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EDITORIAL

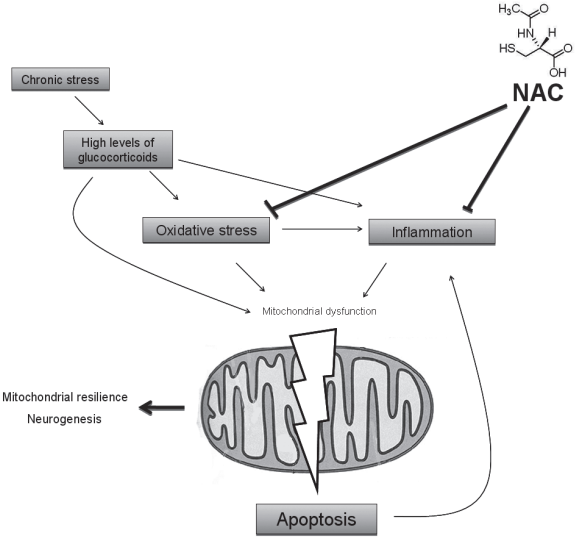
N-acetylcysteine as a mitochondrial enhancer: a new class of psychoactive drugs?

N-acetilcisteína como potencializador mitocondrial: uma nova classe de drogas psicoativas?

The limited available agents effective on the treatment of depressive episodes in bipolar disorder warrants further research on the field. Of note, several drugs have been studied in the light of their mood stabilizing efficacy, including well known supplements commonly used as add-on therapy for a number of conditions. For the past years, attention has been given to N-acetylcysteine (NAC), a chemical with antioxidant properties primarily used as a mucolytic agent and in the treatment of paracetamol overdose. A study by Magalhães et al.[1] published in this issue of RBP shows that add-on NAC therapy improved depressive symptoms and functional outcomes in bipolar disorder patients, which increases the interest in studying the mechanisms by which this drug may present neuroprotective effects.

Among its known mechanisms of action, NAC-induced brain glutathione (GSH) replenishment is the most studied. Glutathione is the primary endogenous antioxidant of the cell, and has the ability to scavenge oxygen and nitrogen species, therefore maintaining the oxidative balance. In addition to restoring GSH levels, NAC modulates inflammation by exerting anti-inflammatory actions, and presents direct effects on glutamatergic and dopaminergic neurotransmission. The inflammatory-modulating effects of NAC may be important for its mood stabilizing efficacy, mainly due to the recently described relevance of systemic inflammation in bipolar disorder pathophysiology (Kapczinski et al.[2]). More specifically, its usefulness on depressive episodes may be linked to innovative mechanisms of action, which we speculate to be taking part throughout its treatment. Among them, modulation of cellular signaling pathways by NAC may ultimately increase mitochondrial resilience, as supported below.

Chronic stress has been thought to play a key role in the pathophysiology of bipolar disorder, although the exact reasons for this association have not yet been fully clarified. The effects of stress are mediated mainly through glucocorticoids, which exert several body changes commonly known as 'stress response'. Dysregulation of glucocorticoids is associated with cognitive impairments and depressive disorder, supporting the notion that stress response may be impaired in affective and mood disorders. In this same vein, chronic stress has been shown to induce mitochondria dysfunction, whereas recent studies have described a biphasic effect of glucocorticoids on mitochondrial function, ultimately leading to the control of apoptosis on neuronal populations. Apoptosis may link chronic stress-induced neuronal death and inflammation, mainly through the release of damage-associated molecular patterns. All together, these features may be responsible for the systemic toxicity found in



NAC may counterbalance chronic stress-induced oxidative stress and inflammation, both pathways known to lead to mitochondrial dysfunction and apoptosis. Thus, NAC-induced neuroprotective mechanisms may increase mitochondrial resilience and neurogenesis.

Figure 1 Putative role of NAC as a mitochondrial enhancer.

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patients (Kapczinski et al.[3]) and underlie the burden associated with the progression of mood disorders.

More recently, adult hippocampal neurogenesis has been found to buffer stress responses and depressive behavior (Snyder et al.[4]). In addition, inflammation downregulates neurogenesis, mainly through modulation of mitochondrial viability (Voloboueva et al.[5]). Thus, neuroprotective properties of NAC may be related to its neurogenesis-inducing ability, which is likely related to mitochondria-protective mechanisms. Of note, mitochondrial dysfunction has been described as one of the pathways underlying neuroprogression in bipolar disorder (Berk et al.[6]). Further studies are warranted in light of NAC effects on treating depressive episodes in bipolar disorder. As far as it seems, NAC may be the first pharmacological intervention that increases mitochondrial resilience and prevents allostatic load in psychiatry (Kapczinski et al.[7]).

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Disclosures

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* Modest

** Significant

*** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

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