Comparison of Methylguanidine Production from Creatinine and Creatol in vivo

T.	Takako	Yokozawa ^a
N.	Naoki	Fujitsuka ^a
H.	Hikokichi	Oura ^a
K.	Kazuharu	Ienaga ^b
K.	Ko	Nakamura ^b

^aDepartment of Applied Biochemistry, Research Institute for Wakan-Yaku, Toyama Medical and Pharmaceutical University, Sugitani, Toyama, Japan; ^bDepartment of Natural Products Chemistry, Institute of Bio-Active Science, Nippon Zoki Pharmaceutical Co., Kato-gun, Hyogo, Japan

Dr. Takako Yokozawa, Department of Applied Biochemistry, Research Institute for Wakan-Yaku, Toyama Medical and Pharmaceutical University, Sugitani, Toyama 930-01 (Japan)

Dear Sir,

A novel creatinine (Cr) oxide, creatol, was isolated from urine of patients with chronic renal failure by Na-kamura and Ienaga [1] in a study of the route of oxidative metabolism of Cr under pathological conditions. In terms of its structure, this compound was considered to be an intermediate arising during the conversion of Cr into methylguanidine (MG), and this possibility was examined in an in vitro experiment [2]. However, the degree of contribution of this compound to in vivo MG production remains to be elucidated. In order to investigate this issue, Cr and creatol (fig. 1) were administered intraperitoneally to normal rats, and the amounts of MG produced from the two substances were compared.

Male Wistar rats (body weight approximately 200 g) were used for the experiment. The rats were fed on an 18% casein diet for 10 days. On the 10th day of the experimental diet, an identical dose (0.24 mmol/kg body weight) of Cr or creatol was administered intraperitoneally to the rats. Urine was collected for 48 h following administration of Cr or creatol, and deproteinized by addition of trichloroacetic acid (final concentration 10%). The supernatant obtained by centrifugation at 3,000 rpm for 10 min was injected into a Japan Spectroscopic liquid chromatograph using a step-gradient system. A fluorescence spectrometer, model FP-210 (excitation 365 nm, emission 495 nm; Japan Spectroscopic Co., Tokyo, Japan) was used for detection of the MG on the column. The urinary excretion of MG in the nontreated rats was about 0.07 μ mol/48 h. Six rats were used for each experimental group. Values were expressed as means $\pm$ SE.

Figure 2 shows the amount of excreted MG after the same intraperitoneal dose (0.24 mmol/kg body weight) of Cr or creatol in normal rats. In rats given creatol, MG excretion increased almost linearly until after 12 h. There-

Fig. 2. Urinary excretion of MG after Cr- or creatol-loading in normal rats.

after, there was a gradual increase, and the amount reached 11.2 μ mol at 48 h. In contrast, in rats given Cr, the amount of MG was 0.06 μ mol at 24 h and 0.1 μ mol at 48 h, accounting for only 0.6

and 0.9% of the corresponding values after creatol administration. It was found that 0.2% of the administered Cr was converted into MG within 48 h after administration, whereas the corresponding proportion was 23.3% for creatol.

MG, which is a low-molecular-weight substance, shows behavior similar to that of a medium-molecular-weight substance, and a low rate of MG elimination by

126

Yokozawa/Fujitsuka/Oura/Ienaga/Nakamura

dialysis has been pointed out by Barsotti and Giovannetti [3]. Therefore, MG is undoubtedly a toxin causing a variety of uremia-like symptoms. Although the route of MG production remains controversial, the idea that Cr is the precursor of MG is predominant [4–8]. We have previously investigated time-course changes in MG production after Cr administration, and found that most of the produced MG is excreted into urine in normal rats [9, 10]. Therefore, in the present study, the amount of MG produced from Cr was compared with that from creatol, using the level of urinary MG excretion as an index. It was found that the amount of MG produced from Cr was 0.1 μmol at 48 h, whereas that from creatol was 112 times higher, 11.2 μmol . Thus, the importance of the role of creatol in MG production was indicated. Aoyagi et al. [11] have proposed a probable oxidizing route as the route of MG production from Cr. However, Nakamura et al. [2] and our group have demonstrated in an in vitro experiment that creatol is involved in the conversion of MG from Cr as an intermediate. In the present in vivo study, the percentage of conversion from creatol into MG was as high as 23.3%. Taking these findings into consideration as a whole, it is speculated that the rate of MG production from Cr depends on the process of creatol production from Cr.

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