Review

DISEASE-INDUCED NEUROINFLAMMATION AND DEPRESSION

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"LINKAGE OF CNS AND IMMUNOLOGY WITH PSYCHOLOGY: SEARCHING FOR NEW PHARMACOLOGICAL TARGETS"

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Abstract:

Progression of major depression, a multifactorial disorder with a neuroinflammatory signature, seems to be associated with the disruption of body allostasis. High rates of comorbidity between depression and specific medical disorders, such as, stroke, chronic pain conditions, diabetes mellitus, and human immunodeficiency virus (HIV) infection, have been extensively reported. In this review, we discuss how these medical disorders may predispose an individual to develop depression by examining the impact of these disorders on some hallmarks of neuroinflammation known to be impaired in depressed patients: altered permeability of the blood brain barrier, immune cells infiltration, activated microglia, increased cytokines production, and the role of inflammasomes.

In all four pathologies, blood brain barrier integrity was altered, allowing the infiltration of peripheral factors, known to activate resident microglia. Evidence indicate morphological changes in the glial population, increased levels of circulating pro-inflammatory cytokines or increased production of these mediators within the brain, all fundamental in neuroinflammation, for the four medical disorders considered. Moreover, activity of the kynurenine pathway appeared to be enhanced. With respect to the inflammasome NLRP3, a new target whose role in neuroinflammation is emerging as being important, accumulating data suggest its involvement in the pathogenesis of brain injury following stroke, chronic pain conditions, diabetes mellitus or in HIV associated immune impairment.

Finally data gathered over the last 10 years, indicate and confirm that depression, stroke, chronic pain, diabetes, and HIV infection share a combination of underlying molecular, cellular and network mechanisms leading to a general increase in the neuroinflammatory burden for the individual.

Keywords: Neuroinflammation, allostasis, depression, stroke, chronic pain, diabetes mellitus, human immunodeficiency virus **infection, pro-inflammatory cytokines,** blood brain barrier **permeability, microglia,** tryptophan catabolites**, inflammasome**

Introduction:

Major depression (MD) is a multifactorial disorder that has been associated with various neurobiological changes like neurotransmitter deficit, endocrine disturbance, impaired neural adaptation and plasticity [1, 2]. Abundant evidence points at neuroinflammation as the common feature behind these alterations [3], and development and progression of the depressive disorder seem to be associated with the disruption of body allostasis [2].

Allostasis is defined as the process of achieving stability of internal physiological and mental processes through dynamic change. The main player in the "allostatic game" is the brain, an organ designed to integrate signals from the periphery that anticipate fluctuations, changes, and needs and coordinates allostatic mediators in order to develop successful coping mechanisms that ultimately lead to an adaptative strategy and resilience (4, 5].

However, when these coping mechanisms become highly and repetitively activated, or ineffective, they may enhance the "allostatic load" that subsequently will take its toll on the individual by making him more vulnerable to the development of a disease. Many factors influence one's ability to either "bend" or "break" in the presence of allostatic overload defining his resilience or vulnerability toward a disease [6]. Resilient people are considered to have a higher threshold to external and internal demands than vulnerable ones. Consequently, the resulting outcome derives from a complex interplay between genes and environment. Vulnerability genes (e.g. allelic variation in the serotonin transporter-linked polymorphic region or brain-derived neurotrophic factor Val66Met polymorphism), external, stressful life events (trauma, adversities, loss) and internal disturbances (diseases) all concur to draw the line between health and disease [7].

But once is the line crossed what happens? At present, multiple coexisting diseases are becoming the norm rather than the exception [8], especially in the field of psychiatry.

High rates of psychiatric comorbidity among specific medical conditions such as stroke, chronic pain conditions, diabetes mellitus (DM), and human immunodeficiency virus (HIV) infection, have been extensively reported [9-12]. Conversely, other studies have described high rates of medical comorbidity among patients with psychiatric illness [13]. However, if the concept of allostasis has helped to change the definition of homeostasis from a one-dimensional/classic model to a complex and centrally integrated set of mechanisms, maybe it is time to change the definition of comorbidity as well. Usually, comorbidity is defined as co-occurrence of two or more different pathological conditions that are often perceived as distinct clinical entities within a single person.

Evidence is accumulating that distinctly occurring diseases are able to influence each other in terms of incidence, vulnerability, trajectory, response to treatment, and ultimately, outcome. For example, depression may modify the course and outcome of stroke and may even act as a risk factor for future cardiovascular disorders, including stroke [14]. Furthermore, depressed patients who received a diagnosis of diabetes and patients with diabetes that are diagnosed with MD should not be perceived in the same way, although they suffer from both depression and diabetes [8], the underlying causes may be different .

Once the allostatic equilibrium is compromised, the body becomes more "vulnerable" or "permissive" to other diseases. This is especially true for psychiatric and stress related disorders, such as, depression. In fact, depression is often associated with other medical disorders with a high accumulative burden of disease [13], like conditions of chronic pain. What happens to the brain in presence of a systemic disease? Does the brain of a patient suffering from stroke/chronic pain/diabetes mellitus/HIV become more vulnerable to the depressive disorder? How so?

Acknowledging that, in many diseases individuals are exposed to treatments as well as to the stress caused by the disease, that these may act on the brain for an extensive period of time, that emotional and behavioural problems are disorders of the brain, and that behaviour is the last step of a cascade that started long before problems manifest

themselves, we probably should start with the brain, with its wiring and connections, with the way it interacts with its surroundings and with its susceptibility to context. Much variation exists in how the brain is wired and how it functions but this variation does not exclude the existence of some possible and predictable set of factors that put some patients at a heightened risk for severe emotional and behavioural problem in concomitance with their medical condition.

While we are often very well equipped to treat or manage complex medical conditions such as, diabetes or cardiovascular problems, we have not been so good at reducing long-term morbidity or disability developed by some of the patients suffering from these conditions, where the nature of the disability is often emotional or behavioural, which are both recognized to constitute a major burden of disease. The question then is what drives the onset of the emotional and behavioural disability?

According to the definition of allostasis, the extra load, that is usually observed in disease states, occurs when the protective mechanisms that are turned on to achieve stability, fail to be turned off or become inefficient [2, 15]. This, then, starts a "domino-effect", sustained by a vicious cycle of mediators of allostasis, that by impairing the brain environment dramatically alters its functionality.

Usually, the extracellular environment of neural tissue is stringently controlled with the blood brain barrier (BBB), acting as a gate keeper [16]. Alterations in the permeability of BBB have been observed in many systemic disorders [17]: plasma components, immune molecules or cells may enter the brain because of BBB disruption [16, 18] and subsequently activate resident microglia [19]. These cells are the main players involved in the brain immune defence network and the first to be activated in the presence of a harmful stimulus [20, 21], but they are also involved in neurodevelopment and in regulating brain connectivity in non-immune contexts [20, 22].

Microglia are particularly responsive to inflammatory signals and may be primed to respond more vigorously to a subsequent disruption of the brain equilibrium, spreading a deleterious wave in the central nervous system (CNS) [23], and being at the onset of a cascade of noxious events.

In fact, primed microglia may produce and release common mediators of allostasis, like pro-inflammatory cytokines. Cytokines are involved in the cross-talk between different types of cells within the CNS. The overproduction of the main pro-inflammatory cytokines, interleukin (IL-) 1β, IL-6, tumor necrosis factor-α (TNF-α) has been reported in the brains of patients suffering from major depression [24]. Recently, growing interest is directed to the role of inflammasomes, the molecular platform that leads to the activation of IL-1β and IL-18, in several neuroinflammation-sustained disorders, like MD, type II diabetes or even aging [25, 26]. In particular, a link between increased levels of IL-1β in MD and inflammasomes has been suggested [25, 26].

Furthermore, the increase in brain levels of pro-inflammatory cytokines (blood borne and transported or locally released by activated glia) is able to induce the expression of the tryptophan-metabolizing enzyme indoleamine 2,3-dioxygenase (IDO) [27, 28], the rate limiting step of the kynurenine pathway (KP).

Also, enhanced production of tryptophan catabolites (TRYCATs) points to a decrease in available tryptophan (TRP) that may be converted to serotonin, thus decreasing serotonin levels [29]. In addition, TRYCATs may exert a plethora of different effects: they can be pro- or antioxidants, neurotoxic or neuroprotective, and may also induce apoptosis [30, 31]. Abundant data from clinical studies as well as animal models associate immune activation and increased activity of KP with the development of depressive symptoms [for extensive review see 31, 32].

Altered permeability of the blood brain barrier, immune cell infiltration, activated microglia, and increased cytokine production [22] are among the hallmarks of neuroinflammation, which is defined as an active response of the brain against injury, infection or disease [33]. The role of prolonged neuroinflammation in the etiopathogenesis of depression (Fig. 1) is being extensively studied. In an exhaustive review, Maes and co-workers suggest how neuroinflammatory

pathways activated in depression may be harmful to the brain and the body and increase the risk of developing or aggravate the course of a series of "medical conditions" [14].

