Enhanced Urea Excretion, Probably by Forming Inclusion Compound with Lutidine

Since VAN SLYKE et al.[1] first introduced the concept of clearance in renal physiology, concerning the mode of excretion of urea, the application of clearance[2] has been expanded to the excretion of variable substances and has brought a heavy crop of knowledge for understanding the kidney function. The mode of excretion of urea, however, is still ambiguous, because urea is one of the very diffusible substances throughout every kind of animal tissue. The movement of urea in the renal tubule cannot be traced simply either by the osmolar gradient or under the influence of ADH. It is also modified by the state of protein uptake in the diet[3].

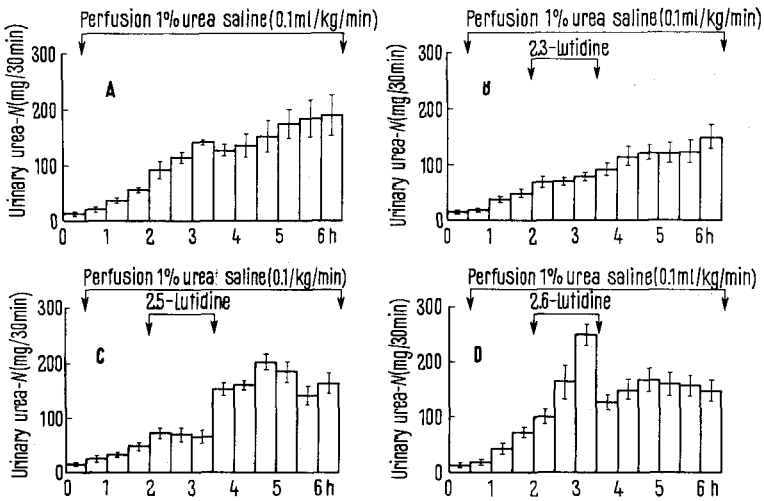
The term 'inclusion compound' was first introduced by SCHLENK[4,5]. In the intensive studies on this kind of compound, 2,6-lutidine (2,6-dimethylpyridine) and urea were found to form inclusion compounds in which 1 *M* of 2,6-lutidine is a guest molecule and 3 *M* of urea are host ones[6]. The finding of inclusion formation with urea attracted the author's attention, because forming inclusion compounds by van der Waal's force must limit the free movement of urea in the lower nephrone where the concentration of urea is increasing. Consequently, this must enhance the urea excretion. Isomers of 2,6-lutidine, i.e. 2,3-, 2,4- and 2,5-lutidines and α-picorine (2-monomethylpyridine), were compared, because these isomers hardly ever form inclusion compounds with urea.

Each of 5 female dogs prepared with perineotomia for easy catheterization of the urinary bladder was chosen at random for each isomer by Raten Square. The animals were anaesthetized with 30 mg/kg body weight of pentobarbital sodium. 1% urea solution in saline (1% urea-saline) was perfused intravenously at the rate of 0.1 ml/kg/min for 7 h throughout the experiment. $1^1/_2$ h after the start of urea loading, 1% solution of 2,6-lutidine or its isomers was administered by Sigmamotor pump at the rate of 0.1 ml/kg/min for $1^1/_2$ h. Urine and blood specimens were collected every 30 min for estimation of urine volume, urea excretion and urea clearance.

The results show quite significant increase of urea excretion accompanied by diuresis after the start of perfusion of 2,6-lutidine (Figure 1, D), while its isomers, 2,5-, 2,4- and 2,3-lutidine and α-picorine, neither acted favourably for excretion of urea nor caused the diuresis (Figure 1, B and C). These isomers rather depressed the urea excretion, among which 2,5- and 2,4-isomer, 2,3-isomer and α-picorine showed very similar effects on the urea excretion.

2,6-lutidine and its isomers have very similar CNS stimulant action. This action, however, was not considered to modify the effect on urea excretion and urine volume, because a selective infusion of 2,6-lutidine in the renal artery caused a definite increase of urine volume and urea excretion.

The above finding may throw light on the way to develop a new type of diuretic, and may provide a new tool for the study of urea excretion in mammals, since many varieties of substances are reported to form an inclusion compound with a urea molecule. Further details will be reported elsewhere[7].



Effects of lutidine and its isomers on urea excretion of dogs. Urea excretion under the continuous infusion of urea and the effect of 2,6-lutidine (D) and its isomers (A, B and C). Each bar and vertical line represents mean ± standard error of 5 experiments. (A) Urea loading by perfusion at a rate of 0.1 ml/kg/min of 1% urea solution in saline; (B) additional infusion of 2,3-lutidine; (C) the same of 2,5-lutidine; (D) the same of 2,6-lutidine.

Zusammenfassung. Die Harnstoffausscheidung wurde durch 2,6-Lutidin i.v. wahrscheinlich über die Bildung der Einschlussverbindung gesteigert. Die isomere Substanz blieb wirkungslos[8].

K. HASHIMOTO, T. KATO, and K. INAGAKI

Department of Pharmacology and Pharmaceutical Institute, Tohoku University School of Medicine, Sendai (Japan), April 22, 1966.

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