GS2-5 Induction of aminolevulinic acid synthase (ALAS) by dioxin affects the glucose metabolism

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Laboratory animals exposed to 2,3,7,8-teterachlorodibenzo-*p*-dioxin (TCDD) develop wasting syndrome, and it has been thought that glycogen depletion and CYP1A1, a hemoprotein, in the liver are involved in the onset of this syndrome. A possible relationship between heme biosynthesis and glucose metabolism has been suggested. Porphyria patients, caused by disorders of heme biosynthetic pathway, were reported to be accompanied with hyperinsulinemia. Because the mRNA of aminolevulinic acid synthase (ALAS), the rate limiting enzyme in the heme synthesis pathway, was induced in liver of TCDD-exposed mice, we here investigated how ALAS is involved in the glycogen metabolism and/or gluconeogenesis. When HepG2, a human hepatoma cell line, was exposed to TCDD, a glycogen amount in the cells was decreased dose-dependently, and ALAS was induced. However, transfection of ALAS specific siRNA suppressed the TCDD-induced decrease in the glycogen amounts, and overexpression of ALAS in HepG2 reduced glycogen amounts indifferent from TCDD exposure. Furthermore, TCDD exposure was found to enhance the phosphorylation of GSK3-β protein, a downstream protein of insulin signal, and induce mRNA of PEPCK that controls gluconeogenesis. On the other hand, ALAS siRNA-transfection abolished TCDD-dependent phosphorylation of GSK3-β protein and significantly decreased the mRNA level of PEPCK that are induced by TCDD. In conclusion, the present results suggest that ALAS is involved in the regulation of glucose metabolism.