On the other hand, evidence is accumulating that chronic inflammation plays an increasingly important role in medical disorders that have a high comorbidity with depression, such as stroke, chronic pain, diabetes mellitus, and HIV infection. This review provides an overview of how neuroinflammation is altered in these four medical disorders, and investigate converging mechanisms that may make the brain more vulnerable to depression.

Materials and methods:

The guidelines prescribed by PRISMA (Preferred reporting items for systematic reviews and meta-analysis) were followed while constructing this review [34, 35].

An electronic database search of PubMed with several specific key terms in various permutations was performed using ProteinQuest (http://www.proteinquest.com), a web-based platform that, by integrating data from the scientific literature, allows the identification of the co-occurrence of biological concepts (e.g., proteins, disease names, drugs). The list of keywords included but was not limited to: pro-inflammatory cytokines, IL-18, IL-1β, TNF-α, cellular, humoral, immune, depression, neuroinflammation, blood brain barrier, TRYCATs, inflammasomes, NLRP3, diabetes, stroke, HIV, chronic pain, cardiovascular disease, comorbidity, microglia and glial cells. At each stage of the search, titles and abstracts were scrutinized and the most appropriate ones, organized into separate lists. In addition, articles relevant to our discussion were retrieved from the reference list of other online articles on each subtopic. This yielded a total of 1800 papers, 243 were used to construct this review. The role of neuroinflammation in depression is the subject of several excellent reviews [32, 33, 36], the focus of our review was to describe how a medical disorder (like chronic pain, diabetes mellitus, stroke or HIV infection) may influence some of the hallmarks of neuroinflammation known to be altered in MD patients. For this review, we chose to include articles published between 2004 and 2015. Articles with anecdotal evidence were excluded from the review (Fig. 2).

1. Stroke

Every year, about 16 million people worldwide have a first-ever stroke [37]: about 5-7 million people die and another 5 million remain disabled [38]. The importance of the immune system in this pathology is crucial: inflammation and immune activation can influence both the risk for stroke and its outcome [39, 40]. Brain inflammation is considered a secondary mechanism producing injury following stroke: the inflammatory response is the consequence of several triggering factors that lead to microglial activation, chemokine up-regulation, inflammatory cell chemotaxis, infiltration of immune cells, synthesis of pro-inflammatory cytokines, matrix metalloproteinases (MMPs), nitric oxide (NO) and more reactive oxygen species (ROS), as well as blood-brain barrier disruption [41]. In contrast, during the chronic phases of stroke, other immune responses cause neurotrophic factors to be released allowing neural repair. In this sense, post-stroke inflammation has both acutely damaging and chronically reparative properties and this balance has to be considered in the development of tailored therapies [41].

Neuropsychiatric disorders commonly occur during the post-stroke period: depression, anxiety, irritability and agitation, emotional liability, apathy, catastrophic reactions, delusions, hallucinations and central post-stroke pain [39, 42]. Depression is the most common neuropsychiatric disorder following stroke: between 29% and 36% of patients have depression up to 1 year after a stroke [10, 43, 44]. Moreover, depression after stroke is a chronic relapsing disorder [45]. Physical disability, stroke severity, and cognitive impairment consistently show a positive association with depressive disorder [45, 46]. The correlation between the neuroanatomic subtypes of stroke and post-stroke depression is not very substantial and contributes little to the prognostic evaluation of the mood disorder [47].

Post-stroke depression could be defined as a depressive syndrome occurring in the aftermath of a clinically apparent stroke and could be interpreted, considering the biopsychosocial model of mental illness, as multifactorial in its pathogenesis [48]. Biological, psychological and social factors interact determining mood symptoms characterized by depression, anxiety and feelings of despair as well as anhedonia [49, 50]. Ischemic insults directly affect neural circuits involved in mood regulation, and social and psychological influences modulate this kind of damage [50], however, there are relatively few hypotheses regarding its pathophysiology: one of these involves increased production of pro-inflammatory cytokines, particularly in limbic areas, and a widespread activation of indoleamine 2,3-dioxygenase with the subsequently depletion of serotonin in paralimbic regions [51].

The BBB consists of brain endothelial cells embedded within a precisely regulated environment containing astrocytes, pericytes, smooth muscle cells, and glial cells [52]. The BBB is modulated by various pathways of intercellular communication and by pathophysiological processes, such as, neurovascular coupling, cortical spreading depression, oxidative stress, and provides a dynamic interface between the peripheral circulation and the central nervous system [53].

Following ischemic stroke, the BBB is disrupted as a result of decreased BBB tight junctions (TJ) integrity [53]. Altered **BBB permeability** and functionality promotes inflammation and vasogenic brain edema, which exacerbate cerebral ischemic injury [52, 54]. The loss of TJ integrity occurs in a phasic manner, with interdependent mechanisms (ionic dysregulation, inflammation, oxidative and nitrosative stress, enzymatic activity, and angiogenesis). These mechanisms, then, could be critical for the development of new therapies [53].

Fang and colleagues reported that 10-O-(N,N-Dimethylaminoethyl)-ginkgolide B methanesulfonate (XQ-1H), a novel analogue of ginkgolide B, alleviates BBB breakdown in hyperlipidemic rats and protects endothelial cells against inflammatory response, possibly by mechanisms that inhibit inflammation [54].

An experimental study conducted on female rats demonstrated the neuroprotective effect of post-stroke treatment with insulin-like growth factor 1 (IGF-1): the administration of IGF-1 to middle-aged female rats reduced infarct volume and BBB permeability [55]. Liu and colleagues found that metformin attenuates BBB disruption and reduces neutrophil infiltration in mice following middle cerebral artery occlusion, resulting in better neurobehavioural outcomes [56].

On the other hand, BBB disruption could be an interesting therapeutic target. Borlongan and colleagues proposed cell therapy as a potential treatment for stroke and other neurological disorders. They suggested a combination of mannitol-induced BBB permeation and nuclear factor kappaB (NF-κB) decoy in order to enhance the therapeutic benefits of cell therapy with stem cells of human umbilical cord blood in stroke [57].

After injury, the immune system has important functions: removal of dead cells, subsequent astrocytosis and prevention of post-ischemic infection [58]. Grønberg and colleagues reviewed the temporal profile of leukocyte **infiltration** following experimental stroke: neutrophil granulocytes peak between day 1 and 3 days after experimental stroke; macrophages/microglia peak later than day 3 and stay in the infarcted area for longer time periods; T-cell infiltration shows a tendency to peak even later, from day 4 onwards [58]. Lehmann and colleagues used a rodent model of stroke to characterize how immune cells invade the ischemia-affected hemisphere. They found an increase in neutrophils and monocytes/macrophages, no numerical alterations in the number of microglia that shifted to an activated phenotype. Lymphoid cells increased in close vicinity to the affected vasculature [59].

Even though some studies correlated the presence of neutrophils to injury, Easton suggests that these immune cells may be subject to a threshold effect: when they reach a critical ratio relative to the volume of injury in the CNS, they adopt an anti-inflammatory phenotype that is able to reduce vascular permeability, possibly resulting in improved outcomes [60].

Lymphocyte subpopulations vary and their modifications correlate with clinical outcome in acute stroke, as underlined by Urra and colleagues [61]. A greater decline (caused by increased apoptosis) in T-helper and T-cytotoxic lymphocytes and increased levels of cortisol and metanephrine were correlated with more severe stroke. Poor outcome was associated with reduced levels of B cells [61]. Mast cells (MC) have an important function in the immune response consequent to stroke as well. In a rat model of transient cerebral ischemia, Strbian and colleagues found that, in the early phase, MCs regulate microcirculation, BBB permeability, and edema formation [62].

Microglia play a key role in brain injury pathology and in the mood and behavioural responses to brain damage [63, 64]. **Microglia activation** consists of progressive morphological and functional changes in response to damage. This process occurs early in the area of the infarct but also in remote regions [65]. When microglia cells are activated, they assume an amoeboid morphology and release inflammatory cytokines (M1 phenotype). An alternative form of activation limits inflammation and phagocytizes tissue debris (M2 phenotype) [66]. These different phenotypes are expressed according to micro-environmental signals and could lead to the implementation of new therapeutic strategies using immune-modulatory interventions [67]. Some studies described the spatiotemporal pattern of microglia morphology during the evolution of cerebral injury after ischemic stroke and reperfusion, revealing a significant spatiotemporal relationship between microglia morphology and evolving cerebral injury in the ipsilateral hemisphere [68, 69]. Wang and colleagues suggested that activated microglia provide a neuroprotective role through neurotrophic factors and TNF-α expression [70]. This protective role was confirmed by Narantuya and colleagues: they observed that the transplantation of human microglial cells in stroke animals reduced ischemic deficits and apoptotic events through the modulation of gliosis, neuroinflammation and neurotrophic factors release [71]. Denes and colleagues proposed that microglia may play a protective function through phagocytosis of infiltrating neutrophils [72]. Furthermore, microglia cells mediate the demonstrated neuroprotective role of oestrogen and insulin-like growth factor -1, where, microglia are the source of IGF-1 and the locus of oestrogen-IGF-1 interactions [73]. However, microglia likely mediate neurotoxicity in the stroke penumbra through the activation of NF-κB, a transcription factor that promotes pro-inflammatory functions [74].

