BIOCHEMICAL MECHANISMS UNDERLYING ENDOCANNABINOID DYSREGULATION IN THE PANCREAS AND ADIPOSE TISSUE OF HIGH FAT DIET-FED MICE

Isabelle Matias[1], Katarzyna Starowicz[1], Luigia Cristino[2], Alessandro Racioppi[1] and Vincenzo Di Marzo[1]

[1,2]Endocannabinoid Research Group, [1]Institute of Biomolecular Chemistry and [2]Institute of Cybernetics, Consiglio Nazionale delle Ricerche, Pozzuoli (NA), Italy

The endocannabinoid (EC) system (comprising the EC ligands, anandamide and 2-arachidonoyl-glycerol, the cannabinoid CB1 and CB2 receptors, and EC biosynthesising and degrading enzymes) is involved in the control of energy homeostasis. There is increasing evidence for peripherally elevated EC levels during conditions of unbalanced energy homeostasis such as abdominal obesity, dyslipidemia and hyperglycemia, but the biochemical mechanisms underlying these alterations are not understood.
Here, we assessed in mice fed for up to 14 weeks with a standard or high fat (HFD) diet: 1) the expression of cannabinoid receptors and EC biosynthesising enzymes (NAPE-PLD and DAGLα) and degrading enzymes (FAAH and MAGL) in pancreatic and adipose tissue sections by immunohistochemistry; 2) the amounts, measured by liquid chromatography-mass spectrometry, of the ECs, 2-AG and anandamide, and of palmitoylethanolamide (PEA) and oleoylethanolamide (OEA), whose levels are regulated by the same enzymes as anandamide.
Whereas CB1 receptors and biosynthetic enzymes were found mostly in α-cells, degrading enzymes were identified in β-cells. Following HFD, a strong upregulation of biosynthetic enzymes in β-cells, and a decrease of FAAH levels, were observed together with an increase of anandamide, but not PEA and OEA, pancreatic levels. Whereas in the visceral fat we observed no changes in the levels of EC metabolic enzymes, in the subcutaneous fat a decrease in EC, OEA and PEA concentrations was accompanied by down- and up-regulation of biosynthesising enzymes and FAAH, respectively. No significant change in cannabinoid receptor levels was observed in any tissue following HFD. These data provide unprecedented information on the distribution of EC metabolic enzymes in the pancreas and adipose organ, where their aberrant expression during hyperglycemia and obesity in part determines dysregulated EC levels.

Supported by a Research Grant from Sanofi-Aventis.