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How smell regulates metabolism: The role of ectopically expressed olfactory receptors in lipid and glucose homeostasis

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Abstract

Olfactory Receptors (ORs) are a large family of G protein-coupled receptors predominantly expressed by the main olfactory epithelium at nasal level and are responsible for the generation of smelling sense. Microarray and deep sequencing analyses, however, have demonstrated that ORs are ectopically expressed in various human tissues including testis, kidneys, adipose tissue and liver and their biological functions become to be unrevealed. Molecular and pharmacological approaches have shown that some of these ORs modulate glucose and lipid metabolism at multiple interfaces, suggesting that ORs might be part of the large family of nutrient sensors, i.e. molecular/ cellular machines that respond to a specific nutrient component. By using nutrient-derived agonists it has been shown that ORs effectively modulates glucose and lipid metabolism raising interest on their possible therapeutic application in the treatment of metabolic disorders including dyslipidemia, obesity and metabolic syndrome.

Abbreviations: ACC: Acetyl-CoA carboxylase; ACIII: Adenylyl cyclase type III; AMPK: AMP-activated protein kinase; ASM: Airway smooth muscle; AzA: Azelaic acid; BAT: Brown adipose tissue; CAC channel: Calcium activated chloride channel; CaMKIV: Calcium / calmodulin-dependent protein kinase IV; cAMP: Cycling adenosine monophosphate; CNG channel: Cyclic nucleotide gated channel; CNVR: Copy number variation region; CREBP: cAMP response element binding protein; CVDs: Cardiovascular diseases; DAG: 1,2-diacylglicerol; ER: Endoplasmic reticulum; FAO: Fatty acids oxidation; FAS: Fatty acid synthase; G protein: GTP-binding protein; G6PC: G6PC; GDP: Guanosine diphosphate; GF: Growth factor; GI: Gastrointestinal; GK: Glucokinase; GLP-1: Glucagon-like peptide 1; GLUT: Facilitated diffusion glucose transporter; GPCR: G protein-coupled receptor; GSIS: Glucose-stimulated insulin secretion; GTP: Guanosine triphosphate; GWAS: Genome-wide association study; HES-1: Hairy and enhancer of split-1; HFD: High fat diet; HGP: Hepatic glucose production; HSL: Hormone sensitive lipase; IP3: Inositol 1,4,5-triphosphate; IP3R: Inositol 1,4,5-triphosphate receptor; IR: Insulin resistance; LXRα: Liver-X-receptor α; MCFA: Medium-chain fatty acid; MetS: Metabolic Syndrome; MOE: Main olfactory epithelium; mtGPAT: Mitochondrial glycerol-3-phosphate acyltransferase; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; OLFR: Olfactory receptor (murine); OR: Olfactory receptor (human); OSN: Olfactory sensory neuron; PCK1: Phospho-enolpyruvate carboxykinase; PGC-1α: Peroxisome proliferator-activated receptor γ coactivator 1α; PIP_2: Phosphatidylinositol 4,5-biphosphate; PKA: Protein kinase A; PLC: Phospholipase C; PPAR-α: Peroxisome proliferator-activated receptor-α; PPAR-γ: Peroxisome proliferator-activated receptor-γ; RF: Risk factor; SCD1: Stearoyl-CoA desaturase 1; SCFA: Short-chain fatty acid; SGLT: Sodium-glucose transporter; SREBP-1a/1c: Sterol regulatory element-binding protein 1a/1c; T2DM: Type 2 diabetes mellitus; TCA: Tricarboxylic acid; TM: Transmembrane; UCP1: Uncoupling protein 1.

Olfactory Receptors (ORs)

Olfactory receptors (ORs) were discovered in 1991 on olfactory cilia of rats' main olfactory epithelium (MOE) by Richard Axel and Linda B. Buck [1], while investigating mechanisms involved in smelling sense generation [2]. ORs are G protein-coupled receptors (GPCRs) [3] that share the pro-typical architecture of these receptors organized in (i) seven transmembrane α-helices (TM1 to TM7) linked one to another by (ii) three extracellular and three intracellular loops, (iii) an extracellular N-terminus domain responsible for ligand binding and (iv) an intracellular C-terminus domain (generally organized in an additional eighth α-helix) interacting with a heterotrimeric complex (α, ß and γ subunits) of GTP-binding proteins (G proteins) [4] (Figure 1). According to a sequence homology categorization, ORs belong to one of the five sub-families of the class A rhodopsin like GPCR family, which encodes for almost the 90% of all GPCRs [5].

At nasal level, multiple subpopulations of Olfactory Sensory Neurons (OSNs) have been identified, each one characterized by the expression of a single OR protein and, thus, able to respond to different chemosensory stimuli (i.e. different ligands, also known as odorants) [6]. Following the binding to its ligand, the OR becomes activated and promotes the classical G protein signaling pathway, triggering the Adenylyl Cyclase type III (ACIII) activation that is followed by a change

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***Keywords:** Olfactory receptors, glucose metabolism, type 2 diabetes mellitus, lipid metabolism, NAFLD, metabolic syndrome*

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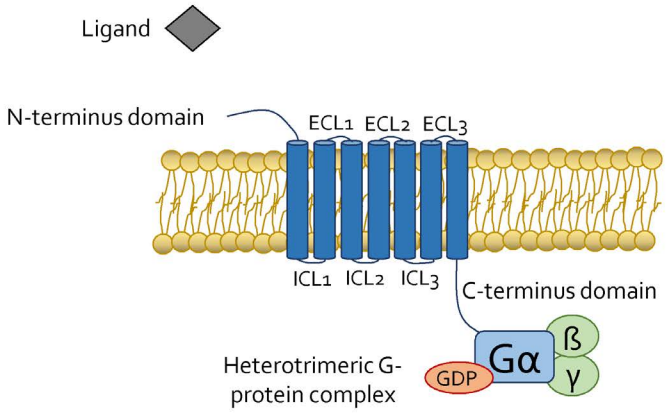


Figure 1. GPCRs structure. The seven transmembrane α-helices counterclockwise arranged are linked one to the other by three extracellular (ECL1-3) and three intracellular (ICL1-3) loops. The extracellular N-terminus domain is deputy to ligand binding, while the intracellular C-terminus domain relates to the heterotrimeric αβγ G-protein complex when the receptor is in its conformational inactive state (unbound ligand) and Gα subunit binds guanosine diphosphate (GDP)

in cyclic adenosine monophosphate (cAMP) levels. cAMP induce cyclic nucleotide gated (CNG) channels opening and increase of intracellular Ca^{++} levels which further stimulates the opening of calcium activated chloride (CAC) channels. This promotes the cell depolarization, action potential generation and neuronal impulse transmission to the central nervous system, allowing the generation of smell perception [7].

