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Mini review

Neuroinflammation in schizophrenia and other psychotic disorders

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Summary. Following the concept that inflammation of the central nervous system is the foundation of some mental health disorders, this review aimed to give a better insight into inflammatory events associated with schizophrenia and psychosis in general. The cascade of events and the change in secreted molecules by microglia occurring during neuroinflammation might predispose or provoke psychotic episodes. Such molecules include cytokines, chemokines, products of arachidonic acid metabolism, reactive oxygen species (ROS) and bacterial products or proteins generated by the host to fight microorganisms. In this review, the role of the major known inflammatory molecules in the disruption of tissue function will be discussed. Among the cytokines frequently examined in schizophrenia such as IL-6, a trait marker, and IFN-γ, a state marker, together with some smaller non-protein molecules were overviewed. Among the discussed markers, it appears that there is no strong evidence supporting a single marker, or a panel of markers for that matter, that would have direct implications for the prevention, diagnosis and treatment. However, the collected data might point to some pathophysiological events associated with schizophrenia and psychosis in general.

Keywords: eicosanoids, interleukins, state marker, trait marker.

INTRODUCTION

Psychosis is a mental health condition characterized by a disconnection from reality, which affects around 3% of the population (Vigo et al. 2016). Individuals experiencing psychosis may have hallucinations, where they see or hear things that aren't there, and delusions, which are strong beliefs that are not based on reality (Arciniegas 2015). These symptoms can significantly impair one's ability to function in daily life. Psychosis can be a feature of several psychiatric disorders, including schizophrenia, bipolar disorder, and severe depression, and can also be triggered by substance abuse or medical conditions. Treatment primarily involves a combination of medication, but also psychotherapy, and support services to help manage symptoms and improve quality of life (Stahl 2011).

The aetiology of psychosis is multifaceted, involving a combination of genetic, biological, psychological, and environmental factors. Understanding the interplay of these factors is crucial for the effective prevention and treatment of psychosis. Patients often have a family history of psychotic disorders, which increases the risk, suggesting a genetic predisposition. Specific genes associated with dopamine regulation and other neurotransmitter systems have been implicated and neurochemical imbalances, particularly involving dopamine and serotonin, play a significant role. Abnormalities in brain structure and function, such as enlarged ventricles or reduced grey matter, are also associated with psychosis. Psychological factors, such as high levels of stress, trauma, and significant life changes, can trigger or exacerbate psychotic episodes. Childhood adversities and abuse are notable risk factors as well. In the prenatal period, exposure to infections,

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malnutrition, or toxins can increase this risk for psychosis in later life. Furthermore, substance abuse, particularly psychoactive substances such as cannabis, LSD, and amphetamines, can also precipitate psychosis. Somatic illnesses such as brain tumours, central nervous system infections, and autoimmune disorders can lead to psychotic symptoms (Boland et al. 2022).

Long long-lasting aspiration of biological psychiatry is to resolve the questions associated with the etiopathogenesis of psychosis and to find adequate biomarkers that could help diagnose and monitor psychosis. Still accepted is the dopaminergic theory, which describes the symptoms through the excess (positive) and insufficiency (negative) of dopamine in mesolimbic and mesocortical dopaminergic projections, respectively (Stahl 2011). Another major hypothesis is the one concerning hypoglutamatergia, which is based on the clinical studies showing that N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine and dizocilpine (MK-801) could provoke and mimic cognitive impairment corresponding to the ones seen in schizophrenia and also on those showing that these drugs could exacerbate schizophrenia (Coyle and Tsai 2004). Serotonergic theory is formed after noting the ability of second-generation antipsychotics to reduce psychotic symptoms. The abundance and distribution of serotoninergic receptors, especially 5-HT_{2A} (but also 5-HT_{2c} and 5-HT_{1}), is on neurons located in the cortex, hippocampus, and ventral striatum which are associated with reality testing, executive function, and selective response to sensory inputs (Meltzer 2012).

In the current state of facts, the absence of a comprehensive biochemical profile, the diagnosis of schizophrenia or any psychotic disorder is currently based on clinical observations, which are broadly subject to the interpretations of medical practitioners and, as a result, are susceptible to errors (Balter 2014). By tracking the changes in blood levels of easily monitored molecules scientists deemed to find the answer for the changes in disease state (Herrera-Imbroda et al. 2023). In the following text, the role of selected molecules with the strongest evidence for their usage as markers for tracing disease predisposition, state, or presence will be discussed, trying to give better insight into the immune-cytokine hypotheses of schizophrenia.

