Diet and gut microbiome regulate a variety of cellular physiological functions. Recent studies published in *Nature* revealed that commensal bacteria produce metabolites, namely, *N*-acyl amines (and *N*-acyl amino acids as their subclass), acting as agonists for human GPR119 receptor (Cohen *et al*., 2017). This receptor belongs to GPCR receptors family and is involved in glucose stimulated insulin secretion (GSIS). Moreover, GPR119 not only affects glucose homeostasis by regulation of insulin secretion from β cells of pancreatic islets (Soga *et al*., 2005), but also gastric emptying and reduction of appetite through GPR119-dependent hormone release of glucagon-like peptide 1 (GLP-1) from intestinal cells (Yea *et al.,* 2009). In recent years GPR119 has become very interesting for the pharmaceutical industry because it is considered as one of the crucial targets for treatment of diabetes and obesity. However, the GPR119-related signaling pathways are very complex and there is a lot of its endogenous agonists including oleoylethanolamide (OEA) and 2-oleoyl glycerol (2-OG) (Hansen *et al.,* 2011). Lysophosphatidylcholines (LPCs), abundantly present in human plasma, also have the ability to activate GPR119 receptor and mediate GSIS (**Drzazga *et al*, 2017a***).

The candidate for the SONATINA grant hypothesizes that bacteria-derived metabolites can activate not only GPR119 but also two other receptors which facilitate GSIS. This hypothesis is based on results of her studies indicating that some LPC can act as ligands for three receptors: GPR119, GPR55 and GPR40 (**Drzazga *et al*, 2017a***). Since OEA and LPCs structurally resemble microbiota-derived N-acyl amines, it seems probable that the latter compounds could also activate all the three receptors. According to this hypothesis, N-acyl amines may influence insulin secretion at much higher level than it was evidenced by Cohen *et al*. (2017).

N-acyl amines (NAA) and *N*-acyl amino acids (NAAA) are produced by commensal bacteria but cooking oils also contain varying levels of these compounds (Bradshaw and Leishman, 2016). Besides, due to their emulsifying properties, synthetic NAAA are considered as candidate amino acid-based surfactants which may be used in food and pharmaceutical industries instead of sodium dodecyl sulphate (Perinelli *et al*., 2016; Bernal *et al*., 2018). However, the potential use of NAAA in food industry should be precluded by careful studies of their cytotoxicity and other potential biological activities which might be responsible for some unknown side effects. Since most of the GPCR activating compounds (OEA, 2-AG, and NAAA) get into the body along with the diet, it is impossible to predict which factors have a greater impact on the activity of receptors present on the surface of enterocytes: type of diet, type of fat consumed or intestinal microflora. Therefore, comparative studies are necessary to estimate their safe levels and influence on human cell metabolism.

Concluding, structurally diverse *N*-acyl amines have probably broad range of biological activities. Taking into account their presence in plant-derived food (oils), their synthesis by commensal bacteria and as well as exploitation as surfactants in food industry, it is necessary to estimate their safe levels and the influence on human cell metabolism, especially in the context of carbohydrate homeostasis.

The objective of the current proposal is to confirm that ligand selectivity of *N*-acyl amines is much wider and not strictly related to GPR119. *N*-acyl amines may be particularly beneficial to diabetic individuals due to activating GPR119, GPR55 and GPR40 receptors in a distinct and specific way. Comparative analysis of *N*-acyl amines', OEA' and LPCs' mechanism of action should yield important insights into basic features of intestinal and pancreatic cells biology. To confirm this, biochemical and microbiological approaches, monitoring downstream signaling activity as well as employing functional assays (secretion of insulin and GLP-1) will be applied.

Projecting forward, the results obtained in the course of this project may significantly improve the knowledge on the pathophysiology of the diabetes mellitus and facilitate the discovery of new treatment/prevention options for metabolic diseases. Activities of *N*-acyl amines are poorly recognized so far, but regulation of GPCRs by diet and microbiota-derived NAA may be a particularly noteworthy strategy, because GPCRs have been extensively validated as therapeutic targets. The proposed studies will provide insight into how commensal bacteria and diet may interact with human physiology via producing small molecules that appear to structurally mimic host signaling metabolites.

•Cohen *et al*., Nature. 549, 48-53, (2017); •Soga *et al*., Biochem Bioph Res Co. 326, 744-751, (2005); •Yea *et al*., Journal of Biological Chemistry. 284, 33833-33840, (2009); •Hansen *et al.*, J Clin Endocrinol Metab. 96, E1409-17, (2011); •Drzazga *et al*. Mol Cell Endocrinol. (2017a); •Bradshaw & Leishman, J Basic Clin Physiol Pharmacol. 27, 247-52, (2016); •Bernal *et al*., Food Chem. 239, 189-195, (2018).

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