ORs are encoded by large family of genes, approximately 1000 genes in the murine genome and at least 400 genes in the human genome and can be classified as class I and class II ORs, depending on their ability to bind and be activated by water-soluble/moderately hydrophobic or highly hydrophobic/volatile compounds, respectively [8].

In addition to the nasal level, an ectopic expression of ORs has been detected in various mammalian tissues [9] including: (i) the testis, where ORs guide spermatogenesis and sperm chemotaxis [10]; (ii) the heart, where ORs seem to be involved in cardiac morphogenesis [11]; (iii) the placenta [12]; (iv) the juxtaglomerular renal apparatus, *Olfr78* recognizes and binds the short-chain fatty acid (SCFA) propionate and regulates renin secretion [13,14]; (v) enterochromaffin cells, *OR73*, *OR17-7/11*, *OR1G1* and *OR17-210* promote secretion of serotonin – a tryptophan-derived neurotrasnmitter involved in gut motility and mucus secretion. These later receptors are timulated by terpenoids such as eugenol, thymol and burgeonal [15]. Moreover, ORs have been detected in other organs such as pancreas, adipose tissue and liver [16], where their function seems to be mostly related to regulation of glucose and lipid metabolism [17] (Table 1).

In contrast to the OSN, however, ORs activation in those tissues is no longer associated to cell depolarization and neuronal impulse generation but linked to AC/cAMP or PLC/IP_3 pathways. Ligand binding to the extracellular N-terminus domain induce a conformational change in the receptor which leads to a GDP/GTP binding exchange at Gα subunit level [51].In the AC/cAMP pathway, mainly regulating lipid metabolism, the Gα subunit dissociates from ßγ heterodimer and diffuses along the inner membrane surface towards the effector protein ACIII, activating it and allowing the production of cAMP, that in turns act on the Protein Kinase A (PKA), a tetrameric complex made up of two regulatory (R) and two catalytic (C) subunits. Binding of two molecules of cAMP to each of the R subunits, triggers PKA activation, which exerts its kinase activity on a large number of cytosolic and nuclear proteins [52]. Additionally, the cAMP can also activate CNG channels located on endoplasmic reticulum, increasing intracellular

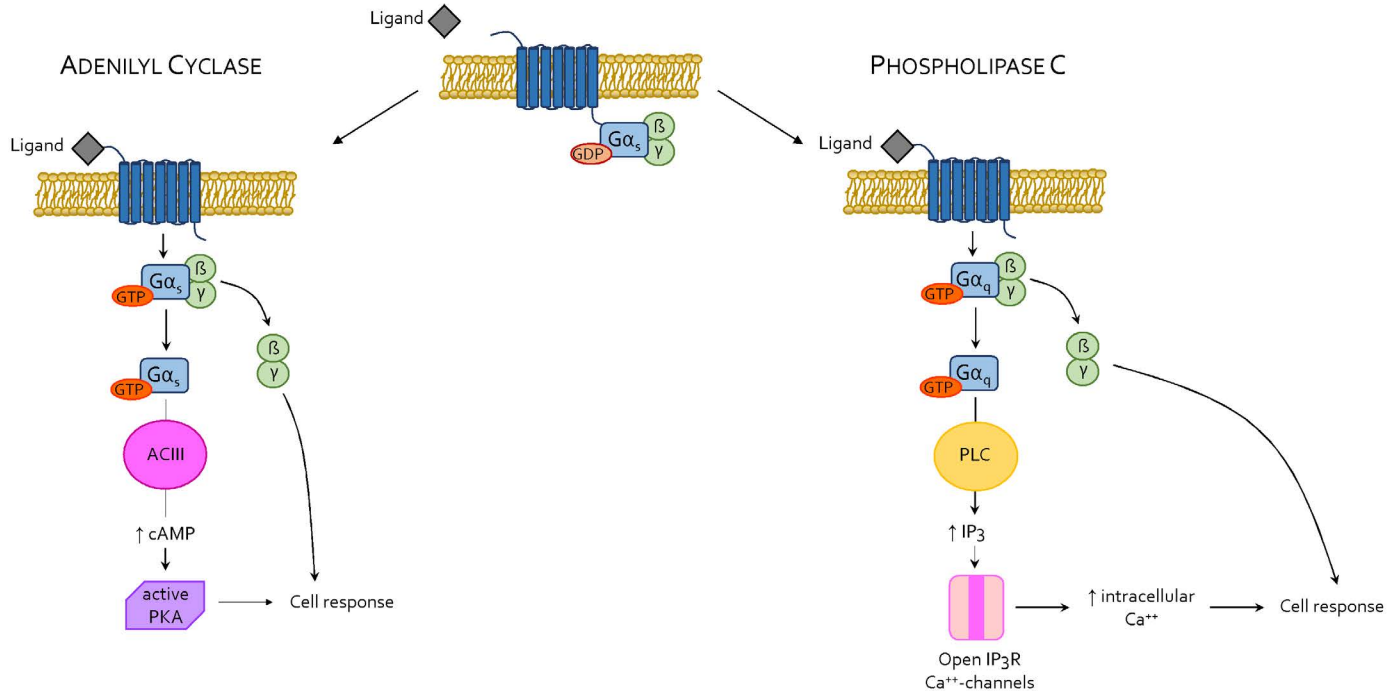


Figure 2. Transition from inactive (unbound ligand) to active (bound ligand) state of a typical GPCR. In ACIII/cAMP GPCR, ligand binding provokes conformational changes in the receptor, inducing a GDP/GTP exchange on Gαs subunit, its activation and dissociation from the αßγ heterotrimer and migration to ACIII. Active ACIII produces cAMP which activates PKA, resulting in phosphorylation and activation of different target proteins. In PLC/IP3 GPCR, ligand binding provokes conformational changes in the receptor, inducing a GDP/GTP exchange on Gαq subunit, its activation and dissociation from the αßγ heterotrimer and migration to PLC. Active PLC produces DAG and IP3 from PIP2 hydrolysis. IP3 in turns activates IP3 sensitive Ca++ channels present on endoplasmic reticulum (ER) membranes where Ca++ is stored, thus increasing intracellular Ca++ levels

