

Inflammatory neuropsychiatric disorders and COVID-19 neuroinflammation

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Review Article

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Abstract

Neuropsychiatric sequelae to coronavirus disease 2019 (COVID-19) infection are beginning to emerge, like previous Spanish influenza and severe acute respiratory syndrome episodes. Streptococcal infection in paediatric patients causing obsessive compulsive disorder (PANDAS) is another recent example of an infection-based psychiatric disorder. Inflammation associated with neuropsychiatric disorders has been previously reported but there is no standard clinical management approach established. Part of the reason is that it is unclear what factors determine the specific neuronal vulnerability and the efficacy of anti-inflammatory treatment in neuroinflammation. The emerging COVID-19 data suggested that in the acute stage, widespread neuronal damage appears to be the result of abnormal and overactive immune responses and cytokine storm is associated with poor prognosis. It is still too early to know if there are long-term-specific neuronal or brain regional damages associated with COVID-19, resulting in distinct neuropsychiatric disorders. In several major psychiatric disorders where neuroinflammation is present, patients with abnormal inflammatory markers may also experience less than favourable response or treatment resistance when standard treatment is used alone. Evidence regarding the benefits of co-administered anti-inflammatory agents such as COX-2 inhibitor is encouraging in selected patients though may not benefit others. Disease-modifying therapies are increasingly being applied to neuropsychiatric diseases characterised by abnormal or hyperreactive immune responses. Adjunct anti-inflammatory treatment may benefit selected patients and is definitely an important component of clinical management in the presence of neuroinflammation.

Summations

- This review summarises the evidence that both acute and chronic inflammation may have significant neuropsychiatric sequelae.
- Although inflammation is present in patients suffering from a number of major neuropsychiatric disorders, factors determining the specific neuronal vulnerability are still unknown.
- Patients suffering from some major neuropsychiatric disorders with abnormal inflammatory markers may experience less than favourable response or treatment resistance when standard treatment is used alone.
- Managing the inflammation with anti-inflammatory agents, disease-modifying therapies, and modulation of the hyperactive immune response are becoming an important part of clinical management of neuropsychiatric disorders where inflammation is present.

Considerations

- Inflammation could be beneficial or harmful. Suppressing overactive immune response has been found to be important to prevent inflammatory-associated damages in COVID-19 but could be harmful in other inflammation, such as viral influenza.
- Inflammation in different neuropsychiatric disorders may require different anti-inflammatory management protocols.
- Results from well-designed clinical trials to test the efficacy of anti-inflammatory agents or immune modulatory therapies, alone or in combination with standard treatment, in each major neuropsychiatric disorder, are not available yet.

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Introduction

Recent reports on serious neuropsychiatric sequelae in coronavirus disease 2019 (COVID-19), SARS, and streptococcal infection in paediatric patients show the important role of the immune system in maintaining health and in disorders of the central nervous system (CNS). Presence of neuroinflammation in neurodegenerative disorders and affective disorders is already well documented and has been extended to include schizophrenia, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), other anxiety disorders, and neuropsychiatric diseases in recent years. If systemic or regional brain inflammation may indeed inflict damage to neurocircuits or neurons, then the factors determining the susceptibility, selectivity, and vulnerability of the neuro-targets should be determined. Clinically, it is important to know if anti-inflammatory medications should be considered in all patients as neuroprotective, such as in COVID-19, or as adjunct treatment, such as in major depression, or only in specific cases. In addition to common anti-inflammatory agents, disease-modifying therapies (DMTs) are becoming an important and novel approach in modulating neuropsychiatric disorders with an inflammatory component. We review the literature on neuroinflammation and management issues associated with major neuropsychiatric disorders.

Method

We searched the English language literature, including foreign language publications with informative abstracts in English, up to November 30, 2020, using PubMed (www.ncbi.nlm.nih.gov), crossing the keyword inflammation and neuroinflammation, respectively, in turn with the following words: COVID-19, psychiatry, psychosis, psychiatric disorders, bipolar disorders, OCD, anxiety disorders, dementia, neuron death, neurodegeneration, brain circuits, neurotransmitters, brain areas, serotonin (5HT), dopamine (DA), glutamine (Glu), cholinergic (ACh), adenosine, herbs, plants, gastrointestinal disorders, gut microbes, probiotics, fecal transplant, and treatment. Manuscripts were identified and then included in this review after evaluation of quality of research and data, and relevancy to our search.

Inflammation in neuropsychiatric disorders

Acute inflammation

Coronavirus disease 2019 (COVID-19)

COVID-19 is an excellent example of neuropsychiatric complications in acute neuroinflammation. The previous Spanish flu epidemic of 1918–1919, the severe acute stress respiratory syndrome (SARS) and the Middle East respiratory syndrome showed that the damage from these virus infections of the respiratory tract is not limited to the lung. Immunopathological studies on a cohort of COVID-19 patients in the Netherlands in the first 3 months of 2020 reported that an extensive inflammatory response was present not only in the lungs, but also in the heart, liver, kidney, and the brain (Schrink *et al.*, 2020). In the brain itself, extensive inflammation was seen in the olfactory bulbs and medulla oblongata, reflecting the loss of smell and many of the CNS symptoms (Banerjee and Vikswanath, 2020). The COVID-19 virus may enter through the angiotensin-converting enzyme two receptors (ACE-2) which are present on endothelial cells of cerebral vessels (Garg 2020) and also likely by crossing the damaged blood–brain

barrier (BBB), which is highly susceptible to peripheral immune changes (Schwartz *et al.*, 2013) and certainly under the characteristic cytokine storm of COVID-19.

