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Review

Inflammation in schizophrenia: A question of balance

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ABSTRACT

In the past decade, there has been renewed interest in immune/inflammatory changes and their associated oxidative/nitrosative consequences as key pathophysiological mechanisms in schizophrenia and related disorders. Both brain cell components (microglia, astrocytes, and neurons) and peripheral immune cells have been implicated in inflammation and the resulting oxidative/nitrosative stress (O&NS) in schizophrenia. Furthermore, down-regulation of endogenous antioxidant and anti-inflammatory mechanisms has been identified in biological samples from patients, although the degree and progression of the inflammatory process and the nature of its self-regulatory mechanisms vary from early onset to full-blown disease. This review focuses on the interactions between inflammation and O&NS, their damaging consequences for brain cells in schizophrenia, the possible origins of inflammation and increased O&NS in the disorder, and current pharmacological strategies to deal with these processes (mainly treatments with anti-inflammatory or antioxidant drugs as add-ons to antipsychotics).

Contents

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Schizophrenia (SCHZ) is a heterogeneous syndrome with unclear molecular mechanisms (van Os and Kapur, 2009; Insel, 2010). Forty years ago, it was suggested that inflammatory processes may play a key role in its pathophysiology (Torrey and Peterson, 1973; Horrobin, 1977). These days, there is renewed interest in immune/inflammatory changes and their associated oxidative/nitrosative consequences as key pathophysiological mechanisms (Kirkpatrick and Miller, 2013) at both the peripheral and central nervous system (CNS) level (Meyer et al., 2011). In this review, we will focus on the inflammatory and oxidative/nitrosative mechanisms underlying brain damage in SCHZ and related disorders and the possibility of pharmacological manipulation of these processes in order to improve psychopathology.

1. General aspects of inflammation and oxidative/nitrosative (O&NS) stress of special interest for schizophrenia

Inflammation is a complex biological protective mechanism aimed at removing dangerous elements and initiating healing processes, although it may be "constitutively" present in areas permanently interacting with external pathogens (skin, respiratory, or digestive epithelia). It occurs in parallel (and overlaps) with other local or systemic defense processes: cell recruitment, O&NS, and apoptosis. Usually, it is a stereotyped, non-specific response, considered a mechanism of *innate immunity* (as compared to *adaptive immunity*, specific to each pathogen). It can be considered a protective mechanism, but when excessive in intensity (non-regulated overactivity of mediators) or time (inefficient resolution), it becomes harmful.

The brain has been classically considered an "*immune privileged*" organ (by the presence of the brain–blood barrier, BBB). However, extensive evidence shows that inflammation within the CNS is directly related to many degenerative processes, and there is growing awareness of its role in psychiatric diseases (depression, post-traumatic stress disorder, and SCHZ, among others) (Najjar et al., 2013). Because increased BBB permeability has been described in SCHZ (Hanson and Gottesman, 2005; Uranova et al., 2010), it is plausible that pro/anti-inflammatory mediators may enter from the periphery or may escape from the brain to the systemic circulation in certain neuropathological scenarios.

Microglia, the resident innate immune cells in the CNS, are immediately activated in response to a harmful signal. Astrocytes, the most abundant cells in the brain (involved in maintenance and support of neurons and structural/functional components of the BBB), also become activated after an insult or by signals released by injured neurons or activated microglia. Neurons themselves may "suffer" the consequences of inflammation – and not just passively – as they release inflammatory mediators (Najjar et al., 2013).

