects the physiological properties of cerebellar Purkinje neurons in primary culture [55]. Two weeks of exposure to IL-6 resulted in altered electrophysiological properties of Purkinje neurons, including a signifi-

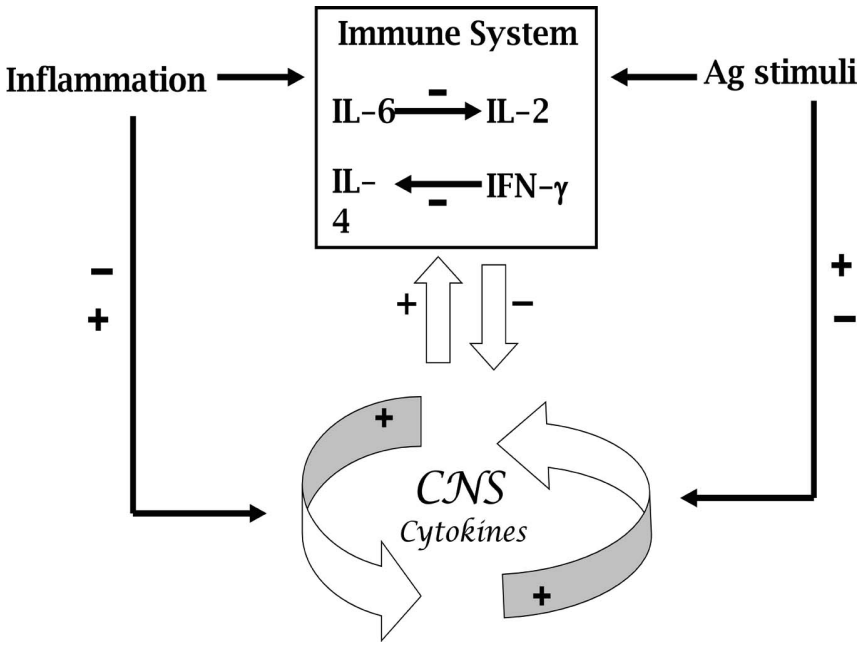

Fig. (2). Proposed neuroimmunological interactions that occur in higher vertebrates.

In physiological conditions there is a crosstalk between the neurological and the immune systems of the host. External stimuli, such as infections, results in a TH1/TH2 systemic cytokine production of the immune response. Also, the central nervous system (CNS) is able to actively induce the expression of cytokines, which may affect the CNS function.

cant reduction in action potential generation, an increase in input resistance, and an enhanced electrical response to the ionotropic glutamate receptor agonist, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA). These effects were mediated by the IL-6 receptor and gp130. Partial chemical lesions of *substantia nigra pars compacta* following 6-hydroxy-dopamine administration led to a sprouting of fibers from the remaining dopaminergic neurons. Also, chronic haloperidol treatment, a D2 receptor antagonist, induces sprouting of axons from dopaminergic neurons of the *Substantia nigra*. Both responses were found greatly attenuated in IL-6 knock-out mice, thus suggesting that IL-6 control the normal arborization and possible regeneration of the nigro-striatal pathway [55].

PHYSIOLOGICAL ACTIONS OF IL-6 IN THE CNS

a). IL-6 Regulation of Excitatory and Inhibitory Transmission

In the mature brain, neurons communicate predominantly through chemical synapses. These synapses are placed in specific sites of the neurons, such that synapse localization defines the final configuration of the neuronal circuits and the way the information passes through them. Information flows through these circuits by means of electrochemical codes that are translated into patterns of neurotransmitter release. Hence, the regulation of the generation of electrochemical codes and/or of the release of neurotransmitters both constitutes effective manners to modulate information processing by neuronal assemblies. Furthermore, glutamic and gamma-amino butyric (GABA) acids are neurotransmitters that, in general terms, facilitate or difficult the transmission of information through synapses. A delicate balance between the excitatory actions associated with glutamate and the inhibitory actions related with GABA, determines whether information will finally flow along neuronal circuits [55, 71]. Most of the work aimed at characterizing cytokine effects on neuronal synaptic communication has shown that they modulate GABA and glutamate-mediated neuronal transmission. Low doses of kainic acid induced severe tonic-clonic seizures and death in GFAP-IL-6 transgenic mice. Moreover, this strain of mice was also significantly more sensitive to NMDA but not to pilocarpine-induced seizures where seen. Kainic acid uptake in the brain of the GFAP-IL6 mice was higher in the cerebellum than in other regions [72]. Kainic acid binding in the brain of GFAP-IL-6 mice had a similar distribution and density as in wild type controls. In the hippocampus of GFAP-IL-6 mice that survived low doses of kainic acid, there was no change in the extent of either neurodegeneration or astrocytosis due to degenerative changes in GABA and parvalbumin-positive neurons in the hippocampus, which progressed to the loss of these cells [49].