After ischemic injury, stressed and dying cells release endogenous signals, which bind toll-like receptors (TLRs) on microglia and astrocytes promoting the activation of NF-κB and/or IRF3-dependent gene transcription [75], and these pathways, in turn, promote the synthesis of **pro-inflammatory cytokines** [76] which have pro-inflammatory and pro-coagulant effects on endothelium [77]. The three major cytokines produced by neurones, astrocytes, microglia and oligodendrocytes are TNF-α, IL-1, and IL-6. Different cytokines are produced by functionally different populations of microglia and macrophages: this is potentially relevant for the development of anti-inflammatory therapies [78].

Also, aetiology of post-stroke depression could be associated with cytokine expression in the hypothalamus and with hypothalamic-pituitary-adrenal axis activity. In a rat model of stroke, TNF-α and IL-1β expression was inhibited by the administration of citalopram, confirming the utility of selective serotonin reuptake inhibitors in post-stroke depression [70].

TNF-α and its receptors, TNF-R1 (p55) and TNF-R2 (p75), are rapidly upregulated in the brain after injury [79]. TNF-α stimulates expression of tissue factor and adhesion molecules for leukocytes, release of IL-1, nitric oxide, factor VIII/von Willebrand factor, platelet-activating factor and endothelin, suppression of the thrombomodulin-protein C-protein S system, reduction of tissue-plasminogen activator and release of plasminogen activator inhibitor-1. TNF-α expression is associated with risk of recurrent stroke [80]. The important role of this cytokine is the rational to develop a decoy receptor and a monoclonal antibody that block the action of TNF-α. These molecules do not cross the BBB, so they have to be re-engineered as IgG fusion proteins with a BBB molecular Trojan horse [81, 82]. Post-injury treatment

with a TNF-α antibody reduced neuroinflammation and improved functional outcomes in a murine model of intracerebral haemorrhage [83].

Both central and haematopoietic-derived IL-1 have an important role in brain ischemic injury [84]. IL-1α is early expressed in areas of ischemic neuronal injury [85], while IL-1β can either inhibit, exacerbate or induce neuronal damage and death [77]. Furthermore, IL-1 drives extracellular matrix re-modelling and has an important function in the development of cerebrovascular inflammation during acute brain damage [86]. An IL-1 receptor antagonist (IL-1Ra), in animal models, plays a protective role against ischemic and haemorrhagic brain damage [87]. Also, IRAK-1/4 (IL-1 receptor associated kinases) inhibition may have a neuroprotective role in brain injury [88].

IL-6 modulation is more complex: IL-1, TNF-α, TGF-beta, prostaglandins and many other mediators are involved in its regulation. However, IL-6 seems to be correlated with the severity and prognosis of the stroke: increased IL-6 concentrations are associated with neurological deficit and stroke outcome [89, 90].

Inflammasomes are multi-protein complexes contained mainly in microglia and macrophages. Cytokine production happens upon activation of the intracellular NLRP3 inflammasome system, a protein complex including the Nod-like receptors NLRP3, apoptosis-associated speck-like protein (ASC) and caspase-1. Activation of NLRP3 leads to oligomerization and recruitment of ASC and pro-caspase-1, with autocleavage and activation of caspase-1 [26], which cleaves both pro-IL-1β and pro-IL-18 into their biologically active mature forms [91]. During cerebral ischemia, inflammasomes are activated, so they and their products represent an important potential target for future treatments [92, 93]. The intracellular Nod-like receptors are key mediators of inflammatory responses. In particular, NLRP3 is supposed to have a critical role in the activation of caspase-1 and to be linked to NOX2-mediated oxidative stress [94]. In mice models, NLRP3 deficiency was associated with a reduction of brain injury, suggesting that NLPR3 could be a therapeutic target [94].

Post-stroke inflammation may induce up-regulation of the oxidative metabolism of tryptophan along the KP, which, by producing **tryptophan catabolites**, plays a key role in the mechanisms underlying neuronal damage and neurodegenerative disorders [95]. This pathway contributes to the oxidative stress generating quinolinic acid (QUIN), an agonist at N-methyl-D-aspartate (NMDA) receptors; kynurenic acid (KYNA), an antagonist at glutamate and nicotinic receptors; and 3-hydroxyanthranilic acid, a redox-active compound [96]. The pathophysiological role of IDO and kynurenine aminotransferase (KAT) seems to be relevant in stroke [97, 98]. The activity of the KP correlates with initial stroke severity, stroke-induced inflammatory responses and long-term stroke outcome [96, 97]. Ormstad and colleagues found post-stroke fatigue to be associated with the activation of the kynurenine pathway and, consequently, with a lower bioavailability of TRP for brain catecholamine synthesis [99, 100]. Concerning post-stroke depression, recent studies have not found significant associations with the KP [100, 101] while Gold and colleagues suggested that IDO activation might be relevant to the development of post-stroke cognitive impairment [102].

Finally, considering the importance of neuroinflammation in the risk, onset, progression and outcome of stroke, the molecular patterns involved in the immune response could be considered as potential therapeutic targets, both acutely and chronically, with immune modulating interventions tailored to the specific phase of stroke [41].

2. Chronic pain

According to the definition of the "International Association for the Study of Pain", pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (http://www.iasp-pain.org/). If a painful condition lasts longer than 3-6 months, it may be diagnosed as chronic. The definition of chronic pain is vast and comprises a large group of clinical syndromes in which pain neither protects nor supports healing and repair and tends to become maladaptive [103].

The resulting severe debilitating condition, affects 20% of adult Europeans [104], and clusters frequently with depression, approximately in 30-60% of the subjects [9]. In fact, the prevalence of depression is higher in chronic pain patients while a diagnosis of depression is associated with an increased risk of developing chronic pain [105].

Such a high co-occurrence and tight relationship suggest the existence of common underlying mechanisms that ask for a stringent regulation of immune-to-brain signalling, mandatory for generating a proper brain-to-periphery response. Disruption of this fine cross-talk may be the key event that adds to and subsequently exceeds to maximum support the allostatic load in patients suffering from chronic pain. A great deal of scientific effort has been spent to study what happens in the presence of peripheral inflammation/peripheral nerve injury at the spinal level [106], while little is known concerning the impact of pathological stimulation of noxious afferents on central higher structures.

Numerous studies showing that inflammatory pain alters **BBB permeability**, come from animal models of inflammatory pain [107]. Neuropathic pain, on the other hand, seems to be associated with disruption of the blood-spinal cord barrier and the blood-nerve barrier [108, 109], but little is known of changes in BBB permeability in the presence of peripheral nerve injury [110].

The central intake of the normally impermeable marker [^{14}C]sucrose and a dysregulation of TJ protein expression levels in microvessels (occludin, Jam, claudin-5) was increased 72 hrs after an injection of the inflammatory agent complete Freund's adjuvant (CFA) in the hind paw of Sprague Dawley (SD) rats [111]. Interestingly, an injection of CFA in the hind paw is able to induce a long lasting hyperalgesic condition, but can also affect depressive-like and anxiety-related behaviours in mice [112, 113] and rats [114].

Increased BBB permeability was also observed in another model of inflammatory pain: a marked change in occludin isoforms (monomeric, dimeric, oligomeric) at TJ of the BBB was induced 3hrs after an injection of λ-carrageenan in the hind paw of female SD rats, possibly through a reduction in disulphide bonds of oligomeric assemblies [115].

Too often in the literature the terms "leakage", "permeability" and "breakdown" are used as synonyms [110]. The increase in BBB permeability induced by peripherally caused central inflammatory pain may be a transient event, not an irreversible process [107, 110, 116]. However, further studies are necessary to better understand the impact of chronic pain on the BBB, considering that current data are limited to short experimental exposure lasting from 3 to72 hrs post injection. Del Rey and co-workers characterized the development and progression of experimentally induced arthritis in female rats for 55 days [117]. They proposed that inoculation of bovine type II collagen and incomplete Freund's adjuvant caused a long lasting disruption in the communication between the CNS and afferent immune signals [118]. Such an impairment in the brain/immune system communication may be present also in pathological conditions characterized by a persistent low grade inflammatory condition, like chronic pain [119].

Inflammation initiated in the periphery can elicit an immune response in the CNS. Several animal models of nociception suggest that peripheral nerve injury or inflammatory insults are at the onset of a systemic response that has important repercussion in the CNS, activating brain cells like microglia and astrocytes. Evidence is accumulating for a role of the glia population in the generation of persistent pain [120, 121]. Once **activated, microglia and astrocytes** exhibit increased production of specific surface markers with respect to their resting phase, for example, CD11b (cluster of differentiation 11b), CD14 for microglia, and glial fibrillary acidic protein (GFAP) and the calcium-binding peptide S100β for astrocytes [122]. Furthermore, activation of glial subtypes following peripheral noxious stimuli is time dependent: microglia activation is rapid and is followed by astrocytic activation, which attributes distinct roles in initiation and maintenance of chronic pain for these cell populations [120, 121].

