Glutathione--Nutritional and Pharmacological Viewpoints: Part V

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PHARMACOLOGICAL VIEWPOINT

GSH is quantitatively the most import biological antioxidant and scavenger. In addition it has a number of important functions in amino acid transport across membranes, in protein synthesis and degradation, in gene regulation and in cellular redox regulation. It becomes more and more evident that depletion of GSH is associated with severe disease states. (1) From this perspective, the possibility of manipulating the availability of GSH becomes a very attractive form of treatment. In view of the strong correlation between the plasma and tissue GSH level and disease progression, several attempts have been made to improve (both plasma and tissue) GSH levels by pharmaco-nutrition.

There are two principle ways to increase plasma and tissue GSH levels in the body: via oral or parenteral administration. When solutions are administered orally, the liver has direct access to dietary amino acids through the portal circulation. The liver can then alter the concentration of amino acids in portal blood before entry into the peripheral circulation and can supply or utilize amino acids rapidly in a manner complementary to the needs of other tissues. Solutions given by the parenteral route bypass the liver and the gut, two important sites in the control of plasma amino acid concentrations.

There is some evidence that individual amino acids (Glutamine, Glutamate, Cysteine, Methionine) and other precursor compounds, behave in different ways depending on the route of infusion. For instance, many TPN solutions are high in glutamate and devoid of glutamine, whereas plasma is relatively high in glutamine and low in glutamate. The infusion of such "standard" solutions through the superior vena cava does not result in increased plasma glutamate concentrations. This indicates that the peripheral tissues are able to adequately metabolise glutamate. (2) In contrast to the rapid metabolism of infused glutamate, synthesis of cysteine from orally administered methionine appears to be somewhat limited even though the entire amino acid intake passes through the liver by means of the portal circulation. Some data show that this synthetic capability is even less when a cysteine – free diet is fed parenterally, a result suggesting that extrahepatic tissues have limited capacity to carry out this conversion. (3)

PHARMACOKINETICS OF GSH AS A DRUG

A study published in 1997 was the first to evaluate the GSH kinetics in normal subjects compared with cirrhotic patients. (4) Following GSH infusion, plasma GSH rapidly increased, reaching a first steady state value approximately twice as high in controls as in cirrhotics (24.63μM vs 11.80μM $p < 0.05$). During the second hour, when the infusion rate was doubled, plasma GSH further increased to a second steady state approximately 50 μM in controls and 25 μM in cirrhosis. In summary, high dose intravenous GSH is safe. It distributes in the extracellular compartment and is eliminated from the circulation (80 ml.min.mt^2) with a half-life of between 5 – 7 minutes.

To date, we are still in doubt as to which is the best way to increase plasma and/or tissue GSH levels. Carefully designed pharmaco-kinetic research studies are necessary to

elucidate the correct place for the various treatment modalities: GSH itself in the form of its sodium salt (TADR, Biomedica Foscama, Italy). Glutathione esters (Gamma-Glutamyl-cysteine ethyl ester) or GSH precursors such as Glutamate, Glutamine, Cysteine, Methionine, N-Acetyl Cysteine (NAC) and L-2-Oxothiozolidine-4-Carboxylic acid are all potential substrates for investigation. (Figure 1).

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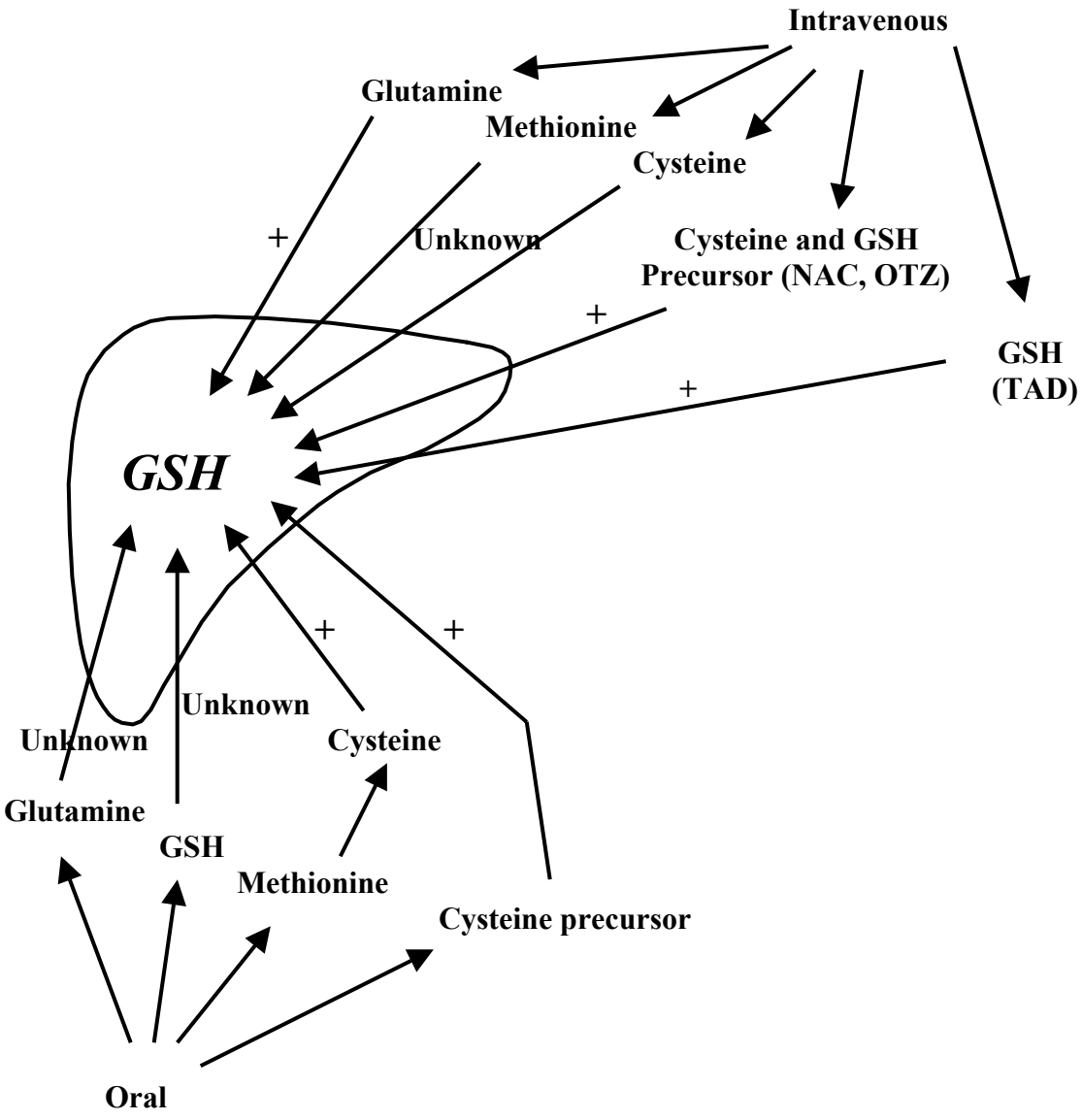

Figure 1. Ways to increase GSH.