IL-6 has been also shown to potentiate evoked GABA release from mediobasal hypothalamic explants and posterior pituitaries in culture. This effect is mediated by prostaglandins and is abolished by indomethacin [73].

The effects of IL-6 on neuronal functioning are not restricted to the CNS. For instance, IL-6 inhibits nociceptive fiber responses to heat both *in vivo* and *in vitro*. Similarly, IL-6 administered systemically to anesthetized rats, with or without neuropathic pain, inhibits all naturally evoked neuronal responses, but, interestingly, only animals with nerve ligation showed heat responses, while intraplantar IL-6 injection lead to thermal hypoalgesia in rats [74, 75].

b). IL-6 Effects on Behavioral States

The effects of IL-6 on neural functioning have not only been analyzed at the level of cellular communication. The

most powerful demonstration that cytokines indeed modulate behavior comes from the fact that intraventricular administration of proinflammatory cytokines, such as IL-6, induces sickness behavior by acting on the amygdalar complex. Nevertheless, the behavioral effect of IL-6 is not restricted to behaviors associated to immunological functions, since it regulates functions as important as learning and memory. IL-6 administration reduced scopolamine-induced amnesia without affecting neurotransmitter level, as monitored by passive avoidance [76].

Even when IL-1β is thought to be a potent mediator of sickness behaviors, it is known that IL-1 potentiates the actions of IL-6, suggesting that most of the effects attributable to IL-6 are on its own, and not by IL-1. Also, it is though that IL-1 induces the IL-6 release in endocrine and neural tissue, thus indicating that many of the effects that have been attributed to IL-1 indeed belong to IL-6. Accordingly, primary astrocyte cultures, obtained from mouse, synthesize IL-6 when exposed to IL-1β, but they do so more importantly after incubation with neuromodulators such as substance P, vasoactive intestinal polypeptide and histamine [51, 77, 78]. It has also been shown that IL-6 and IL-1β regulate their own expression, likely through autocrine mechanisms, in cultured astrocytes. Furthermore, to sustain that cytokines constitutively produced by neural cell lineages indeed play important roles in modulating neuronal functions, it is required not only to show their production within the brain itself, but to demonstrate the presence of receptors at proper targets. In accordance, IL-6 and IL-1 receptors have been detected in various neuronal populations along the peripheral and CNS structures [78-80].

c). IL-6 Effects on Sleep

The interactions between nervous and immune systems have been found to play an important role on sleep. At the central level, cytokines such as IL-6, IL-1 and TNF-α have been shown to exert regulatory functions on sleep [81]. Particularly, IL-6 presents a circadian secretion pattern with an increase during sleep [82, 83], while sleep deprivation increases plasma IL-6 levels [84] suggesting a possible participation on the physiological functions of sleep such as consolidation of memory. Intranasal administration of IL-6 improves sleep-related emotional memory consolidation in healthy men while it does not affect other types of memory this effect is mediated by the interactions of the cytokine to both its membrane receptor and its soluble isoform [85].

The Role of IL-6 in Aging, Inflammation and Neurodegeneration in the CNS

It is widely held that neurodegenerative diseases are accompanied by inflammation, possibly resulting from accumulation of diverse molecules in the brain. The paradigm implies that molecules proper of the inflammatory immune response mediate the damage produced to neurons as a result of the inflammatory process by the host's immune system. This paradigm in neurodegenerative diseases has been around for a long time and in spite of thoughtful recommendations against simplification, it is rarely questioned. It could be a matter of debate the association with many diseases and with mortality trends in humans. It is also involved in broader subjects, including evolution of reproduction, decision making of the host, social hierarchy, mating behavior and the energy costs of infection and of the immune response. However, current evidence so far conflicted with these observations, found in the literature that no evidence (other than the synthesis of cytokine mediators of inflammation) suggests that inflammation indeed exists in the diseased brain. Thus, in the following paragraphs we will try to summarize what is known about pro-inflammatory IL-6 effects and their role in the diseased brain.