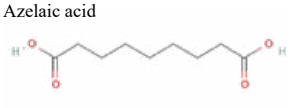
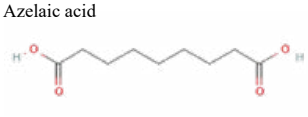
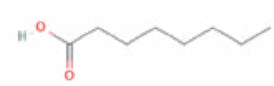
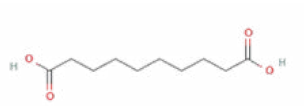
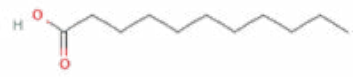
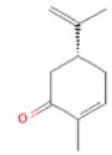
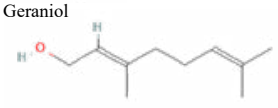
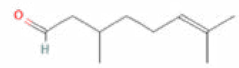
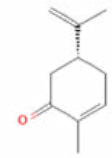
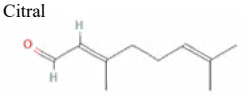
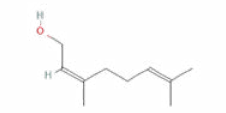
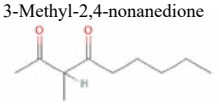
Table 1. Distribution of the main olfactory receptors identified in non-chemosensory tissues

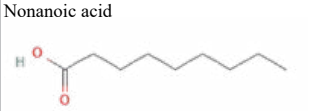
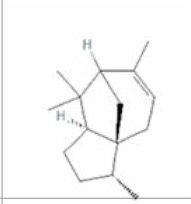
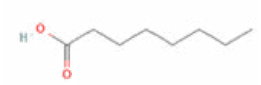
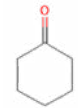
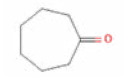
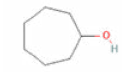
Tissue and/or cell line	Species	Receptor(s)	Main function(s)
Testis	Human	OR7A5, OR4D1, OR1D1, hOR17-4, hOR17-2	Sperm chemotaxis and chemokinesis [10], [18], [19]
	Mouse	MOR23, MOR244-3, MOR139-3, MOR248-11, MOR31-2, MOR171-31, MOR264-10, MOR256-25, MOR144-1, MOR171-31, MOR13-4, MOR281-1, MOR127-2, MOR13-6, MOR174-6, MOR31-2, MOR248-11	Regulation of sperm flagellar motility, chemotaxis, spermatogenesis [20], [21]
Tongue	Human	HTPCR06, HGMP071, JCG1, JCG2, JCG3, JCG4, JCG5, JCG6, JCG9, JCG10, TPCR85, TPCR120	Involvement in taste perception [22], [23]
Heart	Rat Human Mouse	OL1 OR5E1 MOL2.3	Involved in cardiac morphogenesis [11] Regulation of cardiac function [24] Not yet defined [25]
Spleen	Mouse	OL-2	Not yet defined [26]
MIN6	Mouse	OL-2	Possible regulation of insulin secretion [26]
Pancreas	Mouse	OLFR15, OLFR821	Glucose-stimulated insulin secretion (GSIS) [27], [28]
Blood	Human	HPFH1OR	Not yet defined [29]
Prostate	Human	PSGR	Overexpression in tumor specimens: potential prostate cancer marker [30], [31]
Muscle	Mouse	MOR23 (also known as OLFR16)	Involved in muscle regeneration, cell adhesion and migration [32]
Liver	Rat	PSGR	Not yet defined [33]
	Mouse Human	OLFR99, OLFR267, OLFR1393, OLFR1366, OLFR691, OLFR558, OLFR57, OLFR646, OLFR78, OLFR15, OLFR177 OLFR544, OLFR43, OLFR16 OLFR734 OR10J5, OR1A1	Involvement in hepatic physiology [16] Regulation of lipid metabolism (see below) Gluconeogenesis induction [34] Regulation of lipid metabolism (see below)
HepG2	Human	OR1A1, OR10J5	Involved in triglycerides synthesis [35], [36]
Huh7	Human	OR1A2	Inhibition of cell proliferation [37]
3T3-L1	Mouse	OLFR544	Triglycerides hydrolyzation [38]
Adipose tissue	Mouse Rat Human	OLFR544, OLFR16 OLFR788 OLR984 OR6C3, OR4C11, OR4C6, OR4P4, OR4S2	Antiobesogenic effect [36], [38] and brown adipose tissue (BAT) thermogenesis [39] Antiobesogenic effect [165] Antiobesogenic effect [165] Antiobesogenic effect [165] - [167]
Kidney	Mouse Human	OLFR78 OLFR90, OLFR 1373, OLFR1372 OLFR1393 OLFR31, OLFR99, OLFR545, OLFR691, OLFR693, OLFR1426 OR2T1	Involved in renin secretion and blood pression regulation [14] Not yet defined [13] Glucose reabsorption [40] Not yet defined [41] Not yet identified [41]
GI tract	Mouse Human	PSGR OLFR544, OLFR43 OR73, hOR17-7/11, OR1G1, hOR17-210 OR51E1, OR1A1	Not yet defined [33] Glucose metabolism (GLP-1 and glucagon secretion) [42] Involved in serotonin secretion [15] Glucose metabolism (GLP-1 and glucagon secretion) [43]
Placenta	Rat Human	MOR125-1, MOR126-1, MOR140-1, MOR145-5, MOR216-1, MOR263-9 OR2C1, OR4D6, OR2M7, OR10A6, OR4F3, OR8A1, OR2W3, OR1-1	Environmental signaling in fetus-mother interaction [12] Environmental signaling in fetus-mother interaction [12]
HeLa	Human	OR2A4	Regulation of actin cytoskeleton cytokinesis [44]
Brain (and CNS in general)	Rat, mouse Mouse Human	PSGR MOR2.3, M71, C6, OR3 OLFR110/111, OLFR544 OR2L13, OR1E1, OR2J3, OR52L1, OR11H1 OR2H2, OR2A4, OR6K3	Not yet defined [33] Possible involvement in developmental processes such as axon guidance [25], [45] Brain physiology [46] Cerebral cortex physiology [47] Not yet defined [48]
Lung	Human	OR51E2 OR1D2, OR2AG1	Modulation of airway smooth muscle (ASM) cells proliferation [49] Regulation of pathophysiological processes [50]

Ca^{++} concentrations. In the PLC/IP_3 pathway, mostly involving, on the other hand, glucose metabolism, GTP-Gα subunit activates the effector protein Phospholipase C (PLC) which in turns hydrolyzes phosphatidylinositol 4,5-biphosphate (PIP_2) – a constituent of the plasmatic membrane – in inositol 1,4,5-triphosphate (IP_3) and 1,2-diacylglicerol (DAG), critical second messengers responsible for intracellular Ca^{++} signaling regulation [53] (Figure 2). Further on, because its intrinsic GTPase activity, the Gα subunit hydrolyses GTP in GDP and P_i, thereby inducing self-inactivation. Gα-GDP subunit associates again with the heterodimer ßγ and with the GPCR, bringing back the receptor to its inactive state.