Many cases of neuropsychiatric disorders have now been reported in COVID-19 patients, less than 1 year since the pandemic started (Cothran *et al.*, 2020; Huang and Zhao 2020; Rogers *et al.*, 2020; Troyer *et al.*, 2020). Neurological manifestations occur early in the illness (Orsucci *et al.*, 2020). Delirium, from hypoxia and metabolic abnormalities (Garg 2020), particularly occurred in the more vulnerable aged population and those with dementia (Butler *et al.*, 2020; Mcloughlan *et al.*, 2020). Acute neuropsychiatric symptoms which include altered mental status, psychosis, and suicidal ideation (Chacko *et al.*, 2020; Correa-Palacio *et al.*, 2020; Ferrando *et al.*, 2020; Finatti *et al.*, 2020; Ng *et al.*, 2020; Sher 2020; Valdés-Flórido *et al.*, 2020) were the second most common presentation. Encephalopathy or encephalitis occurred in younger patients as well (Varatharaj *et al.*, 2020). An increase of stress response is reflected in the low mood, anxiety, and severe fatigue, which may persist in about 20% of patients following their apparent full recovery (Rogers *et al.*, 2020; Sterdolt and Verkhatsky 2020). PTSD also occurred (Mazza *et al.*, 2020), as well as Guillain-Barré syndrome (Garg 2020; Webb *et al.*, 2020) and other forms of neuropathy and myopathy (Ottaviani *et al.*, 2020). Severe and debilitating fatigue and myalgia could be present, and elevated creatine kinase levels indicate serious myopathy (Garg 2020; Orsucci *et al.*, 2020). Cognitive defects (Troyer *et al.*, 2020; Zhou *et al.*, 2020) may persist for many months after apparent recovery. The damage to neuronal networks initiated by the COVID-19 virus and sustained by the chronic inflammation and disruption of metabolic homeostasis is likely to result in the long-term CNS disabilities, and the term “long COVID” has been applied in the UK and Ireland.

Both acute and long-term neuropsychiatric consequences of viral infections have been documented historically (Davydow *et al.*, 2008). These include schizophrenia cases in the 1918 Spanish flu (Kepińska *et al.*, 2020), depression, anxiety, and PTSD cases in SARS (Mak *et al.*, 2009), and Parkinson’s symptoms with H5N1 influenza (Henry *et al.*, 2010).

The immediate impact of the COVID-19 virus is attributed to its binding to the widely distributed ACE-2, which is distributed along the respiratory and gastrointestinal epithelium as well as endothelial cell surfaces. The spread of the virus into the brain occurs following a high viral load coupled with susceptibility due to the age of the patient, abnormal or over-reactive immune function, chronic medical illness, and frequently a history of neurotropic virus infections (Razanamahery *et al.*, 2020; Singhou 2020). The spread of the virus through the brain is heterogeneous but in experimental studies it has been shown to rapidly infect the olfactory bulbs (approximately after 4 days) and later the piriform cortex (Perlman *et al.*, 2020). The remainder of the cortex, hypothalamus, basal ganglia, and brain stem are affected later. Microglia are important regulators of COVID-19 expression in the brain since their ablation results in increased viral loads, 7–8 days post-infection. Neurons appear to be the main targets of infection *in vivo* (Mangale *et al.*, 2020). As ACE-2 receptors are expressed in the olfactory lining, a main target for COVID-19, this likely accounts for the anosmia and hypo-osmia experienced early in the infection, which occurs with a frequency of 12–32% (Lechien *et al.*, 2020), and loss of smell results from the neurodegenerative effect of the virus on the olfactory bulbs. Dinein and kinesin have been identified as the proteins responsible for the transmission of

the virus and the nucleus solitarius of the brain stem is preferentially affected (Wu et al., 2020), accounting for the central effects of the virus on breathing.

C-reactive protein (CRP) is a commonly used early marker to grade the severity of systemic inflammation from infection (Nehring et al., 2020). Relatively mild to moderate elevations are seen in obesity, diabetes, depression, periodontitis, sedentary lifestyle and cigarette smoking rheumatoid arthritis, myocardial infarction, pancreatitis, and bronchitis, but marked and severe elevations in CRP (more than 10.0 mg/dL and >50.0 mg/dL, respectively) require acute bacterial or viral infections, systemic vasculitis or major trauma. In early-stage COVID-19, CRP levels show a positive correlation with lung lesions and disease severity (Wang, 2020). Importantly, only a subset of COVID-19 patients shows severe elevations in CRP, for which there appears to be emerging evidence of genetic susceptibility (Zeberg and Pääbo, 2020).

The vulnerability of the elderly to severe COVID-19 infection is well known. Ageing is usually associated with overall neurodegenerative changes and diminished homeostatic brain mechanisms. In ageing, synaptic plasticity decreases, brain metabolism is reduced, and the vulnerability to exogenous toxins is increased. The increases in specific pro-inflammatory cytokines have been correlated with specific symptoms of the virus infection. For example, IL-1 beta has been linked to depression in later life, IL-6 with anhedonia and suicidal behaviour, while tumour necrosis factor (TNF)-alpha and IL-2 have been linked to apathy and motor inhibition (Thomas 2005; Schmidt 2016).