EICOSANOIDS

Eicosanoids are one of the best-investigated classes of lipid mediators arriving from polyunsaturated fatty acid oxidation yielding prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (Wang et al. 2018). Prostaglandins are lipid-derived pro-inflammatory signalling molecules generated by cyclooxygenase (COX) from arachidonic acid. Some major prostaglandins include prostaglandin E2 (PGE2), prostaglandin I2, and thromboxane. The production is initiated by stimuli such as injury or infection, thus involving these molecules in the process of inflammation and modulation of the immune response, pain signalling, and regulation of blood flow (Rouzer and Marnett 2009). The activity of PGE2 can be interpreted in two ways as either neurotoxic or neuroprotective, depending on the activated receptors (Wang et al. 2018). The connection between eicosanoids and psychosis has been shown in a recent metabolomic fingerprint study which followed around 158 eicosanoids and correlated their concentrations with psychotic symptomatology (Wang et al. 2018). The results of the study were inconclusive leaving an open question on the utility of these molecules as true disease biomarkers. There are two major enzymes, COX1 and COX2, that are in charge of prostaglandin synthesis, and based on the drugs decreasing their activity (celecoxib, aspirin, etc.), the associations between prostaglandins and psychosis are made. These associations are further corroborated in post-mortem studies showing that COX1 is upregulated in the brain of particular types of patients with schizophrenia, while COX2 expression does not differ from the control (Tang et al. 2012).

Two conducted meta-analyses on the usage of NSAID as a neoadjuvant therapy to antipsychotics present opposite findings (Nitta et al. 2012; Sommer et al. 2014). Although both studies highlighted their limitations and strengths, there is still no valid evidence for justified usage of NSAID in these patients, even though the combination of these drugs with antipsychotics does tend to decrease positive symptom intensity (Nitta et al. 2012; Sommer et al. 2014). Some recommendations for the potential application of NSAIDs, especially aspirin, are reserved for a first and early episode, younger patients, and those with specific/greater pro-inflammatory status (Nitta et al. 2012). Apart from the NSAID, a second-generation antipsychotic clozapine was reported to decrease COX activity and, consequentially, PGE2 concentration (Kim et al. 2012), and its activity can be potentially observed through a decrease in this inflammatory cascade.

CYTOKINES

Cytokines are signalling proteins that play a crucial role in regulating immune and inflammatory responses. In the CNS, they mediate the communication between immune cells and other nervous tissue cells, contributing to both protective and pathological processes. Pro-inflammatory cytokines are key drivers of neuroinflammation, promoting the activation of microglia and astrocytes, which leads to the release of additional inflammatory mediators (Dinarello et al. 2007).

Interleukins (ILs) are a group of cytokines that play a pivotal role in immune regulation and inflammatory re-

sponses, including neuroinflammation. While interleukins are of great importance in the coordination of the immune response, their prolonged or excessive activation, as mentioned, can lead to tissue damage and synaptic dysfunction and contribute to the progression of different CNS-related disorders (Chaney et al. 2021). One such interleukins is IL-6, for which applicability the largest body of evidence has been gathered suggesting it to be a trait marker. At the same time much smaller amount of data for similar purposes has been collected for IL-1ß and tumour necrosis factor α (Herrera-Imbroda et al. 2023).

Interleukin-6

This cytokine is primarily considered pro-inflammatory, and in the IL-6 family of cytokines, eight proteins could bind to either signalling or ligand-binding receptors (Soltani Khaboushan et al. 2022). Receptors could be membrane-bound and soluble in active classic and trans-signalling pathways. The signalling mechanism can be mediated by 130 kDa glycoproteins (gp130) present in all cells, which through a downstream cascade activates Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK), and PI3K pathway. The mentioned gp130 can only bind to a complex formed by IL-6 and soluble receptors and thus can alter its pro-inflammatory properties.

Microglia cells, astrocytes, neurons, and endothelial cells are believed to be the primary sources of IL-6 in the brain (Soltani Khaboushan et al. 2022). In a healthy brain, IL-6 can mediate body weight, food intake and regulate the sleep-wake cycle and some aspects of behaviour, such as emotions (Erta et al. 2012). Brain tissue is dependent on the levels of IL-6, meaning that low levels (or absence) are crucial for normal homeostasis, as it prevents glial activation in some traumatic events, while its overproduction causes neurodegeneration (Rothaug et al. 2016). Through the classical pathway, IL-6 is believed to be involved in the differentiation of oligodendrocytes, neuronal survival, and modification of glutamate release (Soltani Khaboushan et al. 2022).

During inflammation, as the BBB increases its permeability and IL-6 levels increase as well, this is followed by an increase in its receptors (Erta et al. 2012) and also correlates with a surge of NF-κB (Lorigados Pedre et al. 2018). This cytokine, along with other pro-inflammatory ones, could affect GABA transmission through the changes in the GABA transporter profile, leading to a decrease in this neurotransmitter availability (Fu et al. 2015) and, at the same time, increasing glutamate amounts. It is worth mentioning that IL-6 exerted a neuroprotective role in some animal studies, preventing dopaminergic neuron death induced by toxins (Erta et al. 2012). The increased levels of the pro-inflammatory cytokine IL-6 observed consistently across various studies could be regarded as a trait marker for schizophrenia (Herrera-Imbroda et al. 2023). This marker is linked to hereditary and neurodevelopmental factors, indicating susceptibility to the disorder, and tends to remain relatively stable throughout its different stages. Also, in patients with schizophrenia, levels of blood IL-6 mRNA are found to be associated with positive symptom presentation (Chase et al. 2016). These facts could potentially lean in favour of this parameter as a peripheral marker for psychotic disorders.