Ectopically expressed ORs play a role in glucose and lipid metabolism: As mentioned above, many ORs have been detected outside of the MOE, although the function of the large majority of these receptors remains unclear. However, the presence of some ORs in in tissues and organs such as liver, kidneys, pancreas and adipose tissue, may suggest their involvement in the regulation glucose and lipid homeostasis. Up to now, it is possible to confirm the ability of some of those ectopically expressed ORs to exert regulatory function on blood glucose levels and lipid metabolism [54], opening the possibility for their exploitation in managing metabolic disorders such as type

Table 2. State of the art of the main ORs involved in glucose and lipid metabolism, their relative odorant ligands and pathways activated.

OR	Odorant(s)/ligand(s)	Pathway(s)	Main function(s)
OLFR544	Azelaic acid  Azelaic acid  Octanoic acid  Sebacic acid  Undecanoic acid 	cAMP/Ca++ cAMP/HSL and cAMP/CREB	Ca++-dependent glucagon secretion [42] HSL-induced triglycerides breakdown [38] PPARα-induced FAO and inhibition of triglycerides synthesis via HES-1 repression [38]
OR1A1/OLFR43	(-)-Carvone  Geraniol  Citronellal  (-)-Carvone  Citral  Nerol  3-Methyl-2,4-nonanedione 	cAMP/Ca++ cAMP/CREB	GLP-1 and Ca++-dependent glucagon secretion [59], [60] PPARα-induced FAO and inhibition of triglycerides synthesis via HES-1 repression [35], [61]–[63]

OR51E1	Nonanoic acid 	cAMP/Ca++	Ca++-dependent GLP-1 secretion [43]
OR10J5/OLFR16	α-cedrene 	cAMP-CREB cAMP-HSL cAMP-AMPK	PPARα-induced FAO and inhibition of triglycerides synthesis via HES-1 repression, hepatic steatosis improvement [36], [64], [65] HSL-induced triglycerides breakdown, hepatic steatosis improvement [36], [64] LXRα and SREBP-1c repression, inhibition of lipogenic genes (ACC, FAS, SCD-1, hepatic steatosis improvement [36], [64], [65]
OLFR15, OLFR821	Octanoic acid 	PLC/IP3	Increased expression of GK, potentiation of glucose absorption and GSIS [27], [28]
OLFR734	Asprosin (endogenous)	cAMP/CREB	Increased expression of G6PC and PCK1, gluconeogenesis stimulation [34]
OLFR1393	Cyclohexanone  Cycloheptanone  Cycloheptanol  Cyclooctanone 	cAMP-?	Glucose reabsorption at renal tubules level via increasing expression of SGLT1 and SGLT2 [40]

2 diabetes mellitus (T2DM) and nonalcoholic fatty liver diseases (NAFLD) or nonalcoholic steatohepatitis (NASH) [55-57], i.e. a family of human disorders that develop in association with the Metabolic Syndrome [58] (Table 2).

ORs in glucose homeostasis

Glucose metabolism: Glucose is a 6-carbon sugar found in different foods both in simple (mono- and di-saccharides, such as fructose and lactose, respectively) and complex (e.g., starch) forms, and used as principal source of energy by our organism, reason why glucose transporters are present on surface membranes of all our cells [66]. Those transporters, classified in Sodium Glucose Transporters (SGLTs) and facilitated diffusion Glucose Transporters (GLUTs), are differently distributed among different cell types [67] and allow glucose uptake from blood circulation to (i) produce energy (ATP) via a series of biochemical reactions (glycolysis) or, in case of excess glucose, to (ii) store it under the form of glycogen (glycogen synthesis) in liver and skeletal muscles [68-70]. The balance between blood glucose, glucose absorption and glycogen deposition is finely regulated by the two peptide hormones insulin and glucagon, produced in Langerhans pancreatic islets, by ß- and α-cells respectively [71]. In a simple way: after a meal, blood glucose levels are increased (causing hyperglycemia) and insulin secretion is stimulated. After its release in the bloodstream, insulin reaches its main target tissues such as hepatic, skeletal and adipose tissues, binds to its receptor and increase translocation of GLUT4 transporter to the surface membrane, potentiating glucose uptake [72,73], as well as enhancing free fatty acids and amino acids uptake for lipogenesis and protein synthesis. These processes are furthermore potentiated by glucagon-like peptide-1 (GLP-1), released by gut enteroendocrine cells and responsible for increase of insulin secretion [74].

Conversely, during fasting periods glucagon [75], that is released by pancreatic cells, exerts several counter-regulatory effects including (i) reduction of hepatic glucose uptake, (ii) I breakdown of the previously stored glycogen (glycogenolysis) and, (iii) *de novo* glucose synthesis (gluconeogenesis) [76-78].

ORs and glucose metabolism in human disorders: In pathological conditions, glucose metabolism is altered generally due to an improper insulin production and subsequent long-lasting high blood glucose levels in T2DM, also known as adult-onset diabetes, is one of the most common widespread chronic metabolic disorders worldwide, accounting for almost the 90% of all diabetic patients [79]. T2DM is characterized by persistent hyperglycemia mainly due to defective insulin secretion by pancreatic ß-cells and/or loss of responsiveness of insulin-sensitive tissues, causing the development of insulin resistance (IR) and hyperinsulinemia onset [80]. Persistent high levels of blood glucose in non-treated patients are responsible for micro- and

macro-vascular complications such as retinopathy, nephropathy and cardiovascular comorbidities [81-86].

