URATE AS A PHYSIOLOGICAL SUBSTRATE FOR MYELOPEROXIDASE

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Myeloperoxidase is the predominant protein in neutrophils and its levels in plasma predict the risk for the development of cardiovascular disease. Hyperuricemia is also a risk factor for cardiovascular disease. Interestingly, uric acid can be oxidized by myeloperoxidase. However, it is not known whether this occurs under physiological conditions and what products are formed. We have investigated the mechanisms by which uric acid is oxidized by myeloperoxidase to determine whether there is a link between the enzyme and this potential substrate in the development of cardiovascular disease. Spectral analyses showed that uric acid was readily oxidized by myeloperoxidase in the presence of hydrogen peroxide. The products of oxidation identified by LC/MS (liquid chromatography/mass spectrum) were allantoin and the intermediate imine alcohol. Spectral analysis of myeloperoxidase revealed that the enzyme oxidized uric acid through its classical peroxidise mechanism, with the formation of a free radical intermediate. The presence of a free radical intermediate was confirmed by measuring the conversion of glutathione (GSH) to glutathione disulfide (GSSG). The calculated rate constant for the second order reaction between uric acid and the intermediate compound I of myeloperoxidase was $(3.7 \pm 0.2) \times 10^5$ M^{-1} s^{-1}. This demonstrates that uric acid can be a preferred substrate for the enzyme in human plasma. The presence of chloride in the system decreased the oxidation of uric acid, showing that chloride and uric acid are competitive substrates for myeloperoxidase. Uric acid was oxidized by activated human neutrophils. Oxidation required myeloperoxidase and hydrogen peroxide. Our results demonstrate that uric acid will act as a substrate for myeloperoxidase in plasma and get oxidized to reactive free radicals. Thus, high levels of myeloperoxidase and hyperuricemia may exacerbate oxidative stress in the vasculature and contribute to the development of cardiovascular disease.

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