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GLUTATHIONE AS A RADICAL SCAVENGER AND THE BIOLOGICAL CONSEQUENCES OF THIYL RADICAL PRODUCTION

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A large number of compounds that have toxic effects can be metabolised to free radicals and secondary reactive oxygen species. These may be directly damaging or affect cell function by altering regulatory mechanisms through changing redox status. Protection is provided by an integrated system of antioxidant defences. This includes reduced glutathione (GSH), one of the functions of which is as a free radical scavenger. Radical scavenging by GSH generates thiyl radicals (reaction 1) whose fate is dictated by equilibrium 2:

$$R^{\cdot} + GSH \Leftrightarrow RH + GS^{\cdot}$$

$$GS^{\cdot} + GS^{-} \Leftrightarrow GSSG^{\cdot -}$$

$GS^{\cdot}$ is oxidising and able to abstract hydrogen atoms from a variety of compounds including polyunsaturated fatty acids, whereas $GSSG^{\cdot -}$ is reducing. It reacts rapidly with oxygen and in aerobic solution this provides the driving force to displace equilibriums 1 and 2 and accounts for the good scavenging ability of GSH. It also generates superoxide. For GSH to be an effective radical scavenging antioxidant, therefore, it must act in concert with superoxide dismutase to remove the superoxide so generated.

Superoxide is produced in a variety of metabolic processes. It is also a secondary product of radicals reacting with oxygen either directly or through GSH. The biological reactivity of superoxide has been the subject of much debate ever since the discovery of superoxide dismutase in 1968. It has more recently become apparent that its rapid reaction with nitric oxide to give peroxynitrite, and its ability to reversibly oxidise and inactivate iron sulphur enzymes, contribute to the toxicity of superoxide. Another mechanism that could be important involves addition reactions of superoxide with other radicals to give organic peroxides. This reaction, to form a tyrosine peroxide, has come to our attention through the study of the scavenging of tyrosyl radicals by GSH. We have also shown that a tyrosine peroxide is a major product of the oxidation of tyrosine by neutrophils. Superoxide addition to phenoxyl radicals has been observed in chemical systems, but to date the biological significance of these rapid reactions has received little attention.