Recent studies have confirmed that some ectopically expressed ORs exert a regulatory function in glucose metabolism. *Olfr43* (homologous of the human *OR1A1* gene) and *OR51E1*, expressed by L and K enteroendocrine cells and respectively activated by geraniol, citronellal and (-)-carvone or nonanoic acid binding, participates in glucose homeostasis by inducing GLP-1 secretion which, in turns, stimulates insulin production [43,59,60]. Thus, ORs add to the many GPCRs that regulate GLP-1 release from L cells. These promotes GLP1 secretion in response to various nutrients or microbial products and exert a critical role in regulating insulin secretion and sensitivity. L cells expressed various lipid sensing receptors, including the free fatty acid receptor (FFAR)2/GPR43 and FFAFA3/GPR41, two receptors for short chain fatty acids (SCFA) [87], along with FFAR1/GPR40 and FFAR40/GP120 two receptors for long chain fatty acids [88], GPR119 that is activated by fatty acid metabolites such as ethanololemanie such as N-acylethanolamines and 2-monoacylglycerols [89], and GPBAR1 (also known as TGR5) a receptor for secondary bile acids litocholic acid (LCA) and deoxycholic acid (DCA), generated from the intetsinal microbiota [90]. These array of receptors are mostly known for their ability to sense microbial product, and, in addition to ORs provide an intricated network of chemical signaling that integrate nutrients, intstinal microbiota and host metabolism and immune system, that could be exploited for therapeutic purposes [91-93].

To further highligt these interactions, *Olfr15* and *Olfr821*, detected in ß-pancreatic islets and ß-cell line MIN6, are capable to recognize and bind the medium-chain saturated fatty acid (MCFA) octanoic acid (also known as caprylic acid, naturally found in coconut and palm oils [94]), thus activating downstream PLC/IP_3 pathway, inducing glucokinase (GK) expression and potentiating glucose absorption and glucose-stimulated insuline secretion (GSIS) [27,28]. In both cases, activation of those receptors exerts an hypoglycemic and anti-diabetic function, finally lowering blood glucose levels via increasing insulin secretion.

On the other hand, different ORs have been linked to be directly involved in diabetes pathogenesis. In particular, *Olfr1393*, expressed in the kidneys by the proximal tubules, has been confirmed to be involved in glucose reabsorption at renal level by increasing expression and membrane translocation of the sodium-glucose cotransporters SGLT1 and SGLT2 [40], thus increasing blood glucose levels and emerging indeed as an important contributor to T2DM development. Despite the molecular mechanism is not so clear, further studies have confirmed *Olfr1393* capability to modulate SGLT1 and SGLT2: infact, SGLT2 expression was reduced in *Olfr1393* KO mice, resulting in improvement of hyperglycemia and glucose tolerance [95,96]. Both *in vitro* and *in vivo* studies revealed and increased expression of SGLT2, and thus of glucose reabsorption, in T2DM patients [97]: although not yet completely understood, it seems that SGLT2 overexpression should be due to a hyperphosphorilaton guided by insulin via PKA and PKC [98,99]. Conversely, SGLT2 genetic mutations and/ore deletions have been associated to familial renal glicosuria (FRG), with persistent high levels of glucose in the urine [100]. Importantly, SGLT2 inhibitors (i.e., canagliflozin, dapagliflozin, and empagliflozin) have been shown effective in the treatment of T2DM by reducing glucose reabsorption in the proximal renal tubule thus lowering blood glucose levels and glucose toxicity [101-103]. SGLT2 inhibitors have gain approval for the treatment of T2DM patients [104,105] and targeting *Olfr1393* thus preventing SGLT2 expression offers novel therapeutic possibilities in tyhis setting. *Olfr734*, that is expressed by hepatocytes, is activated by asprosin, an endogenous fasting-induced hormone produced by adipose tissues [106], that in its turn incraeses the expression of glucose-6-phosphatase (G6PC) and phospho-enolpyruvate carboxykinase (PCK1) thus promoting gluconeogenesis and blood glucose release as well as stimulating appetite at hypotalamic level [34]. The expression of *Olfr543*, *Olfr544*, *Olfr545* and *Olfr1349* has been detected also in the pancreatic α-cells, but only the stimulation of *Olfr544* by azelaic acid results in Ca^{++}-dependant glucagon secretion [42] (Figure 3).

ORs and lipid metabolism

Lipid homeostasis: Lipids are an eterogeneous group of hydrophobic molecules majorly belonging to fatty acids (FAs), triglycerides (TGs), phospholipids, steroids and glycolipids classes [107] all necessary for our organism due to their implications in many different aspects of cellular homeostasis and metabolism. Cholesterol, is the starting molecule in the biosynthesys of hormones such as progesterone, aldosterone, cortisol and testosterone, other than be a fundamental costituent of cell membranes[108,109] together with phospholipids [110], regulating important aspects of the bilayer such as fluidity, permeability and rigidity [111]. Glycolipids are important membrane constituent as well due to their role in facilitating cell-cell interactions [112, 113]. However, almost the 90% of the lipid intake in a normal diet is represented by triglycerides, suppling most of the lipidic energy source [114]. After enzymatic digestion (borne by lingual, gastric and pancreatic lipases) and instestinal bile salts emulsion, FFAs, free cholesterol and 2-monoacylglycerols are the main products ready to be absorbed by enterocytes under the form of micelles [115]. Once inside the cell, FFAs and 2-monoacylglycerols are converted again in TGs, cholesterol is esterified and together are incorporated in small particles named chylomicrons. Those chylomicrons, constituted up to 90% by TGs, are reversed into the lymphatic system and transported to (i) skeletal and cardiac tissues, where TGs are released to be used for energy production or to (ii) the adipose tissue to be stored as tryglycerides [116]. After TGs release, what remains of chylomicrons is absorbed by hepatocytes to form very low-density lipoproteins (VLDLs, costituted up to 60% by TGs), to bring lipids from the liver to peripeheral tissues. TGs depletion converts VLDLs in low-density lipoproteins (LDLs), predominantly made up of cholesterol which can be brought to peripheral tissues or, thanks to the activity of high-density lipoproteins (HDLs), back to the liver for biliary acids synthesis or to steroidogenics cells for hormones production [117]. Role of HDLs in fundamental in cholesterol homeostasis since by removing excess cholesterol molecules from the periphery (including atherosclerotic plaques) can be associated to a reduction of cardiovascular risk [118, 119].

During fasting periods, in glucose shortage, FFAs represents the primary source of energy for [120]: via the mitochondrial ß-oxidation pathway, fatty acids are converted in Acetyl CoA, which enters tricarboxylic acid cycle (TCA, also know as Krebs cycle) to finally obtain NADH and $FADH_2$ molecules, used as final electron acceptor for ATP production [121]. At the same time, reduction of the ATP/ADP ratio induce phosphorilation and activation of AMPK [122], inhibiting lipogenesis by preventing expression of lipogenic genes [123], reducing hepatic lipid accumulation [124] and potentiating fatty acids oxidation via PPARα transcription factor [125].

