

Review

How Smell Regulates Metabolism: The Role Of Ectopically Expressed Olfactory Receptors In Lipid and Glucose Homeostasis

Ginevra Urbani¹, Eleonora Distrutti², Michele Biagioli¹ and Silvia Marchianò¹, Stefano Fiorucci^{1*}

¹ Department of Medicine and Surgery, University of Perugia, Italy

² SC di Gastroenterologia ed Epatologia, Azienda Ospedaliera di Perugia, Perugia, Italy

* Correspondence: stefano.fiorucci@unipg.it

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 nutrients- 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.

Keywords: Olfactory receptors; glucose metabolism; type 2 diabetes mellitus; lipid metabolism; NAFLD; Metabolic Syndrome

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 (ECL1 to ECL3) and three intracellular (ICL1 to ICL3) 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 , β and γ

subunits) of GTP-binding proteins (G proteins) [4] (Fig.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].

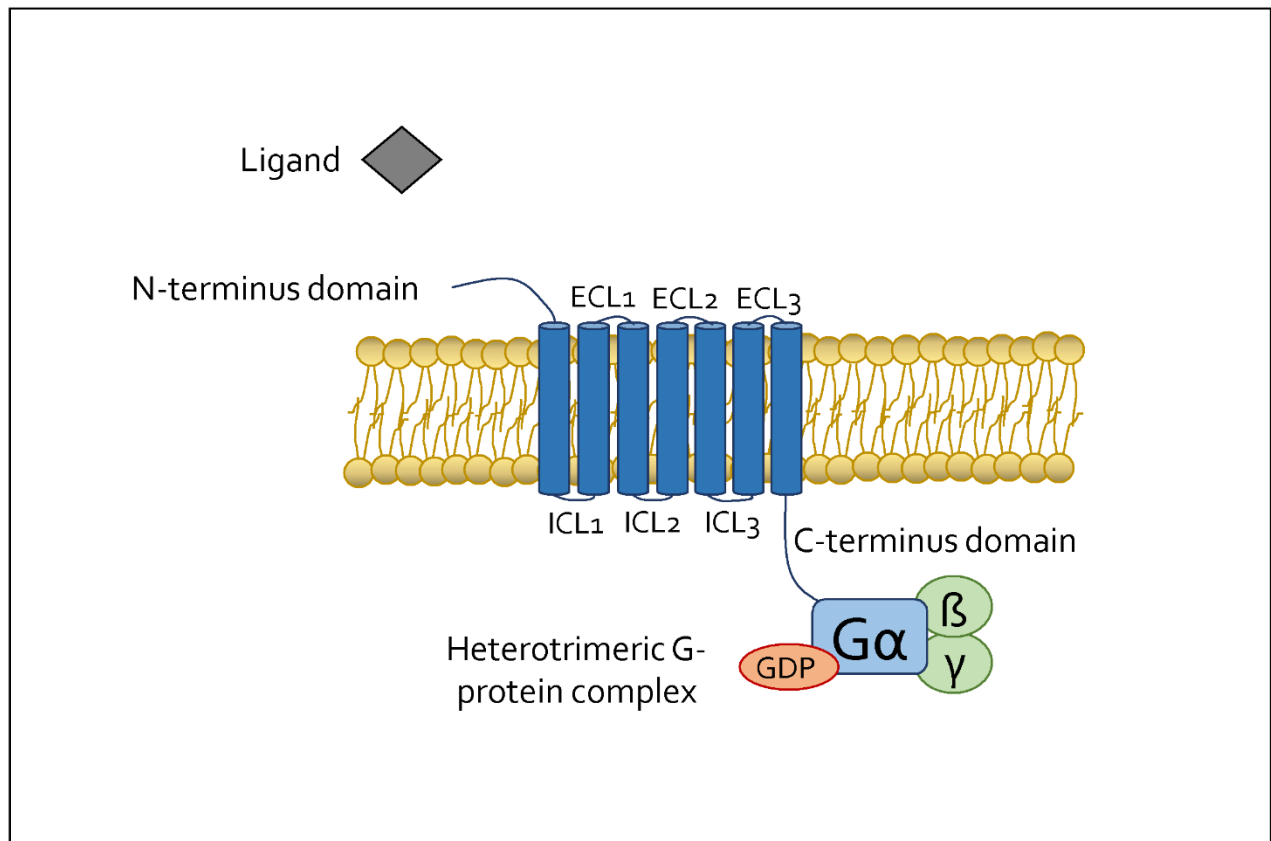


Figure 1

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 $\alpha\beta\gamma$ G-protein complex when the receptor is in its conformational inactive state (unbound ligand) and $G\alpha$ subunit binds guanosine diphosphate (GDP).

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 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 (CNS), allowing the generation of smell perception [7].

