FREE FATTY ACIDS RECEPTORS AS POTENTIAL DRUG TARGET IN THERAPY AND TREATMENT OF TYPE 2 DIABETES

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Type 2 diabetes (T2D) is the most common form of diabetes mellitus, and condition followed by hyperglycemia and disturbances in fat as well as protein metabolisms. There are many risk factors involved in the development of T2D such as nutrition, the environment and genetics. In 1963, Randle et al proposed a vicious "glucose and fatty acid cycle" which include stimulation of hepatic glucose output by fatty acids (FA), potentiation of glucose-stimulated insulin secretion (GSIS) by FAs, and the cellular mechanism whereby high glucose and insulin concentrations inhibit FA oxidation. Fatty acids as an energy fuel in the body, are important as well as biomolecules, particular as free fatty acids (FFAs) and play a key role in various metabolic functions by acting as signaling molecules and regulators or stimulators of biological functions. Recent studies, including lipidomics and pharmacological investigations have been shown that different type of FFAs (short-, medium- and long-chain fatty acids) activated several G-protein coupled receptors (GPCR) and represent important receptors for FFAs termed as FFA1–4 (*Figure 1)*. These FFA receptors (FFARs) are mediate various physiological functions, such as peptide hormone secretion and inflammation related conditions and thereby contribute energy homeostasis. Since imbalance in energy homeostasis lead to metabolic disorders, such as obesity and T2D, FFARs are considered to be a potential drug and therapeutic targets in these diseases. Novel findings have been shown that the administration of selective agonists of FFAR1 and FFAR4 improved glucose metabolism and ameliorated systematic metabolic disorders by increasing GSIS as well a direct positive effect on GSIS, while activation of FFAR2 and FFAR3 are linked with metabolic function of saturated fatty acids (SFAs) in anti-inflammation and energy metabolism by reducing inflammation and improvement in insulin sensitivity. Based on obtained data and new aproaches and protocols of synthesis using cyclopropanecarbocylic acid, several synthetic compounds were reported as FFAR3 and 4 agonists or antagonists. The presence of small molecule i.e. carboxylic acid in the structure of FFARs, enchanced selectivity as allosteric modulators of compounds. This work, presented a recent finding of FFARs physiological as well biological functions and their potential as selective ligands for development as novel drugs to treatment metabolic disorders such as obesity and T2D as well other inflammation related conditions (*Table 1*).