Cytokines such as interleukins, interferons, tumor necrosis factor alpha (TNFα), and chemokines are crucial elements of a proper intra- and intercellular inflammatory response, both in the CNS and periphery. Furthermore, cytoplasm–nuclear transcription factors, mainly kappaB (NFκB) and others (AP-1), control the expression of many oxidative and nitrosative mediators through activation of enzymes (i.e., cyclooxygenases —COX— and nitric oxide synthases —NOS—). There are three isoforms of nitric oxide synthase (NOS), two constitutive: neuronal (nNOS or NOS1) and endothelial (eNOS or NOS3), and one inducible: NOS (iNOS or NOS2). iNOS is characterized by its calcium independence to synthesize NO and citrulline from L-arginine and the larger quantities of NO it can generate as compared with the other isoforms after determinate immune stimuli (i.e., infection, stress). In a pathological context, over-activation of iNOS produces high amounts of NO and the superoxide anion (O_2^-) producing enzymes NADPH oxidase and xanthine oxidase. The simultaneous production of NO and O_2^- results in the generation of peroxynitrite ($ONOO^-$), which in turn damages target molecules including proteins, glutathione (GSH), mitochondria, and DNA. This could be considered a protective cytotoxic effect against potential infection agents such as viruses or bacteria. However, iNOS has also been implicated in cell death in many clinical and experimental settings by lipid peroxidation, disruption of the blood–brain barrier, and decreased mitochondrial function. However, there are two major forms of COX enzymes, designated COX-1 and COX-2, in mammalian tissues. COXs isoforms are responsible for the synthesis of endoperoxides, PGG2 and PGH2, which are transformed into specific prostanoids in each tissue by tissue-specific synthase types. Finally, these molecules and their derivatives interact with their specific receptors to modulate cell function (Phillis et al., 2006). COX-1 is constitutively expressed in tissues, including brain tissue, and is responsible for the physiological production of prostaglandins (PGs) (Phillis et al., 2006). Inflammatory mediators such as cytokines, growth factors, and bacterial endotoxins rapidly induce COX-2, which is normally undetectable in healthy tissues, but is constitutively expressed in the kidney, stomach, and brain (Hoffmann, 2000). COX-2 expression could be induced in certain brain regions and it is able to produce peroxides and other free radicals (ROS) and prostanoids such as PGE2 in toxic amounts (10–20 times above the physiological levels produced mainly by COX-1) in pathological processes with a clear inflammatory component (Seibert et al., 1995). Brain COX-2 activity can be also neurotoxic because, during the production of PGE2, ROS are generated and these contribute to the oxidative/nitrosative damage observed (Phillis et al., 2006), and also because PGE2 is able to induce glutamate release by astrocytes generating cellular death by apoptosis (Takadera et al., 2002).

Intracytoplasmatic clusters of molecules called inflammasomes also play a central role in inflammation, mainly by detecting a large range of pathogen-associated molecular patterns and promoting the maturation of cytokines (Latz et al., 2013). All of these molecular signals are activated by cells in order to fight against pathogens and to recruit other CNS and peripheral immune cells for appropriate response.

Such a complex defense mechanism is finely regulated by compensatory anti-inflammatory pathways. One of these mechanisms involves the cyclopentenone prostaglandins (PGs). The most thoroughly studied is 15-deoxy-PGJ_2 (15d-PGJ_2) (Prasad et al., 2008). This is the proposed endogenous ligand for the gamma isoform of peroxisome proliferator-activated nuclear receptors, PPARγ, a transcription factor whose main effect is to mitigate inflammation by repressing the expression of proinflammatory cytokines and of the inducible isoforms of COX and NOS: COX-2 and iNOS (García-Bueno et al., 2008). PPARγ may be pharmacologically activated by a number of synthetic ligands such as the antidiabetic drugs thiazolidinediones, which exert anti-inflammatory, anti-excitotoxic, and proenergetic effects (promote glucose transport and ATP production) in the brain (García-Bueno et al., 2007, 2008, 2010).

Oxidative/nitrosative stress (O&NS) was first described 18 years ago when it was defined as "an imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage" with the ratio of oxidants to antioxidants >1 (Sies, 1997). Thus, O&NS is the result of a lost battle between components necessary to fight against pathogens – but also toxic to healthy cells – and the mechanisms to detoxify them. Some of the by-products of mitochondrial function used to kill pathogens or foreign cells are *radicals* (more precisely, *free radicals*: compounds with unpaired electrons, which make them highly reactive). Most radicals react immediately, looking for stability with other molecules (or even themselves). The majority are oxygen (ROS) or nitrogen species (RNS). At moderate concentrations, free radicals play an important role as regulatory mediators in signaling processes, such as the