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Review

Pharmacological targeting of redox regulation systems as new therapeutic approach for psychiatric disorders: A literature overview

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ABSTRACT

Redox dysregulation occurs following a disequilibrium between reactive oxygen species (ROS) producing and degrading systems, i.e. mitochondria, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and nitric oxide synthase (NOS) on one hand and the principal antioxidant system, the glutathione, on the other hand.

Increasing recent evidence points towards a pathogenetic role of an altered redox state in the development of several mental disorders, such as anxiety, bipolar disorders, depression, psychosis, autism and post-traumaticstress disorders (PTSD). In this regard, pharmacological targeting of the redox state regulating systems in the brain has been proposed as an innovative and promising therapeutic approach for the treatment of these mental diseases.

This review will summarize current knowledge obtained from both pre-clinical and clinical studies in order to descant "lights and shadows" of targeting pharmacologically both the producing and degrading reactive oxygen species (ROS) systems in psychiatric disorders.

Contents

1. Introduction

There is increasing evidence that dysregulations of the redox system are directly implicated in the pathogenesis of several psychiatric diseases, including anxiety [1], psychosis [2–6], bipolar disorders [7], autism [8], depression [9] and post-traumatic stress disorders (PTSD) [10]. Redox dysregulation occurs when reactive oxygen species (ROS) and reactive nitrogen species (RNS) production is increased, while antioxidant systems are deficient [11]. A large amount of ROS production derives from mitochondrial electron transport chain of the inner mitochondrial membrane, which directly generate superoxide [12], dismutating, in turn, in hydrogen peroxide and, consequently, in hydroxical radical [13,14]. Moreover, the monoamine oxidase enzyme, located at the outer membrane of mitochondria, catalyses biogenic amines deamination, representing an important source of hydrogen peroxide [15]. Another important source of ROS is the family of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase NOX enzymes. These enzymes, distributed in different body districts, transport electrons across the plasma membrane, inducing the generation of superoxide and other free radicals [16]. They have been also

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demonstrated to be crucial contributors of various physiological functions as well as pathological processes, going from alterations of the immune system, cardiovascular disorders, dysfunctions of endocrine pathways and neuropsychiatric disorders [2,3,5,17,18]. On the other hand, to reduce the ROS-induced damage, the organism utilizes enzymatic and non-enzymatic antioxidant systems. The first group includes superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT), reduced glutathione (GSH), while vitamin A, ascorbic acid (vitamin C) and alpha-tocopherol (vitamin E) are part of the second group [19].

In this review, we will summarize current knowledge on the pharmacological targeting of producing and degrading ROS and RNS systems in psychiatric disorders. Data derived from pre-clinical and human evidences will be descanted in the light of the recent scientific literature, focused on the pharmacological targeting of the redox dysregulation as an innovative therapeutic approach for the treatment of mental disorders [20].

2. Pharmacological targeting of ROS producing systems

2.1. Pharmacological targeting of mitochondria

Targeting mitochondrial functions is actually considered as a novel avenue for the development of therapeutics for several psychiatric disorders [21]. There is growing evidence that anxiety, mood disorders and PTSD are associated with impairment of the diverse mitochondrial functions in the central nervous system (CNS) [22,23]. In a very recent pre-clinical study, Hollis and co-workers observed that, in the nucleus accumbens of anxious animals with a tendency to social subordination with respect to less anxious rats, proteins of the mitochondrial complex I and II were significantly decreased, together with adenosine trisphosphate (ATP) levels and ROS release [24]. In this regard, cerebral micro-infusion of specific inhibitors of mitochondrial complex I or II decreased the probability to become dominant, observed in high anxious animals. Conversely, administration of nicotinamide in the brain was able to prevent subordination behaviour in anxious rats [24]. In the same line, it has been recently demonstrated that selective pharmacological targeting of specific mitochondrial pathways displays anxiolytic effects in vivo. In particular, treatment of anxiety-like symptoms in mice with mitoquinone mesylate (MitoQ), an antioxidant that selectively targets mitochondria, decreased anxiety-related behaviour by altering brain metabolome [25]. Emerging data suggest that mitochondrial Ca^{2+} sequestration acts as a key modulator of synaptic plasticity in several brain regions, involved in anxiety disorder development [26]. B-cell lymphoma 2 (Bcl-2) protein, located in the inner mitochondrial membrane, is one of the major modulators of mitochondrial function. Its overexpression is known to increase mitochondrial Ca^{2+} uptake and resistance to Ca^{2+}-dependent inhibition of respiration [27]. In particular, Bcl-2 mutant mice have reduced mitochondrial levels and show a significant increase of anxiety-like behaviours [28], suggesting that Bcl-2 crucial role in anxiety disorders possibly originates from its functions in mitochondria. Importantly, clinical observations suggest that anxiety-related symptoms are increased in mothers of children with maternally inherited mitochondrial disorders, confirming that the frequency of this mental state is higher among subjects belonging to the mother's line, because of the sharing of the same mitochondrial DNA of the affected individual [29].

