Neuroinflammation is a common characteristic of many neurodegenerative conditions including Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS), stroke, and epilepsy. Neuroinflammation is also associated with mental health conditions such as depression, bipolar disorder, posttraumatic stress disorder (PTSD), and schizophrenia. Recent evidence suggests that individuals with these conditions have inflammatory and oxidative processes in the brain, which are susceptible to being alleviated by analgesic, anti-inflammatory, pro-neurogenic, and pro-neurotrophic treatments. The neuroinflammatory process in the brain is characterized by the activation of glial cells, changes in glucose metabolism and perfusion, and the activation of several pro-inflammatory factors. Such factors include the eicosanoids, cRaf-1, nuclear factor kappa B (NF-κB), cyclooxygenase-2 (Cox-2), tumor necrosis factor-α (TNF-α), interleukins, and the inducible nitric oxide synthase (iNOS). The activation of individual factors such as NF-κB can further increase the expression of other pro-inflammatory “partners in crime” including interleukins, eicosanoids, and iNOS. For example, the inhibition of the cRaf-1/NF-κB signaling pathway protects neurons against amyloid β peptide (Aβ) toxicity, considered the main cause of neurodegeneration in AD. Moreover, the multikinase and cRaf-1 inhibitor sorafenib restored memory and inhibited the expression of amyloid precursor protein (APP), NF-κB, Cox-2, and...
In this chapter, we will discuss potential benefits of targeting neuroinflammatory factors for the treatment of psychiatric and neurological disorders.

“To be lost, if it must be so!
To feed the remainder of life with one hour of fulness and freedom!
With one brief hour of madness and joy.”
— Walt Whitman [1]

INTRODUCTION

Neuroinflammation has been identified as an important mediator of neurodegeneration in many neurological disorders including Alzheimer’s disease (AD) [2-4], Parkinson’s disease (PD) [5, 6], epilepsy [7-9], ischemic stroke [10], autism [11], and amyotrophic lateral sclerosis (ALS) [12]. Chronic neuroinflammation continuously activates the immune response including acute phase protein response, cytokines (interleukins and interferons), dendritic cells, macrophages, lymphocytes, and glia in the brain. Microglia is a type of glial cell that plays an immunocompetent and phagocytic role in the central nervous system. It has been postulated that the neuroinflammatory process in the brain can be the result of the abnormal release of pro-inflammatory cytokines, nitric oxide (NO), and reactive oxygen species (ROS) by overactive microglial cells [13, 14], the main source of cytokines in the brain. Also, a role for other glial cells such as astrocytes in mediating neuroinflammation in neurological disorders including AD [15, 16] and ALS [17] has been documented. In fact, microglial activation has been shown to be toxic for oligodendrocyte precursor cells [18].

Within the last few years, numerous reports have postulated a role of neuroinflammation in psychiatric conditions such as schizophrenia [13], bipolar disorder [19], and depression [20]. It is not likely a coincidence that a large number of patients with conditions that are associated with neuroinflammation (e.g., AD and PD) or those who had suffered an ischemic stroke also develop psychiatric conditions. These conditions include depression and psychosis with symptoms such as hallucinations, delusions, sadness, agitation, and aggressiveness. A link between neuroinflammation and the appearance of these disorders needs to be further investigated.

SCHIZOPHRENIA

Schizophrenia is a chronic illness that affects approximately 1% of the world population (approximately 70 million people). The DSM-IV (American Psychiatric Association, 1994) describes five core features of schizophrenia. The “positive” symptoms include catatonic behavior, delusions, disorganized speech, and hallucinations. The “negative” symptoms include affective flattening (numbness) and alogia (poverty of speech). The etiology of schizophrenia is puzzling and several hypotheses have been postulated, some of them deriving from the known mechanistic actions of effective drugs. These include a dysregulation of the dopaminergic, GABAergic, and glutamatergic systems in the brain [21]. For example, the role of dopamine in schizophrenia is supported by the fact that most treatments involve anti-dopaminergic drugs affecting genes such as the dopamine D2-like
receptors (DRD2, DRD3), dopamine- and cAMP-regulated phosphoprotein of Mr 32 kDa (DARPP-32), brain-derived neurotrophic factor (BDNF), and catechol-O-methyltransferase (COMT; EC 2.1.1.6) associated with the dopaminergic system.

