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Therapeutic potential of glutathione-enhancers in stress-related psychopathologies

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panelIoannis Zalachoras [a], Fiona Hollis [a], Eva Ramos-Fernández [a], Laura Trovo [b], Sarah Sonnay [b], Eveline Geiser [b], Nicolas Preitner [b], Pascal Steiner [b], Carmen Sandi [a], Laia Morató [a]
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Highlights

- •
  Mitochondria meet the high energetic demand of the brain during psychogenic stress.
- •
  Chronic stress leads to oxidative stress and lower glutathione (GSH) levels.
- •
  Depression and anxiety are associated with decreased levels of GSH.

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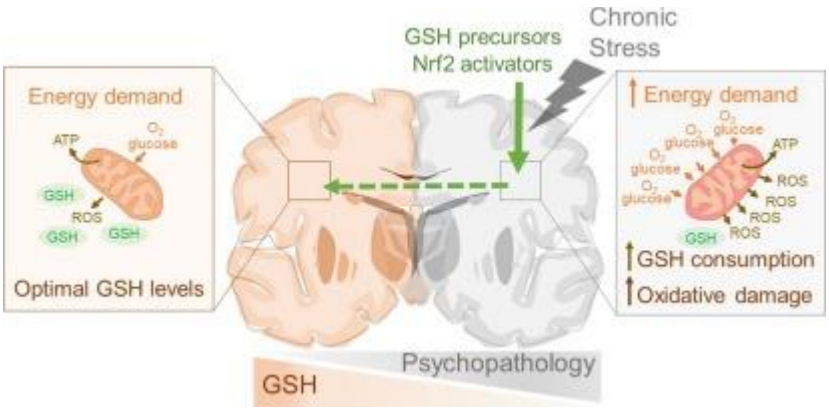
  The nuclear factor erythroid-2-related factor 2 (Nrf2) regulates GSH synthesis.
- •
  GSH precursors and Nrf2 activators prevent stress-induced behavioral alterations.

Abstract

The mammalian brain has high energy demands, which may become higher in response to environmental challenges such as psychogenic stress exposure. Therefore, efficient neutralization of reactive oxygen species that are produced as a by-product of ATP synthesis is crucial for preventing oxidative damage and ensuring normal energy supply and brain function. Glutathione (GSH) is arguably the most important endogenous antioxidant in the brain. In recent years, aberrant GSH levels have been implicated in different psychiatric disorders, including stress-related psychopathologies. In this review, we examine the available data supporting a role for GSH levels and antioxidant function in the brain in relation to anxiety and stress-related psychopathologies. Additionally, we identify several promising compounds that could raise GSH levels in the brain by either increasing the availability of its precursors or the expression of GSH-regulating enzymes through activation of Nuclear factor erythroid-2-related factor 2 (Nrf2). Given the high tolerability and safety profile of these compounds, they may represent attractive new opportunities to complement existing therapeutic manipulations against stress-related psychopathologies.

Graphical abstract



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Section snippets

The link between psychogenic stress, brain energetics and oxidative stress

Psychogenic stress is defined as a state of imminent or perceived threat to homeostasis, where the brain and body invoke various physiological responses to adapt (de Kloet and Joels, 2005; de Kloet et al., 2019). In acute situations, the stress response helps the organism mobilize the resources needed to either meet or prepare for a physical or psychological challenge (Herman and Tasker, 2016). For instance, during stress, cerebral energy metabolism, including the oxidation of glucose and the

Evidence of GSH decrease under conditions of psychogenic stress

A number of preclinical studies have reported a link between exposure to stress and decreased levels of GSH and GSH-related enzymes. Glucocorticoids, the main hormone from the hypothalamic-pituitary-adrenal (HPA) axis secreted in response to stress, have been shown to negatively impact the levels of antioxidants, including GSH. in vitro, glucocorticoids were found to decrease GSH levels and inhibit GPx activity in hippocampal neuronal cultures (Patel et al., 2002). Additionally, several studies

Compounds with potential to modulate brain GSH levels

Identifying treatments that enhance brain GSH levels may help develop therapies against stress-related neuropsychiatric diseases. In this section, we explore possible methods of increasing GSH levels in the brain.