Apart from psychological support and treatment of accompanying neuropsychiatric disorders such as anxiety, depression, psychosis, and neuropathic and myopathic pain (Drożdżal et al., 2020), management of the neuroinflammation is important. Intravenous immunoglobulins (Novak 2020) and careful steroidal immunosuppressant therapy appear to be useful in some cases to avoid complications (Rajabally et al., 2020). A recent report summarised the recommendations from the Italian Societies of Neurology, Clinical Neurophysiology, and Peripheral Nervous System Association in the management of COVID-19 immune-mediated neuropathies (Dubbioso et al., 2020).

Because of the very recent occurrence of the pandemic, much still has to be learned about the chronic effects of the virus on the brain and behaviour. However, it is already apparent that its impact, both direct and indirect, could result in neuroprogressive changes (as seen in Parkinson's disease (PD)) and long-term neuropsychiatric consequences. Increased vigilance for all neuropsychiatric symptoms in patients with COVID-19 is certainly warranted (Brown et al., 2020). Minimising the relevance of the psychiatric aspects of COVID-19 and mistakenly explaining that "sometimes an abnormal behavior in an abnormal situation is a normal behavior" could be an unforgivable mistake (Stearo and Verkhatsky, 2020).

Autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

Compared to the multiple neuropsychiatric consequences of COVID-19 infection, acute neuroinflammation causing a specific psychiatric disorder is highlighted in PANDAS (Frick and Pittenger 2016). PANDAS is a medical emergency, in which sudden and severe OCD, with cognitive and behavioural symptoms, developed in children after streptococcal infection. The exact neuro-mechanism is still unclear. It is not known whether serotonin (5HT) or other types of neurons were involved or damaged (Chiarello et al., 2017; Jasper-Fayer et al., 2017), but there is

evidence suggesting that human anti-brain autoantibodies induced by *Streptococcus pyogenes* infections target DA receptors (Cox et al., 2013; Cunningham and Cox 2016; Orefici et al., 2016). Acute infections in adults have not been reported to cause OCD, but depression is a fairly common consequence, as reported in influenza (Bornand et al. 2016). Acute systematic inflammation induced by endotoxin also may precipitate sad mood (Benson et al., 2017) and exacerbation of schizophrenic symptoms has been reported with oseltamivir administration (Lan et al., 2015). Penicillin, azithromycin, intravenous immunoglobulin, plasma exchange, tonsillectomy, cognitive behaviour therapy, non-steroidal anti-inflammatory drug (NSAID), and corticosteroids (CSs) have been used in the treatment of PANDAS. The rationale and efficacy of antibiotics and immunomodulatory therapies have been reviewed and discussed (Burchi and Pallanti 2018; Sibra et al., 2018).

Traumatic brain injury (TBI)

Acute physical trauma to the brain, as in boxing and after head injury, triggers a reactive inflammatory process. Though inflammation serves defence and neuroprotective purposes in the early stages when the brain sustains physical injuries, it is a double-edged sword (Loane and Kumar 2016; Konoshi and Kiyama 2018). The consequences of inflammation are dictated by multiple local and systematic cues of the host. It is hard to predict which direction the multiple processes will end up, but the results could be quite different. In physical head injuries, hyperactivation of glutaminergic (Glu) neurotransmission after injury may result in neuronal death. Amantadine is neuroprotective, supposedly through its N-methyl-D-aspartate receptor (NMDAR) antagonist action. The antioxidants glutathione and N-acetylcysteine reduce brain damage and improve recovery, glial limitans breakdown, and parenchymal cell death by up to approximately 70%, suggesting that reactive oxidative stress may be a primary inducer of cell death and inflammation after focal brain injury (Corps et al. 2015). The benefit of NSAIDs is controversial as they block both the tissue damaging and repair-promoting aspects of inflammation. Likewise, the benefit of systemic glucocorticoid treatment in COVID-19 patients is not straightforward (Keller et al., 2020). Glucocorticoid administration appears beneficial when CRP levels are high (greater than 20.0 mg/dL) but harmful when CRP levels are low (less than 10 mg/dL), perhaps due to the association between glucocorticoid use and delayed viral clearance (Keller et al., 2020).

In traumatic brain injury (TBI), salsalate, an unacetylated salicylate, has been found to be effective, through blockade of NF-κB, pro-inflammatory gene expression and nitrite secretion by microglia, increasing expression of genes associated with neuroprotection and neurogenesis, including neuropeptides, oxytocin, and thyrotropin-releasing hormone (Lagraoui et al. 2017). Apart from these small molecules, cell-based therapeutics are being pursued as well, to manipulate the immune response into a neuroprotective direction (Xiong et al. 2018). Apart from neurodegenerative disorders triggered by chronic neuroinflammation post-TBI, it is important to mention that about 1/3 of ischemic stroke patients with neuroinflammation also end up with post-stroke depression. Low mental health literacy in many elderly subjects may result in patients not being able to voice the mental symptoms properly, making a diagnosis difficult (Lee et al., 2009). Though there were some studies on the relationship between brain areas affected by inflammation and the subsequent development of depression, the specific neurocircuits affected are unclear, and anti-inflammatory

measures again seemed to be beneficial in these patients (Villa et al. 2018).

The cause for the widespread CNS damage following acute neuroinflammation, whether it is from viral or bacterial infections, or physical trauma, appears to be an acute activation and subsequent dysregulation of the immune system (Becher et al., 2006; Rostami and Ciric 2013; Kostic et al., 2015), especially the eicosanoids and cytokine systems (cytokine and eicosanoid storms). Cytokine activations in inflammation has been well studied. Eicosanoids and related bioactive lipid mediators derived from polyunsaturated fatty acids were viewed as pro-inflammatory until recently when unique eicosanoids and related docosanoids with anti-inflammatory and pro-resolution functions were discovered (Dennis and Norris 2015).