Increasing data point towards a crucial role of intensifying mitochondrial functions as possible therapeutic option for mood disorders [30]. Indeed, it has been shown that antidepressant compounds, lithium and electroconvulsive therapy might positively impact the process of mitochondrial energy production [31,32]. More specifically, complex 1 and 2 functioning, associated to ATP production, can be increased by lithium administration [33], as also reported by Bachmann and co-workers [34]. With regard to both electroconvulsive therapy and transcranial magnetic stimulation, they have been shown to be able to enhance mitochondrial system functioning [35]. In the same line, cellular degeneration caused by oxygen and glucose deprivations, as well as the decrease of mitochondrial membrane potential, might be inhibited by treatment with nortriptyline [36]. Heterocyclics, including tricyclic antidepressants, mediate dose-dependent protection of mitochondria, i.e. inhibition of the mitochondrial permeability transition [37]. Also, a recent work of Maes and co-workers points towards the possibility to consider several agents, interfering with mitochondria activity and functioning, such as nuclear factor erythroid 2-related factor (Nrf2) activators and glycogen synthase kinase-3 (GSK-3) inhibitors, as potential new pharmacological targets for depression treatment [38].

A crucial role of mitochondrial dysfunctions has been also observed for the pathogenesis of PTSD [39,40]. Thus, in a recent work, Garabadu and co-workers evaluated possible effects of risperidone and paroxetine on mitochondrial dysfunctions and mitochondria-dependent apoptosis, in specific brain regions, in the modified stress/re-stress animal model of PTSD, showing that risperidone ameliorated the activity of mitochondrial respiratory complex (I, II, IV, and V) and decreased the levels of mitochondrial membrane potential, cytochrome-C and caspase-9 in the hippocampus, hypothalamus, pre-frontal cortex (PFC) and amygdala [41].

The relationship between autism spectrum disorders and mitochondrial dysfunctions is an area of ongoing research [42]. In particular, clinical data point towards the presence, in autistic patients' serum, of higher levels of extracellular mitochondrial DNA which could be efficiently decreased by infusion of neurotensin and flavone luteoline in the same patients [43]. In a very recent work, Yui and co-workers observed the recovery of behavioural abnormalities relevant to autism spectrum disorders by administration of the mammalian targetof rapamycin (mTOR) signalling inhibitor, rapamycin, in an animal model of this psychiatric disorder, i.e. the Tuberous Sclerosis 2 (Tsc2)+/− mice, suggesting that mTOR inhibitor may be useful for autism pharmacological treatment [44].

Several scenarios have been proposed to explain the development of psychosis and schizophrenia, one of which is mitochondrial dysfunctions [45,46]. Electron microscopy applied on *post-mortem* brain samples of subjects suffering from schizophrenia, including specific cerebral areas such as PFC and caudate nucleus, revealed a significant decrease in the number and density of mitochondrial population [47], as well as altered mitochondrial cross-sectional profile in the caudate and putamen [48] and enlarged mitochondria, associated with disruption of astrocytic cristae, consequent to long-duration schizophrenia [49]. Other studies, conducted using peripheral blood of drug-free schizophrenic patients, showed decreased number and lower volume of lymphocytic mitochondria [50–53]. Among the common anti-psychotic compounds, several are reported to be mitochondrion-toxic [54]. Therefore, given the possible worsening of the psychotic clinical status which can be induced by the toxic effects of anti-psychotic medication on mitochondria functioning, it is essential to exclude basal mitochondrial dysfunctions before treating schizophrenic patients with these compounds [55]. In particular, treatment with quetiapine or trazodone, which have been shown to possibly function as mitochondrial Complex-I inhibitors [54] and inducers of lower mitochondrial membrane potential [56], might induce severe and even fatal reactions. In the same line, it has been reported that the functioning of the respiratory chain and pyruvate-dehydrogenase complexes may be disrupted following anti-psychotic medication [57]. Moreover, phenothiazine derivatives have been described