Increased microglia activation in the brain and brainstem was demonstrated in a surgical model of neuropathic pain. After a double ligation of the sciatic nerve (chronic constriction injury, CCI), rats showed a significant increase of

CD11b-positive microglia in the periaqueductal gray, hypothalamus [123], and thalamus [124], 4 and 7 days after CCI respectively, as compared to the sham operated control group. Time following surgery is a critical factor when evaluating the effects of neuropathic pain on glia activation: no effect on the expression of GFAP and CD11b was observed in the amygdala, hippocampus and prefrontal cortex, 22 days after a spinal nerve ligation (SNL) [125, 126]. As for inflammatory pain, Raghavendra and co-workers have demonstrated that following CFA injection in the hind paw of SD rats, the expression of microglia markers increased as early as 4 hours post injection and was still upregulated 14 days after treatment. In the same experimental conditions, the increased expression of astrocyte markers (GFAP and S100β) showed a delayed pattern and was observed only after the subacute phase (4 days) [127].

Recently, in humans, a general increase in binding of [^{11}C]-PBR28 in the brain of patients diagnosed with chronic low back pain (LBP) was observed [128]. ^{11}C-PBR28 is a newly developed PET/MRI radioligand that binds TSPO, a traslocator protein (18 kDa), known to be upregulated in activated microglia and reactive astrocytes in animal models of nociception [129, 130]. Increased tracer binding was observed especially in the thalamus and somatosensory cortex of patients with chronic low back pain with respect to their matching controls (TSPO polymorphism, age, sex). This is the first evidence *in vivo* of central glial activation in human pain disorders [128].

More interestingly, an increase in TSPO density has been recently demonstrated in a substantial sample of patients with depressive disorder using [^{18}F]FEPPA, another TSPO PET radioligand. The finding was prominent in the prefrontal cortex, anterior cingulate cortex and insula [131].

Peripheral circulating cytokines may exert central effects by entering the CNS through diffusion or infiltration of a more permeable BBB, but may also be released within the brain by activated glial cells [132]. An increase in the levels of **pro-inflammatory cytokines** in patients suffering from depression or chronic pain has been reported [133-135], however little is known regarding the central effect on cytokine expression in animal models of nociception in specific brain areas.

An intraplantar injection of CFA induced an upregulation of TNF-α in the anterior cingulate cortex (ACC) [136] and in the basolateral amigdala (BLA) [137] in mice during the chronic phase of inflammation (days 3–7), while after 48 hrs the effects of CFA on expression levels of IL-1β, IL-18, IL-6 in several brain areas (hippocampus, thalamus, hypothalamus) were less marked and different depending on the mouse strain [138]. In the rat, an increase in mRNA and protein levels of cytokines (IL-6, TNF-α, IL-1β) in the brainstem and forebrain induced by CFA was demonstrated to last at least 14 days after injection [127]. This type of sustained imbalance in cytokine levels has been demonstrated also in several animal models and seems common to the central effects of neuropathic pain as well [119].

Following spinal nerve injury (SNI), brain levels of IL-1β and TNF-α were increased, peaking approximately three days following surgery [139]. IL-1β expression was regulated in a time and area specific pattern following a chronic constriction injury [140, 141]. An increase in hippocampal mRNA levels of IL-1β was demonstrated in both SNI and CCI rats (SD and Wistar) 10 days after surgery. This effect was still present 24 days after nerve injury [142], while in the same experimental condition, an induction of IL-6 expression was observed in the hippocampus of SNI rats only in the early phase and only in the Wistar strain. Increased protein levels of IL-6 and IL-1β were observed in cingulum and hippocampus in SD animals 21 days after either CCI or SNI when compared with their respective control group [143]. Interestingly, in another surgical model of neuropathic pain, SNL, expression levels of IL-1β, TNF-α and IL-6 in hippocampus and prefrontal cortex of both male and female SD rats were not altered 22 days after nerve injury [126].

The connection between brain cytokine concentration and nociception has been supported by numerous studies using animal models of both inflammatory and neuropathic pain. In particular, converging evidence points to a pivotal role played by IL-1β [116, 144, 145]. Another member of the IL-1 superfamily, IL-18 and its receptor system [146, 147],

implicated in the pathogenesis of peripheral inflammatory diseases and in the CNS [148], has been recently involved in mediating pain facilitation at the spinal level [149-152]. No data are actually available regarding its contribution to the central mechanisms underlying and sustaining chronic pain and we are aware of only one study investigating the role of **inflammasomes**, protein complexes involved in activation of IL-18 and IL-1β, in chronic pain. Here, NLRP3 and caspase-1 gene expression and protein levels were increased in blood mononuclear cells of patients suffering from fibromyalgia, a common chronic pain syndrome. This increase was coupled to an increase in serum levels of IL-1β and IL-18 with respect to matching controls [153]. Central NLRP3 has been shown to be involved in the lipopolysaccharide (LPS)-induced sickness behaviour syndrome [154], but its role in chronic pain remains to be elucidated.

Numerous data suggest that increased activity of the IDO enzyme may be involved in the development of depressive-like behaviour [155, 156], by decreasing serotonergic tone and increasing the production of **TRYCATs** [31].

Similarly, an upregulation of IDO expression in rats with coexistent nociceptive and depressive-like behaviour has been observed [157]. A CFA injection in the joints of Wistar rats produced long lasting alterations in nociception (thermal and mechanical) as well as in immobility in the forced swimming test which was accompanied by a steady increase in mRNA and protein levels of IDO1 and in its activity (increase in kynurenine/tryptophan ratio and decrease in serotonin /tryptophan ratio) in the hippocampus (but not in the thalamus) of CFA-exposed animals with respect to their controls. A causal role for IDO in nociceptive and depressive behaviours was demonstrated by administering an IDO competitive inhibitor (1-methyl tryptophan) to CFA treated rats and by using IDO1KO mice: in both approaches the authors observed an attenuation of CFA-induced nociceptive and depressive behaviour [157].

In a recent paper, no induction of central expression of IDO1 was observed in the model of spared nerve injury. Given that SNI is associated with a mild inflammatory state, this suggests that IDO is not involved in mechanical allodynia in neuropathic pain [158].

Human data on the role of IDO in central pain processing are still incomplete, in the study by Kim and co-workers patients with both LBP and depression showed increased plasma IDO levels and enzyme activity, with respect to normal control subjects [157]. However, data on patients with chronic pain without depression were not included in this study. Enhanced plasma IDO activity was demonstrated also in patients suffering from complex regional pain syndrome (CRPS), a chronic neuropathic pain condition. Moreover, 66% of CRPS patients enrolled in the study were diagnosed with depression, but its severity was not evaluated [159].

Finally, shared mechanisms underlying chronic pain and depression are supported also by the efficacy in both conditions of tricyclic antidepressants (TCAs) and minocycline in clinical and preclinical studies. In fact, evidence suggests that TCAs possess anti-inflammatory properties [160, 161] and are effective in several chronic pain syndromes: neuropathic pain, chronic low back pain, fibromyalgia (for an extensive review see 162). Moreover, minocycline, a second generation tetracycline, has been proposed to possess both antidepressant [156, 163, 164] as well as anti-inflammatory properties [165, 166], as it prevents hyperalgesia in inflammatory model of nociception, prevents microglia activation and decreases the release of pro-inflammatory cytokines [167, 168].

Thus, converging evidence suggests the existence of an altered communication between immune and nervous system in both MD and chronic pain that may drive and sustain the transformation of a singular or isolated “physiological” event, like acute pain or sickness behaviour, into “pathological” conditions [116].

3. Diabetes mellitus

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia. Two main types have been etiologically recognized, type 1 and type 2, but more than 85% of total diabetes prevalence is represented by type 2. Type 1 is an insulin-dependent form of DM, which results from a deficiency of insulin secretion. Type 2, the non-

insulin-dependent DM, involves insulin resistance by target organs and inadequate insulin secretion. The latest estimates show a global prevalence of 382 million people with diabetes in 2013 which is expected to rise to 592 million by 2035. Despite that the two types of diabetes have different etiological characteristics and variation according to age, sex, and geographical location, both forms can lead to multisystem complications of microvascular endpoints, including retinopathy, nephropathy and neuropathy, and macrovascular endpoints, including ischaemic heart disease, stroke, and peripheral vascular disease [169].

Chronic hyperglycemia leads to various pathological changes both in peripheral organs as well as in the central nervous system [170]. Neuroinflammation, together with impaired vascular function, reduced blood flow, oxidative stress, and abnormal lipid metabolism, have all been proposed to play a role in the pathogenesis of both peripheral neuropathy and CNS disease associated with diabetes [171].

Data indicate that type 2 DM is associated with alterations in the innate immune system and the endocrine system, and that the associated inflammatory imbalances are involved in the development of secondary disease complications or comorbidities [172, 173]. In particular, type 2 DM driven neurodegenerative disease depends on neuroinflammation. Accumulating evidence strongly suggests that chronic inflammation contributes to the pathogenesis of type 2 DM which points to a bidirectional relationship between diabetes and the innate immune system [12, 174].

