Alcohol and Aldehyde Metabolizing Systems

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Edited by

Ronald G. Thurman

Department of Pharmacology
University of North Carolina
Chapel Hill, North Carolina

John R. Williamson **Henry R. Drott**

Britton Chance

The Johnson Research Foundation
University of Pennsylvania
Philadelphia, Pennsylvania

between hepatic catalase activity and the ability of the rat to metabolize formate to CO_2. For example, aminotriazole-treated rats which have 5-10% of control catalase activity showed no inhibition of formate oxidation . A correlation coefficient of 0.37 was obtained when information was submitted to linear regression analysis. Thus, we suggest that formate is metabolized to CO_2 via a folate-dependent pathway in the rat and that by reducing the rate of formate metabolism it is possible to sensitize the rat to methanol poisoning. Recent studies in this laboratory have shown that the monkey is exquisitely sensitive to methanol poisoning and that formate accumulates in the blood coincident with the production of metabolic acidosis. Other studies have shown (10) that low level chronic formic acidemia leads to ocular toxicity in the rhesus monkey and that formate infusion alone at normal pH, produces this toxicity. Thus, formate is a major determinant in methanol poisoning and further studies are underway to determine which catalyst is responsible for formate oxidation to CO_2 in the rat and monkey.

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VII. REFERENCES

(1). McMartin, K., Makar, A.B., Martin-Amat, G., Palese, M., and Tephly, T.R., Biochem.Med. 13, 319 (1975).
(2). Clay, K.L., Murphy, R.C., and Watkins, W.D., Toxicol.Appl. Pharamcol. 34, 49 (1975).
(3). Roe, O., Pharmacol. Rev. 7, 399 (1955).
(4). Gilger, A.P., and Potts, A.M. Amer.J.Ophthalmol. 39, 63 (1955).
(5). Palese, M., and Tephly, T.R. J. Toxicol. Environ. Hlth. 1, 13 (1975).
(6). Friedmann, B., Nakada, H.I., and Weinhouse, S., J. Biol. Chem. 210, 413 (1954).
(7). McMartin, K., Martin-Amat, G., Makar, A.B., and Tephly, T.R., Alcohol and Aldehyde Metabolizing Systems (R.G. Thurman, T. Yonetani, J.R. Williamson, H. Drott, and B. Chance, Eds.) Vol, II Acad. Press, New York, In Press (1977).
(8). Longo, D.L., and Herbert, V., J.Lab.Clin.Med. 87, 138 (1976).
(9). Makar, A.B., McMartin, E.Ke., Palese, M., and Tephly, T.R., Biochem. Med. 13, 117 (1975).
(10). Martin-Amat, G., McMartin, K.E., Makar, A.B., Baumbach, G., Cancilla, P., Hayreh, M.M., Hayren, S.S., and Tephly, T.R. Alcohol and Aldehyde Metabolizing Systems, (R.G. Thurman, J.R. Williamson, J.R. Drott and B. Chance, Eds.) Vol. II Acad. Press, New York, In press, (1977).
(11). Makar, A.B., and Tephly, T.R., Nature 261, 715 (1976).

THE MONKEY AS A MODEL IN METHANOL POISONING

G. Martin-Amat, K.E. McMartin, A.B. Makar, G. Baumbach, P. Cancilla, M.M. Hayreh, S.S. Hayreh, and T.R. Tephly

The University of Iowa

Methanol poisoning in man is characterized by a mild central nervous system depression, metabolic acidosis and ocular toxixity followed by coma and death. Previous work from this laboratory has described the production of metabolic acidosis, coma and death in rhesus and pigtail monkeys without the demonstration of definitive ocular lesions. Since animals used in those studies died rapidly after methanol administration a prolonged and less intense state of intoxication was deemed necessary for the production and recognition of ocular toxicity. Thus, methanol was administered at a dose of 2 g/kg followed by subsequent doses of 0.5 g/kg until signs of ocular toxicity were observed: usually at 48 hours, or later, after the first dose of methanol. Ocular toxicity was characterized as optic disc edema with dilated pupils and a slow reaction of the pupillary reflex to light. A rapid intraarterial perfusion of appropriate fixatives was used in order to minimize autolysis of tissues. Histopathologic changes included intracellular swelling and mitochondrial disruption in the area of the optic disc but otherwise retinal histology was normal. Clinical symptoms appeared to be similar to those described in man and may provide a basis for our understanding of the mechanism of methanol toxicity with respect to the ocular lesions observed in man.

I. INTRODUCTION

A marked species difference in susceptibility to methanol poisoning is well known and has been the subject of numerous reviews (1.2.3.4). It has been shown recently that the rat does not accumulate formate in the blood after methanol administration whereas the monkey rapidly accumulates formic acid coincident with the production of a metabolic acidosis (5,6). Potts and coworkers (2,7) observed metabolic acidosis in the rhesus monkey and certain signs of ocular toxicity, but Cooper and Felig (8) were unable to confirm these results. Recently, Clay et.al. (6) and McMartin et.al. (5) have reproduced certain of