Abstracts of the European Behavioural Pharmacology Society Workshop 'Eating Behaviour and Obesity', Lecce, 7–9 September 2012

Behavioural Pharmacology 2012, **23**:626–635

PLENARY LECTURE

LIPID SIGNALS AS FAT SENSORS: THE ROLE OF OLEOYLETHANOLAMIDE IN ENERGY BALANCE

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Oleoylethanolamide (OEA), the naturally occurring amide of ethanolamine and oleic acid, is an endogenous lipid mediator that modulates feeding, body weight and lipid metabolism by binding with high-affinity to the ligand-activated transcription factor, peroxisome proliferator-activated receptor-alpha (PPAR-alpha). In my presentation, I will briefly describe the biochemical pathways responsible for the initiation and termination of OEA signaling, the pharmacological properties of this compound in relation to its ability to activate PPAR-alpha, and its impact on feeding behavior in rats and mice. I will then outline the role of dietary fat in the regulation of OEA biosynthesis in the rat small intestine, which suggests that activation of small-intestinal OEA mobilization serves as a molecular sensor linking fat ingestion to satiety, and provide evidence that activation of oxytocinergic neurons of the hypothalamus is responsible for mediating the anorexic effects of OEA. Finally, I will describe new data integrating the actions of OEA with those of the endocannabinoids, another class of lipid mediators involved in the sensing of dietary fat.

SYMPOSIUM SPEAKERS

TISSUE MICROBIOTA: THE NEXT PARADIGM OF METABOLIC DISEASES

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We recently discovered that feeding a fat-enriched diet increases the blood concentration in lipopolysaccharides (LPS) in human and mice. These bacterial fragments are causally responsible for the initiation of inflammation, adipose tissue development, hyperglycemia, and insulin resistance. We now further established the phylogenetic profiles of bacterial genes in blood samples from diabetic and controls, and described the major importance of the Proteobacteria family. This group of Gram negative and LPS releasing bacteria was also present in feces and correlated with metabolic features which further validate the LPS hypothesis. In mice, the intestinal bacteria translocated to the adipose tissue and the liver and established a metabolic infection leading to a metabolic inflammation. More evidence from our laboratory also suggest an important role of the intestinal immune system in the regulation of the bacterial translocation process and consequently metabolism. The microbes associated molecular pattern receptors NOD1, CD14, and the leptin genes were involved in the regulation of bacterial translocation and its impact on diabetes and obesity. Hence, the identification of tissue microbiota should be the basis of discoveries leading to the identification of biomarkers and new therapeutic targets.

ROLE OF THE ADIPOSE ORGAN IN OBESITY

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White and brown adipocytes, are contained together in visceral and subcutaneous depots (adipose organ) in all mammals (Frontini and Cinti, 2010). A growing body of evidence suggests that the reason for this mixture could reside in the fact that adipocytes can convert directly each other under appropriate stimuli. Under chronic cold exposure white convert into brown to support the need for thermogenesis and under obesogenic diet brown convert into white to satisfy the need of energy storing. Adipocytes in the mammary gland offers another example of plasticity: during pregnancy and lactation adipocytes transdifferentiate into milk-producing epithelial glands and vice versa in the post-lactation period. The white into brown transdifferentiation is of great medical interest because the brown phenotype of the adipose organ is associated with obesity resistance and drugs inducing the brown phenotype cure obesity and related disorders.

Macrophages infiltrating the adipose organ are responsible for the inflammation dealing to insulin resistance and T2 diabetes. This inflammation is caused by the need of removal debris deriving from the death of adipocytes. Death of adipocytes is tightly related to their hypertrophy up to the critical death size. Visceral adipocytes have a critical death size smaller than subcutaneous adipocytes, thus explaining the higher inflammation and higher morbidity of visceral fat.

BODY WEIGHT LOWERING EFFECT OF GASTRIC BYPASS (RYGB) SURGERY

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Roux-en-Y gastric bypass (RYGB) surgery is an effective anti-obesity therapy. The weight reducing effect of RYGB seems to depend on a variety of factors such as lower spontaneous eating and lack of a compensatory decrease in energy expenditure (EE) that often is associated with weight loss. Mechanical restriction and caloric malabsorption seem to play only minor roles. Early studies suggested that changes in eating behavior induced by RYGB may be related to humoral factors because recipient rats ate less when they received postprandial plasma from RYGB than from sham rats. It is now generally believed that the enhanced synthesis and release of satiation hormones like glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and perhaps amylin contribute to the eating inhibitory and weight reducing effect of RYGB. This is consistent with the typical meal pattern after RYGB (reduction in average meal size and only partial compensation by an increase in meal frequency). Weight reduction by dieting typically leads to a compensatory decrease in EE; this reaction is markedly attenuated by RYGB, i.e., RYGB rats expend more energy than weight matched controls. Unlike the effect of RYGB on eating, it is unclear whether the changes of EE are also mediated by altered release or action of gastrointestinal hormones. Further, RYGB also changes food preferences

0955-8810 DOI: 10.1097/FBP.0b013e328357eb02