34 Does carbon monoxide inhibit cytochrome oxidase in vivo?

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The action of nitric oxide (NO) in the control of blood pressure by has been well characterised [1,2]. NO activates soluble guanylate cyclase (GC-s) by binding to the haem iron. This results in a rise in intracellular cyclic GMP and subsequent relaxation of vascular smooth muscle.

Carbon monoxide (CO) shares some of the chemical properties of NO; it is therefore possible that CO may also exert similar physiological effects. NO and CO can both bind ferrous haemoproteins in the sixth coordinate position producing low-spin complexes [3]. Recent studies indicate that carbon monoxide [CO] can also regulate GC-s in a similar manner to NO [4,5] and it has been suggested that CO may play a significant role as a vasodilator *in vivo*.

CO is formed from several endogenous sources [3] including as a product of haem degradation. It is produced when haem oxygenase catalyses the breakdown of haem, forming CO, iron and bilverdin. Some of the CO formed from heam degradation is exhaled and a portion is present as carbonmonoxy-haemoglobin (HbCO), even in the blood of non-smoking adults.

We have recently shown that nanomolar levels of NO, as well as activating GC-s, also inhibit mitochondrial oxygen consumption by binding to the haem-copper enzyme, cytochrome *c* oxidase[6]. As CO is also an inhibitor of cytochrome oxidase we were interested in determining whether *in vivo* levels of CO could inhibit this enzyme.

CO competes with oxygen at the active site of the enzyme. Figure 1 demonstrates the competitive nature of this inhibition. At low oxygen tensions CO is a more effective inhibitor. The Ki calculated from Figure 1 is 0.3 uM. This Ki is very similar to the Km for oxygen of the enzyme. At 30uM O2, 30 uM CO inhibits 50% of enzyme activity. This makes CO a 500 x less effective inhibitor of cytochrome oxidase than NO [6]. However, when considering the *in vivo* situation it is necessary to remember that CO is also a much less potent activator of GC-s than NO. The amount of CO required to activate GC-s is 20μM [7] (compared to nanomolar levels for NO).Therefore the relative affinities of cytochrome oxidase and GC-S for CO and NO appear similar. We suggest that if CO really activates GC-S *in vivo* it is also likely to inhibit cytochrome oxidase.

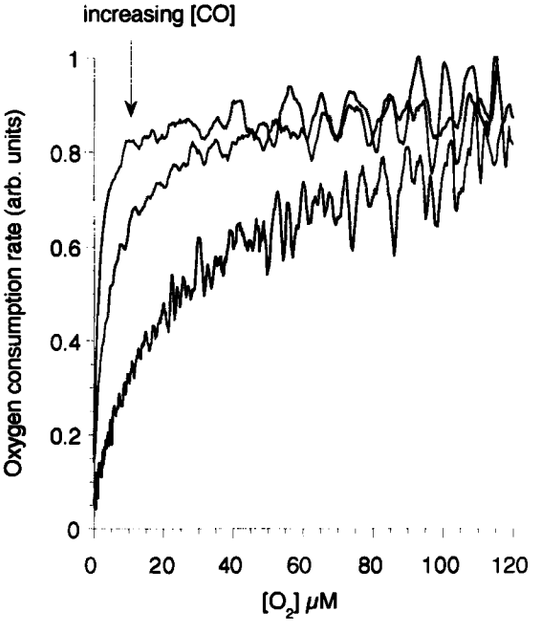

Fig. 1 Effect of CO on steady state activity of cytochrome oxidase

Increasing concentrations of CO used (0, 7 and 36 μM)

We also find that similar levels of CO inhibit HEP G2 (human hepato-blastoma) cells, although the Ki appeared somewhat higher than for the isolated enzyme These findings suggest the possibility that some of the metabolic effects attributed to guanylate cyclase activation by CO may be attributed to a localised inhibition cytochrome oxidase.

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