In particular, DM is a risk factor for cerebrovascular disease which can exacerbate cognitive dysfunction. Patients with type 2 DM have twice the risk of developing Alzheimer's disease or other types of dementia. This association may be explained by DM-mediated cerebrovascular damage affecting cognition through multiple mechanisms, including oxidative stress and deregulated innate immunity characterized by persistent subclinical chronic inflammation, recently linked to states of insulin resistance and hyperglycemia [170, 175]. Furthermore, a relation between type 2 DM and depression has been suggested by several clinical reports. Possible explanations for this correlation refer to chronic dysregulations of the hypothalamic-pituitary-adrenal axis, such as, high cortisol levels and reduced insulin sensitivity or to the activation of the immune system, leading to inflammatory processes [174, 176]. An additional explanation can be found in stress vulnerable patients in which high amounts of diabetes-related distress or a deficit in coping with diabetes-related problems could result in symptoms of depression [177, 178].

The link between diabetes and inflammation is based mostly on findings in type 2 DM conditions, where hyperglycemia and hyperinsulinemia display a clinical increase in pro-inflammatory markers and acute phase reactants, like IL-1β, TNF-α, IL-6, chemokines, C-reactive protein, and cortisol [12]. Inflammation, and more specifically pro-inflammatory cytokines, and other molecules with a relevant role within the inflammatory process, may be critical factors in the development of microvascular diabetic complications [179]. IL-1, IL-6 and TNF-α are involved in the proliferation of meningeal cells and extracellular matrix synthesis besides their implication in the hemodynamic disbalance between vasodilatory and vasoconstrictive mediators, which may result in alterations of endothelial permeability, glomerular blood flow and glomerular filtration rate. Consequently, these altered processes induce intraglomerular microcirculatory abnormalities responsible for diabetic nephropathy [180-183].

Unlike in the peripheral nervous system, where tight junctions of the blood-nerve barrier are less restrictive and diabetes causes severe neurodegenerative changes, in the brain, hyperglycemia has been shown to alter the vascular homeostasis of the BBB [184, 185]. Increased **permeability of the BBB** has been demonstrated experimentally in streptozotocin (STZ)-induced diabetes in rats (type1 DM model) using peripheral infusion of tracers such as glucose and mannitol. The estimated distribution of sucrose in the brain indicated that the BBB was indeed compromised in this model of diabetes and treatment with insulin of the STZ animals normalized blood chemistry and attenuated the change in

sucrose distribution [186]. This study demonstrated that BBB permeability was not affected only by acute hyperglycemia, but that the changes in BBB permeability were time dependent.

Interestingly, treatment with statins, cholesterol-lowering medications, reduced the permeability of the BBB in STZ-induced diabetic animals [187]. Regarding the BBB level, increased vascular permeability, accelerated pathologic angiogenesis, excessive apoptosis of endothelial cells through the activation of protein kinase C, has been observed which in turn seems to activate a pathway resulting in an inflammatory response. Moreover, hyperglycemia induces excessive production of ROS that causes pathological changes in the endothelium of the BBB and the **activation of microglia**. All these events induce chronic inflammation resulting in pathological changes in the BBB [175]. The interaction of oxidative stress with inflammatory pathways complicates hyperglycemia mediated neuronal damage. Structural features of neurons are affected because the glycosylation of myelin protein alters its antigenicity causing infiltration of monocytes, macrophages, neutrophils from peripheral blood, and activation of glial cells in the CNS. These infiltrating immune cells secrete inflammatory cytokines like IL-1β, IL-6, IL-17, TNF-α and chemokines, and increase nerve excitability, thus leading to oedema and neuroinflammation. Diabetes linked hypoxia and ischemia also aggravate neuroinflammation through the release of NO, a physiological mediator of inflammation [188].

Dey and collaborators demonstrated that the corticosterone mediated accumulation of microglia in the hippocampus of leptin receptor deficient mice is accompanied by elevated levels of **pro-inflammatory cytokines,** IL-1β and TNF-α, in the same area [189]. Other data supports this evidence: Hwang and co-workers observed the activation of microglia and the production of the cytokines IL-1β and IFN- γ in the hippocampus of a rat model of chronic diabetes [190]. On the contrary, treatment with minocycline in diabetic rats did not alter the increase of IL-1β and TNF-α [191]. Moreover, this study showed that inhibiting microglia activation in diabetic retinopathy, correlates with neuronal protection. In STZ treated mice, the gene expression of several cytokines changes in the spinal cord, which is probably essential for the development of neuropathic pain, a common complication of DM. Proteins of the TNF-family and various interleukins (IL-1β, IL-2, IL-4, IL-6, IL-9, IL-17, IL-12p70) resulted upregulated in activated microglia which suggests their involvement in the development of diabetic neuropathy because treatment with minocycline directly inhibits microglia activation in the spinal cord and diminishes the onset of pain [192]. In addition, neuro-immunological interaction is modulated by changes in the proportion of immune cells invading the spinal cord and by the release of cytokines from these cells. In this way, minocycline suppresses peripheral inflammation induced in mice by STZ by decreasing peripheral inflammatory signals and attenuating immune-to-CNS-communication [191, 193, 194].

Elevated concentrations of TNF-α were detected in the blood of patients with type 2 DM [195]. This increase coexists, especially, in the presence of obesity [196]. IL-1β has long been implicated in the development of type 1 DM. Increasing evidence suggests an important role for this cytokine in the early processing of the inflammatory signal and may represent an early biomarker of the disease. Moreover, IL-1β results closely correlated, especially, to the pathogenesis of type 2 DM [197, 198]. The effect of IL-1β on β –cells is due to the decreased number and secretion of pancreatic β –cells, this supports a strict relation between inflammation and induction of insulin resistance [196, 199]. Therefore, this cytokine is thought to have a critical role in driving neuroinflammation and is induced by various mechanisms.

Also, IL-18 seems to be involved in the pathogenesis and progression of diabetes. IL-18-stimulated mouse islets produce nitric oxide and ultimately undergo apoptosis [200]. In humans, increased IL-18 levels have been observed in the serum of patients at high risk for developing diabetes [201], as well as in children and adults diagnosed with type 1 and type 2 diabetes [202-206]. The secretion of IL-1β and IL-18 is mediated by a complex signalling pathway guided by the activation of TLR and by NLRP3 **inflammasome** [207]. This protein complex plays a pivotal role in the

production of IL-1β and IL-18 in response to various danger signalling molecular patterns and caspase-1 is considered a rational and effective target for modulating the initiation and progression of various autoinflammatory and autoimmune diseases [208]. Emerging evidence investigates the role of inflammasomes as one of the mechanisms underlying the pathogenesis of diabetes. The activation of NLRP3 inflammasome has been observed after obesity-induced signalling and induction of the production of IL-1β in adipose tissue of type 2 diabetic patients [209]. Moreover, levels of chemokines CXCL10, CCL2 and IFN-γ were reduced in the adipose tissue of NLRP3-deficient mice. Wen and collaborators also showed that the saturated fatty acid palmitate, induced the activation of the NLRP3 inflammasome in hematopoietic cells, which are responsible for the impairment in insulin signalling and in the inhibition of glucose tolerance in mice [210]. Also, in peripheral blood mononuclear cells and monocyte-derived macrophage cells of patients with type 2 diabetes, elevated levels of NLRP3, ASC, IL-1β and IL-18 mRNA as well as protein levels were observed. Additionally, these patients presented increased activation of caspase-1 and maturation of IL-1β and IL-18 [208], which suggests a strong association between the NLRP3 inflammasome and the pathogenesis of type 2 diabetes.

Various enzyme activities involved in the production of **tryptophan catabolites** such as kynurenine (KYN), KYNA, 3-hydroxy-kynurenine (3-HK), QUIN and picolinic acid have been reported to be affected by insulin-dependent diabetes [211]. The insufficient production or compromised action of insulin leads to increased blood glucose levels and trigger a complex panel of metabolic disturbances, accompanied by inflammation, oxidative stress and vascular damage [212, 213]. Therefore, it could be useful to examine the production of biologically active TRYCATs in diabetes in order to better comprehend its pathophysiology. Emerging data revealed an alteration in the production of these metabolites in diabetic patients, but we are just at the beginning and additional research is still needed to help understand their role. Clinical and experimental data suggest an increased metabolism of TRP in diabetes, most likely, resulting from an up-regulation of the KP. A recent study, by Chmiel-Perzynska and co-workers, specified the influence of experimental diabetes on kynurenic acid synthesis in the rat brain, observing a prominent increase of KYNA the hippocampus, while cortical and striatal levels were not affected [214]. Furthermore, KYNA was increased in urine of non-human primates and in mouse models of type 2 diabetes mellitus [215], as well as in patients with diabetic retinopathy [216].

Xanthurenic acid (XA) was the first KP metabolite to be enhanced in type 2 diabetic patients when compared to healthy subjects. High levels of XA precursors, KYN and 3-HK, were found in samples of serum of retinopathy patients [216].

Moreover, in the hepatocytes of STZ-induced diabetic rats, increased production of both KYN and QUIN has been detected, suggesting that these TRP metabolites may affect the pathophysiological state of insulin dependent DM, especially in the immune and the neuronal system [186, 211]. These data have been further confirmed by the authors, that is, mRNA levels of tryptophan 2,3-dioxygenase (TDO), a constitutive enzyme that catabolizes TRP, were higher in hepatocytes of diabetic patients, which indicates enhanced TDO activity [211].

