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The nuclear receptor FXR is expressed in pancreatic β-cells and protects human islets from lipotoxicity

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ABSTRACT

Farnesoid X receptor (FXR) is highly expressed in liver and intestine where it controls bile acid (BA), lipid and glucose homeostasis. Here we show that FXR is expressed and functional, as assessed by target gene expression analysis, in human islets and β-cell lines. FXR is predominantly cytosolic-localized in the islets of lean mice, but nuclear in obese mice. Compared to FXR+/+ mice, FXR−/− mice display a normal architecture and β-cell mass but the expression of certain islet-specific genes is altered. Moreover, glucose-stimulated insulin secretion (GSIS) is impaired in the islets of FXR−/− mice. Finally, FXR activation protects human islets from lipotoxicity and ameliorates their secretory index.

1. Introduction

Type 2 diabetes is characterized by the progressive deterioration of β-cell secretory function and its capacity to compensate for increased peripheral insulin resistance [1].

Nuclear receptors are transcription factors that regulate glucose and lipid metabolism in a variety of metabolically active tissues, including the pancreatic β-cell [2]. The farnesoid X receptor (FXR; NR1H4), which is highly expressed in liver, intestine and adrenal glands, is a receptor of bile acids (BA) [3–5]. BA-activated FXR protects the liver from BA-overload by controlling the transcription of genes responsible for their synthesis, biotransformation and cellular excretion [6]. FXR also modulates hepatic lipid and lipoprotein metabolism. Recent data identified a role for FXR in glucose homeostasis [7]. FXR gene expression is induced by glucose in rat hepatocytes, whereas insulin reversed this effect [8]. Moreover, FXR mRNA levels are increased in livers of diabetic db/db mice [9]. Treatment of type 2 diabetic dyslipidaemic patients, with intestinal-acting bile acid sequestrants, such as cholestyramine or colesevelam, resulted in lower plasma glucose and HbA1C concentrations [10]. Several authors suggested that BA decrease hepatic glucose production by the liver and therefore improve hyperglycemia by regulating enzymes of gluconeogenesis [11–13]. In addition, FXR−/− mice display impaired glucose and insulin tolerance due to blunted insulin signaling pathways in skeletal muscle and white adipose tissue [13,14]. Moreover, treatment with GW4064 enhances insulin sensitivity in db/db [13] and ob/ob mice [14], suggesting that FXR agonists could be promising therapeutic agents for type 2 diabetes treatment.

In our previous studies, we have speculated that the decreased clearance of plasma glucose observed in FXR−/− mice upon intraperitoneal glucose tolerance test (IPGTT) could be explained, besides the peripheral insulin resistance, by an impaired insulin secretion of the pancreas [14]. In order to investigate this

Abbreviations: BA, bile acids; BSA, bovine serum albumin; FGF, fibroblast growth factor; GSCN, guanidinium thiocyanate; FXR, farnesoid X receptor; GSIS, glucose-stimulated insulin secretion; IAPP, islet amyloid polypeptide; IPGTT, intraperitoneal glucose tolerance test; LXR, liver X receptor; PDX-1, pancreatic duodenal homeobox gene-1; PPAR(α,δ,γ), peroxisome proliferator-activated receptor (α,δ,γ); SHP, small heterodimer partner; SST, somatostatin; TG, triglycerides; VLDL-R, very low density lipoprotein-receptor

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hypothesis, we studied whether FXR is expressed in pancreatic β-cells and whether it participates in the regulation of glucose homeostasis by the β-cell. Our results show that FXR is expressed and active in β-cells and pancreatic islets, both in rodents and humans. Using islets isolated from FXR−/− mice or human islets treated with FXR ligands, we show that FXR controls the proper response of β-cells to a glucose challenge and that FXR activation protects human islets under lipid-induced metabolic stress.

2. Materials and methods

2.1. Cell culture

Rat INS1E and mouse βTC6 pancreatic β-cells were routinely maintained in RPMI1640 medium (Gibco, Invitrogen) supplemented with 1 mM sodium pyruvate, 2 mM L-glutamine, 100 mM gentamycine, 50 μM β-mercaptoethanol, 10% FCS and incubated at 37 °C in 5% CO_2.

2.2. Protein extraction and Western blotting

See Supplementary data.

2.3. Animals

All studies performed with laboratory animals were approved by the institutional review boards for the care and use of experimental animals. Lean C57Bl6/J wild type and ob/ob male mice were obtained from Charles Rivers Laboratory (France). Homozygous FXR−/− and sex- and age-matched FXR+/+ littermates, bred on the C57Bl6/J genetic background, housed in a pathogen-free barrier facility with 12 h light/12 h dark cycle, were maintained on a standard laboratory chow diet (A03/R03).