ORs are encoded by a 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, *Olf78* 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 neurotransmitter involved in gut motility and mucus secretion. These later receptors are stimulated 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).

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	OL1	Involved in cardiac morphogenesis [11]
	Human	OR5E1	Regulation of cardiac function [24]
	Mouse	MOL2.3	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	OLFR99, OLFR267, OLFR1393, OLFR1366, OLFR691, OLFR558, OLFR57, OLFR646, OLFR78, OLFR15, OLFR177 OLFR544, OLFR43, OLFR16 OLFR734	Involvement in hepatic physiology [16] Regulation of lipid metabolism (see below) Gluconeogenesis induction [34]
		OR10J5, OR1A1	
	Human		Regulation of lipid metabolism (see below)
	Human	OR1A1, OR10J5	Involved in triglycerides synthesis [35], [36]
HepG2	Human	OR1A2	Inhibition of cell proliferation [37]
Huh7	Human	OR1A2	Inhibition of cell proliferation [37]
3T3-L1	Mouse	OLFR544	Triglycerides hydrolyzation [38]
Adipose tissue	Mouse	OLFR544, OLFR16 OLFR788	Antiobesogenic effect [36], [38] and brown adipose tissue (BAT) thermogenesis [39] Antiobesogenic effect [165]
	Rat	OLR984	Antiobesogenic effect [165]
	Human	OR6C3, OR4C11, OR4C6, OR4P4, OR4S2	Antiobesogenic effect [165] - [167]
	Mouse	OLFR78 OLFR90, OLFR 1373, OLFR1372 OLFR1393	Involved in renin secretion and blood pression regulation [14] Not yet defined [13] Glucose reabsorption [40] Not yet defined [41]

	Human	OLFR ₃₁ , OLFR ₉₉ , OLFR ₅₄₅ , OLFR ₆₉₁ , OLFR ₆₉₃ , OLFR ₁₄₂₆	Not yet identified [41]
		OR _{2T1}	
GI tract	Mouse	PSGR OLFR ₅₄₄ , OLFR ₄₃	Not yet defined [33] Glucose metabolism (GLP-1 and glucagon secretion) [42]
	Human	OR ₇₃ , hOR _{17-7/11} , OR _{1G1} , hOR ₁₇₋₂₁₀ OR _{51E1} , OR _{1A1}	Involved in serotonin secretion [15] Glucose metabolism (GLP-1 and glucagon secretion) [43]
Placenta	Rat	MOR ₁₂₅₋₁ , MOR ₁₂₆₋₁ , MOR ₁₄₀₋₁ , MOR ₁₄₅₋₅ , MOR ₂₁₆₋₁ , MOR ₂₆₃₋₉ OR _{2C1} , OR _{4D6} , OR _{2M7} , OR _{10A6} ,	Environmental signaling in fetus-mother interaction [12]
	Human	OR _{4F3} , OR _{8A1} , OR _{2W3} , OR ₁₋₁	Environmental signaling in fetus-mother interaction [12]
HeLa	Human	OR _{2A4}	Regulation of actin cytoskeleton cytokinesis [44]
Brain (and CNS in general)	Rat, mouse	PSGR MOR _{2.3} , M ₇₁ , C ₆ , OR ₃	Not yet defined [33] Possible involvement in developmental processes such as axon guidance [25], [45]
	Mouse	OLFR _{110/111} , OLFR ₅₄₄	Brain physiology [46]
	Human	OR _{2L13} , OR _{1E1} , OR _{2J3} , OR _{52L1} , OR _{11H1} OR _{2H2} , OR _{2A4} , OR _{6K3}	Cerebral cortex physiology [47]
			Not yet defined [48]
Lung	Human	OR _{51E2} OR _{1D2} , OR _{2AG1}	Modulation of airway smooth muscle (ASM) cells proliferation [49] Regulation of pathophysiological processes [50]

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/IP₃ 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 G α subunit level [51]. In the AC/cAMP pathway, mainly regulating lipid metabolism, the G α subunit dissociates from $\beta\gamma$ heterodimer and diffuses along the inner membrane surface towards the effector protein adenylyl cyclase (AC), 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 Ca^{++} concentrations. In the PLC/ IP_3 pathway, mostly involving, on the other hand, glucose metabolism, GTP- $\text{G}\alpha$ subunit activates the effector protein Phospholipase C (PLC) which in turns hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) – a constituent of the plasmatic membrane – in inositol 1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG), critical second messengers responsible for intracellular Ca^{++} signaling regulation [53] (Fig.2).