Research, during the past decade, has demonstrated that diabetes and comorbid pathologies are not only disorders involving peripheral tissues but imply changes in neurological process resulting in neural dysregulation and altered neuro-physiological processes as well. Interdisciplinary research in neuro- endocrine- immunology has linked metabolic disorders, such as DM, to inflammation in the brain [217].

Neuroinflammation impairs neuronal regulatory mechanisms and induces multiple pathological changes that contribute to the onset of metabolic and neurodegenerative diseases and ultimately may lead to depression.

4. HIV infection

Human immunodeficiency virus is a variable ribonucleic acid (RNA) retrovirus that affects human cells (including cells of the immune system), possibly leading to acquired immunodeficiency syndrome (AIDS). According to the World Health Organization (WHO), in 2013, approximately 35.0 million people were living with HIV/AIDS worldwide.

HIV/AIDS has been estimated to be the first global leading cause of burden of disease by 2030, immediately followed by major depressive disorder (MD) [218]. This fact is particularly relevant considering that depression is the most common psychiatric comorbidity of HIV infection. Comorbid HIV infection and MD negatively impact on the course and prognosis of these diseases reciprocally [11]. In fact, when depressive symptoms were assessed before HIV testing, HIV+ individuals with depressive symptoms had a lower CD4+ count with respect to patients with no symptoms. Moreover, in newly diagnosed HIV-infected individuals, depression had a negative impact on initial health-seeking behaviour [219].

However, even if an high incidence of depressive disorders has been reported in HIV+ individuals [220], the rate of prevalence of clinical depression in this population differs widely (from 0% to up to 80%) [221]. Reasons for this variability include, the study population (age, gender, route of HIV infection, ethnicity, HIV strains and stage of the pathology) and the instruments used to assess depression, considering that several confounding factors render MD diagnosis even more difficult in HIV+ subjects [222-225].

Nevertheless, most studies demonstrated that people living with HIV or AIDS tend to have a higher probability to develop MD than non-HIV-infected individuals. MD in HIV+ individuals may be the consequence of cellular and molecular effects induced directly or indirectly by the virus itself or may include pathophysiological responses triggered by the stress of receiving a diagnosis of HIV/AIDS (a chronic disabling medical illness), social isolation and stigma related to the pathology [226, 227].

Stressful life events as well as viral infection have been shown to cause inflammation and provoke **pro-inflammatory cytokines** production, both known to constitute contributing factors to the development of depression [228-230]. Chronic immune activation in HIV-infected individuals is an almost pathognomonic feature of progressive infection [228]. Markers of inflammation (including IL-6) are related to heightened mortality in patients with HIV infection and are independent predictors of disease progression [231, 232].

One of the hypotheses that may explain systemic immune activation during HIV infection assumes that it is due to the dramatic HIV-induced immunological and structural damages in the gut mucosa. Starting during the early phase of HIV infection and continuing throughout the entire course of the disease, $CD4^+$ T cells are depleted in the gastrointestinal (GI) tract, thus, providing a breakdown in mucosal immune surveillance [233-235]. Together with T cells loss, HIV-induced enteropathy is also associated with local inflammation, alteration of the microbiota, malabsorption, lymphocyte infiltration, T_H17 cells loss, epithelial injury, increased permeability of the mucosa and thus microbial product translocation [231, 236-242].

Consequently, HIV-induced damage to the gut barrier, together with local inflammation of the GI tract, is hypothesized to cause systemic inflammation by inducing translocation into the blood of microbial TLRs agonists derived from bacteria that stimulate innate immune as well as nonimmune cells to produce inflammatory cytokines [242-244]. HIV-mediated breakdown of the integrity of the gut mucosal barrier enhanced translocation to the blood of bacterial products, like LPS and bacterial DNA (e.g. 16S rDNA, common to most bacteria) [245, 246]. HIV+ individuals had significantly increased levels of plasma LPS when compared to HIV negative (-) individuals [245]. The endotoxin LPS is the major component of the outer membrane of Gram-negative bacteria known to induce a robust immune response, and produce pro-inflammatory cytokines, in mammalian cells. In HIV+ subjects, plasma LPS stimulates the production of pro-inflammatory cytokines (including TNF-α, IL-1 and IFN-γ) by activated monocytes/macrophages [245, 247], while high peripheral levels of LPS have been correlated with activation of innate and adaptive immune responses.

Furthermore, the LPS-induced production of IFNs in tissue-resident dendritic cells (DC) may partially account for the reduced levels of tryptophan and increased IDO activity measured in the plasma of HIV infected subjects. In DC, IFN-γ

induced indoleamine 2,3-dioxygenase, activating the kynurenine pathway [248]. IDO activity (as measured by the kynurenine to tryptophan ratio) is elevated in HIV+ individuals and positively correlates with plasma LPS concentrations [231]. Moreover, HIV-induced dysbiosis has been associated with increased tryptophan catabolism along the KP with **TRYCATs** production. Indeed gut-resident bacteria that metabolize tryptophan through the KP are enriched in HIV infected subjects [241].

More recently, the role of **inflammasomes** in HIV associated immune impairment has been observed. Activation of inflammasomes has been hypothesized to contribute to both local and systemic inflammation [249, 250], and that the NLRP3 inflammasome may participate in the disruption of the gut epithelial lining by inducing IL-1β [251]. HIV has been shown to induce NLRP3 in immune cells and this effect has been associated with IL-1β maturation and secretion [252-254]. As already mentioned, NLRP3 is involved also in the maturation of IL-18. Interestingly, IL-18 levels increase in the serum and plasma of HIV-infected patients [255, 256]. *In vitro* experiment performed by Chattergoon and colleagues demonstrated that HIV stimulates IL-18 production in monocytes through activation of the NLRP3 inflammasome [249]. Even if further studies are needed to clarify the role of NLRP3 and other inflammasome in HIV associated inflammation, it is convincible that inflammasomes may participate in the immune response following HIV infection. Indeed, HIV induces ROS production and pathogen-associated molecular patterns (PAMPs) translocation from the gut (e.g. LPS, DNAs and flagellin) that may prime and activate inflammasomes [243, 252].

Increased peripheral levels of pro-inflammatory cytokines are involved in HIV-associated neuroinflammation by mechanisms described earlier [32]. Circulating LPS may stimulate brain endothelial cells to produce pro-inflammatory cytokines (including IL-6) that increase virus and viral protein entry in the CNS, across the BBB [257-259]. Even though HIV is unable to enter the CNS via retrograde nerve transmission, it can "seek refuge" into the brain in a number of ways, almost immediately after peripheral infection has occurred [260]. Once inside the brain, HIV (as cell-free virus or infected peripheral blood mononuclear cells according to the "Trojan horse" hypothesis) infects microglia and perivascular macrophages, astrocytes and oligodendrocytes as well as neuronal progenitor cells (that are all permissive to the virus) and stimulates the *in loco* production and release of cytokines [261-263]. HIV-induced neuroinflammation is promoted by reduced integrity, and increased **permeability of the BBB** also because of the direct effects against neurovascular components of the virus and its proteins (e.g. glycoprotein 120 –gp120) [264-266].

Consequently, CNS-infiltrating and CNS-resident immune cells are the principal contributors to HIV-induced neuroinflammation. **Activated microglia** cells release neurotoxic agents, including pro-inflammatory cytokines (e.g. TNF and IL-1β), quinolinic acid and glutamate [260]. In human monocyte-derived macrophage and foetal microglia culture, HIV-1 infection increased the production of glutamate [267, 268]. In microglia, this is due to up-regulation of the enzyme glutaminase C and leads to neurotoxicity through the NMDA receptor [267]. Moreover, glutamate and glutaminase C levels are higher (and positively correlate) in post-mortem brain tissues of HIV infected patients with dementia as compared to HIV- controls [267]. Another endogenous modulator of the NMDA receptor, whose production is stimulated by HIV in microglia cells, is the metabolite of the KP: QUIN. HIV-induced QUIN released from microglia cells stimulate astrocyte apoptosis thereby inducing neuronal dysfunction and death [269]. Furthermore, neurotoxic viral proteins (including gp120 and the HIV transactivator protein – Tat) may also stimulate central cytokine (e.g. IL-1β) and QUIN production [270].

As for the GI, a role for **inflammasomes** in HIV-induced encephalopathy and the maturation of IL-1β has been proposed. Moreover, inflammasome activation may affect IL-18 and caspase-1 levels in the cerebral white matter of HIV+ patients [91] both known to play important roles in the CNS, with their production possibly inducing neuronal

injury [148, 271]. Microglia cells represent the major contributor to inflammasome-dependent IL-1β release within the brain following HIV infection in an envelope-depended manner [91].

