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Inhibition of inflammation-induced damage by low-molecular-mass selenium compounds

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The formation of oxidants at sites of inflammation by activated white cells (leukocytes) is critical for the killing of invading pathogens (e.g. bacteria, yeasts, fungi etc). Oxidant generation is however associated with damage to host cells, and has been linked to multiple human diseases including cardiovascular disease, some cancers, rheumatoid arthritis, asthma, cystic fibrosis and multiple neurodegenerative conditions. Leukocytes generate multiple oxidants including hypohalous acids (HOX, X = Cl, Br, SCN, via the heme enzyme myeloperoxidase, MPO), and peroxynitrous acid (ONOOH, from reaction of $O_2^{-\cdot}$ with $NO^{\cdot}$).

There is now abundant experimental and epidemiological evidence for a key role for myeloperoxidase, MPO, in human cardiovascular disease. This evidence includes: the detection of MPO RNA and protein in human cardiovascular lesions, the detection of MPO enzymatic activity in lesions, the presence of products derived from MPO-generated oxidants, a strong association between increased levels of protein modification by MPO with disease severity, and epidemiological data indicating that MPO levels in blood and plasma are both diagnostic of disease and prognostic of poor outcomes. There is therefore considerable interest in modulating the oxidants formed by this enzyme and this is an active area of pharmaceutical development.

Myeloperoxidase is a promiscuous enzyme that uses H_2O_2 to oxidize halide (Cl^-, Br^-, I^-) and pseudohalide anions such as SCN^-. This occurs via the so-called halogenation cycle, in which H_2O_2 oxidizes the resting state Fe^{3+} form of the enzyme to a formal Fe^{5+} state (Compound I) that subsequently oxidizes the halide/pseudohalide anions to their corresponding hypohalous acids (HOCl, HOBr, HOI, HOSCN). Other anions and aromatic compounds can also be oxidized via a competing peroxidase cycle. Under normal physiological conditions, Cl^- is the major MPO substrate because of its high plasma concentration, despite this being much less rapidly oxidized than other anions. However, other anions (e.g. SCN^-) compete successfully with Cl^- when these are present at elevated levels. Elevated levels of SCN^- have been achieved *in vivo* via dietary means, and also via oral dosing. As HOSCN is a weaker and less reactive oxidant than HOCl, the increased formation of HOSCN over HOCl, has been shown to limit biological damage, including the development of atherosclerotic lesions, the underlying cause of most cardiovascular disease.

In the light of these data, we hypothesized that selenocyanate, $SeCN^-$, should also be rapidly oxidized by MPO, and that this may give rise to the weak oxidant HOSeCN. Elevated levels of $SeCN^-$ might therefore also limit damage induced by MPO in biological systems by competing with Cl^- during the enzymatic cycle of the enzyme Furthermore, $SeCN^-$ may also be protective by directly scavenging HOCl if this is generated at significant levels.

Data will be presented to show that $SeCN^-$ is indeed a competitive substrate for MPO, and that this is more effective than SCN^-. In addition, $SeCN^-$ and SCN^- have additive effects. Both of these anions also act as effective direct scavengers of HOCl and can protect cells from damage. Oxidation of $SeCN^-$ by MPO and HOCl is shown to generate a species believed to HOSeCN which is a modest oxidant that oxidizes thiols and also (slowly) some aromatic compounds.

Together these data suggest that elevated levels of $SeCN^-$ and SCN^- can be important modulators of inflammation-induced damage.

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References:

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