Cholesterol and FAs are are not just introduced with the diet, but are also synthesized *de novo* in the liver starting from Acetyl CoA: sterol regulatory element binding protein (SREBP)-1a, -1c and -2 is activated in presence of low sterols levels, inducing the transciptional activation and expression of genes involved in FAs and cholesterol biosynthesis like fatty acid synthase (FAS), stearoyl-CoA desaturase (SCD1), mitochondrial glycerol-3-phosphate acyltransferase (mtGPAT),

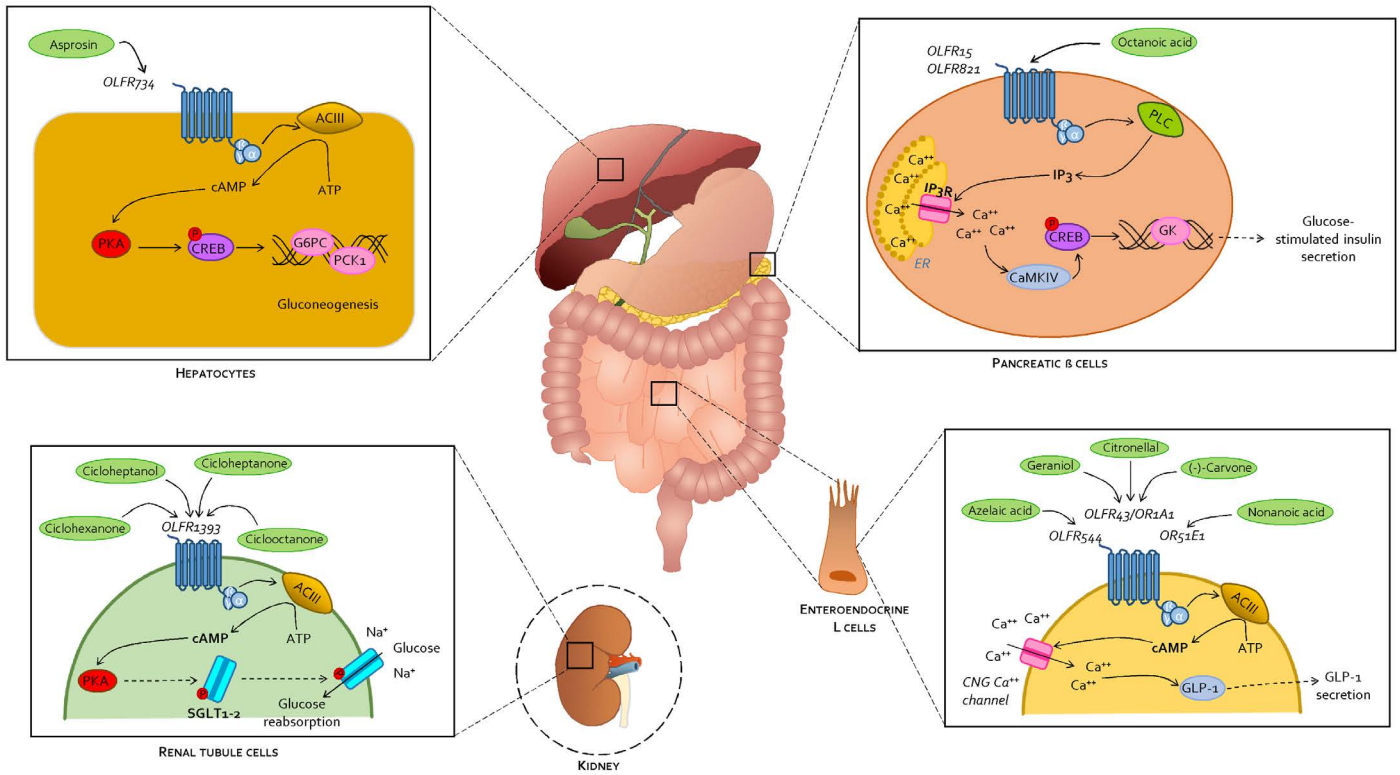


Figure 3. Modulation of glucose metabolism by ectopically expressed ORs via cAMP/CREB and PLC/IP3 pathways. In the liver, PKA-activated CREB induces the expression of G6PC and PCK1 genes, indeed promoting gluconeogenesis. In renal tubule cells, PKA seems to be involved in SGLT1-2 phosphorylation and subsequent membrane translocation, potentiating renal glucose reabsorption. In enteroendocrine L cells, cAMP acts directly on activating CNG Ca++ channels: increase intracellular Ca++ induces GLP-1 secretion. In pancreatic β-cells, IP3 binds IP3 receptors (IP3R) located on endoplasmic reticulum (ER) where intracellular Ca++ is stored, inducing their opening and cytoplasmic Ca++ increase. Ca++ activates calcium/calmodulin-dependent protein kinase IV (CaMKIV), subsequent CREB phosphorylation and activation and GK gene expression, resulting in final glucose-stimulated insulin secretion