Furthermore, we should consider that coinfection by HIV and other opportunistic pathogenic agents, as well as, drug and alcohol abuse, are factors that may enhance neuroinflammation [272-274]. In the highly active anti-retroviral therapy (HAART) era, that transformed HIV infection from a deadly into a chronic disease with a long-term life perspective, age represents a risk factor for HIV-associated neuroinflammation [275]. Also, HAART itself may affect CNS inflammation given that enhanced neuroinflammation was observed in the hippocampus and basal ganglia following HAART treatment [276].

Finally, although outside the scope of this review, other molecular mechanisms, likely linked to inflammatory processes, should be taken into consideration to better understand how HIV contributes to the development of depression, including HIV-induced alterations in: i) monoaminergic systems, ii) neurotrophic support and iii) neurogenesis [261, 277]. The role of persistent and uncontrolled systemic immune activation in disease morbidity and mortality associated with HIV/AIDS and response to HAART has been extensively explored because of its relevance to HIV disease progression. Current studies are mainly focused on exploring the role of HIV-induced inflammation in HIV-associated neurocognitive disorders (HAND), whereas little is known concerning its role in leading to MD [260].

In conclusion, even if it is now recognized that HIV+ positive individuals have a higher probability to develop depression than the general population, much research remains necessary to unravel the precise molecular mechanisms that lead to an enhanced vulnerability for the development of psychiatric disease in these individuals. Growing evidence indicates that neuroinflammation and related neurotoxicity may contribute to HIV-induced MD. Nevertheless, clear evidence of a causative, or even correlative, role for a biochemical chain of events activated by HIV and leading to MD, remain to be confirmed.

This is particularly important, especially because MD in HIV+ individuals leads to heightened HIV progression, increased mortality rate and reduced HAART response. Given that MD may affect the immune response and disease progression in HIV+ individuals, prospective longitudinal studies should be performed, to unravel the role of HIV-induced inflammation leading to depression, which together with *in vivo* models could represent a useful integrated approach to achieve this goal [278].

Conclusions:

At this moment in time, it is hard to assert clear causal relationships, however, an increasing number of studies indicates that converging mechanisms underlie the significant higher incidence of depression in stroke, chronic pain, diabetes mellitus or HIV infection, suggesting that disease induced neuroinflammatory processes do alter the risk for or the life trajectory leading to depression in a meaningful way.

In this review, we have summarized recent data concerning six biological mechanisms that are among the fundamental players in neuroinflammation and that are activated by these chronic and severe medical disorders.

The medical conditions considered for review are characterized by altered signalling in the brain or from the periphery to the brain, involving inflammatory or neuroinflammatory mediators [23, 24, 40, 116, 171, 260]. Whether considering stroke, chronic pain, diabetes mellitus or HIV infection, significant overlap seems to exist among the activated pathways in the brain that eventually may lead to a heightened risk for developing depression. We hypothesized that in these medical conditions, allostatic load is the result of a combination of intrinsic (gene) or extrinsic (time and environment) factors that ultimately may lead to depression (Fig. 3).

Our review advances evidence that substantial interaction exists between the activation of neuroinflammatory processes, observed in depression, and the activation of the same inflammatory and neuroinflammatory factors found to play essential roles in stroke, chronic pain, diabetes mellitus, HIV infection, thus, representing a possible important common substrate, explaining the high co-occurrence of depression in these medical disorders [9-12].

Especially, neuro-immune factors, such as, pro-inflammatory cytokines (e.g. IL-1β, TNF-α), activated glia and microglia, monocyte-derived macrophages as well as other factors involved in neuroinflammation, for example, BBB integrity, TRYCATs, and inflammasomes play an active role in the altered neuronal functioning of the sick brain.

In all four pathologies, an alteration of BBB integrity was observed [52, 108, 186, 258, 264], leading to infiltration of peripheral factors that are known to activate resident microglia. Evidence demonstrating morphological changes in the glial population, increased levels of circulating pro-inflammatory cytokines or increased production of these mediators within the brain were reported for stroke, chronic pain, diabetes mellitus or following HIV infection [77, 116, 190, 247]. In general, the activity of the kynurenine pathway appeared to be increased in the medical disorders considered. We also present evidence that the NLRP3 inflammasome, a new target whose role in neuroinflammation is emerging [26], may be involved in the pathogenesis of brain injury following stroke, chronic pain conditions, diabetes mellitus or in HIV associated immune impairment [92, 154, 209, 249]. This then, results in a generalized "vulnerable" brain that, over time, accumulates allostatic load [4, 5, 15].

Furthermore, the concepts of allostasis and allostatic load help to explain why patients suffering from the same disease, for example diabetes or stroke, with a very similar pathophysiological profile, receiving the same therapy, often have very different or even opposite outcomes. Given the extreme complexity of the problem, most risk factors by themselves will contribute only a small amount of risk, but together with other factors may help to explain a dynamic relationship among the cumulative burden of risk factors and predict a substantial part of future vulnerability or resilience. Thus, by considering that depression and stroke, chronic pain, diabetes, and HIV infection share a combination of underlying molecular, cellular and network mechanisms, we may be able to redefine how to think about psychological, emotional and cognitive difficulties common to these four pathologies, emphasizing that they are undeniably the late events of multidimensional neuro-inflammatory processes that started much earlier.

Finally, the cumulative burden associated with prolonged neuro-immune dysregulation in the presence of a long-lasting pathological condition may increase the vulnerability of an individual to other disorders.

In our review we propose a working model that stresses the fundamental role of neuro-immune factors that are activated by various medical pathologies while also being risk factors for the development of depression. When a person is diagnosed with stroke, chronic pain, diabetes, and HIV infection treating the disease should not be the only goal.

A significant proportion of patients go on to develop clinically meaningful deficits in emotional and psychosocial functioning often leading to depression [13].

Acknowledging that these long lasting pathological conditions are associated with prolonged neuro-immune dysregulation which in turn enhances the vulnerability of an individual to psychiatric disorders may lead to include mood disorder screening in routine assessment of overall health in these patients or to develop potential intervention strategies that target upstream inflammatory process. However, no simple solution exists to the complex problem of long-term well-being, but failure to comprehensively assess and closely consider the molecular consequences of a disease in a patient may lead to confusion surrounding his day-to-day struggles.

Our challenge lies in the complexity of translating and applying an interdisciplinary, multidimensional approach to clinical practice.

Early detection, using common neuro-immune risk factors as biomarkers and indicators of risk susceptibility may represent a valuable step in searching for new treatment targets and the development of innovative therapeutic approaches, offering important tools to help us intervene in a timely manner.

Figure captures:

Figure 1: Activation of the neuro-immune system may represent the link underlying the high co-occurrence of depression and medical disorders. Neuro-immune factors are known to be altered in depressive patients, here we gather evidence demonstrating that these hallmarks of neuroinflammation are altered in medical disorders with a high accumulative burden of disease like stroke, chronic pain conditions, diabetes mellitus, HIV infection, as well (BBB: blood brain barrier; CNS: central nervous system; TRYCATs: tryptophan catabolites; HIV: Human immunodeficiency virus).

Figure 2: Study inclusion flowchart.

Figure 3: Allostatic load is the result of a combination of intrinsic (gene) or extrinsic (time and environment) factors that interact with medical conditions or depression. Pro-inflammatory cytokines are allostatic mediators that promote neuroinflammation through several mechanisms. The cumulative burden associated with prolonged neuro-immune dysregulation in the presence of a long-lasting or chronic pathological condition may increase the vulnerability of an individual to other disorders. (TRYCATs: tryptophan catabolites; BBB: blood brain barrier)

List of Abbreviations:

AIDS = Acquired immunodeficiency syndrome

ASC = Apoptosis-associated speck-like protein

BBB = Blood brain barrier

CCI = Chronic constriction injury

CD = Cluster of differentiation

CFA = Complete Freund's adjuvant

CNS = Central Nervous System

DM = Diabetes Mellitus

GFAP = Glial fibrillary acidic protein

GI = Gastrointestinal

HAART = Highly active anti-retroviral therapy

HIV = Human immunodeficiency virus

IDO = Indoleamine 2,3-dioxygenase

IFN = Interferon

IGF-1 = Insulin-like growth factor

IL = Interleukin

KP = Kynurenine pathway

KYN = Kynurenine

KYNA = Kynurenic acid

LPS = Lipopolysaccharide

MD = Major depression

NF-κb = Nuclear factor κb

NLRP3 = NOD-like receptor family, pyrin domain containing 3

NMDA = N-methyl-D-aspartate

NO = Nitric oxide

QUIN = Quinolinic acid

ROS = Reactive oxygen species

SD = Sprague Dawley

SNI = Spinal nerve Injury

STZ = Streptozotocin

TH_{17} = T Helper 17

TJ= tight junctions

TLRs = Toll-like receptors

TNF = Tumor necrosis factor

TRP = Tryptophan

TRYCATs = Tryptophan catabolites

TSPO = Translocator protein

Conflict of Interest:

The authors confirm that they have no conflict of interest.

