Editorial

Linkage of CNS and Immunology with Psychology: Searching for New Pharmacological Targets

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Scientists have striven since ancient times to improve mankind's physical health. In so doing, the state of psychological health is often overlooked, especially as concerns its close connection with the central nervous system (CNS) and immunology. Two challenging questions thus arise: 1. "how to maintain one's healthy status from birth to death in terms of physiology and mind"? 2. Which are the neurobiological links between CNS and immunology relating to physical and mental health? Studying these neurobiological links could help us to better understand the pathophysiology of CNS diseases and, hopefully, improve their treatment.

Epidemiological data show CNS disorders to be some of the most prevalent, devastating and yet poorly treated illnesses. The development of new drugs for these disorders has the potential to provide patients with significant improvements in quality of life, and to reduce future economic burden on healthcare systems. The approval of CNS drugs with novel mechanisms of action has been rare in recent years, creating a strong need to improve the drug discovery processes in this field [1]. Focusing on treatments that target disease pathophysiology will improve the chances of developing therapeutics that go beyond current symptomatic treatments. Indeed, identifying new molecular targets involved in the pathogenesis of CNS disorders is an essential first step in designing new and efficacious disease-modifying drugs [1, 2].

Over the last decade significant progress has been made in diverse areas of neuroscience such as neurobiology, neuroimaging, neuroimmunology, social neuroscience and the 'network approach' to brain function. These advancements have suggested new pharmacological approaches for the treatment of CNS disorders which should be validated in the next years [3].

According to the current *pathology-to-drug* discovery approach, analysis of the pathophysiology of neuropsychiatric disorders represents the first step in identifying novel disease pathways and validating new pharmacological targets. A more complete understanding of these disease pathways can facilitate both the selection of novel drug targets and the development of disease-relevant models for the development of new psychotropic drugs. Working on multiple targets within favoured biological pathways, using both small-molecule and biotherapeutic approaches, can help to balance pipeline risk and increase the chances of delivering truly novel compounds to the clinic [2]. The aim of this special issue is to provide the reader with evidence on new potential pharmacological targets for the treatment of neurological and psychiatric disorders.

In the first article, Bengesser and coauthors [4] examine peripheral oxidative stress parameters and antioxidative markers in sera from 115 euthymic bipolar disorder (BD) individuals, as well as the effects of mood stabilizers on oxidative and antioxidative systems. Interestingly the authors found that bipolar patients taking lithium have significantly lower oxidative parameters, as opposed to individuals taking atypical antipsychotics who showed high oxidative stress markers. The observed effects of lithium on oxidative markers might provide a mechanistic basis for understanding lithium's neuroprotective effects.

The neurobiology of BD is not completely understood, but recent evidence suggests a central role of disturbed endoplasmic reticulum (ER) homeostasis in the pathogenesis of BD. In line with this, Wallner-Liebmann and coworkers [5] discuss recent data on impairment of ER homeostasis in light of the stress-vulnerability model. These authors highlight candidate pharmacological targets for the treatment of BD, such as the chaperon BiP, which is highly expressed in the ER and up-regulated by chronic treatment with different classes of mood stabilizers. They also examine the role of unfolded protein response-related proteins associated with BD and propose the hypothesis that ER stress may represent a common interface between obesity, which is over-represented in BD patients.

Recent studies suggest that different neurobiological and clinical links exist between autistic spectrum disorder and Alzheimer disease (AD). In this special issue Khan and coauthors [6] investigated common clinical phenotypes and factors in the pathophysiology of these two disorders such as amyloid precursor protein, metals and neuro-inflammatory phenomena, finally suggesting that common molecular targets might be found in these two disorders with the potential advantage to identify new pharmacological targets.

Over the last two decades several studies have demonstrated that inflammation of the CNS (neuroinflammation) plays a central role in the pathophysiology of CNS disorders as diverse as chronic neurodegenerative diseases, chronic pain, stroke, spinal cord injury and neuropsychiatric disorders [7]. Originally viewed as an immune-privileged organ, the CNS is now recognized to have a constant interplay with the innate and adaptive immune systems, where resident microglia and infiltrating immune cells from the periphery have important roles. Indeed, activation of innate immune system cells in the periphery can affect CNS behave and cognitive performance [7]. Common diseases of the CNS, such as major depression, schizophrenia, AD, Down syndrome (DS) and autistic spectrum disorders elicit a neuroinflammatory response, making them attractive targets for

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treatments that limit the extent of the disease and support repair and regeneration. However, various disease mechanisms leading to neuroinflammation contribute to the disease process itself. An extensive dataset describes neuroinflammation to have detrimental consequences, but results emerging largely over the past decade have indicated that aspects of the inflammatory response can also be beneficial for CNS outcomes.