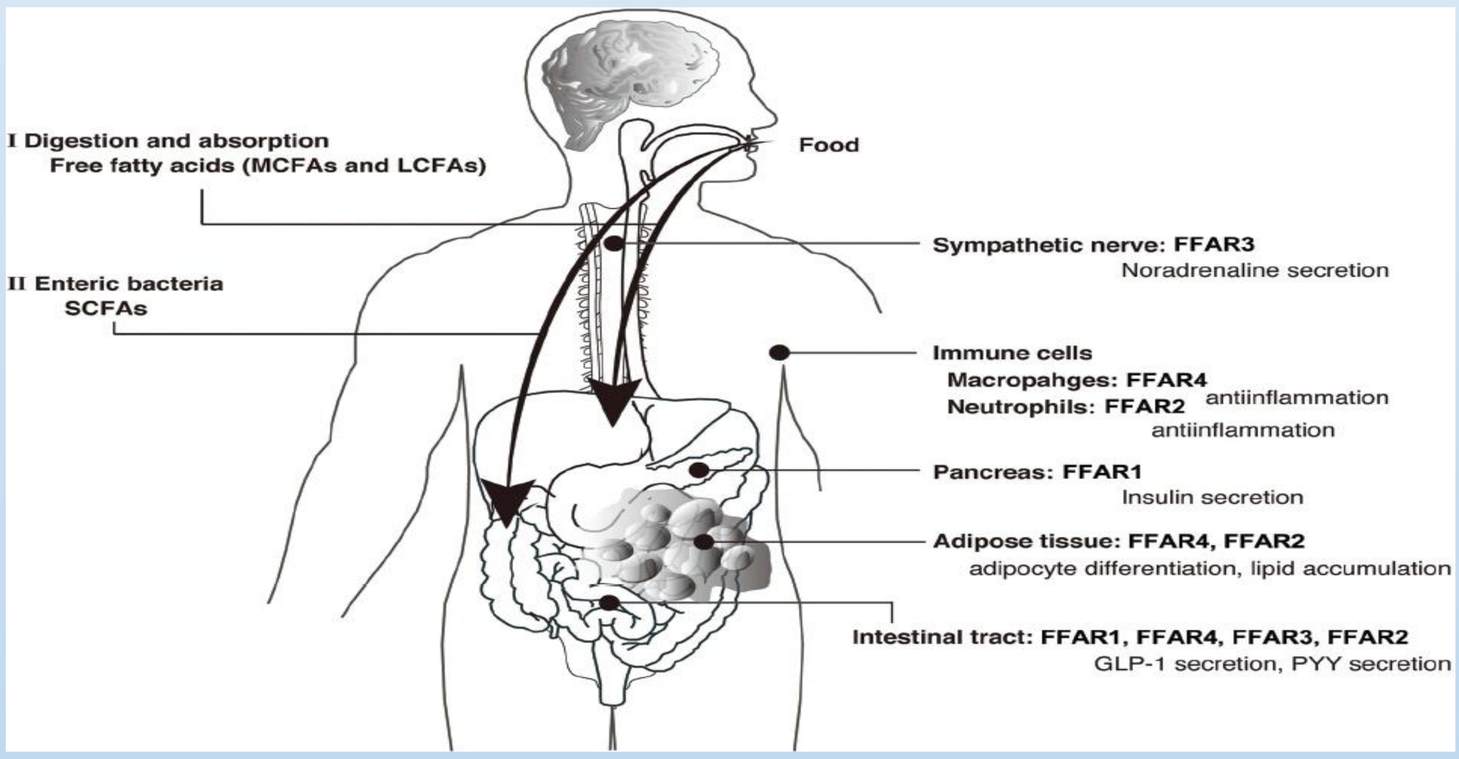

***Figure 1.* Physiological functions of free fatty acid receptors (FFARs).** Medium- and long-chain fatty acids derived from dietary fat act as ligands for FFAR1 or FFAR4 (I). Short-chain fatty acids produced by gut microbes from indigestible dietary fiber act as ligands for FFAR2 or FFAR3 (II).

***Table 1.* Summary of Free fatty acid receptors, FFARs (FFAR1, FFAR2, FFAR3, and FFAR4), their expression and biological functions**

FFA receptor	FAs	Expression	Biological functions
FFAR1(GPR40)	MCFA LCFA	Pancreatic β cells	Enhanced GSIS; Improved fasting hypoglycemia and glucose tolerance in diabetic animal models; Stimulation of glucagon secretion
FFAR4(GPR120)	MCFA LCFA	Various tissues and cell types (intestinal tissue, AT, pancreas, macrophages, adipocytes,)	Reduction of energy efficacy and regulation of inflammation; Improved insulin sensitivity and glycemic control; Increased insulin secretion; Adipocyte differentiation and maturation, glucose uptake, lipid accumulation; Protection against diet-induced obesity and diabetes
FFAR2(GPR43)	SCFA	Intestinal L cells, AT, Pancreatic β cells	Improved glucose uptake; Increased GLP-1 secretion; Inhibition of leukocyte activation; Reduction of lipolysis, reduction of fat accumulation, suppression of insulin signal
FFAR3(GPR41)	SCFA	Intestinal L cells, Pancreatic β cells	Increased GLP 1 secretion; Production of chemokines and cytokines, Inhibition of GSIS

*FFAR-free fatty acid receptor; GPCR- G-protein coupled receptor; FA-fatty acid; MCFA-medium chain fatty acid; LCFA- long chain fatty acid; SCFA- short chain fatty acid; GSIS- glucose-stimulated insulin secretion; AT-adipose tissue; GLP 1- glucagon like peptid 1;

In Summary, regulation of glycemia as well as fat accumulation and maintenance of body energy homeostasis, increasing insulin secretion, fololowed with improvement of insulin resistance and chronic inflammation, free fatty acid receptors molecule represents an important tool of research in novel drug development for the treatment of obesity and therapy monitoring of Type 2 diabetes.

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