*Physiol. Res. 48: 79-81, 1999*

**SHORT COMMUNICATION**

# The Effect of Goldthioglucose on Peroxidative Processes in Mice

D. KOŠŤOVÁ, E. MICHNOVÁ

*Department of Pathophysiology, University of Veterinary Medicine, Košice, Slovak Republic*

*Received May 28, 1998*
*Accepted October 27, 1998*

## Summary

Experiments were conducted to study the effect of goldthioglucose (GTG) upon the processes associated with lipid peroxidation. The glucose-6-phosphate dehydrogenase activity (G6PD; E.C.1.1.1.49) in red blood cells (RBC) and the amount of malonaldehyde precursors (MDA) per gram of brain, liver and kidney were determined. Adult mice received i.p. injections for three consecutive days of either saline (controls) or GTG dissolved in saline, in a dose of 0.10 $mg.g^{-1}$ or 0.15 $mg.g^{-1}$ b.w. In mice receiving higher dose of GTG the G6PD activity was significantly increased (349.38±17.46 $mU.10^{-9}$ RBC compared to 258.2±14.46 $mU.10^{-9}$ RBC in control animals). The content of MDA precursors rose significantly from 4.8±0.81 $\mu mol.g^{-1}$ of the liver in controls to 8.12±1.41 $\mu mol.g^{-1}$ and 7.88±0.51 $\mu mol.g^{-1}$ and from 18.71±1.01 $\mu mol.g^{-1}$ of the kidneys in controls to 24.25±1.25 $\mu mol.g^{-1}$ and 24.88±1.7 $\mu mol.g^{-1}$ respectively. The GTG-induced higher levels of MDA precursors and increased G6PD activity in RBC corresponds to the rise in lipid peroxidation and its participation in producing the lesions after experimental and therapeutic use of gold-containing substances seems possible.

**Key words**

Goldthioglucose • Glucose-6-phosphate dehydrogenase • Malonaldehyde precursors • Mice

The ability of goldthioglucose (GTG) to produce experimentally necrotic lesions in the murine hypothalamus with subsequent hyperphagia (Marshall *et al.* 1955) and lesions, e.g. in the liver and myocardium (Šimková *et al.* 1971) has long been known. GTG is still of interest as an important model of food intake regulation (Blair *et al.* 1996, Malaise 1997) and in anti-rheumatic therapy as an anti-inflammatory agent (Stein 1987, Laurence and Bennett 1996). In therapeutic use, different toxic effects were also described in as many as 30 % of patients (Laurence and, Bennett 1996), but the reasons for the production of lesions by gold-based substances are not clear. The biological and biochemical properties of cells can be impaired by increased peroxidation in cell membranes (Gutteridge 1995) with changes in the defense mechanisms induced by gold (Hu *et al.* 1988a,b). This paper considers the *in vivo* GTG effects on the cytosolic protective enzyme activity and lipid peroxidation evaluated according to the amount of malonaldehyde precursors and the activity of the first



E-mail physres@biomed.cas.cz Fax +420 2 293 894
http://www.lf2.cuni.cz/physiolres/physiolres.htm

enzyme of the pentose cycle, glucoso-6-phosphate dehydrogenase (G6PD), involved principally in RBC antioxidative protection (Pačin *et al.* 1991).

The activity of G6PD (E.C.1.1.1.49) in RBC was analyzed by Boehringer Mannheim tests. The peroxidative state of the liver, kidneys and the brain were considered in relation to the level of substances reacting with thiobarbituric acid, such as malonaldehyde (MDA) precursors, expressing on a larger scale the amount of MDA (Uchiyama and Mihara, 1978). Three groups of six ICR adult male mice each received i.p. injections for three consecutive days of either saline (controls) or GTG dissolved in saline, in a dose of 0.10 or 0.15 mg.g$^{-1}$ b.w. Samples for analyses were removed under ether anesthesia two hours after the last GTG or saline injection. The RBC count and osmotic resistance were estimated by standard methods. For statistical evaluation, analysis of variance and the t-test were used for comparison of mean values ± S.E.M.