The study of neuroimmune interactions might represent therefore an important step to identify new pharmacological strategies and finally to improve physical and mental health in neuropsychiatric disorders. Within this context, this special issue presents several studies on the role of neuroinflammation in CNS disorders such as depression [8, 9], DS associated with AD [10], disorders associated with intellectual disability such as autism [11] and, finally, schizophrenia [12]. Neuroinflammatory phenomena play a central role in the pathophysiology of major depression and AD [7, 13]. Neuroinflammation is also strongly associated with a reduced response to treatment with second-generation antidepressants [14] and may also account for the complex interaction of depression and cognition in older adults [15]. Further, neuroinflammation might represent a biological link between depression and different medical disorders characterized by high co-morbidity with depressive disorders. Within this scenario an innovative approach proposed by Benatti, Blom and colleagues [8] in this special issue reconsiders the fundamental role of neuroinflammation and neuroimmune factors activated by various pathologies such as stroke, chronic pain, diabetes mellitus and HIV infection as new relevant risk factors for the development of depression. Interestingly these investigators identified six different neuroimmune factors that can define and individual's neuroinflammatory burden and explain the high risk to develop depression in these medical disorders. In particular, the authors show the central role of interleukin-1β, tumor necrosis factor-α, activated glia and microglia, and monocyte-derived macrophages, as well as other factors involved in neuroinflammation such as blood-brain barrier integrity, activity of the kynurenine pathway and inflammasomes. All these neuro-immune factors might represent biomarkers of risk susceptibility as well as new potential pharmacological targets for the development of innovative antidepressant drugs.

Moving to drug discovery processes, Crupi and Cuzzocrea [9] examine the role of neuroinflammation and immunity as a new pharmacological target in depression. The authors explore preclinical and clinical evidence supporting the causative role of immune system activation, hypothalamus-pituitary-adrenal axis hyperactivity and neuroinflammatory phenomena in the pathophysiology of major depression. Interestingly, they show a central role for pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6 in the pathogenesis of depression and examine the molecular mechanisms underlying glucocorticoid receptor dysfunction in depression as new pharmacological targets for the treatment of major depression.

As discussed above, neuroinflammation has been proposed as a neurobiological link between depression and neurodegenerative diseases [13]. Neuroinflammation strongly affects cognitive function [7] and seems to be an early event in the pathogenesis of AD and DS [16-18]. Both AD and DS are marked by a progressive degeneration of basal forebrain cholinergic neurons, which depend on nerve growth factor (NGF) for the phenotypic maintenance of their cell bodies and synaptic terminals. Along this line, Iulita, Caraci and Cuello [10] discuss recent evidence for a deficit of NGF pathway in AD and in DS brains and examine how an early, disease-aggravating pre-plaque pro-inflammatory process promoted by amyloid β -peptide oligomers can adversely affect the extracellular metabolism of NGF, thus promoting degeneration of cholinergic basal forebrain neurons both in diseases. According to this scenario, inhibition of this early pro-inflammatory process and rescue of the NGF metabolic pathway might represent new pharmacological strategies to slow down the neurodegenerative process in AD and DS.

The central role of neuroinflammation has been confirmed also in other CNS disorders such as autism and schizophrenia. Within this context, Di Marco and coworkers [11] examine the neuroinflammatory mechanisms in developmental disorders associated with intellectual disability and autism spectrum disorder. The authors first discuss the physiological role of CNS immune cells and inflammatory cytokines in neuro-developmental processes and in synaptic and structural plasticity during development before examining inflammatory changes and immune system dysfunction in syndromic forms of autism and intellectual disability. Di Marco *et al*. then show how an abnormal immune response during critical windows of development and consequent abnormal production of neuroinflammatory mediators may impact brain function and structure, thereby playing a role in the pathogenesis of non-syndromic autism. Finally these authors discuss recent evidence on the central role of neuroinflammatory phenomena in Fragile X syndrome and Rett syndrome.

Immune system dysfunction is an early event in the pathogenesis of schizophrenia, and immune system activation and pro-inflammatory cytokines influence dopaminergic, serotonergic, noradrenergic, and glutamatergic neurotransmission [19]. In their chapter, Karim *et al*. [12] present a meta-analysis linking neuroimmune interaction with psychological disorders in schizophrenia, by means of a global expression approach and pathway analysis [12]. The authors retrieved genome-wide mRNA expression data and clinico-pathological information from five independent studies for schizophrenic patients from the Gene Expression Omnibus database. Their pathway and gene ontology analysis showed alterations of interleukin-1 signaling pathways and networks combined with alterations of γ-aminobutyric acid receptor signaling and nuclear factor of activated T cells activity in regulation of the immune response. Interestingly, these results suggest strong neurobiological links between immune system activation and the pathophysiology of schizophrenia.

The link between immune system dysfunction and the pathogenesis of CNS disorders is a hot topic in the field of neuroscience with a relevant impact on drug discovery processes. We hope that this special issue will stimulate debate and discussion on this topic and a reappraisal of the immune system's role in the pathophysiology of CNS disorders, with the final aim to identify new pharmacological targets and improve current therapeutic strategies.

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