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Figure 1:

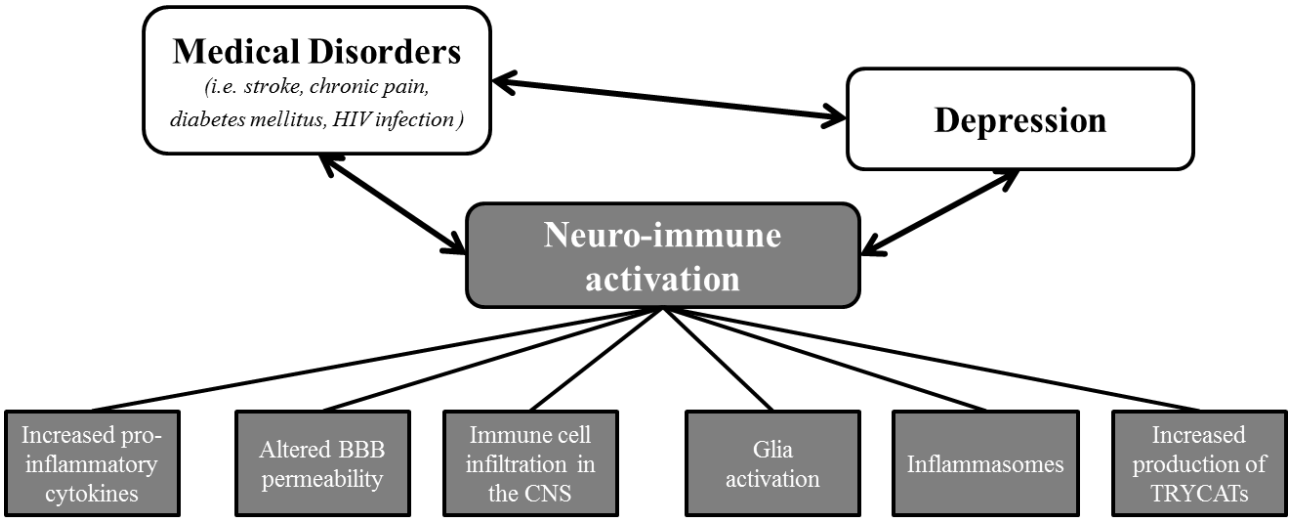


Figure 2:

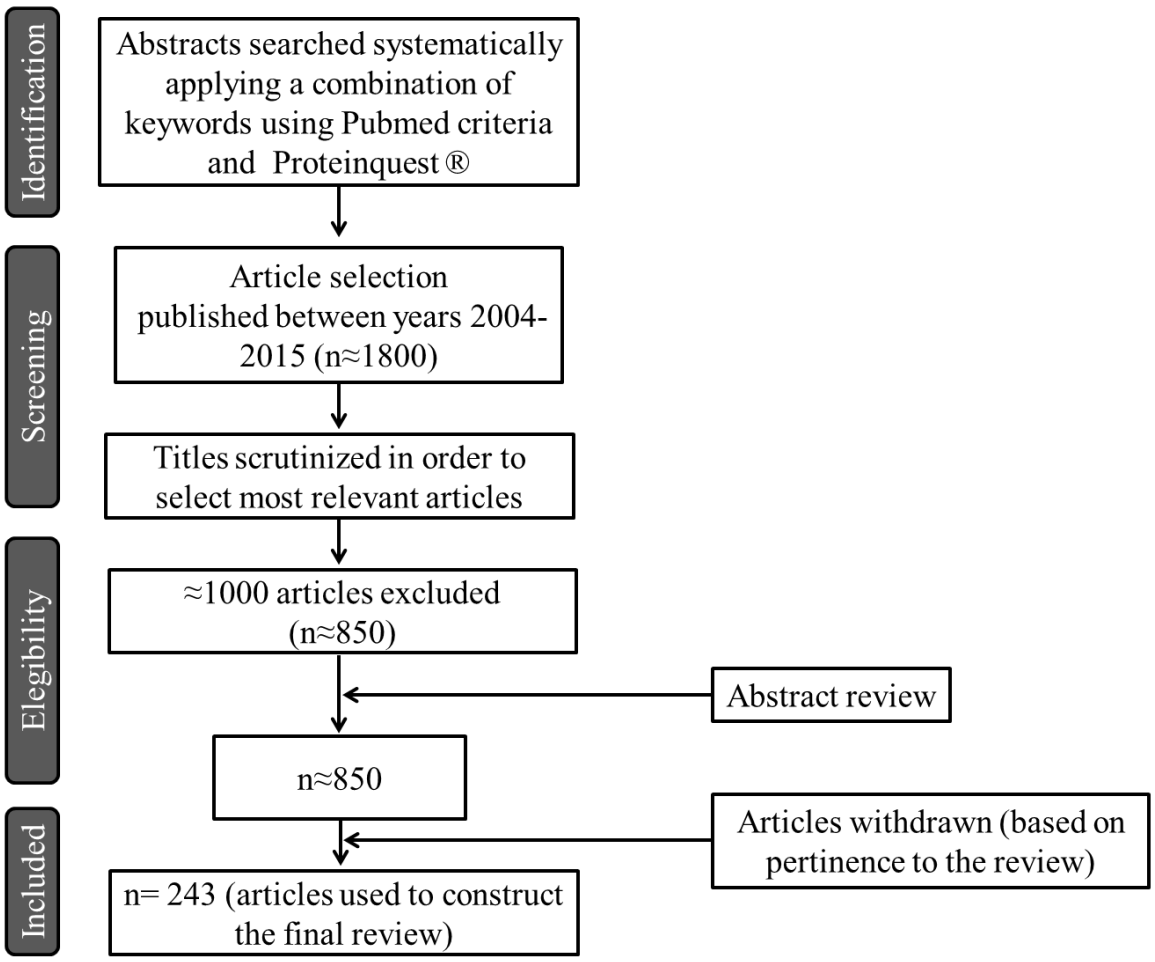
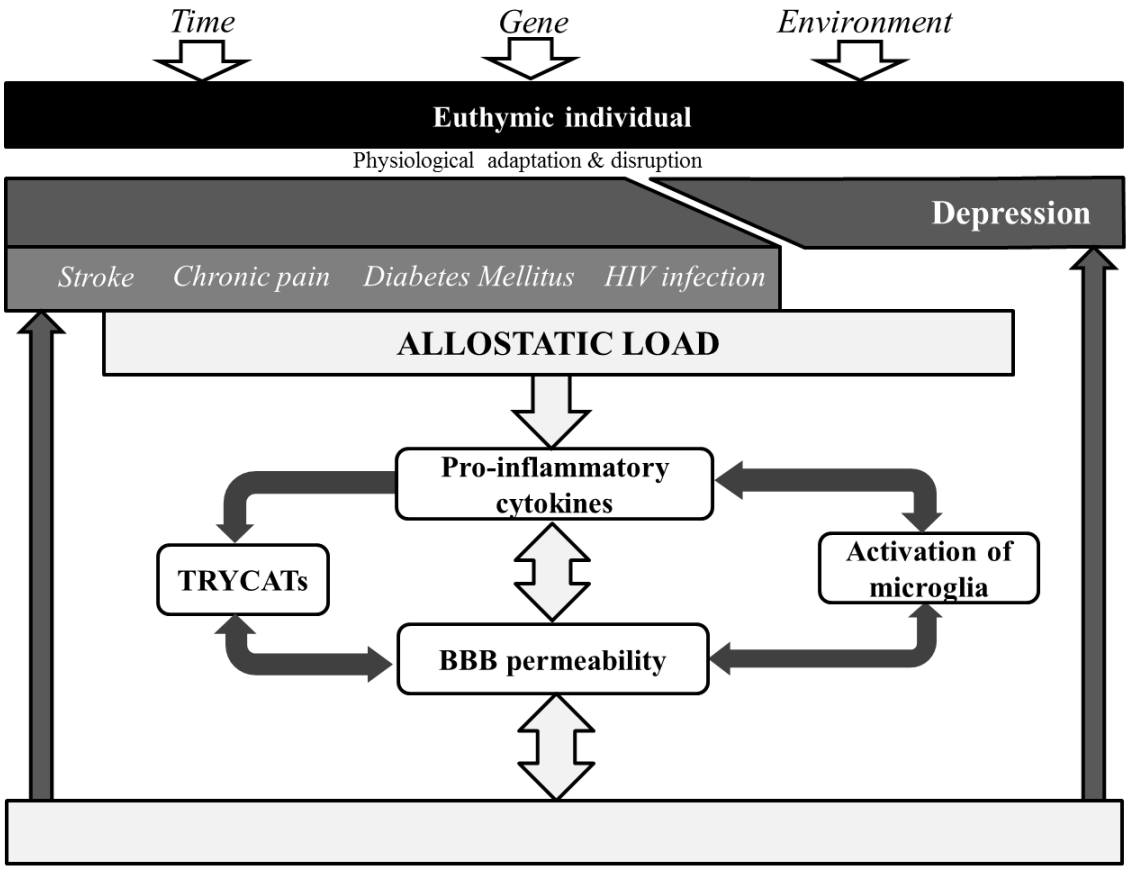


Figure 3


Time
Gene
Environment
Euthymic individual
Physiological adaptation & disruption
Depression
Stroke
Chronic pain
Diabetes Mellitus
HIV infection
ALLOSTATIC LOAD
Pro-inflammatory cytokines
TRYCATs
Activation of microglia
BBB permeability

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