Inflammatory processes that occur within the CNS can produce illness-induced behaviors which include fever, sleep and the development of allodynia and hyperalgesia. IL-6 appears to participate in the process of aging in the brain. Evidences have shown that IL-6 is augmented in the brain of aged humans and rodents [86, 87]. This increase might reflect the decrease of steroid hormone levels and of their immuno-supressing actions, both associated with aging. Changes in the expression of Sp1, Sp3 and Sp4 transcription factors also occur in the aged brain. These factors downregulate NF-κB expression, thus favoring inflammatory conditions in the elder [88, 89]. Interestingly, the elevation of IL-6 has been documented in the brain suffering neurodegenerative diseases, such as Alzheimer disease [90-92], dementia [93], multiple sclerosis [94] and mayor depression [95] and this circumstance has led to the idea that maintaining the balance between pro-inflammatory and non-inflammatory cytokines determines, to some extent, the outcome of CNS injuries or neurodegeneration [96-100]. High IL-6 peripheral levels have been correlated to hippocampal degeneration as well as impairment in memory [101].

The discovery that several proinflammatory cytokines act as endogenous pyrogens and that other cytokines can act as antipyretic agents provided a link between the immune and the CNS and stimulated the study of the central actions of cytokines. IL-6 has been most investigated for their pyrogenic or antipyretic actions [102-106]. The experimental evidence demonstrating the role of these secreted proteins in modulating the fever response is as follows: 1) association between IL-6 levels in serum, cerebrospinal fluid, and fever; 2) presence of IL-6 receptors in various cell types in the brain and demonstration of the effects of the pharmacological application of cytokines and of their neutralizing antibodies on the fever response; 3) fever studies on IL-6 and IL-6 receptor- transgenic models.

Studies on the peripheral and the central action of cytokines demonstrated that peripheral IL-6 can communicate with the brain in several ways, including stimulation of afferent neuronal pathways and induction of the synthesis of a non-cytokine pyrogen, i.e. PGE2, in endothelial cells in the periphery and in the brain. IL-6 synthesized in the periphery may act by crossing the blood brain barrier and acting directly via neuronal IL-6 receptors [107]. The mechanisms that ultimately mediate the central action of IL-6 on the temperature-sensitive neurons in the preoptic hypothalamic region involved in thermoregulation, directly or via second mediators, remain to be fully elucidated (Fig. **2**).

Lipopolysaccharide (LPS), causes the release of IL-6 from immune cells, that can reach the brain by several routes. Furthermore, IL-6 is induced in neurons within the brain by systemic injection of LPS. Then, IL-6 determines

the pattern of hypothalamic-pituitary secretion that characterizes infection. It has been shown that IL-6 induces an activation of both microglia and astrocytes in different brain regions of the same hemisphere [108]. Also, treatment of astrocyte cultures with IL-6 significantly altered the astrocyte functions and ultrastructure, findings that suggests that LPS affects astrocyte function and structure via the release of proinflammatory cytokines [109].

It has been shown that IL-6 is chronically expressed at elevated levels within the CNS in many neurological disorders and may contribute to the hystopathological, pathophysiological, and cognitive deficits associated with such disorders. Therefore, chronic IL-6 exposure can disrupt normal CNS function and thereby contribute to the pathophysiology associated with many neurological diseases. The induction of IL-6 by lesion, infection or experimentation, induced a marked and dose-dependent decrease in the expression of PTP and LTP that was counteracted by the simultaneous treatment with the tyrosine kinase inhibitor lavendustin A (LavA), but did not significantly affect PPF [61]. The IL-6-induced inhibition of PTP and LTP was accompanied by a simulation of STAT3 tyrosine phosphorylation and an inhibition of MAPK/ERK dual phosphorylation, in the absence of changes in the state of activation of SAPK/JNK, in the same fashion as in the activated immune system [61], indicating that the tyrosine kinases and MAPK/ERK are involved in hippocampal synaptic plasticity and may represent preferential intracellular targets for the actions of IL-6 in the adult nervous system. Previous experiments in which a strain of transgenic mice with the GFAP promoter driven-astrocyte production of IL-6 was used to determine whether the pre-existing production of these cytokines *in vivo* might modulate the sensitivity of neurons to exocytotoxic agents, and it was suggested that pre-existing IL-6 production and inflammation in the CNS not only causes spontaneous neurodegeneration but also synergizes with other neurotoxic insults to induce more severe acute functional neurological impairment [49].