Autoimmune encephalitis includes those with systematic lupus erythematosus (Bendorius et al., 2018), cases of autoimmune anti-NMDAR antibodies (Kayser and Dalmau 2016), or anti-GABA (γ -aminobutyric acid) receptor antibodies. Regarding anti-GABA antibody encephalitis (Dalmau 2017), there may be differences in vulnerability in terms of age, as the antibodies in childhood cases appeared to be more viral-related while adult cases are more tumour-related (Spatola et al., 2017), highlighting the age effect on vulnerability of inflammation again. Kawasaki disease is a good example of age-dependent vulnerability. The excessive inflammatory response is seen in a minority of preschool infants, with Asian ancestry being a suspected vulnerability factor, while adults in the same household rarely experience anything more serious than transient conjunctivitis (Chen et al., 2018; personal communication).

In summary, there are neuropsychiatric consequences following acute neuroinflammation. Apart from the potency of the causative agent such as COVID-19, or SARS, or streptococci bacteria, and co-existing medical disorders such as diabetes and cardiovascular disorders, age appears to be an important factor for susceptibility. Other factors, including genotype, determine the pro- or anti-inflammatory outcome of initial immune responses, selectivity of neuroinflammatory insult, neuronal vulnerability, and the neuropsychiatric consequences.

Chronic neuroinflammation

Chronic inflammation is defined here as inflammation which lasts for long durations, usually years. Acute inflammations, such as viral infections and TBI, may trigger reactions that turn chronic. For example, dementia may result from chronic neuroinflammation after physical traumatic injuries in boxing. Chronic microglial activation and sustained immune response are well known in neurological disorders such as Alzheimer's disease (AD), PD, and multiple sclerosis (MS) (Pulli and Chen 2014; Hoehn 2015; Albrecht et al., 2016; Hagens et al., 2016; Bevan Jones et al., 2017; Lagarde et al., 2018; Tommasin et al., 2019). In MS, myelin-specific CD4(+) T cells, activated in the periphery, infiltrate the CNS and start an inflammatory cascade by secreting cytokines and chemokines (Rostami and Ciric 2013), followed by BBB disruption, demyelination, and neurodegeneration (Kostic et al., 2015). Semi-acute factors which may create chronic inflammatory reactions include oxidative loads, toxic metals such as aluminium, copper, and iron, nutritional factors, dietary or environmental toxins, and contaminants such as insecticides (Yegambaram et al., 2015).

Dementia and ACh neurons

ACh neurons appear to be particularly vulnerable to neuroinflammation. ACh neuronal deaths in the basal forebrain occur early in AD (Whitehouse et al., 1981) but not in normal ageing (McQuail et al., 2011). On the other hand, the ACh system has been discovered to exert significant modulatory action on the immune system (Gatta et al., 2020; Hoover 2017). Muscarinic and nicotinic receptors stimulate pro- and anti-inflammatory cytokines, respectively, to modulate the immune/inflammatory responses (Di Bari et al., 2017). Acetylcholine esterase inhibitors (AChE) or vagal nerve stimulation modulate neuroinflammation via the $\alpha 7$ nicotinic acetylcholine receptor (Treinin et al., 2017).

PD and DA neurons

The susceptibility or vulnerability of DA neurons to neuro- and peripheral inflammation is demonstrated in PD (Matheoud et al., 2019). DA-dependent motor function being easily testable, urinary tract, and chest infections have been reported to cause transient worsening of PD symptoms. Neuromelanin is a catecholamine-derived pigment in DA neurons of the substantia nigra and also in norepinephrine neurons of the locus coeruleus. They are both known to be damaged by inflammation in PD. A close relationship has been described between iron, DA, and neuromelanin. Excess iron or DA is toxic. Excess DA is converted into neuromelanin, and excess iron is chelated by neuromelanin, which also removes pesticides and some other oxidants. Microglia become activated when this DA-iron neuromelanin balance is lost (Fedorow et al., 2005; Haining and Achat-Mendes 2017), resulting in neuronal death. In PD, it is the neurons containing neuromelanin that degenerate (Zecca et al., 2003, 2008; Zucca et al., 2017). Similar to the relationship between ACh neurons and the immune system, dysregulation of DA transmission may also induce dysfunction in the immune system (Vidal and Pacheco 2019). Astrocyte DA D2 receptor (DRD2) was also shown to modulate immunity through αB -crystallin (CRYAB), which is part of the small heat shock protein family and is anti-neuroinflammatory (Shao et al., 2013; Zhang et al., 2015).

