

S04-4 Effect of cadmium on erythropoietin production

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Itai-itai disease, which has been endemic in the heavily cadmium (Cd)-contaminated area in the Jinzu River Basin, Toyama prefecture, is a severe form of chronic Cd intoxication characterized by renal tubular dysfunction, osteomalacia, and anemia. The mechanism of anemia had been thought to be iron deficiency or hemolysis, as opposed to a renal mechanism, despite the existence of extensive renal injury. However, clinical and hematologic investigations of patients with Itai-itai disease showed that the anemia was caused by hypoproduction of erythropoietin (Epo) from the kidneys. After that discovery, experimental studies using rats or Hep3B cells derived from human hepatoma cells showed that Cd could destroy renal Epo-producing cells and lead to hypoproduction of Epo, as well as that Cd had a functional inhibitory effect on Epo production before cell destruction. Furthermore, inhibition of activation of hypoxia inducible factor-1 (HIF-1), an important transcriptional factor for Epo mRNA induction, or an indirect inhibitory effect of over-accumulation of iron in the organs due to Cd-induced abnormal iron metabolism in the body, is involved in the inhibition of Epo production. These results not only indicate that Cd induces anemia by inhibiting Epo production through various mechanisms, but also suggest the need to revise the current criteria defining Itai-itai disease to include renal anemia as one of the conditions for diagnosis.