In addition to the dopaminergic theory of schizophrenia, it has also recently been proposed that schizophrenia is a type of neurodegenerative disease that is associated with neuroinflammation. For example, a progressive reduction of global gray matter volume has been shown postmortem in schizophrenic individuals at an early stage of the illness [22]. Neuroinflammation is characterized by the activation of microglia, which have a higher expression of the peripheral benzodiazepine receptor. In a study performed with the benzodiazepine receptor ligand (R)-N-[11C]-methyl-N-(1-methylpropyl)-1-(2-chlorophenyl) isoquinoline-3-carboxamide ([11C]-(R)-PK11195) that is used for the imaging of microglia with positron emission tomography (PET), it was found that schizophrenic patients have a significantly higher binding of [11C]-(R)-PK11195 in the hippocampus than healthy individuals [23] and an increased microglial density in the brain [24].

Immunological research in schizophrenia was initially motivated by observing schizophrenia-like psychosis after the influenza pandemic [25]. Today, numerous amounts of evidence further support a role of neuroinflammation in the pathophysiology of schizophrenia, including the presence of increased serum levels of pro-inflammatory cytokines in patients with schizophrenia [25]. The investigation of the effect of three atypical antipsychotic drugs perospirone, ziprasidone, and quetiapine on the release of cytokines by microglia and NO showed that these three drugs decreased NO release by activated microglia, while only quetiapine and perospirone inhibited the release of the cytokine tumor necrosis factor-alpha (TNF-α) [14]. In another study, it was reported that risperidone, an antipsychotic used to treat schizophrenia symptoms, also decreased the release of the pro-inflammatory NO, inducible NO synthase (iNOS), interleukin (IL)-1β, IL-6, and TNF-α in activated microglial cell cultures [26]. The inhibition of microglial activation by these antipsychotic drugs is proposed to reduce its toxic effect over neurogenesis and oligodendrogenesis, both of which are involved in the pathology of schizophrenia.

In addition, the function of intracellular phospholipases A2 (inPLA(2)) has attracted attention in schizophrenia research. Cytosolic PLA(2) (cPLA(2)) enzymes are involved in the synthesis of arachidonic acid-derived lipid metabolites and in the remodeling of the neural membrane by degrading constituent phospholipids as well as in processes of synaptic pruning and neuroplasticity. The upregulation of PLA(2) has been associated with neuroinflammation, oxidative, and neurodegenerative processes [27, 28]. Increased activity of inPLA(2) has been found in the serum of young patients with first episode schizophrenia. The extent of this increase was also associated with the severity of negative symptoms and improvement outcomes with antipsychotic drug treatments several weeks later [28]. Overall, this evidence implicates an inflammatory process in patients with schizophrenia.

**Bipolar Disorder**

Bipolar Disorder (BD) is defined by the DSM-IV as recurrent episodes of depression and mania. This chronic disease affects approximately 1–2% of individuals globally and carries a substantial risk of suicide [29, 30]. Although initial efforts to elucidate the neurobiology underlying BD focused on monoamines, current understanding has shifted toward a focus on
inflammatory processes. The association between BD and neuroinflammation is based on new evidence showing that several inflammatory factors are dysregulated in the brains of BD patients, including molecules derived from the arachidonic acid (AA) cascade and cytokines [31].