Although a fraction of dietary GSH can cross the intestinal barrier and enter the blood stream directly, this process is inefficient and most GSH in humans is thought to be synthesized endogenously. Direct supplementation with GSH is a challenging approach, because it can be rapidly

Alternative strategies to increase glutathione levels

Apart from the main strategies to increase GSH levels through precursor supplementation or activation of Nrf2 pathway, there is substantial evidence that shows the ability of other antioxidants to increase or rescue GSH levels under conditions of oxidative stress. Ergothioneine, L-carnitine, and puerarin are discussed below, as novel possibilities for therapeutic applications. While the exact mechanism of action for some of these antioxidants is not yet well characterized, we include this

Safety and tolerability of GSH precursors and Nrf2 activators

One major aspect in using GSH precursors and Nrf2 activators as potential therapeutic approaches to treat anxiety and stress disorders is their safety and tolerability profile. As one of the main reasons for therapy discontinuation of antidepressant treatments is their severe side effects (van Geffen et al., 2007), the compounds discussed here may offer an attractive alternative or complementary option. Indeed, several GSH precursors have been tested in clinical trials for safety and

Conclusions and discussion

GSH is the main antioxidant in the brain (Dringen, 2000). Its action is essential to neutralize excessive ROS production and prevent oxidative damage under conditions of high energy demand in the brain. Stress-related and anxiety disorders have been associated with reduced levels of GSH, increased levels of oxidative damage and/or reduced levels of expression of enzymes involved in GSH synthesis or recycling (Krömer et al., 2005; Brocardo et al., 2012; Krolow et al., 2014). We propose in this

Authors' contributions

IZ, FH, ER-F, CS and LM drafted the original manuscript, designed tables and figures. IZ, FH, ER-F, LT, SS, EG, NP, PS, CS and LM critically reviewed the drafts. All authors approved the final version.

Declaration of Competing Interest

Laura Trovo, Sarah Sonnay, Eveline Geiser, Nicolas Preitner, and Pascal Steiner are employees of Société des Produits Nestlé S.A.

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  Regarding the inflammatory factors, the pro-inflammatory cytokines TNF-α and CRP were relevant for the differentiation of the group of patients from the HC group and regarding the metabolic risk variables, the waist circumference differentiated between both groups. The inflammatory disturbances that exhibit MDD patients could be the consequence of an hyperactivation of the hypothalamic pituitary adrenal (HPA) axis (Fiksdal et al., 2019) motivated by chronic stress (Horowitz et al., 2020; Liu et al., 2017), impacting on the production of antioxidants through the dysregulation of the glucocorticoid production (Zalachoras et al., 2020). Thus, the increased production of glutathione, TNF or CRP in MDD patients (Beurel et al., 2020; Ma et al., 2016; Mazereeuw et al., 2015; Osimo et al., 2019; Rae and Williams, 2017; Zalachoras et al., 2020) is an important factor in the differentiation between healthy subjects and MDD patients.

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  Glutathione degradation releases glutamate, the major excitatory neurotransmitter, involved in the control of many

physiological and pathological processes. Glutamate is associated with the onset and progression of various neuropsychiatric disorders [63], including anxiety, depression, stress, and sleep disorder [64], all of them reported as MTK's adverse side effects. As mentioned before, the neuropsychiatric ADRs are mainly reported among children.

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  Several preclinical studies have shown that exposure to environmental toxicants or xenobiotics causes a depletion of GSH and related enzymes, leading to a severe imbalance in the redox cycle. This cascade of events invites inflammation-related molecules and activates microglia in the brain, ultimately implicating in psychiatric disorders including stress-related psychopathologies [65]. Xenobiotics exposure to the early stage of zebrafish embryos interferes with neurogenesis and causes impairment in motor-cognitive functions such as locomotion.

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  These findings add to evidence suggesting the involvement of oxidative stress and redox imbalance in depressive disorders (Sushma and Mondal, 2019). Compounds that activate NRF2 signaling, such as sulforaphane, dimethyl fumarate, curcumin, and melatonin, could help replenish GSH stores and combat oxidative damage in stress-related pathologies, including depression and anxiety (Zalachoras et al., 2020). The GSH antioxidant system is also negatively impacted in T2DM.