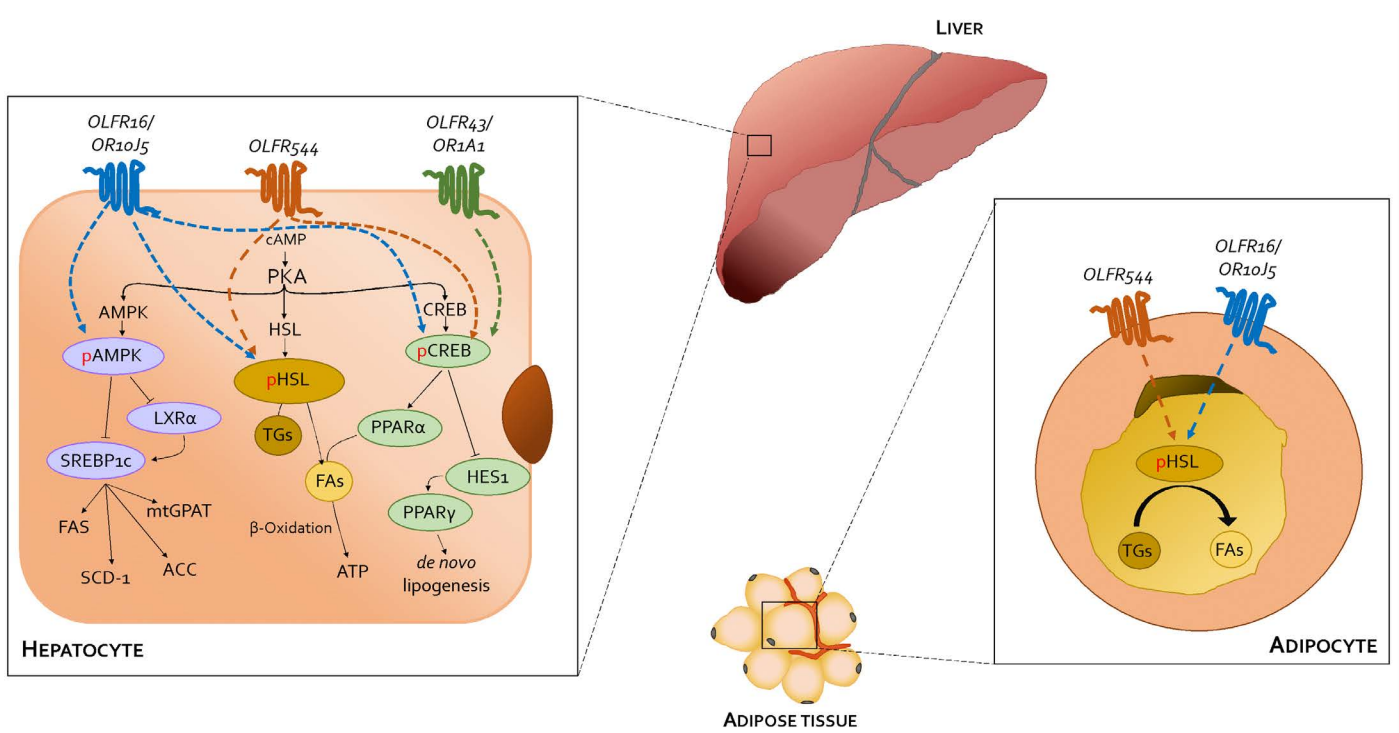


Figure 4. Modulation of lipid metabolism in hepatocytes and/or adipocytes by activation of ectopically expressed ORs through cAMP/HSL, cAMP/CREB and cAMP/AMPK pathways. In the former case, PKA phosphorylates and activates HSL, enzyme responsible for triglycerides decomposition, thus enhancing fatty acids β-oxidation. In the second case, PKA-dependent CREB phosphorylation indirectly inhibits PPARγ via HES1 inhibition thus reducing triglycerides synthesis on the one hand and inducing PPARα expression and, thus, stimulating fatty acids β-oxidation, on the other hand. In the latter case, active p-AMPK down-regulates LXRα and RXR, thus inhibiting expression of the key lipogenic transcription factor SREBP-1c and all its downstream genes, such as aP2, FAS, SCD1, ACC, and mtGPAT, finally reducing lipogenesis

acetyl-CoA carboxylase (ACC) [126], and simultaneously decreasing ß-oxidation. Alongside, high levels of glucose activate PPARγ resulting in *de novo* lipogenesis and hepatic lipid deposition [127].

ORs and NAFLD/NASH

In pathological conditions, the balance between *de novo* lipogenesis and fatty acids ß-oxidation can be altered, resulting in dyslipidemia, excessive lipid accumulation and an increase risk for atherosclerosis and cardiovascular diseases [128]. Nonalcoholic fatty liver disease (NAFLD, also known as fatty liver or hepatic steatosis) is characterized by the abnormal deposition of lipids within the hepatic tissue and represents nowadays one of the most diffuse liver diseases in developed countries, affecting about the 30% of the US population. Anomalous storage of triglycerides in hepatocytes as a result of the imbalance in lipid metabolism (increased *de novo* lipogenesis, adipose tissue lipolysis and free fatty acids uptake vs impaired lipid ß-oxidation), owing to hepatic lipotoxicity, can induce NAFLD progression and worsening in nonalcoholic steatohepatitis (NASH), marked by the onset of inflammation and fibrosis, till cirrhosis and, at worst, hepatocellular carcinoma [129,130]. Typical NAFLD patient's features are represented by IR, increased plasma triglycerides, high levels of circulating AST and ALT, abdominal obesity and fatty liver [131,132]. As seen also for T2DM, physical activity and healthy diet (with special reference to Mediterranean and ketogenic diets) are the starting point for ameliorating lipid homeostasis in NAFLD patient [133]. In addition to this, although no approved treatments are currently available for NAFLD/NASH, animal data and recent human trials seem to identify statins (e.g., atorvastatin, fluvastatin and rosuvastatin) as possible drugs to be used in NAFLD/NASH patients, giving beneficial results in terms of hyperlipidemia improvement, liver steatosis and inflammatory decrease, anti-fibrotic effect, as well as reduction for cardiovascular diseases risk and hepatocarcinoma [134-140]. Also, agonists of PPARα nuclear receptors could be used, thanks to their ability to induce mitochondrial ß-oxidation and reduce lipogenesis, finally resulting in decreased liver steatosis [127,141,142]. Liver-x-receptor α (LXRα), particularly expressed in metabolic tissues such as liver and adipocytes, is a nuclear transcriptional receptor mainly activated by cholesterol-derived endogenous ligands (e.g., oxysterols) which induces SREBP-1c and all its derived lipogenic genes expression [143]: for this reason, treatment with LXRα antagonist might be beneficial for NAFLD treatment by suppressing the activity of its target genes and alleviating lipogenesis [144-146].

During last years, several ORs have been investigated for their potential role in regulating lipid homeostasis in hepatic steatosis and lipolysis and, as a consequence, could be considered potential targets in the development of new drugs for NAFLD prevention [147]. ORs activation in hepatic and adipose tissue is linked to cAMP production and PKA activation resulting, finally, in phosphorylation and activation of three principal target proteins massively involved in lipid metabolism: hormone-sensitive lipase (HSL), cAMP response element binding protein (CREBP) and AMP-activated protein kinase (AMPK) [148] (Figure 3*)*. Each of these different pathways (i.e., cAMP/HSL, cAMP/CREB and cAMP/AMPK) can be activated by binding of various ligands to specific ORs.

Stimulation and activation of mouse OLFR16 and its human homolog OR10J5, both expressed in liver, adipose and muscular tissues, using the sesquiterpene α-cedrene (a natural odorant compound found in cedarwood essential oils [149]), resulted in modulation of lipid metabolism via all the three different pathways previously cited [65,149,150]. Indeed, ligand-receptor binding induces phosphorylation and activation of HSL, by increasing triglycerides hydrolyzation, as well as CREB activation, with subsequent decreased expression of HES-1 and PPAR-γ resulting in reduction of triglycerides, cholesterol and free fatty acids in hepatocytes [151,152]. In parallel, CREB phosphorylation induce the expression of peroxisome proliferator-activated receptor γ coactivator1-α (PGC-1α) and its downstream thermogenic genes such as UCP1, involved in thermogenesis, energy balance and control of body weight [65,153-155]. Moreover, PKA-induced p-AMPK inhibits *in-vitro* LXRα expression, leading to SREBP-1c and its target genes downregulation, such as ACC, FAS and SCD-1, and alleviates *in-vivo* hepatic steatosis in mice fed HFD [36,64]. It has already been confirmed that inactivation of both SREBP-1c and SREPB-1a phosphorylation prevents the onset of fatty liver disease in mice, avoiding FAs and cholesterol synthesis [156,157]. Moreover, even if characterized by a lower binding affinity with respect to the natural α-cedrene, the synthetic lyral derivatives also binds and activates OLFR16 and OR10J5 [158]. In addition, current studies are still ongoing to unveil the specific endogenous ligand compound that seems to be released by injured muscle tissues and involved in cell adhesion and migration [32].