In 1922 AA was detected for the first time in the brain. Since its discovery, many new functions of this fatty acid in brain homeostasis and disease have been elucidated [32]. The unesterified AA in the plasma is supplied in part from adipose tissues and later esterified and incorporated into brain phospholipids [32]. PLA(2) has been shown to catalyze the release of AA from the neuronal phospholipids in response to receptor-mediated signal transduction [33] such as by neurotransmitters including dopamine, serotonin, and acetylcholine [32]. It is possible that the overactivity of these neurotransmitters can be involved in the abnormal activation of PLA(2) in psychiatric disorders.

The chronic treatment of rats with mood stabilizers used in the treatment of BD reduced the upregulated expression of AA cascade components induced by excitotoxicity and neuroinflammation [19]. This evidence suggests that AA cascade markers are upregulated in the brains of individuals with BD and that some of the beneficial actions of mood stabilizers may be the result of their downregulating actions on AA cascade markers. Supporting this idea, a recent report showed evidence that expression of AA-selective cytosolic cPLA(2) IVA, secretory PLA(2) IIA, cyclooxygenase-2 (Cox-2), and membrane prostaglandin E synthase (mPGES) were significantly elevated postmortem in the cortex of individuals with BD. Levels of Cox-1 and cytosolic PGES (cPGES) were significantly decreased in comparison to controls tissues, while Ca(2+)-independent iPLA(2)VIA, 5-, 12-, and 15-lipoxygenase, thromboxane synthase, cytochrome P450 epoxygenase protein and mRNA levels were not significantly different. These results reinforce the idea that the brain AA cascade is disturbed in BD, and that certain enzymes associated with the release of AA from membrane phospholipids and with its downstream metabolism are upregulated [19]. Currently, the feasibility to synthesize [11C]-labeled AA facilitates its measurement in humans using PET as well as the examination of the effect of new drugs against BD on the metabolism of this relevant marker [32].

Bipolar disorder progresses over time and it has been postulated that the aggravation of the neuropathology may involve neuroinflammation. In a recent study [34], the analysis of the levels of pro-inflammatory factors postmortem in the frontal cortex from patients with BD and control individuals revealed that BD brains showed higher expression of IL-1β, IL-1 receptor (IL-1R), myeloid differentiation factor 88, and nuclear factor-kappa B (NF-κB) subunits in comparison with control age-matched brain tissues. An upregulation of astroglial and microglial markers (i.e., glial fibrillary acidic protein, iNOS, c-fos, and CD11b) were also found in the same study [34].

Although the role of cytokines in BD is still controversial, other studies have similarly found an upregulation of pro-inflammatory cytokines in postmortem BD brains. In one of these studies performed with 37 manic patients with bipolar disorder and 74 control subjects, higher baseline levels of IL-6 and TNF-α were found in the brains of bipolar manic patients than in normal controls. Additionally, the anti-inflammatory cytokine IL-4 was reported to be significantly decreased relative to normal controls [35]. After six weeks of treatment with psychotropic drugs, the levels of IL-6 significantly decreased. Another study showed that changes in the cytokine profile in plasma of BD patients were more pronounced during acute
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 episodes than in euthymia. Of the pro-inflammatory cytokines, IL-2, IL-4, and IL-6, were increased during mania, and only IL-6 was upregulated during depression [36]. The overall inflammatory response will promote a cascade of events that include the production of free radicals that may promote oxidative stress and neuronal cell death in BD brains.

An important implication in the upregulation of cytokines in BD subjects involves the activation by these factors of the hypothalamic-pituitary-adrenal (HPA) axis and the consequential alteration of behavior in subjects with BD and other psychiatric conditions [20]. For example, anxiety, hyperarousal, and irritability have been observed to appear after administration of the cytokine interferon (IFN)-α to humans. Indeed, a significant percentage of patients receiving IFN-α therapy have been shown to experience hypomanic and/or manic episodes, including hyperactivity, aggressiveness, and sleep disturbances [37].

