Letter to the Editor

Blood Purification

Blood Purif 2010;30:96–97
DOI: 10.1159/000318587

Published online: July 13, 2010

Clear Correlation of Tetrahydrobiopterin with Nitric Oxide Bioavailability in Continuous Ambulatory Peritoneal Dialysis

Seiichi Mochizuki[a, b] Aya Takayama[b, c] Tamaki Sasaki[d] Toyotaka Yada[a, b] Kousuke Endo[e] Hideyuki Horike[d] Naoki Kashihara[d] Yasuo Ogasawara[a, b] Fumihiko Kajiya[a, b]

[a]Department of Medical Engineering, Kawasaki Medical School, [b]Department of Medical Engineering, Faculty of Health Science and Technology, Kawasaki University of Medical Welfare, [c]Medical Engineering Center, Kawasaki Medical School Hospital, [d]Division of Nephrology, Department of Internal Medicine, and [e]Department of Physiology, Kawasaki Medical School, Kurashiki-City, Japan

Nitric oxide (NO) plays diverse physiological roles including vasodilatory and anti-atherogenic actions [1]. In continuous ambulatory peritoneal dialysis (CAPD), NO has been thought to regulate permeability of the peritoneal membrane and suppress angiogenesis in the peritoneum [2–4]. Thus, abnormal production and/or metabolism of NO would lead to peritoneal dysfunctions. Previous studies suggested that changes in NO bioavailability induce the dysfunction of peritoneal membranes [3, 5]. Recently, we demonstrated that NO exists in spent dialysates at measurable levels over a wide range [6].

Tetrahydrobiopterin (BH_4) is a cofactor for NO synthase (NOS) and plays an important role in maintaining the NOS activity. Depletion of BH_4 would result in NOS uncoupling and NOS-derived superoxide release [1, 7, 8]. Yokoyama et al. [9] reported that a significant positive correlation between creatinine clearance and the BH_4/BH_2 ratio (BH_2 = biopterin, an oxidized form of BH_4) in the patients with chronic renal failure. Yamamizu et al. [10] demonstrated the involvement of BH_4 deficiency in endothelial dysfunction in rats with chronic renal failure. Recently, we also reported the possible involvement of BH_4 in the NO production rate of hemodialysis (HD) patients [11]. However, there have been no investigations on the roles of NO and BH_4 in CAPD. Therefore, we measured both NO and BH_4 concentrations in spent dialysates of CAPD patients to investigate the relation between the two.

The NO concentration was measured by an NO sensor [6, 12] and BH_4 and BH_2 concentrations were measured fluorometrically by the HPLC-based method [13]. This study protocol was approved by the Ethical Committee of Kawasaki Medical School. Written informed consent was obtained from each patient.

Both NO and BH_4 in the spent dialysates (dwelling time about 5 h) showed diverse distribution among the patients (n = 28; NO, 0.5–11.8, 4.7 ± 0.6 nmol/l; BH_4, 0.6–17.0, 3.8 ± 0.7 ng/ml). There was a positive correlation between NO and BH_4 (fig. 1; $p < 0.001$). This result suggests that NO is produced in dependence on BH_4 availability. Similarly to BH_4, BH_4/BH_2 also showed diverse distribution (2.3–122.3, 42.2 ± 6.8). There was a positive correlation between NO and BH_4/BH_2 (fig. 2; $p < 0.002$). This result may also sup-

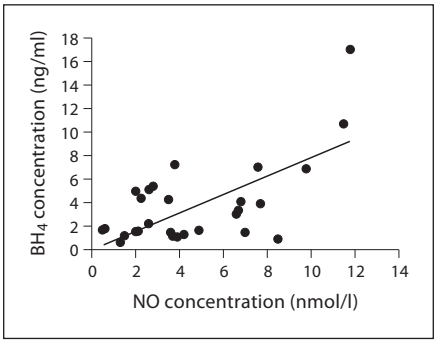

Fig. 1. Relation between nitric oxide (NO) and tetrahydrobiopterin (BH_4) concentrations.

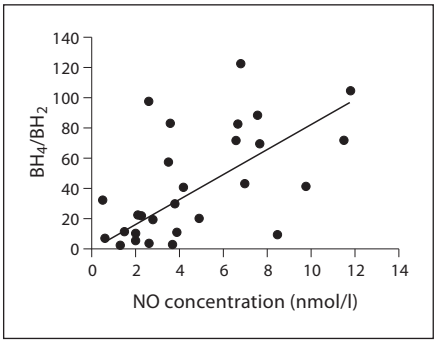

Fig. 2. Relation between nitric oxide (NO) concentration and tetrahydrobiopterin/biopterin (BH_4/BH_2) ratio.

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Seiichi Mochizuki, PhD
Department of Medical Engineering, Kawasaki Medical School, 577 Matsushima
Kurashiki, Okayama 701-0192 (Japan)
Tel. +81 86 462 1111, ext. 83750, Fax +81 86 463 2975
E-Mail mochi@me.kawasaki-m.ac.jp

port the dependence of NO availability on BH_4.

Recently, we reported the plasma BH_4 concentrations and the BH_4/BH_2 ratios for the HD patients and the healthy volunteers [11]. The BH_4 concentration in the spent dialysates of the CAPD patients in the present study (3.8 ± 0.7 ng/ml) was nearly at the same level as that of healthy volunteers (3.0 ± 0.2 ng/ml) and that of HD patients before HD (3.8 ± 0.6 ng/ml). The BH_4/BH_2 ratio of the CAPD patients (42.2 ± 6.8) seems higher than that of the HD patients (12.7 ± 7.4 before HD; 16.1 ± 10.3 after 4-hour HD) but almost at the same level as that of the healthy volunteers (31.4 ± 15.2). Thus, it is implied that CAPD is a milder therapy (similar to the healthy conditions) than HD in terms of BH_4 bioavailability and resultant NO bioavailability.

A wide distribution of BH_4 levels was observed (fig. 1). Although the exact reason for the distribution is not clear, some possible mechanisms may be inferred. GTP cyclohydrolase I, one of the key enzymes for the BH_4 synthesis, may be adversely affected by high oxidative stress [7]. BH_4 itself has reducing capacity and thus may be oxidized to BH_2 by high oxidative stress. Therefore, depending on the oxidative stress levels, BH_4 bioavailability may differ among the patients studied.

In case of depletion of BH_4, NOS uncoupling is induced and causes release of superoxide from NOS [14]. This may lead to detrimental effects on the peritoneal membrane. In our preliminary studies, we observed lower NO production in cultured mesothelial cells with increasing glucose content (increasing oxidative stress) in culture solutions [15]. A recent report demonstrated the effectiveness of oral supplementation of BH_4 on recovery of endothelial dysfunction in the rats of chronic renal failure [10]. Thus, in case of BH_4 deficiency, exogenous BH_4 intake may be beneficial to maintenance of peritoneal functions.

Acknowledgments

This study was supported in part by Grant-in-Aid for Science Research, Japan Society for the Promotion of Science. The authors thank Ms. Mayumi Ono for her superb technical assistance.

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