Affective disorders and NMDARs (glutamate)

Chronic neuroinflammation appeared to be present in some patients with affective disorders. Transition into depression in these patients has been attributed to the activation of the toxic kynurenine metabolic pathway, resulting in the formation of toxic quinolinic acid, an NMDAR agonist (Leonard 2010, 2015, 2017, 2018; Müller 2010; Müller and Schwarz 2006, 2007; Dantzer and Walker 2014; Won and Kim 2016; Dantzer 2017). Bringing in this inflammatory toxicity factor, an integrated toxic brain hypothesis of depression (Tang et al., 2017a) would supplement the other two hypotheses of depression, namely the amine hypothesis (Bunney 1975) and the stress hypercortisolemia hypothesis (Duman and Monteggia 2006). In addition to the neurotoxic effects on neurons and astroglia cells, quinolinic acid is also an important substrate for nicotinamide adenine dinucleotide (NAD⁺), a key component of the electron transport system. As discussed by Leonard (2018), in severe depression, the synthesis of NAD⁺ is reduced. Unlike non-nervous tissues, brain energy metabolism is largely dependent on glucose and the transport of glucose across the BBB is an insulin-dependent process. As the resistance of the insulin receptors is increased in the inflammatory state associated with severe depression, the transport of glucose into the brain is compromised. The

concurrent increase in the activity of superoxide dismutase and the rise in reactive oxygen species further compromise the integrity of neurons and, in addition, damage the mitochondria (Burkunina et al., 2015). As a result of the damage to the mitochondria, the synthesis of ATP and other high-energy intermediates is decreased. These metabolic changes caused by the neurotoxins and metabolic stress help to understand the causes of the neurodegenerative changes associated with chronic depression, particularly in elderly patients.

OCD and anxiety disorders

Recently, heightened inflammatory activities have been described in patients suffering from PTSD, fear, and anxiety disorders (Frick and Pittenger 2016; Attwells et al., 2017; Michopoulos et al., 2017; Zaas et al., 2017).

This is also the case in OCD. Altered gut flora has been discovered in OCD (Turna et al., 2016; 2019) and in animal models (Scheepers et al., 2019). Pregnancy may induce OCD with gut flora changes in pregnancy suggested as possible causes (Rees 2014). Reintroduction of beneficial microbes and probiotics into the gut has been proposed as a possible treatment for OCD.

Psychosis

Early clinical evidence arose from epidemiological studies of the 1957 influenza pandemic in which maternal infection during pregnancy was found to correlate with the development of schizophrenia in the offspring in later life (Brown and Patterson, 2011; Mednick et al., 1988). A growing body of experimental and clinical evidence supports the role of neuroinflammation in the pathophysiology of psychosis and schizophrenia (Doorduyn et al., 2009), with theories pinpointing parvalbumin interneuron development impacted by inflammation and NMDAR hypofunction (Barron et al., 2017; Najjar et al., 2018). These parvalbumin interneurons are fast spiking GABAergic neurons that synchronise the pyramidal neurons in the cortex and contribute to the generation of cognitive processes and working memory (Zandi et al., 2011). Support for the importance of neuroinflammation in schizophrenia and psychosis also comes from genetic studies. Multiple genome-wide association studies implicate the major histocompatibility site on chromosome 6, in particular complement C4 within the human leucocyte antigen. C4 is involved in pathogen opsonisation and synaptic pruning which could be involved in the initiation of the early disruption of the neuronal network in schizophrenia (Sekar et al., 2016).

Post-mortem studies of schizophrenic patients have also demonstrated the presence of activated microglia in brain tissue, though results of several studies are inconsistent or confined to a limited number of brain regions and without a specific selection of the patients studied. An early positive emission study using 14C-PK-11195, a peripheral benzodiazepine receptor ligand, showed that neuroinflammation occurred in the hippocampus of schizophrenic patients in the psychotic phase of the illness (Doorduyn et al., 2009). Later positron emission tomography (PET) studies using a more specific radioligand showed no difference between medicated and drug-naïve first episode psychosis or schizophrenia compared to healthy controls (Hafizi et al., 2017; Coughlin et al., 2016). This suggests that neuroinflammation may be confined to a subgroup of patients and present at an early stage of the illness.

A meta-analysis by Miller et al., (2011) of 40 studies involving over 2500 schizophrenic patients found that the pro-inflammatory cytokines, TNF-alpha, interferon (IFN)-gamma, IL-12, and IL2 receptor were consistently increased independent of the stage of

the illness, suggesting that these cytokines might be trait markers. Conversely, IL-1 beta, IL-6, and TGF-beta were positively associated with the active phase of the illness and were therefore possible state markers.

Finally, celecoxib, a cyclo-oxygenase 2 inhibitor, can enhance the efficacy of risperidone and amisulpride in the treatment of chronic schizophrenia (Muller 2010; Muller et al., 2010), while the anti-inflammatory tetracycline, minocycline, improves the negative symptoms and cognitive dysfunction of schizophrenic patients in the early and acute phases of the disorder (Levkovitz et al., 2009).

MS and 5-HT

Although disruption of the BBB and demyelination are known consequences of neuroinflammation in MS, an interesting relationship between 5-HT and MS exists. 5-HT disturbances of gut origin have been suggested to play a pivotal role in demyelinating disorder, including MS (Malinova et al., 2018). PET showed differential expression of 5-HT transporters in several brain regions in relapsing MS. Lower levels of serotonin reuptake transporters (SERTs) have been reported in the cingulate cortex, the thalamus, insula, and hippocampus, with higher SERTs in the prefrontal cortex. Lower SERT in the insula was correlated with depression scores (Hesse et al., 2014).

Chronic stress causes widespread health problems, including malignancies, ageing, gastrointestinal disorders, and skin problems. Psychological stress and mental disorders have been shown to activate the peripheral immune system (Bendorius et al., 2018). The composition of gut microbes, which are far away from the brain, is known to be affected by psychological factors, including pregnancy-related stress, and *vice versa* (Rees 2014). Toxic metabolites generated from pathological microbes in the gut could travel to the CNS and trigger neuroinflammation. Thus, a dynamic triple relationship exists between the CNS, immune system, and gut axis and this intricate balance could be lost in the presence of external insults or stress. Dysregulation of the eicosanoids and cytokine systems is suspected to be the mediator of the psychological stress-damaging effects (Umamaheswaran et al., 2018).

