Major Role of Hydroxyl Radical in the Conversion of Creatinine to Creatol

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that induced by Cr (fig. 1). This suggested that nonenzymatic oxidation of creatol to MG by the •OH radical is negligible in the mammalian body. Therefore, the target step of •OH radical scavengers is not the degradation of creatol to MG, but rather the first, probably nonenzymatic, oxidation step (Cr– > creatol). Since we have already shown that MG production from Cr via creatol (Cr– > creatol > MG) is generally operative in mammals [3], Cr appears to be of physiological importance as an intrinsic radical scavenger, especially specific for •OH. Cr consumes an equimolar amount of •OH.

Dear Sir,

In a previous study [1], we obtained direct evidence that hydroxyl (•OH) radical scavengers inhibit the conversion of creatinine (Cr) to creatol (5-hydroxycreatinine) in Fenton’s reaction, thus providing a possible mechanism for the indirect inhibition of methylguanidine (MG) production reported by Nagase et al. [2]. This suggests that Cr may be an intrinsic radical scavenger, specific for the •OH radical. Since Cr never reacts with other active oxygen species (superoxide, hydrogen peroxide and singlet oxygen) (data not shown) but only with the •OH radical, we think that the main contributor to the Cr– > •OH radical oxidation step is the •OH radical [1]. However, we have not shown how the results obtained in vitro correlate with phenomena occurring in vivo. Therefore, we carried out a study to determine whether the •OH radical scavenger inhibits the production of MG via creatol formation in the rat in vivo.

We analyzed the level of MG in urine collected for 3 h after intraperitoneal administration of Cr (1.00 g/kg body weight) or an equimolar amount of creatol (1.14 g/kg body weight) in saline to normal rats (body weight approximately 250-260 g). At 30 min before and 30 min after Cr administration, saline with or without a half volume of N,N'-dimethyl thiourea (DMTU: 20, 100 and 500 mg/kg body weight), a well-known and strong •OH radical scavenger, was administered intraperitoneally to rats given both types of treatment. The administration of DMTU had no effect on the urinary MG induced by creatol, but had a significant dose-dependent effect on
not only in vitro [1] but also in vivo, to give creatol, which can be converted easily in the body to MG [4] without consuming the •OH radical. The resulting creatol and MG are excreted into urine, and never accumulate in serum [3]. However, patients with renal failure suffer from hypocalcemia of not only Cr, but also creatol and MG, and the accumulation of these products, especially MG, which is a uremic toxin [7-9], becomes significant. Therefore, for such patients, Cr is a double-edged sword, and another •OH scavenger safer than Cr is required for them. We are now seeking such a scavenger.

![Fig. 1. Effect of DMTU on MG production from Cr (left) and creatol (right). *p < 0.001 significantly different from the value in rats given no DMTU.](image)

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References


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