Insulin action is viewed as a set of branching pathways, with some actions serving to regulate energy metabolism and others to regulate cellular growth and development[1]. Thus far, available genetic evidence has supported this view. In humans, complete lack of insulin receptors due to mutations of the insulin receptor gene results in severe growth retardation and mild diabetes[2,3]. In mice, targeted inactivation of insulin receptor sub-strate-1, an important substrate of the insulin receptor kinase, leads to inhibition of growth and mild resistance to the metabolic actions of insulin[4,5]. To address the question of whether both metabolic and growth-promoting actions of insulin are mediated by the insulin receptor, we have generated mice lacking insulin receptors by targeted mutagenesis in embryo-derived stem (ES) cells. Unlike human patients lacking insulin receptors[6–9], mice homozygous for a null allele of the insulin receptor gene are born at term with apparently normal intrauterine growth and development. Within hours of birth, however, homozygous null mice develop severe hyperglycaemia and hyperketonaemia, and die as the result of diabetic ketoacidosis in 48−72 hours. These data are consistent with a model in which the insulin receptor functions primarily to mediate the metabolic actions of insulin.