It can be concluded that an increase in pro-inflammatory cytokines and an imbalance between pro-inflammatory and anti-inflammatory cytokines may be playing a role in the pathophysiology of BD.

**Depression**

From a philosophical point of view, psychological depression has been considered by ancient cultures including South and Native Americans as a healing response that can lead to personal transformation [38]. From a clinical perspective, depression is a psychiatric disorder and a major health concern, being the fourth leading cause of disability worldwide. Symptoms that are common to depression include altered mood (e.g., feelings of worthlessness or recurrent thoughts of death or suicide), attention deficits, lack of motivation, anxiety, sleep disturbance (insomnia), and loss of appetite, as well as other symptoms as per the DSM-IV.

The molecular mechanisms underlying depression are still largely unclear. Nonetheless, the link between clinical depression and immune function is well established [39]. Depression is characterized by higher expression of adhesion molecules, which increase leukocyte adhesiveness and aggregation [40] as well as the production and release of pro-inflammatory cytokines [41]. Neuroinflammation involves the presence of higher levels of pro-inflammatory cytokines in the brains and blood of individuals with major depression and of animal models of the disease. The genetic deletion of the cytokines IL-6 [42] and IL-1 has been shown to decrease depressive-like behavior in mice [43]. These changes associated with depression can be triggered by chronic psychological stress negatively affecting the HPA axis. The hypersecretion of glucocorticoids associated with chronic stress can provoke a desensitization of central glucocorticoid receptors to the negative feedback inhibition of the HPA axis. As previously mentioned, cytokines can induce the HPA axis to release glucocorticoids, which in turn can act alone or together with the cytokines to induce the activation of glial cells and neuronal damage [20]. The corticotrophin releasing factor (CRF), a stress factor, plays a key role in activating the central sympathetic and serotonergic systems. CRF is expressed in limbic regions of the brain such as the hippocampus as well as in the hypothalamus and immune cells. By acting on the dorsal raphe nucleus, CRF can change the serotonergic system, contributing to the onset of anxiety and depression.

The link between neuroinflammation and its involvement as a causal role in depression is further supported by studies showing that the administration of inflammatory mediators such
as IFN-α to humans can trigger major depressive (MD) syndrome [44]. Furthermore, anti-inflammatory therapies have been shown to have antidepressant effects. Recent studies have reported higher levels of prostaglandins in saliva and acute phase proteins in the plasma of depressed individuals. In several clinical trials, the use of Cox-2 inhibitors such as celecoxib as adjunct therapies to SSRIs has been investigated for the treatment of depression [45, 46]. These studies showed a decrease in depressive symptoms in the patients treated with non-steroidal anti-inflammatory drugs (NSAIDs) plus SSRIs, in comparison with those treated with SSRIs alone. Even aspirin has been reported to have similar effects to celecoxib in a pilot study in depression [47].

It has also been shown that anti-depressive drugs inhibit microglial activation (For review please see [48]). For example, it has been reported that both SSRIs sertraline and paroxetine decreased the production of NO and TNF-α from microglia activated by IFN-γ through a mechanism involving the inhibition of intracellular Ca(2+) elevation [49].

Altogether, this evidence suggests that neuroinflammation play an important role in the development and/or maintenance of clinical depression.

**PARKINSON’S DISEASE**

Parkinson’s disease (PD) is the most common neurodegenerative movement disorder and the second leading neurodegenerative disease [6]. This progressive and age-related disease is characterized by resting tremors, postural instability, slowed movement, and muscle rigidity [50]. There are few hypotheses to explain the causes of this disease, including genetic and environmental factors. Several lines of evidence suggest that systemic infections can be associated with the development of sporadic PD [51-53]. At the neuropathological level, the brains of people with PD show a severe loss of dopaminergic neurons in the substantia nigra (SN) and the presence of Lewy body (LB) inclusions, which are mainly constituted by fibrillar α-synuclein and ubiquitinated proteins [54].