A neuroprotective role of the endocannabinoid system and a modulating role of the cannabinoid receptor 1 (CB1) have been debated, using data from animal models (Zoppi et al., 2011; Rabasa et al., 2015). The potential neuroprotective usage of anti-inflammatory CB1 and CB2 agonists would need further research (Mastinu et al., 2018).

In these different neuropsychiatric disorders, finding the clues to address the specificity and vulnerability issue of chronic neuroinflammation is important. It is difficult to accept general inflammation as the aetiology of any specific neuropsychiatric disorder, as one would have to explain why the same inflammation would end up with neurodegeneration in some patients and depression, OCD, or schizophrenia in others. In fact, the same difficulty happened in the early hypercortisolemia hypothesis of depression; a question of whether it is the inflammation or hypercortisolemia that created the neurocircuit damage or suppressed neurogenesis (Lau et al. 2007; Qiu et al. 2007). The damages are not specific to depression (Tang et al., 2012; Tang et al., 2017b).

Profiles of neuroinflammation, anti-inflammatory agents, and disease-modifying agents

In neuroinflammation, chronic activation of astrocytes and microglia, infiltration of peripheral leucocytes, and secretion of

inflammatory cytokines are well known. Astrocytes and microglia are key regulators of innate and adaptive immune responses. Their coordinated activities can be pro- or anti-inflammatory, neuroprotective, or neurotoxic (Colombo and Farina 2016; Jha et al., 2019). A good example is the observation that Th1 cells produce IFN- γ and mediate neuroinflammation in MS. In contrast, Th2 cells produce IL-4 which would antagonise Th1 cells and therefore would be beneficial (Rostami and Ciric 2013). These kinds of checks and balances are typical of the immune system but when off-balance, these result in many run-away inflammatory responses and autoimmune disorders. More precise manipulation of the immune system may be useful. One approach is the use of a designer monoclonal antibody to bind directly to the targeted chemo/cytokine or the use of soluble receptors to bind the chemo/cytokine molecules. Small molecule antagonists and neutralising molecules to precisely target one or more cytokine are also possible (Pranzatelli 2018).

The neuroinflammation-triggered immune response may be heterogeneous and cytokine/chemokine profiling might provide new insights into disease pathogenesis and improve our ability to monitor inflammation and respond to treatment (Kothur et al., 2016). Different inflammatory markers or profiles of immune response have been described for different neuropsychiatric disorders. The best examples are in neurodegenerative disorders where the profiles of immune responses have been rigorously investigated (Oeckl et al., 2018; Abu Rumeileh et al., 2019). Profiling immune response may eventually provide directions for the type of anti-inflammatory measures to be used. For example, patients with high YKL-40 (glycoprotein marker of inflammation) might benefit from compounds targeting specific neuroinflammatory mechanisms, independently of the initial clinical diagnosis (Baldacci et al., 2019).

Alcoholism is an example of the heterogeneity and complexity of the immune response to inflammation (Orio et al., 2019). Alcoholism induces both peripheral and CNS inflammation and activates toll-like receptors 4 (TLR4). The innate lipid transmitter oleoethanolamide (OEA) is potentially anti-inflammatory and neuroprotective in alcohol abuse. In animal models, it has been demonstrated that OEA blocks the alcohol-induced TLR4-mediated pro-inflammatory cascade. The release of pro-inflammatory cytokines and chemokines is blocked, resulting in the blockade of inflammatory neuro damage in the frontal cortex (Sayd et al., 2014).

Pro-inflammatory cytokines, such as IL-6, TNF- α , IL-1 β , as well as TNF-alpha and IFN-gamma, have been reported to be elevated in patients suffering from major depression (O'Brien et al., 2004; Schiepers et al., 2005; Brites and Fernandes 2015; Benatti et al., 2016). Activated pro-inflammatory cytokines may cause HPA axis hyperactivity through interference with the negative feedback inhibition of circulating CSs on the HPA axis. These patients may benefit from anti-inflammatory agents (Kopschina Feltes et al., 2017). There are other signature cytokines such as interleukin-17A (IL-17A) produced by T helper 17 cells (Th17) that have been suspected to mediate the damaging effects of neuroinflammation (Beurel and Lowell 2018). Intestinal Th17 cells are regulated by gut microbes. Immune profiling is therefore the step to target therapy.

Considering the profiles of neuroinflammation, the dynamic interaction between the cytokines and the glucocorticoid system (Kim et al., 2016) is an important consideration. The profiles may not be static when the glucocorticoid system is activated, or

in response to steroid therapy, when treating hyperinflammatory states, as in cytokine storms in COVID-19.

Neuronal damage in peripheral inflammation and innate neuroinflammation may differ. It has been pointed out that in degenerative diseases, brain resident cells, not blood-borne leucocytes, are the predominant producers of pro-inflammatory cytokines. In neuroinflammatory diseases, such as in MS, invading leucocytes are the main producers of pro-inflammatory cytokines (Becher et al., 2017). This may translate into targeted therapeutics with further research.

Use of anti-inflammatory agents such as NSAIDs has been found to be associated with reduced risks in AD studies (Wang et al., 2015), especially if used early (McGeer et al., 2016). This contrasts with the ineffectiveness of NSAID in treating acute inflammation in TBI as mentioned above. COX-2 inhibitors have been reported to be effective in some but not all studies (Sethi et al., 2019; Westwell-Roper C, Stewart 2020).

