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## **Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid.**

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Peroxynitrite, a biological oxidant formed from the reaction of nitric oxide with the superoxide radical, is associated with many pathologies, including neurodegenerative diseases, such as multiple sclerosis (MS). Gout (hyperuricemic) and MS are almost mutually exclusive, and uric acid has therapeutic effects in mice with experimental allergic encephalomyelitis, an animal disease that models MS. This evidence suggests that uric acid may scavenge peroxynitrite and/or peroxynitrite-derived reactive species. Therefore, we studied the kinetics of the reactions of peroxynitrite with uric acid from pH 6.9 to 8.0. The data indicate that peroxynitrous acid (HOONO) reacts with the uric acid monoanion with  $k = 155 \text{ M}^{-1} \text{ s}^{-1}$  ( $T = 37 \text{ degrees C}$ , pH 7.4) giving a pseudo-first-order rate constant in blood plasma  $k(\text{U}(\text{rate}))/(\text{plasma}) = 0.05 \text{ s}^{-1}$  ( $T = 37 \text{ degrees C}$ , pH 7.4; assuming  $[\text{uric acid}](\text{plasma}) = 0.3 \text{ mM}$ ). Among the biological molecules in human plasma whose rates of reaction with peroxynitrite have been reported,  $\text{CO}_2$  is one of the fastest with a pseudo-first-order rate constant  $k(\text{CO}_2)/(\text{plasma}) = 46 \text{ s}^{-1}$  ( $T = 37 \text{ degrees C}$ , pH 7.4; assuming  $[\text{CO}_2](\text{plasma}) = 1 \text{ mM}$ ). Thus peroxynitrite reacts with  $\text{CO}_2$  in human blood plasma nearly 920 times faster than with uric acid. Therefore, uric acid does not directly scavenge peroxynitrite because uric acid can not compete for peroxynitrite with  $\text{CO}_2$ . The therapeutic effects of uric acid may be related to the scavenging of the radicals  $\text{CO}(\cdot)(3)$  and  $\text{NO}(\cdot)(2)$  that are formed from the reaction of peroxynitrite with  $\text{CO}_2$ . We suggest that trapping secondary radicals that result from the fast reaction of peroxynitrite with  $\text{CO}_2$  may represent a new and viable approach for ameliorating the adverse effects associated with peroxynitrite in many diseases. Copyright 2000 Academic Press.

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