

On infusion of high-dose ascorbate in treating cancer: Is it time for *N*-acetylcysteine pretreatment to enhance susceptibility and to lower side effects?



ABSTRACT

Ascorbate administered intravenously gives a high plasma concentration of this drug. Clinical trials with pancreatic carcinoma patients revealed their prolonged survival if treated with intravenous ascorbate. On the other hand, high plasma ascorbate concentration leads to severe side effects, such as nephrotoxicity. In the present paper, we advocate to lower intravenous ascorbate dosage along with monothiol *N*-acetylcysteine pretreatment due to anticipation of the same therapeutic effect but less or none of side effects. We describe in detail molecular mechanism of ascorbate action to be potentiated by *N*-acetylcysteine, as observed under *in vitro* conditions. Providing further arguments, we believe that the same mechanism may be employed *in vivo*.

Letter to the editor of journal Medical Hypotheses

Cieslak and Cullen [1] focused on the treatment of pancreatic carcinoma (PaC) with intravenous dose of ascorbate (Asc) at millimolar concentrations. PaC incidence gradually increases with current 5-year survival less than 25%. The Asc-mediated inhibition of PaC lines viability was found to correlate with the dose-dependent H_2O_2 production.

We wish to suggest another mechanism, which allows administration of ascorbate at markedly lower concentration to prevent its nephrotoxic effects with the addition of a thiol agent *N*-acetylcysteine.

Tumor cells overexpress on their surface the CD44 antigen, which can anchor high-molar-mass hyaluronan (HMM HA), and thus makes tumor cells invisible for the immune system. Our group has been focused on degradation of HMM HA by $\cdot OH$ radicals generated by Asc and Cu(II) ions, which produce H_2O_2 under aerobic conditions, whereas Cu(I)—complex is simultaneously formed. This complex decomposes H_2O_2 to highly-reactive $\cdot OH$ radicals: $H_2O_2 + Cu(I)\text{—}complex \rightarrow \cdot OH + HO^- + \{Cu(II)\text{—}complex\}$. Moreover, redox cycling of copper ions has been indicated to be a basis of copper cytotoxicity towards

tumor cells [2,3].

The formed low molar mass HA fragments are immunogenic and may be involved in the immune system reactivation. We believe that the same mechanism of HMM HA degradation happens *in vivo*. As a result, uncovering “the cape of invisibility” of tumor cells and exposing their aberrant glycocalyx to the immune system may contribute to effective tumor treatment.

By means of electron paramagnetic resonance (EPR) and spectrophotometry we observed that NAC was particularly effective in producing Cu(I)—complex (Fig. 1A and B).

Fig. 1, panel C illustrates that addition of NAC at micromolar concentration remarkably potentiated peroxidative degradation of HMM HA initiated by $\cdot OH$ radicals (green curve). In conclusion, we emphasize that the described mechanism may be of clinical significance, in particular for treating PaC. We believe that to maintain Asc therapeutic effect, the pretreatment with a low dose of non-toxic NAC will allow to decrease the intravenous dosage of Asc substantially and thus enable to minimize the undesired effects of Asc, including nephrotoxicity.

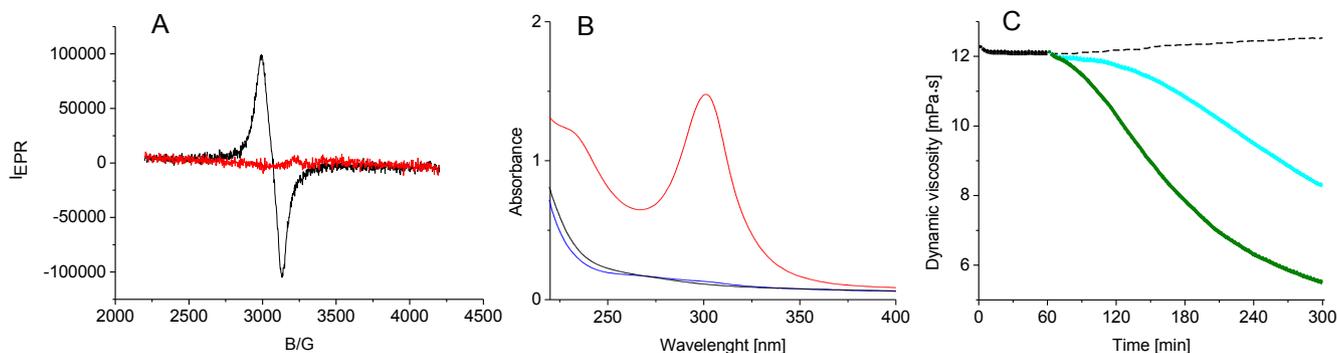


Fig. 1. Panel A – EPR spectra of Cu(II) ions alone (2.5 mmol/L, black curve), and with addition of NAC (5 mmol/L), indicating the Cu(I)—complex formation (red curve). Panel B – UV-spectra of Cu(II) ions alone (0.8 mmol/L, black curve), NAC alone (0.8 mmol/L, blue curve), and the mixture of Cu(II) ions (20 $\mu\text{mol/L}$) and NAC (40 $\mu\text{mol/L}$) (red curve). Panel C – Addition of Cu(II) ions (1 $\mu\text{mol/L}$) to the HA solution (black curve); peroxidative degradation of HMM-HA initiated by $\cdot OH$ radical generated by Cu(II) ions (1 $\mu\text{mol/L}$) and Asc (100 $\mu\text{mol/L}$) added one hour later (cyan curve). The same under presence of NAC (2 $\mu\text{mol/L}$) (green curve); NAC was added before Asc. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Conflict of interest

The authors report no conflict of interest.

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