Apart from anti-inflammatory agents such as NSAID, an important advancement in targeting the dysregulated immune system in neuroinflammation is in the area of disease-modifying agents or therapies (DMT). There is a paucity of such agents at present for neuropsychiatric disorders other than MS. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have already approved a number of DMTs for MS, such as β -IFN-1 α , teriflunomide, and natalizumab (Doshi and Chataway, 2016). The use of IFNs to modify inflammatory damage in viral infection is already a common practice. In COVID-19 infections, the virus has been discovered to impair IFN λ induction, resulting in severe hyperinflammation. IFN-lambda (IFN λ) is thus a possible DMT for COVID-19-associated hyperinflammation (Andreaskos and Tsiodras 2020). Cell-based therapies have also been considered. Examples include mesenchymal, neuronal, human embryonic, and induced pluripotent stem cell and hematopoietic stem cell therapy for suppressing hyperinflammation in relapsing MS, thereby improving neurological disability (Cuascut and Hutton 2019).

Neuroprotection and therapeutics

The diagnosis of the cause of acute neuroinflammation is usually straightforward. Treatment would involve targeting and removal of the causative factors and applying neuroprotective measures as fast as possible. In COVID-19 infection, application of steroids and a full plethora of disease-modifying agents illustrate the contemporary approach to mitigating the potential damage of a hyperinflammatory condition, which may proceed into a chronic neuroinflammatory state, such as MS. In PANDAS, for example, prophylactic NSAIDs given within 30 days of onset may shorten neuropsychiatric symptom duration (Brown et al. 2017). Small doses of DA antagonists may help to relieve the hallucinations, which are different from the intrusive images of OCD (Thienemann et al. 2017). Repinotan, a highly selective 5-HT1A receptor agonist, was found to have pronounced neuroprotective effects in ischemic stroke (Berends et al. 2005). Other treatment and activities such as enhancing BDNF, Bcl-2, and other neurotrophic hormones, and physical exercise (Tang et al. 2008), are important in facilitating or enhancing neurogenesis and synaptogenesis.

One of the most exciting developments is repurposing of existing medications for neuroprotection. Fluvoxamine, an SSRI antidepressant with high (agonist) affinity for sigma1 receptors, is beneficial in pre-clinical models of inflammation and sepsis

(Rosen et al., 2019). It also lowers clinical deterioration in COVID-19 outpatients (Lenze et al., 2020). The effect appears related to the fact that sigma1 receptors control production of inflammatory cytokines via the endoplasmic reticulum stress sensor IRE1. For reviews on sigma-1 receptor's role in neurodegeneration and neuroprotection, please see (Nguyen et al., 2015, 2017).

Interestingly, a number of important psychiatric drugs have been found to label sigma receptors in human brain (Helmeste et al., 1996, 1999; Tang et al., 1997). Considering the emerging role of sigma1 receptors in neuroprotection, it is significant that post-mortem brain studies in schizophrenic subjects have shown marked reductions (50%) in sigma receptor numbers compared to normal controls (Helmeste et al., 1996). How this affects long-term neurodegeneration is an important area for further study.

Different neurons exhibit different vulnerabilities to insults. GABA neurons appear to be particularly vulnerable to psychological stress resulting in depression in early life (Gabbay et al., 2017) or schizophrenia later (Modinos et al., 2018a, b; Romeo et al., 2018).

ACh neurons are the vulnerable neurons in AD and degenerate early. Their number is a good correlate of disease progression while drugs that protect the ACh system are still one of the most promising treatments for AD (Ferreira-Vieira et al., 2016; Hampel et al., 2018).

Serotonin (5HT) neurons are vulnerable to certain hormone deficiencies, 5HT depletion medications, and certain psychedelics, which bind strongly to the 5HT_{2A} receptors. Normal function of the 5HT system depends on ovarian steroidal hormones, especially estradiol and deficiency of these hormones in early development adversely influenced the development of 5HT neurons and resulted in fewer 5HT neurons in animal models (Bethea et al., 2011, 2017). Decrease in female steroid hormones in middle age or in those with ovariectomy correlates with an increase in the onset of AD and depression. Oestrogen enhances the effect of antidepressant treatment (Hernández-Hernández et al., 2019). All these illustrate the value of adjunct or supportive therapeutics.

Drugs of abuse and many psychedelics tend to damage 5HT neurons, by binding strongly to 5HT_{2A} receptors and via perturbation of 5HT uptake and release. Well-known examples include amphetamine and its analogues. 3,4-methylenedioxyamphetamine and its analogues damage serotonin (5-HT) neurons through mitochondrially mediated oxidative stress and activate autophagy, with dieback of 5-HT neurone. Rilmenidine antagonises this neurotoxic effect (Mercer et al. 2017). Whether damaged 5HT axons in the adult mammalian brain have the capacity to regrow is controversial (Jin et al. 2016).

Glutamatergic pyramidal neurons in hippocampus are sensitive to ischemia and may degenerate after recurrent seizures and stroke. Interestingly, susceptibility differs between CA1 pyramidal neurons, which tend to degenerate after global ischemia and CA3 neurons after limbic seizures. The basis for these differential vulnerabilities is unclear and might be related to the differential entry of Zn²⁺ into CA1 (delayed and long-lasting) and CA3 (rapid) (Medvedeva et al. 2017).