Interleukin-18

Interleukin-18 belongs to the IL-1 family and is a pleiotropic pro-inflammatory cytokine. It is primarily produced by macrophage-like cells, while in brain tissue, it is produced by astrocytes, microglia, neurons, and ependymal cells. It is recognized as a linking molecule between innate and adaptive immune responses and a regulator of both cellular and humoral immunity (Alboni et al. 2010). It acts costimulatory with IL-12 in the production of interferon γ (IFN-γ) from Th1 cells (Alboni et al. 2010).

During brain development and in some disorders, IL-18 could affect tissue function via its receptors located at neurons and through its influence on the hypothalamic-pituitary-adrenal axis (Sugama and Conti 2008). In response to CNS infection, IL-18 has been shown to activate microglial cells, which, as has been described previously, is believed to be the main culprit for psychosis and schizophrenia.

A recent meta-analysis revealed that IL-18 is significantly increased in patients with chronic schizophrenia, while it is borderline increased in those with the first episode (Syed et al. 2021). Thus, these indicate that IL-18 might be an adequate marker for chronic schizophrenia rather than the first episode. Higher levels of IL-18 have been vaguely associated with total PANNS score, while much more correlated with cognitive dysfunction and depression (Syed et al., 2021). It has been shown that increased hippocampal neurons IL-18 enhance both synaptic glutamate release and postsynaptic AMPA receptor expression which might been associated with symptoms seen in psychosis (Kanno et al. 2004).

Transforming growth factor β (TGF-β)

Transforming growth factor β (TGF-β) has mainly inhibitory action on different types of T cells by decreasing exocytosis of granules and through the inhibition of cytokines production (IL-2, TNF-α, IFN-γ, IL-4, etc.). It also polarizes T cells towards regulatory T cells, and when the IL-6 and soluble IL-6 receptors are present, TGF-β facilitates the development of Th17 cells (Corsi-Zuelli et al. 2021). Also, one should not overlook its immense impact on the development and maturation of the CNS through the processes

of cell growth, differentiation, migration, synapse formation, and pruning (Corsi-Zuelli et al. 2021). The presence of IL-10, secreted by microglia, acts as a direct stimulation of astrocytes to secrete TGF-β, and thus to maintain nervous system homeostasis. However, if more significant amounts of TGF-β are secreted, genes for phagocytotic processes and nerve cell pruning are activated, while the inflammation is tuned down (Corsi-Zuelli et al. 2021). Also, in animal models, excess TGF-β was found to be associated with a decreased production of neurotrophic factors (e.g., insulin-like growth factor 1), which is involved in the survival of cortical neurons (Endo et al. 2015). Thus, targeting the TGF-β can potentially be beneficial in preventing and/or maintaining the associated disease.

Among the studied genes, TGF-β was found to be the only immune gene set to be increased enrichment in schizophrenia (Birnbaum et al. 2019), and these conclusions are drawn from a large number of studies (Corsi-Zuelli et al. 2021). Together with this cytokine, the levels of glutamate in astrocytes, but not in neurons, in the frontal cortex of patients with schizophrenia were increased (Abdolmaleky et al. 2019). Apart from theoretical and partially confirmed findings about the role of TGF-β in the brain of patients with psychosis, there is evidence suggesting that TGF-β is increased in drug-naive patients and also in those with repeated episodes. Also, a significant decrease in plasma levels of TGF-β was noted in those after antipsychotic treatment (Corsi-Zuelli et al. 2021). Bearing in mind the mentioned fact related to TGF-β, this cytokine has gained a name as a state marker of schizophrenia (Herrera-Imbroda et al. 2023).

INTERFERON Γ (IFN-Γ)

A cytokine belonging to the Th1-immune response is IFN-γ. It is produced by different lymphocytes, both peripheral and those infiltrating CNS, as well as by astrocytes (Kak et al. 2018). Up to now, studies show that IFN-γ is associated with some neurological disorders such as multiple sclerosis and epilepsy (Gao et al. 2017). An important study debated the influence of IFN-γ on brain functioning and changes under different conditions in animals, showing the importance of its signalling (Barichello et al. 2019). However, in human studies, the levels of IFN-γ in different fluids/tissues yield opposite results (Barichello et al. 2019). Some studies observed an increase in IFN-γ, as well as some other Th1 response-associated molecules, in acute exacerbations of psychosis, which all correlate with increased neopterin and kynurenic acid (Barichello et al. 2019). Interestingly, some authors suggest that levels of IFN-γ could be considered trait markers of psychosis, as they were found to remain elevated in acute exacerbations and following antipsychotic treatment (Miller et al. 2011).

CONCLUSIONS

Although several known molecules are suggested to be adequate for monitoring psychosis (and schizophrenia), there is still no specific nor sensitive one which could be called a biomarker. Some of them, such as IL-6, can be considered a state marker, while others, such as IFN-γ, might be considered as trait markers. It remains to be seen in future basic studies and meta-analyses will there be some other molecule(s) which could help monitor changes in the human psyche seen during psychotic episodes.

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