Epidemiological studies support the view that neuroinflammation is a contributing factor in the development of PD. For example, a large prospective clinical study showed that patients using NSAIDs have an incidence of PD that is 46% lower than age-matched non-user individuals [55]. Another report showed that individuals treated with NSAIDs had elevated IL-6 plasma concentrations that correlated with an increased risk of developing PD [56].

Coherent with these findings, postmortem brain examinations also suggest a central role for chronic neuroinflammation in the progressive degeneration of dopaminergic neurons in PD. One of these investigations has revealed higher levels of activated microglia and pro-inflammatory cytokines such as TNF, IL1β, and IFN-γ in the brains of patients that suffered PD [57]. Another report conducting a microarray analysis of the cerebral expression of pro-inflammatory factors showed an increased expression of cytokines in the brains of patients with PD relative to age-matched controls [58].

The *in vivo* brain imaging analysis of microglial activation, using the peripheral benzodiazepine receptor binding ligand [11C]-(R)-PK11195 in PET scans, showed that patients with PD have markedly elevated neuroinflammation in the pons, basal ganglia, striatum, and frontal and temporal cortex compared to age-matched healthy controls [59]. Also, a dopamine transporter marker, [11C] CFT, which binds to the dopamine transporter and shows the viability of the presynaptic dopaminergic neurons, has been used to study
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microglia activation in PD [60]. This study showed that changes in microglia seem to occur early in the pathology prior to or simultaneously with the degeneration of dopaminergic neurons. In untreated PD patients, [11C]-(R)-PK11195 binding in the midbrain inversely correlated with [11C] CFT binding in the putamen. Moreover, [11C]-(R)-PK11195 binding in the midbrain positively correlated with the severity of motor dysfunction in PD. As the disease progressed, the [11C]CFT binding continued to decrease, and the microglial activation spread throughout the entire brain. These results suggest that early suppression of glial activation may be favorable in PD. Further studies using these tracers can permit to monitor in vivo the correlation between the inhibition of neuroinflammation and changes in the progression of PD.

The idea that neuroinflammation is involved in PD progression is supported by another study investigating the possible neuroprotective effect of the selective Cox-2 inhibitors, valdecoxib and NS-398 [61], in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-model of PD. MPTP administration to mice induced Parkinson-like symptoms, oxidative stress, mitochondrial dysfunction, and the upregulation of caspase-3 and NF-κB in comparison with vehicle-treated mice. In these mice, the authors found that a one-week treatment with valdecoxib or NS-398 reversed behavioral and biochemical abnormalities as well as attenuated oxidative stress and neuroinflammation. These findings highlight the importance of the pro-inflammatory process in the development of the disease and support the investigation of Cox-2 modulators as therapeutic drugs against PD [61].

**ALZHEIMER’S DISEASE**

AD is a progressive neurodegenerative condition and the main cause of dementia in the elderly [62]. According to the amyloid hypothesis, this disease originates from the toxicity of the amyloid-beta (Aβ) peptide [63] that accumulates in the brain, inducing oxidative stress, neuroinflammation, synaptic deficits, and neuronal cell death.

Neuroinflammation is a common link among many neurodegenerative conditions, where the increase in ROS and the resultant oxidative stress parallels with a persistent activation of the protein kinases cRaf-1, extracellular regulated kinases (ERKs), and other downstream pro-inflammatory factors such as the transcription factor NF-κB, cytokines, iNOS, and Cox-2. Oxidative stress and the associated activation of inflammatory factors are major neurochemical changes associated with neurodegeneration in AD brains and other neurological conditions.

