Response of muonium to oxygen contents in hemoglobin and other biological aqueous solutions for cancer research

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Hypoxia, or low oxygenation, is known as an important factor in tumor biology; in cancer patients, an accurate measurement of O_2 concentration ($c(O_2)$) or partial pressure in specific regions is critical[1)] therefore, improved methods for detecting O_2 are required. Several trials that employ PET, MRI and EPR have been conducted[1)].

We have proposed the use of μ^+ as a new sensitive method to probe the existence of paramagnetic O_2 in cancer tumors in the human body. The μ^+ in water is known to take the states of diamagnetic μ^+ such as μ^+OH (60%), paramagnetic muonium (Mu, $\mu^+ + e^-$) (20%), and a missing fraction (20%). In Mu, 50% fraction becomes an ortho state with spin 1, providing a spin rotation signal with a precession pattern (1.39 MHz/G) that is 100 times faster than that of diamagnetic μ^+. Some experimental studies have been conducted on the oxygen-dissolving effects of the spin relaxation rate (λ_{Mu}) of paramagnetic Mu in pure water due to electron spin exchange interactions with paramagnetic O_2 in water; the rate change of λ_{Mu} against $c(O_2)$ is $(1.8 \pm 0.1) \times 10^{10}$ (L/mol)/s [2)]. A problem that remains to be solved is the effect of other magnetic molecules, which is the objective of the present study.

Experiment was conducted at Port 2 of RIKEN-RAL using 60 MeV/c decay μ^+. Spin rotation and relaxation were detected under 2.2 G transverse fields at room temperature.

The biological samples used were as follows: 1) Albumin**;** Bovin serum (plasma) albumin 2) Serum**;** Donor horse serum 3) Hemoglobin (Hb); Polymerized hemoglobin of bovine origin in a lactated Ringer's solution at 13% concentration in the form of deoxy-Hb.

Before measuring the O_2 dependence of λ_{Mu}, its dependence on the concentration of each biological molecule was systematically measured. The increasing rates of λ_{Mu} were obtained as 25 μs^{-1}/(g/L) for albumin, 1 μs^{-1}/(vol.%) for serum and 3.1 μs^{-1}/(g/L) for Hb.

Then, by determining the relevant concentration for each molecule, the O_2 dependence of λ_{Mu} was measured. In these biological aqueous solutions, λ_{Mu} showed an almost similar change in relaxation against increasing O_2 concentration as that for pure water.

For higher Hb concentrations, by introducing O_2, a part of deoxy-Hb (magnetic) becomes oxy-Hb (non-magnetic) so that the O_2 dependence of λ_{Mu} becomes non-linear.

Measurements were made upto 2.0 g/L c(Hb) and 20% $c(O_2)$ (Fig. 1). The O_2 dependence of λ_{Mu} at higher Hb concentrations was predicted by assuming the following relation[3)]: $\lambda_{Mu} = R_{Hb}(Mu) + R_{O2}(Mu)$. There, $R_{Hb}(Mu)$ is the relaxation rate due to the amount of deoxy-Hb obtained by solving the Hill's equation for the total Hb amount and $c(O_2)$ [4)], while $R_{O2}(Mu)$ is the relaxation rate due to the free molecular O_2 in solution obtained by the O_2 dependence data of the pure water and by the amount of free O_2 which is estimated by subtracting the O_2 amount used for oxy-Hb formation obtained by the Hill's equation. As summarized in Fig. 1, λ_{Mu} increases with increasing Hb at any fixed $c(O_2)$; slower increasing rate at Hb higher than 1 g/L due to oxy-Hb formation. The λ_{Mu} becomes undetectably large ($\geq$ 10 μs^{-1}) at $c(O_2)$ lower than 6% at higher c(Hb) of 100 g/L expected for human body.

Before carrying out the clinical application of the proposed method to studies on hypoxia, it is important to conduct further systematic studies on the behavior of O_2 in various other biological aqueous systems, especially with high-concentration Hb. Significant features of the present muon method can be summarized as follows: a) non-invasive nature, b) no need of a high magnetic field and c) sub-mm probing region confinement by the advanced beam method.[5)]

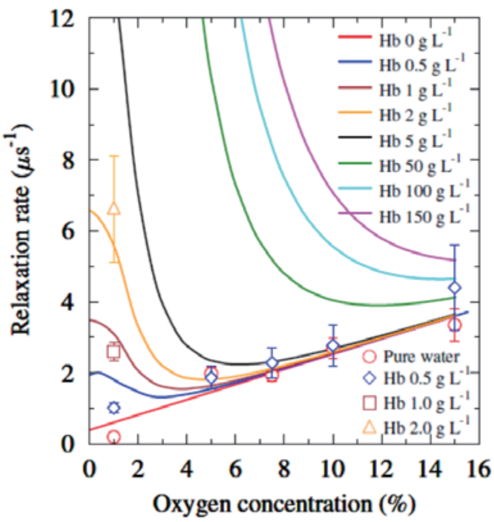

Fig. 1 Summary of dependence on O_2 concentration of muonium relaxation rates in Hb aqueous solution; experimental data upto 2.0 g/L and predictions upto 150 g/L by the method described in the text.

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