PICTURES & PROSE

Picturing emotional distress?

In the context of mood disorders, stressful life events have long been implicated in the onset and maintenance of depression (1,2). In relation to this, the role of the hypothalamic pituitary adrenal axis in mood disorders has been investigated extensively and this research has provided a better understanding of the underlying neuroendocrine pathophysiology of depression (3,4). However, the picture remains incomplete and in recent years the role of oxidative processes in the aetiopathogenesis of mood disorders has attracted increasing interest.

Broadly speaking, depression occurs because of complex genetic and environmental factors and their interactions (5). Differing contributions from these two sources and a whole host of additional psychosocial factors conspire to produce the vast array of manifestations of depression that range from seemingly biologically driven disorders to those that are largely context-dependent. Given that life stressors, and stress *per se*, play a significant role in maintaining a depressive state or at least in the precipitation of depressive episodes, and in some cases perhaps contribute significantly to the cause of depression in the first place, examination of the neurobiology of stress is warranted. One such type of stress that is experienced by the brain is *oxidative stress*.

Oxidative stress arises because of an imbalance in redox homeostasis that favours an excess of free radicals. This can be caused by the overproduction of free radicals or because of anti-oxidant deficiency. The main sources of oxidative stress to a cell are the by-products of mitochondrial energy generation such as the radical superoxide. Two anti-oxidants that defend against such reactive oxygen species are superoxide dismutase and glutathione (GSH) peroxidase. The first converts the superoxide radical (O_2^-) to peroxide (H_2O_2), whereas the second, in conjunction with GSH, reduces peroxide to water (6).

In comparison to other tissues in the body, the brain is more susceptible to oxidative stress because it utilizes large amounts of oxygen that generate free radicals, and because it has relatively poor anti-oxidant defences. Further, biochemically it provides a good substrate for oxidation by virtue of its lipid-rich composition (6).

Individuals with psychiatric illnesses are known to experience greater emotional distress and oxidative stress and in general have poor cerebral anti-oxidant defences. In this regard the anti-oxidant GSH has emerged as a promising potential therapeutic target for psychiatric disorders (6,7). However, GSH does not pass through the blood-brain barrier and therefore N-acetyl cysteine (NAC), a GSH precursor, is proving to be a useful means of providing an exogenous boost to cerebral anti-oxidant activity (Fig. 1).

Biochemically, GSH is a tripeptide that consists of glutamate, cysteine and glycine. To date, brain GSH levels cannot be measured reliably but using proton spectroscopy (8) cerebral concentrations of glutamate, a metabolite of GSH, can be quantified with reasonable confidence (Fig. 2). This provides an indirect 'assay of anti-oxidant activity' (9).

Therefore measuring both glutamate and GSH, along with other metabolites, should provide valuable insights into the oxidative processes thought to underpin

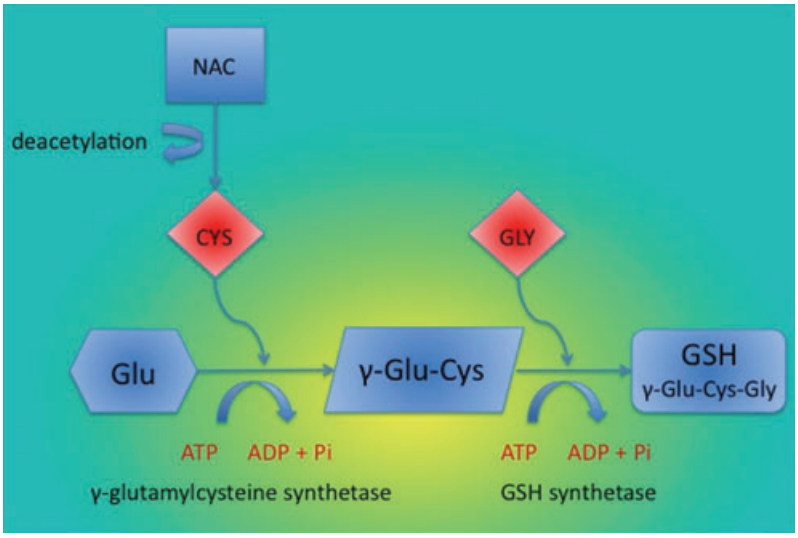

Fig. 1. The formation of glutathione (GSH). Cysteine (CYS) and glutamate (Glu) form a dipeptide catalysed by γ-glutamylcysteine synthetase. Glycine (GLY) is then added to this dipeptide by GSH synthetase. N-acetyl cysteine (NAC) is able to increase GSH production because the availability of cysteine is the rate-limiting factor.

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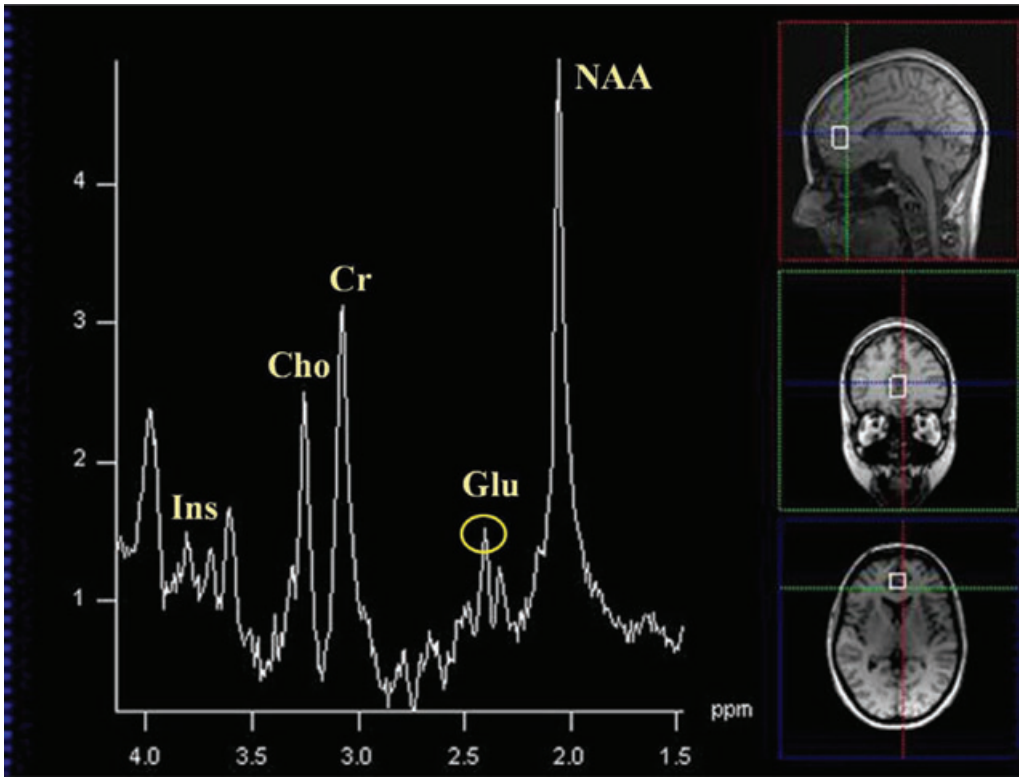

Fig. 2. Example of an *in vivo* Proton Magnetic Resonance Spectroscopy spectra acquired using a PRESS sequence on a 3T scanner from a voxel in the anterior cingulate of a healthy volunteer. The yellow oval indicates the glutamate (Glu) peak.

depressive disorders. Future research aims to directly measure the oxidative stress incurred by the brain as a consequence of mood disorders, and eventually determine how this ameliorates with anti-oxidant therapy.

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