Journal of the Korean Society of
Tobacco Science, Vol. 2, No. 1 (1980),
Printed in Republic of Korea.

Communication

The Effect of N'-nitrosodiethylamine and N'-nitrosodimethylamine on the Formation of Cyclic GMP in Rat's Urine.

Quae Chae and Kil-Lyong Kim

Korea Tobacco Research Institute,

Seoul, Korea

(Received Feb. 10. 1980)

Sir:

Cyclic GMP stimulates the cell growth and its transformation(1). It is also observed that the level of cyclic GMP is substantially higher in the cancer cell compared with the one in the normal cell(2). The enzyme activity of guanylate cyclase, which catalyzes the reaction of GTP to cyclic GMP, is remarkably enhanced by the NO gas(3,4). At the moment, the physiological implication of this phenomenon in conjunction with the occurrence of tumor and/or cancer is not cetain.

Among the carcinogens of nitrosamine compounds, we selected the two compounds (DEN and DMN) which have nitroso group (NO) as a substituent in order to see the formation of cyclic GMP in rat's urine. The intra-peritoneal injections of DEN and DMN to rats are carried out and the levels of cyclic GMP formation in its urine have been checked by the radioimmunoassay method.

In this communication we present the results on the effects of injection dose and time in both DEN and DMN to the formation of cyclic GMP. In the case of DEN, the formation of cyclic GMP in the living rats is quite independent of the dose and time during 3 days (Fig.1). However, the drastic increase of cyclic GMP's level (70%—80%) is shown after 3days of injection. The enhancement is about same in 3 different concentrations of DEN.

Dose independent behavior might be interpreted to be that an excess amount of DEN and/or its metabolite (most probably, activator for guanylate cyclase) dose not function as an inhibitor. Most N-nitroso compounds undergo biotransformation in vivo and the carcinogenic effects are due to their metabolic products(5). The long term enhancement of cyclic GMP by DEN could be speculated as a long time course to be metabolized into an biologically active form to activate guanylate cyclase.

DEN: N'-nitrosodiethylamine
DMN: N'-nitrosodimethylamine

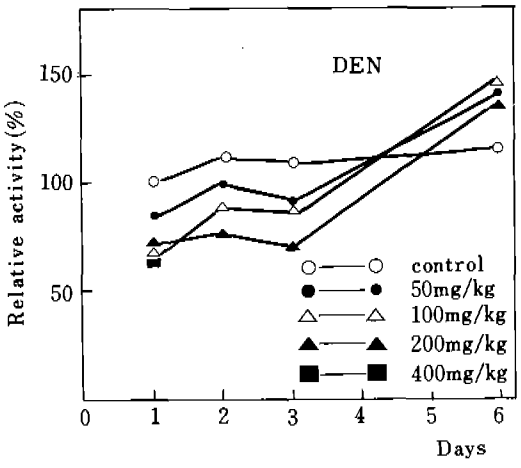

Fig. 1. Effects of DEN to the formation of cyclic GMP in rat's urine as a function of injection dose and time.

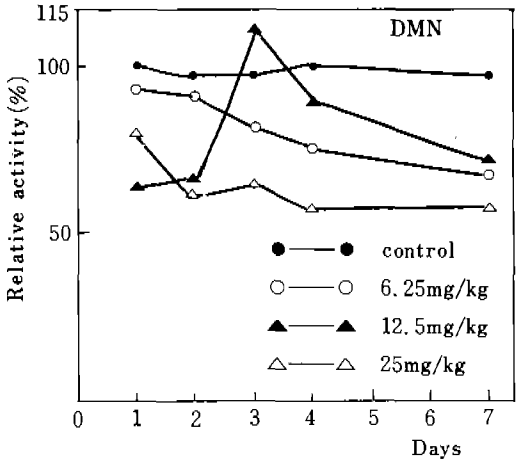

Fig. 2. Effects of DMN to the formation of cyclic GMP in rat's urine as a function of injection dose and time.

In contrast with DEN, DMN shows dose dependent formation of cyclic GMP and short term activation to reach maximum concentration of cyclic GMP (Fig.2).

Only at 12.5 mg/kg dose the enhancement of cyclic GMP formation is observed and the maximum value is obtained at 3 days after injection.

This fact implies that the optimum concertration of DMN is required to activate guanylate cyclase and also excess DMN and/or its active molecular species may inhibit enzyme activation. The short term enhancement can also be explained to be that it takes less time to be metabolized as a biologically active species through enzymatic α-C-hydroxylation(6).

In this communication we can not certainly present the physiological behavior concerned with the formation of cyclic GMP by these two nitroso compounds. Particularly, in connection with the biochemical enzymatic mechanism of guanylate cyclase with these compounds, further study is necessarily required in future.

References

1) De Rubertis, F.R. and Carven, P. A., Science, 193: 897(1976).
2) Thomas, E.W., Murad. F., Looney, W. B., and Morris, H.P., Biochem. Biophy. Acta. 297: 564(1973).
3) Arnold, W., Mittel, C. K., Katsuki, S., and Murad, F., Proc. Natl. Acad. Sci., 74: 3202 (1977).
4) Arnold, W., Adlred, R. and Murad, F., Science; 198: 934(1977).
5) Olajos, E. L., Ecotoxicol. Envirom. Safety, 1: 175(1977).
6) Druckery, H., Preussmann. R., and Ivankovic, S., Ann. N.Y, Acad. Sci., 163: 676(1969)