**Depression and Alzheimer’s Disease**

The occurrence of a high comorbidity between AD and depression has been known for many years. In fact, depressive episodes are associated with increased risk of AD [64]. Thus, in individuals with a genetic linkage to depression, there may be an increased vulnerability toward developing this disease. This correlation can be explained by the existence of a common mechanism behind depression and AD. It is possible that neuroinflammation is the common link that predisposes the individuals with depression to AD.
cRaf-1 Kinase as a Target to Inhibit Neuroinflammation in Alzheimer’s Disease

Craf-1 is a key protein kinase expressed ubiquitously and its inhibition involves the phosphorylation of the inhibitory site, serine 259, by protein kinase A (PKA) and the dephosphorylation of the activation site, serine 338 [65]. Craf-1 is part of a protein kinase cascade whose components including cRaf-1, MEK, and ERK are dysregulated in AD brains [66-71]. After stimulation, cRaf-1 is recruited to the membrane where it activates the ERK kinase (MEK), which in turn phosphorylates and activates the ERK enzymes. The abnormal activation of cRaf-1 may promote neuroinflammation and cell death by stimulating the expression of pro-inflammatory signaling factors that induce apoptosis/necrosis in the brain. Craf-1 has been found to be overactive postmortem in the brains of persons who suffered from AD. The hyperactivation of this pro-inflammatory kinase can be the result of a decrease in the expression of endogenous inhibitors of cRaf-1 such as PKA and the Raf kinase inhibitory protein (RKIP) in AD brains [72]. Furthermore, this deficit in the inhibition of cRaf-1 can be reinforced by the Aβ-induced abnormal activation of protein kinases that activate cRaf-1 such as p21-activated kinase (PAK) [73-76].

Craf-1 is able to induce the expression of cytokines and other pro-inflammatory factors by promoting the activation of NF-κB, a transcription factor that mediates inflammatory responses and is broadly expressed in the nervous system [77]. Before activation, NF-κB is inactive and sequestered in the cytosol by the inhibitory subunits, IκB-α/β. The activation of NF-κB involves the phosphorylation of the IκB subunits by the IκB kinase (IKK) complex [78], which are subsequently degraded by the proteosome [79]. Freed NF-κB then travels to the nucleus where it can stimulate the expression of cytokines and other factors such as IL-2, IL-6, TNF-α, TNF-β, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), c-myc, IκB-α, p53, Bcl-xL, FasL, and other proteins involved in AD pathology such as Aβ precursor protein (APP) and APP-cleaving enzyme (BACE1) [80]. We have previously shown that inhibition of cRaf-1 can be beneficial in neurological conditions such as AD by reducing the expression or activation of neuroinflammatory factors including NF-κB in the brain. We found that the inhibition of Raf in cultured cortical neurons inhibited the activation by phosphorylation of NF-κB.

cRaf-1 Inhibitors as Neuroprotective Agents

It has been reported that the cRaf-1 kinase inhibitor GW5074 [5-Iodo-3-[(3,5-dibromo-4-hydroxyphenyl) methylene]-2-indolinone] is neuroprotective against the toxic effects of MPP+ and methylmercury in cerebellar granule cells as well as against oxidative stress induced by glutathione depletion in cortical cells [81]. In the same report, the authors investigated the effect of GW5074 on cell death in a mouse model of Huntington’s disease (HD) [82]. In this study, mice were treated with the succinate dehydrogenase inhibitor, 3-nitropropionic acid (3-NP), to produce mitochondrial dysfunction [82]. A unique dose of GW5074 prevented neuronal cell death and behavioral abnormalities in the HD mice [81]. Similarly, we found that GW5074 protected cortical neurons against Aβ toxicity and inhibited Aβ-induced activation of NF-κB [83]. It has been reported that the inhibition of NF-κB with a
double stranded kappa B decoy oligonucleotide \textit{in vitro} decreased Aβ production and signs of apoptosis in primary neurons and post-mitotic human neuronal cells [84], while other NF-κB inhibitors also decreased Aβ production [85]. It seems that the inhibition of NF-κB by inhibiting cRaf-1 can potentially decrease both neuroinflammation and Aβ synthesis.