The above discussion highlights the differential vulnerabilities of neurons to inflammatory insults. The remaining difficulty is to differentiate neuroinflammation from other aetiological factors in causing functional impairment or neuronal degeneration/death in the particular disorder.

Regarding neuroprotection, toll-like receptors (TLRs), such as TLR2 and TLR4, are known inducers of tissue inflammation in trauma and infections. Binding to TLRs, hyaluronan (HA) oligomer and HA tetrasaccharide (HA4) could suppress the expression of pro-inflammatory cytokine IL-1 β and was found to significantly prevent hippocampal pyramidal neuronal death even 7 days after ischemic injury (Sunabori et al., 2016). The polyphenol resveratrol, present in red wine, potently protects against ischemia neuronal damage through its oxygen-free radical scavenging and antioxidant properties (Zhang et al., 2008). Delayed pyramidal neuronal death in ischemia might be due to apoptosis; the NSAID indomethacin, a prostaglandin inhibitor, has been shown to be neuroprotective in an animal model (Kondo et al., 2000). Extensive but selective pyramidal neuronal death occurred in the neocortex and hippocampus in AD. In normal ageing, there is no neuronal death, but synaptic NMDARs, no longer protected by oestrogen, are decreased in certain hippocampal circuits (Morrison and Hof, 2002). NMDAR antagonists are known to be neuroprotective against hippocampal neuronal death in cell culture models (Pozzo Miller et al., 1994). Pyramidal neuron damage may lead to deafferentation and degeneration of GABAergic neurons (Shih et al., 2004).

Another type of glutamatergic neuron in the anterior cingulate cortex and frontal-insular cortex, the Von Economo neurons, are especially vulnerable to AD pathology, particularly in later stages of pathogenesis. Their densities do not change throughout normal ageing but are more numerous in super-agers with high memory functioning. They are selectively destroyed in frontotemporal dementia (Kaufman et al., 2008), in which activated microglia are prominent (Lall and Baloh 2017). The intrinsic vulnerabilities, whether high metabolism or high oxidative load of these glutamatergic neurons, which push them into degeneration, will require further investigation (Gefen et al., 2018). Attempts to ameliorate glutamate-induced cytotoxicity were illustrated in the anti-allergic and anti-inflammatory actions of N-Palmitoyl-5-hydroxytryptamines (Pal-5HT), a cannabinoid, which demonstrated a dose-dependent inhibition of oxidation-induced cell death and suppressed glutamate-induced apoptosis and enhanced Bcl-2 and BDNF (Yoo et al., 2017).

Many other compounds and medications, as well as physical exercise, have been examined for their neuroprotective properties, but their neuroprotective actions appear to be general and not specific nor selective for specific neurons.

There are other less known but emerging novel neuroprotective compounds and measures to antagonise neuroinflammation. Psychological stress has been shown to change the composition of the gut flora, resulting in the passage of neurotoxic metabolites through the BBB to create damages or changes in the brain. The brain-gut-microbe-inflammation hypothesis of mental disorders and fecal transplantation as treatment is a rapidly emerging area of new research and new concept of treatment (Choi and Cho 2016; Evrensel and Ceylan 2016; Fung et al. 2017; Inserra et al. 2018; Lin et al. 2018; Sun and Shen 2018; Cerovic et al. 2019; Kim et al. 2019; Sochocka et al. 2019). Interestingly, processed fecal preparation has been used in traditional Chinese medicine for the treatment of all mental disorders from depression to psychosis (Tang and Tang 2019). The recently announced seaweed-based drug oligomannate (Wang et al. 2019), which also works through restoration of normal gut flora, shows that small molecules are not necessarily the only compounds for neuroinflammation treatment.

Imaging inflammation

Investigation of neuroinflammation in psychiatric disorders benefited from recent advances in imaging techniques to visualise and quantify neuroinflammation *in vivo* (Wu et al., 2013; Felger 2018). Cellular, immunoproteins, and other elements involved in inflammation and infection can now be imaged. Examples include tracking inflammation by PET, tagging targets such as the translocator protein in microglia, with ^{18}F or ^{11}C ligands (Wu et al., 2013). Other techniques included the use of 2-[(^{18}F)-fluoro-2-deoxy-d-glucose or gallium -68 ligands to label leucocytes and other elements of immune responses (Vaidyanathan et al., 2015). Diagnosis and management of patients suffering from a broad spectrum of infections, such as human immunodeficiency virus (HIV) infections, disorders such as sarcoidosis, autoimmune disorders, and IgG4-related systemic diseases, can benefit from these imaging techniques now. It is foreseeable that more inflammation markers could be imaged soon with new techniques, such as the hybrid PER/magnetic resonance imaging systems (Sollini et al., 2018). These advanced imaging techniques have yielded much data in patients with neurodegenerative disorders. Applications to other neuropsychiatric disorders such as OCD (Attwells et al., 2017) are in the early phases. These new techniques may enable us to quantify or differentiate the types of neuroinflammation in different psychiatric disorders and design targeted therapy to replace a general anti-inflammatory strategy such as the use of COX-2 inhibitors.

Conclusion

Neuroinflammation, triggered by a variety of causes, including viral infections such as COVID-19, plays an important role in the initiation, progression, or enhancement of many neuropsychiatric disorders, including depression and anxiety, OCD, AD, PD, and MS. In patients showing clear and marked elevations of inflammatory activities, or abnormal anti-inflammatory response, management or immune modulation may be crucial and useful as adjunct therapy to the standard medication.

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