ENDOCRINE EFFECTS OF IL-6

The endocrine effects of this cytokine have been extensively demonstrated. For instance, it has been shown to stimulate the secretion of LH and FSH in cultured pituitary cells [110], and to stimulate the release of prolactin from the anterior pituitary gland [111]. On the other hand, IL-6 inhibits FSH-stimulated progesterone production by rat granulosa cells *in vitro* [112]. In some reports, the IL-6 activity has been shown to be an important factor that affects the activity of P-450 aromatase, mainly in estrogen-dependent breast cancer cells [113, 114]. IL-6 has been suggested to be capable of performing those immunoendocrinological interactions that lead to the feminization process in the cysticercotic male mice because of its effect on P450 aromatase. IL-6 expression is involved in the paracrine control of testicular function, and the fact that FSH could be involved in the induction of IL-6 expression in the testes of infected male mice is supported by previous studies in human Sertoli cells, in which FSH only stimulated IL-6 production by Sertoli cell-enriched preparations, but increased the release of both IL-1 and IL-6 in germ cell-depleted Sertoli cell cultures [115]. In addition, LPS and latex beads enhanced the production of IL-6 by Sertoli cell cultures, whereas human chorionic gonadotropin and LPS enhanced the release of IL-6 by Leydig cells [115]. The molecular mechanisms of testicular aromatase activation induced by IL-6 are not clear, but could involve its regulation by a distal promoter, namely promoter I.4, as has been shown for other steroidogenic tissues [116]. The stimulation of expression in adipose stromal cells by IL-6 is mediated via the JAK-STAT3 signaling pathway and a GAS element upstream of promoter I.4.82. IL-6 has been shown to enhance the secretion of adrenocorticotropic hormone (ACTH) through the stimulation of the production of hypothalamic corticotropin-releasing hormone (CRH), which produces heightened HPA activity characterized by increases in cortisol, to be reported elevated in major depression.

CONCLUDING REMARKS

The present literature search revealed an extremely complex NIE-network involving many molecules and IL-6 that foresees potent interactions in events generally attributed to the exclusive operation of single systems in response to simple precepts (reproduction, defense). So much plasticity and multifunctionality in a network are not without a risk. Loss of control could lead to the loss of tolerance and autoimmunity, to be involved in the immune compromise of aging, and/or in the physiopathology of some infections in which inflammation is a prominent effector of pathology. Also, the NIE network could connect IL-6 with diseases that seem distant from the immunologic and endocrinologic domains, such as arterial hypertension, cystcercosis and cancer.

New neuroscience data rapidly accumulating in the past years call for radical revision of many long-established and widely accepted paradigms. This paper reviews some data leading to new concepts of the life and functions of neurons. The adult brain contains stem cells that are the source of the precursors for all the main types of brain cells: neurons, astrocytes, and oligodendroglia. These cells can substitute the deteriorating elements in the adult and even in the old brain. The neurons happen to be highly resistant to lesions in their processes as well as to anoxia, and inhibitory neurons are shown to be especially stable in some pathological conditions. Changes in the afferent input result in various types of rapid compensatory morphological and functional reorganizations at different levels. Thus, the previous fatalistic view of the nervous system is now substituted for an optimistic one, which considers various possibilities of prolongation and restoration of normal functioning of the brain. Simultaneously, our concepts of the neuron have drastically changed. A unitary neuron may operate by several neurotransmitting substances; their synaptic influences upon dendrites may evoke the active propagation of calcium and sodium spikes, their axons may differentially release transmitter substances depending on the parameters of excitation. All neuronal functions are helped and controlled by astroglia, which participate in the synthesis of transmitters and protect the neurons from exocytotoxic death. In addition to synaptic interactions between neurons, there exist other types of communications, such as volume conduction of transmitters after their spillover from the excited synapses and non-synaptic (varicose) zones, as well as exchange of molecules and ions through the gap junctions. A complex picture of interneuronal communications with multiple synaptic, pre-

synaptic, and parasynaptic interactions is further complicated by the intimate participation of cytokines in these processes. The mutual regulatory influences between neurotransmitters, neurotrophic, and neuroimmune systems show that in normal conditions they are all working in concert. This increase in the number of factors that determine the final result of interactions between neurons adds new difficulties to the development of theoretical concepts or simulation of brain functions. Finally, the development of drugs specifically targeted against IL-6 may be useful in the prevention of plaque formation, myocardial infarction and restenosis. Based on the literature data, blocking the effect of IL-6 in humans may probably improve lupus by interacting with the autoinflammatory process both systemically and locally. The specific targeting of the complex IL-6/sIL-6R pathway will be a promising new approach for the treatment of autoimmune, parasitic and neurodegenerative diseases.

Even when it could be hard to think that IL-6 alone has all the effects in the central, endocrine, and immune systems by itself, other proinflammatory cytokines could create redundancy in the system and work together to elicit several of the discussed effects that are attributed to IL-6.

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