It has been previously reported that NF-κB inhibitors improved memory as well as reduced neurodegeneration and the expression of neuroinflammatory factors such as Cox-2 and iNOS [86-88] in the brains of animal models of PD [89, 90] and AD [91, 92]. Accordingly, we found that sorafenib (Bay 43-9006, Nexavar®, Onyx-Bayer), a strong but non-specific cRaf-1 inhibitor (IC\textsubscript{50} for cRaf-1 of 6 ± 3 nM) and anti-cancer agent [93], inhibited NF-κB and cRaf-1 and normalized the expression of other pro-inflammatory factors such as IκB-α, Cox-2, iNOS, and APP in the brains of aged 17-19-month-old APPswe mice [94]. This decrease correlated with an improvement in working memory abilities in these mice. Since sorafenib also inhibits other protein kinases, such as the VEGF receptor, other synergistic mechanisms can co-exist.

These results suggest that the use of Raf inhibitors as therapeutic tools against neurodegeneration need to be further investigated in animal models using specific cRaf inhibitors.

\textbf{Targeting Cox-2 in Alzheimer’s Disease}

The increase in the levels of Cox-2 has been associated with several neurological disorders [95], including AD [96-99], ALS [100], epilepsy [101], PD [102-104], and ischemic stroke [105]. Cox-1/2 enzymes participate in the synthesis of prostaglandins (PGs) from their precursor arachidonic acid that is converted to PGH\textsubscript{2}. This in turn generates the prostanoids PGE\textsubscript{2}, PGF\textsubscript{2α}, PGD\textsubscript{2}, PGI\textsubscript{2}, and thromboxane A\textsubscript{2}, which stimulate the PG receptors. Because the stimulation of some of these receptors promotes neurodegeneration, a reduction in Cox-2 in the brains of individuals suffering from neurological conditions is considered beneficial. In fact, the reduction in Cox-2 expression has been reported to reduce the neuropathology in animal models of neurodegenerative diseases, such as AD [106], stroke [95, 105], PD [107], and ALS [108, 109].

It has been known for several years that NSAIDs, whose main targets are the Cox-1/2 enzymes, reduce inflammation and amyloid burden [110] as well as improve synaptic plasticity and memory in mouse models of AD [99]. However, the inhibition of Cox-2 activity as a therapeutic strategy for the treatment of neurodegenerative conditions has not been very successful. For example, an investigation of NSAID in ALS shows no therapeutic value [111]. Moreover, numerous studies performed to evaluate the use of NSAIDs for the treatment of AD indicate that Cox-2 inhibition is not successful in preventing the clinical progression of AD [112-114].

An alternative to the enzymatic inhibition of Cox-2 is the reduction of its expression by inhibiting the cRaf-1/NF-κB/Cox-2/iNOS cascade. Advantageously, the inhibition of this signaling pathway can also inhibit the expression of iNOS and the oxidative damage of the neuronal membrane and proteins caused by the production of NO-derived reactive nitrogen species (\textit{e.g.}, peroxynitrite) under pathological conditions. Our previous findings suggest that
the inhibition of the cRaf-1/NF-κB/Cox-2/iNOS pathway may downregulate the molecular events underlying neurodegeneration in AD [94].

**MELATONIN**

Melatonin, N-acetyl-5-methoxytryptamine, is a hormone synthesized mostly in the pineal gland during the dark phase [115]. This versatile molecule has been shown to have a large number of therapeutic uses and is being extensively investigated as a drug against neurological and psychiatric disorders including BD, depression, schizophrenia, and AD as well as against other pathological conditions such as cancer [116-118], fibromyalgia [119], and cardiovascular disorders [120]. Melatonin is also an antioxidant [121, 122] that has been shown to be critically involved in regulating circadian rhythms, sleep [123], and lipid metabolism. As a drug, it has been recommended against schizophrenia to correct the circadian rhythms and low endogenous melatonin levels in individuals suffering from this disease [124].