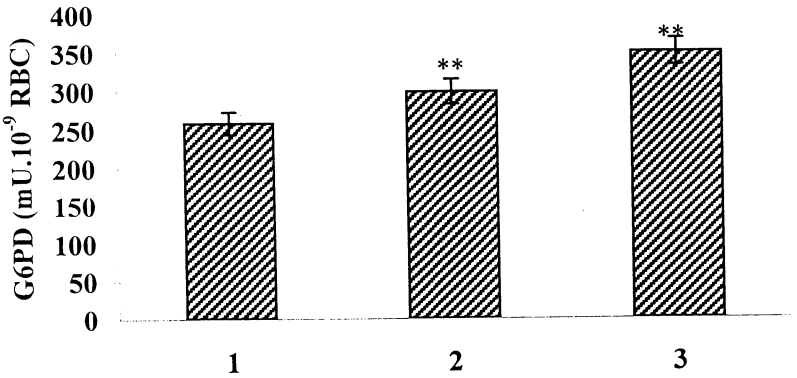


**Fig. 1.** *Activity of glucose-6-phosphate dehydrogenase (G6PD) in red blood cells (RBC) expressed in mU.10$^{-9}$ RBC ± S.E.M. after goldthioglucose (GTG) injection in mice. Animals groups in the experiment: controls (1), mice after injection of GTG in a dose of 0.10 mg.g$^{-1}$(2) and 0.15 mg.g$^{-1}$ (3).* ** *P<0.001.*

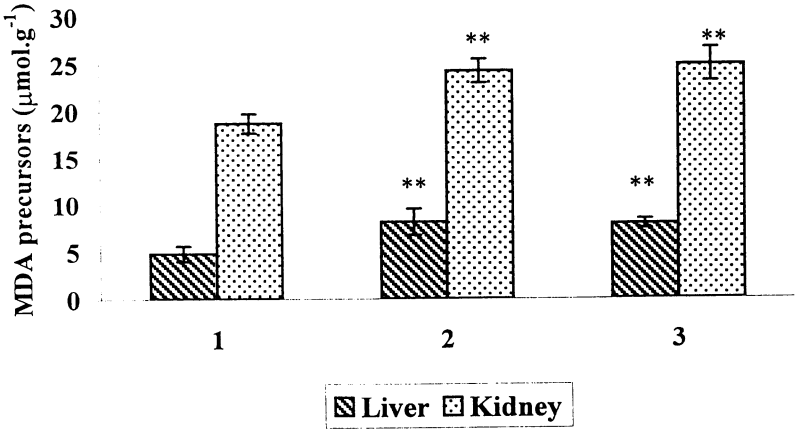


**Fig. 2.** *Malonaldehyde precursors (MDA) in the liver and kidneys of mice after goldthioglucose (GTG) injection, expressed in μmol.g$^{-1}$ ± S.E.M. of tissue. Animal groups in the experiments: controls (1), mice after injection of GTG in a dose of 0.10 mg.g$^{-1}$(2) and 0.15 mg.g$^{-1}$(3).* ** *P<0.001,* $^{x}$*P<0.05.*

In the GTG-treated mice, G6PD activity of RBC rose dose-dependently from 258.20±14.46 mU.10$^{-9}$ RBC in the controls to 298.60±16.20 mU.10$^{-9}$ RBC and significant values of 349.38±17.46 mU.10$^{-9}$ RBC (P<0.001), respectively (Fig. 1). The MDA precursors increased in the liver from 4.80±0.81 μmol.g$^{-1}$ in the controls to 8.12±1.41 μmol.g$^{-1}$ (P=0.05) and 7.88±0.51 μmol.g$^{-1}$ (P<0.01), respectively, and in the kidney from 18.71±1.01 μmol.g$^{-1}$ in the controls to 24.25±1.25 μmol.g$^{-1}$ (P<0.01) and 24.88±1.77 μmol.g$^{-1}$ (P<0.01), respectively (Fig. 2). The RBC count decreased dose-dependently from 7.42±0.20 . 10$^{-9}$ RBC in controls to 6.41±0.36 . 10$^{-9}$ RBC and 6.45±0.32 . 10$^{-9}$ RBC, respectively (P<0.01), with unchanged RBC osmotic resistance. The increased level of MDA precursors in the liver and kidneys of the GTG-treated mice, as in sheep exposed to emissions predominantly of fluorine and mercury (Michnová *et al.* 1997), can be related to the metal accumulation and/or way of metal excretion. This assumption is supported by several observations. There is a high level of mercury in the liver and kidneys of animals exposed to emissions predominantly of mercury (Krupicer 1995) and prolonged body retention of gold (Stein 1987). Furthermore, the route of gold excretion is mainly by urine and partly in the feces (probably due to secretion into the bile) (Gilman *et al.* 1980). The overwhelmed or decreased activity of antioxidative mechanisms in the exposed cells can participate in