Targeting OLFR544 with azelaic acid (AzA), a non-toxic dicarboxylic acid naturally found in wheat, rye and barley [159], results in similar biological effects by acting via the cAMP/HSL and cAMP/CREB pathways. Highly expressed both in liver and adipose tissue, the activated receptor participates in regulation of cell metabolism, inducing transcriptional repression of genes involved in lipogenesis. AzA was confirmed to be able to reduce and revert adiposity [39] in mice fed HFD as a consequence of (i) increased triglycerides hydrolyzation (cAMP/HSL) and (ii) PPAR-α-induced fatty acid oxidation (FAO) and ketogenesis (cAMP/CREB) [38], together with AzA ability to restore hepatic markers to values close to normal [160,161]. Despite azelaic acid results to be the strongest agonist capable of activating OLFR544, octanoic acid, sebacic acid and undecanoic acid can activate the receptor, too, even though in a milder way [162].

cAMP/CREB pathway is also triggered when (-)-Carvone, a monoterpene presents in high quantity in fennel, caraway and spearmint essential oils [163], binds and activates the mouse OLFR43 and its human homolog OR1A1, both strongly expressed in the liver [35]. *In-vitro* decrease of intracellular triglycerides levels and lipid accumulation was furthermore confirmed by *in-vivo* reduction of hepatic steatosis [61], together with reduced expression of lipogenic genes such as PPAR-γ and SCD1 [62]. Besides recognizing (-)-carvone, it has been established OR43/OR1A1 binding ability towards about 30 different compounds among esters, terpenes (e.g., citral), alcohols (e.g., nerol), aldehydes and ketones (e.g., 3-Methyl-2,4-nonanedione) [63,164] (Figure 4).

Interestingly, three new olfactory receptors (i.e., OR4C11, OR4P4 and OR4S2) have been detected in the adipose tissue and, as demonstrated in different linkage analysis, their disruption (associated to the deletion of the 11q11 region where they are mapped) leads to fat accumulation, confirming them as new risk factors for obesity [165] and corroborating the hypothesis that ORs might have a protective role against fat accumulation in hepatic and adipose tissue [166]. Another genome-wide associated study (GWAS) allowed to confirm the 11q11 region as a copy number variation region (CNVR) associated to early-onset extreme obesity, confirming reduced number of CNV of that region [167]. Anyway, further studies are needed to unveil the molecular mechanism which underlies beyond the activation of these antiobesogenic ORs.

Conclusions

T2DM and NAFLD commonly exist together in the so-called Metabolic Syndrome (MetS) [168,169]. Atherogenic dyslipidemia, abdominal obesity, hypertension and insulin resistance are typical clinical features of the MetS and represent all together a cluster of risk factors (RFs) for the development of cardiovascular diseases (CVDs) [170]. Therefore, managing to control and restore glucose and lipid metabolism back to normality is fundamental to treat symptomatology and pathophysiology of T2DM and NAFLD and solve the burden of the Metabolic Syndrome.

Already well-known in literature is the onset of olfactory impairment in diabetic and obese patients [171], unveiling the connection between olfaction (i.e., ORs), glucose and lipid metabolism. Not only: day after day, an increasing number of ectopically expressed ORs are discovered, together with their ability to take part in glucose and lipid metabolism. Thus, a deepened knowledge is required in order to understand how those ORs work on modulating glucose and lipid metabolism, what pathways they are able to trigger and what are the biological effects induced by their activation.

As previously mentioned, diverse ORs can activate different intracellular signaling pathways, leading to different biological effects; moreover, triggering the same receptor with the same ligand makes possible to activate simultaneously multiple pathways and even if the function of the large majority of them is still unclear, it has been possible to link some of them to specific pathways regulating glucose and lipid metabolism. Activation of Olfr43/OR1A1, OR51E1, Olfr15 and Olfr821 such as inhibition of Olfr734 and Olfr1393 can induce kidney hyperfiltration, renal glucose reabsorption and blood glucose levels reduction, giving relieve to diabetic patients. At the same time, triggering Olfr16/OR10J5 and Olfr43/OR1A1 while inhibiting OR4C11, OR4P4 and OR4S2 potentiate lipids breakdown and adiposity reduction, being a possible successful approach for patients affected by NAFLD. Nevertheless, *Olfr544* results to be an ambiguous target: indeed, its activation could be useful to induce triglycerides hydrolyzation but unfavorable due to the subsequent blood glucose increase.

Therefore, it is possible to infer that (i) the large majority of odorants known so far are ORs agonists both in glucose and lipid metabolism regulation and (ii) they mainly belong to two types of biological molecules, i.e., saturated fatty acids and terpenes/terpenoids, indicating those two compound classes of primary interest in the continuous search for new natural ligands.

Regrettably, only for some of the above mentioned ORs it has been possible to define an endogenous ligand (e.g., Asprosin for OLFR734) or exogenous one; indeed, the great major of them (about the 80%) are identified as "orphan receptors", that is why further and more in-depth studies are still needed to define new ORs odorants and their biological role in cell metabolism.

Moreover, the large majority of those studies have been developed by using mouse models that, despite their genetic and physiological similarities with the human species and their diffuse use for human diseases modeling [172], still may have some differences in term of tissue-specific ORs expression or different ability to trigger intracellular signaling pathways.

Finally, taking in consideration all these aspects, it is clearly affirmable an ORs' involvement in glucose and lipid metabolism. Despite that, additional studies are still needed to find out new ORs and respective odorants, as well as their possible targeting for the treatment of diseases marked by dysregulation in glucose and lipid metabolism such as T2DM and NAFLD, with the final aim to relieve hypertension, dyslipidemia, obesity, hyperglycemia and insulin resistance, typical clinical features of the Metabolic Syndrome.

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