It was reported that patients with psychiatric conditions show significant differences in melatonin production and secretion [125]. Based on these findings, it has been hypothesized that melatonin can be a beneficial drug to co-treat psychiatric disorders due to its anti-inflammatory, anxiolytic, anti-nociceptive, and drug detoxification properties (For review please see [126]). For example, it has been shown using a transgenic mouse model of AD that melatonin decreased Aβ deposition into senile plaques and improved cognitive abilities in AD mice [127].

Additionally, melatonin has been proposed as a good adjuvant to mood stabilizers. Psychostimulants have many positive effects over neuroplasticity and mood. Nonetheless, they have negative side effects including the metabolic syndrome, obesity, diabetes, and increased blood pressure commonly observed in treated patients with BD, schizophrenia, and schizoaffective disorder [128, 129]. Melatonin can potentially be beneficial against these undesirable side effects by reducing blood pressure and protecting cardiac and brain tissues against various insults by its antioxidant and anti-inflammatory effects [126]. Also, melatonin may be able to diminish the bone debilitating effects of some antidepressants such as the serotonin transporter inhibitors and SSRIs [126].

Several studies suggest that depressed individuals have higher levels of cytokines and show signs of neuroinflammation and oxidative stress in the brain [44, 130], which are associated with a higher risk of cardiovascular disease and infections in this population. It has been proposed that endogenous melatonin can add to antidepressant effects depending on the expression pattern of melatonin receptors in the brain. For example, prolonged treatment with antidepressants such as fluoxetine, desipramine, and clomipramine has been found to increase the number of melatonin (MT1 and MT2) receptors in the brain. This effect enables endogenous melatonin to synergize the antidepressant effects of these drugs [131]. Due to melatonin’s capacity to reduce oxidative stress as well as the expression of cytokines and adhesion molecules, it can be further beneficial in the treatment of depression.
TARGETING NEUROINFLAMMATION IN NEUROLOGICAL DISORDERS: A DOUBLE-SIDED COIN

In addition to the mounting evidence supporting the role of neuroinflammation in the development of neurological disorders, it is important to take into account that immunocompetent cells and neuroinflammatory factors have beneficial effects in neurological disorders. For example, it has been postulated that the activation of microglia is required for the clearance of senile plaques in AD brains and was found that under certain circumstances, prostanoids can be neuroprotective against Aβ toxicity [132]. Another illustrative example is the role of metalloproteinases (MMPs) in cerebral ischemia [133]. After giving the broad-spectrum MMP inhibitor FN-439 on day one of focal cerebral ischemia in rats, (a time in which several MMPs are increased after stroke), infarct volume was reduced at fourteen days. However, when administered seven days after insult, the infarct volume after fourteen days was worsened, indicating that timing is fundamental. The final outcome may depend on the level and temporality of the neuroinflammation process. However, a sudden activation of immunocompetent cells and the consequent upregulation of inflammatory factors are mostly regarded as deleterious for the brain [134]. Therefore, a careful study of the role of neuroinflammation at different stages of specific neurological disorders needs to be investigated to indentify the therapeutic value of targeting specific neuroinflammatory factors in neurological disorders.

CONCLUSION

Neuroinflammation undoubtedly plays a central role in mediating the neurodegenerative and detrimental functional changes in the brain that occur in many neurological disorders. This complex process involves multiple and concatenated biochemical cascades. However, it is possible to target upstream individual components of the neuroinflammatory pathways to downregulate or inhibit multiple inflammatory effectors with great repercussions in the course of neurological disorders. Specifically, we propose that inhibition of cRaf-1 in AD brains may result in the inhibition of several neuroinflammatory factors (iNOS, NF-κB, Cox-2) downstream of the cascade leading to a restoration of higher-order cognitive abilities. The normalization of the inflammatory response rather than its suppression seems to be the more adequate therapeutic strategy in neurological disorders.

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