2.4. Mouse and human islet isolation

Mouse pancreatic islets were obtained by the collagenase digestion method [15], adapted as described in Supplementary

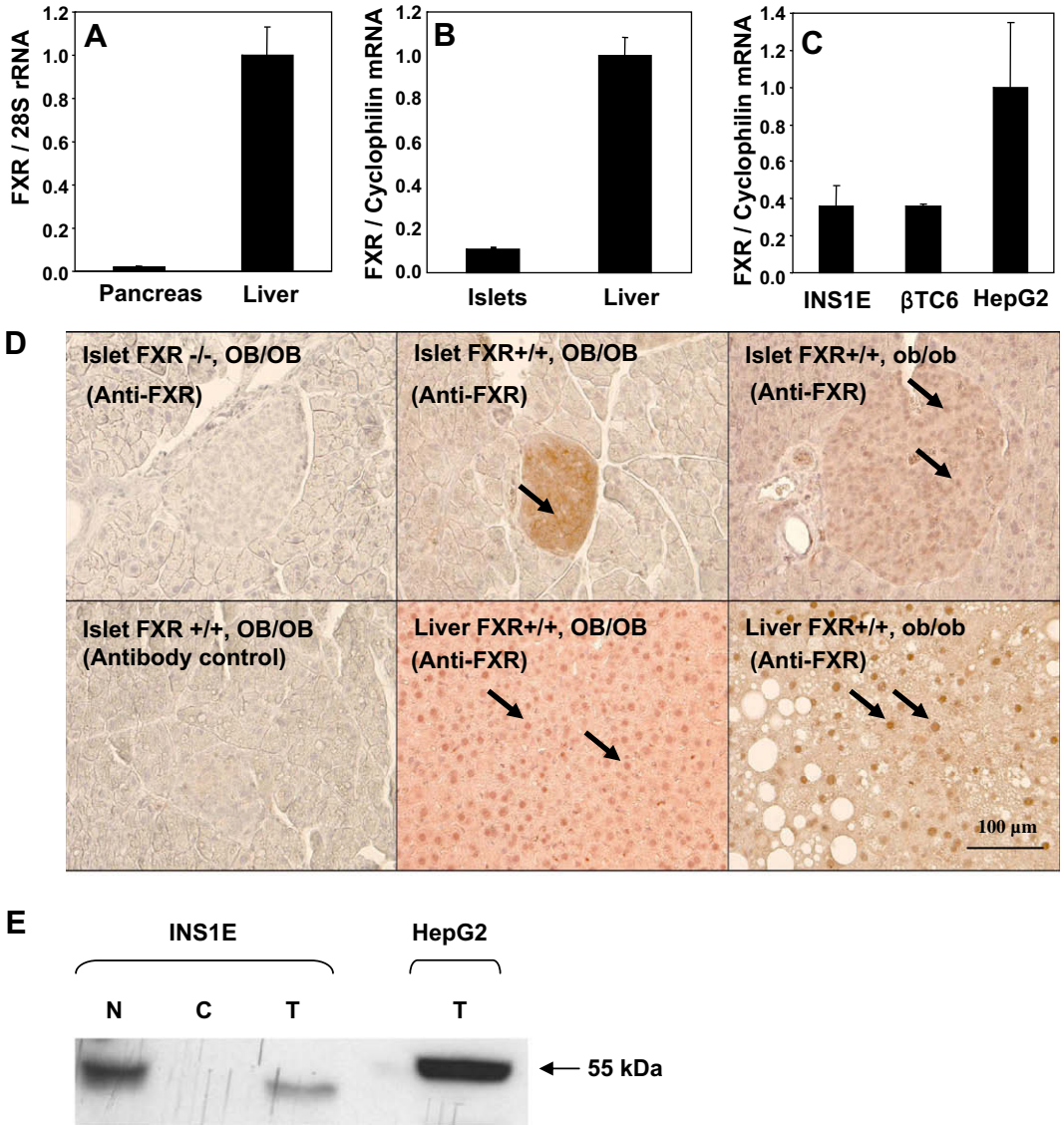

Fig. 1. FXR is expressed in pancreatic islets and β-cells. (A, B) FXR mRNA levels in the pancreases and islets of 20–26 week-old mice (n = 3–5) vs. liver set at 1 (mean ± S.D.). (C) FXR mRNA levels measured in INS1E and βTC6 cells vs. HepG2 hepatoma cells, set at 1 (mean ± S.D.; n = 3). (D) Immunohistochemical staining of FXR protein in pancreatic islets of lean (OB/OB) and obese (ob/ob) mice vs. FXR−/− mice as negative control. Liver sections of OB/OB and ob/ob mice were analyzed as positive controls. Pancreatic sections obtained from lean mice were also stained only with the secondary antibody and compared with anti-FXR stained sections, in order to verify the specificity of the antibody ("antibody control") – see Supplementary data for details. Images are representative of three independent experiments. (E) Immunodetection of FXR in total (T) or nuclear protein fraction (N) of INS1E and HepG2 cells.