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Regulation of gluconeogenesis by Aldo-Keto-Reductase 1a1b in zebrafish

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Regulation of glucose homeostasis is a fundamental process to maintain blood glucose at a physiological level, and its dysregulation is associated with the development of several metabolic diseases. The zebrafish has been established as a model for diabetes research in the past decade, because glucose homeostasis in zebrafish is very similar to humans and other mammals, and alterations in glucose homeostasis are associated with organ damage, including the kidney, eyes, and nerves. Akr1a1b belongs to Aldo-keto reductase (Akr) superfamily in zebrafish. In this study, adult akr1a1b-/- mutant zebrafish developed fasting hypoglycemia, which was caused by inhibiting phosphoenolpyruvate carboxykinase (PEPCK) expression as rate-limiting enzyme of gluconeogenesis. Subsequently, glucogenic amino acid glutamate as substrate for gluconeogenesis accumulated in the kidneys, but not in livers, and induced structural and functional pronephros alterations in 48 hpf akr1a1b-/- embryos. Akr1a1b-/- mutants displayed increased nitrosative stress as indicated by increased nitrotyrosine, and increased protein-S-nitrosylation. Inhibition of nitrosative stress using the NO synthase inhibitor L-NAME prevented kidney damage and normalized PEPCK expression in akr1a1b-/- mutants. Thus, the data have identified Akr1a1b as a novel regulator of gluconeogenesis in zebrafish and thereby controlling glucose homeostasis.