increased peroxidation in the respective tissues with a rise of MDA precursors. This seems to be confirmed by the decreased activity of catalase in the kidneys and glutathione peroxidase in the liver and kidneys after GTG injection (Hu *et al.* 1988a,b). The absence of differences in brain MDA precursors is probably related to localized lesions after GTG injection (Marshall *et al.* 1955). The similar rise of G6PD activity of RBC as in GTG-treated mice was also found in sheep after administration of a metal mixture predominantly containing mercury (Koštová *et al.* 1995), This can represent a compensatory reaction to increased *in vivo* peroxidation, related to blood metal transport with e.g. gold peak 2-6 hours after the gold/based therapy (Gilman *et al.* 1980). The lower RBC count with unchanged osmotic resistance can be related to marrow suppression as described after gold therapy (Kahl 1988).

The elevated MDA precursors in kidneys and the liver as well as increased G6PD activity of RBC in GTG-treated mice concern increased peroxidation and its possible participation in lesions after experimental and therapeutic use of gold-based substances.

## References


BLAIR SC, CATERSON ID, COONEY GJ: Insulin response to a spontaneously ingested standard meal during development of obesity in GTG injected mice. *Int J Obes* **20:** 319-323, 1996.

GILMAN AG, GOODMAN LS, GILMAN A (eds) In: *The Pharmacologic Basis of Therapeutics.* Sixth Edition. MacMillan Publishing Co., New York, Collier MacMillan Canada, Toronto, Bailliere Tindal, London, 1980, pp. 714-715.

GUTTERIDGE JMC: Lipid peroxidation and antioxidants as biomarkers of tissue damage. *Clin Chem* **41:** 1819-1828, 1995.

HU ML, DILLARD CJ, TAPPEL AL: Effect of chronic aurothioglucose treatment of rats on kidney catalase and cytochrome. *J Inorg Biochem* **33:** 175-181, 1988a.

HU ML., DILLARD CJ, TAPPEL AL: Aurothioglucose effects on sulphhydryls and glutathione-metabolizing enzymes: in vivo inhibition of selenium-dependent glutathione peroxidase. *Res Commun Chem Pathol Pharmacol* **59:** 147-160, 1988b.

KAHL LE: Aplastic anemia in adult onset Still disease during gold therapy. *J Rheumatol* **15:** 1877-1878, 1988.

KOŠŤOVÁ D, MICHNOVÁ E, LEGÁTH J, KRUPICER I: Intoxication by heavy metals in relation to the activity of glucose -6-phosphate dehydrogenase of erythrocytes in sheep. *Vet Med Czech* **40** : 371-375, 1995.

KRUPICER I: Vplyv imisií ťažkých kovov s dominanciou ortuti na priebeh pasienkových helmintóz oviec. *Vet Med Czech* **40:** 1-15, 1995.

LAURENCE DR, BENNETT PN: *Clinical Pharmacology.* Churchill Livingstone, 1996, pp 22-223.

MALAISSE WJ: Stimulation of insulin release by aurothioglucose. *Med Sci Res* **25:** 759-760,1997.

MARSHALL NB, BARNETT RJ, MAYER J: Hypothalamic lesions in goldthioglucose injected mice. *Proc Soc Exp Biol Med* **90:** 240-244, 1955.

MICHNOVÁ E, KOŠŤOVÁ D, LEGÁTH J, BÍREŠ J, ELIÁŠ V: Vplyv priemyslových emisií na lipoperoxidáciu v niektorých tkanivách oviec. In: *Zborník prednášok. Vedecké sympozium o ekologii*, Hrádok, 1997, pp 170-173.

PAČIN J, RÁCZ O, DIALLO ST: Antioxidačné enzýmy v červených krvinkách žien s neskorou gestozou. *Cs gynekol* **56:** 393-396, 1991.

STEIN JH: Diseases-modifying antirheumatic drugs. In: *Internal Medicine.* Little Brown Co., Boston, 1987, pp 1330-1331.

ŠIMKOVÁ D, ŠKARDA R, BOĎA K: Patologicko-histologické zmeny pečene a myokardu po aplikácii aurothioglukózy. *Folia Vet* **15:** 57-62, 1971.

UCHIYAMA M, MIHARA M.: Determination of malonaldehyde precursors in tissues by thiobarbituric acid test. *Anal Biochem* **86:** 271-278, 1978.



**Reprint requests**

Dr. D. Košťová, Department of Pathophysiology, University of Veterinary Medicine, Komenského 73, 040 01 Košice, Slovak Republic.