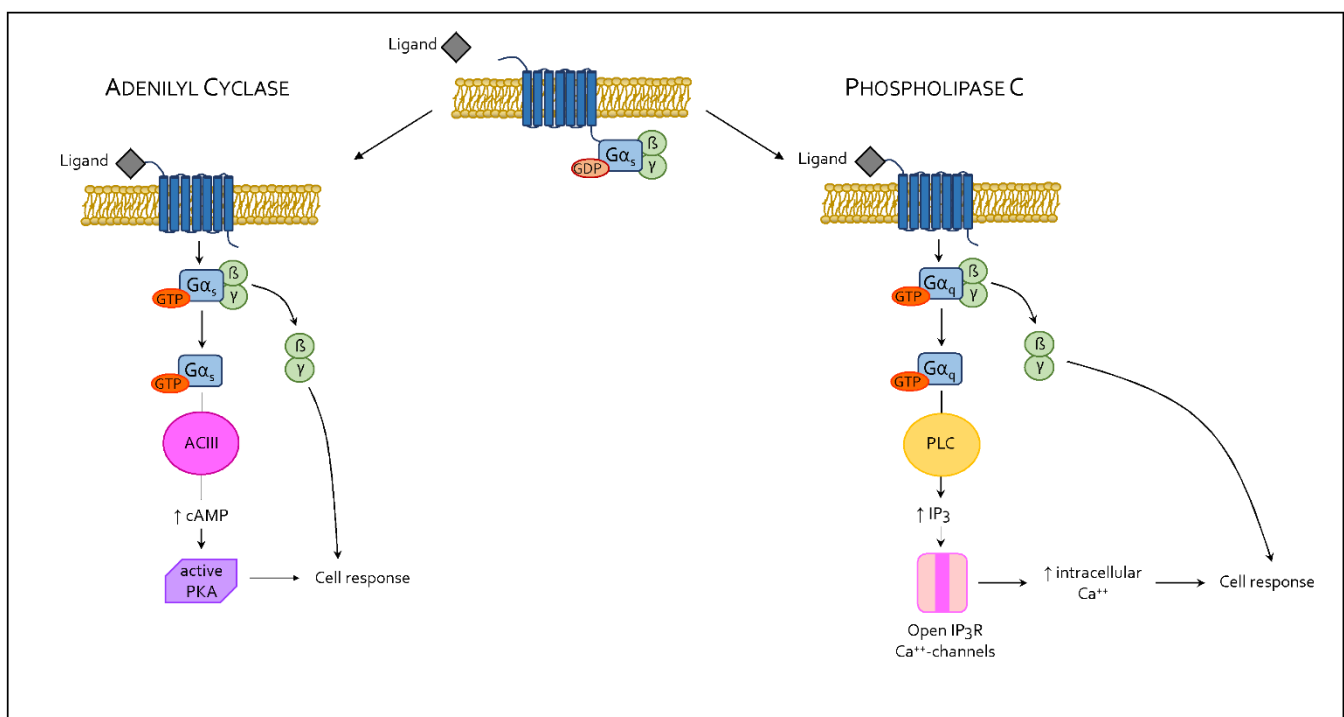


Figure 2

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 $\text{G}\alpha_s$ subunit, its activation and dissociation from the $\alpha\beta\gamma$ heterotrimer and migration to ACIII. Active ACIII produces cAMP which activates PKA, resulting in phosphorylation and activation of different target proteins. In PLC/ IP_3 GPCR, ligand binding provokes conformational changes in the receptor, inducing a GDP/GTP exchange on $\text{G}\alpha_q$ subunit, its activation and dissociation from the $\alpha\beta\gamma$ heterotrimer and migration to PLC. Active PLC produces DAG and IP_3 from PIP_2 hydrolysis. IP_3 in turns activates IP_3 sensitive

Ca⁺⁺ channels present on endoplasmic reticulum (ER) membranes where Ca⁺⁺ is stored, thus increasing intracellular Ca⁺⁺ levels.

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 βγ and with the GPCR, bringing back the receptor to its inactive state.

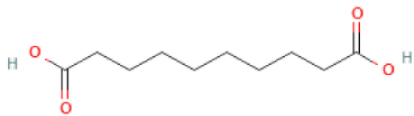
2. Ectopically expressed ORs play a role in glucose and lipid metabolism

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 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).

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

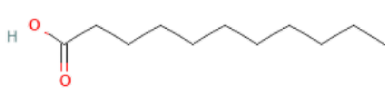
OR	Odorant(s)/ligand(s)	Pathway(s)	Main function(s)
OLFR544	Azelaic acid	cAMP/Ca ⁺⁺	Ca ⁺⁺ -dependent glucagon secretion [42]
	Azelaic acid		
	Octanoic acid	cAMP/HSL and	HSL-induced triglycerides breakdown [38]

Sebacic acid



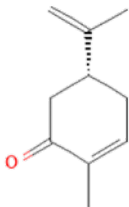
cAMP/CREB
PPARα-induced FAO and inhibition of triglycerides synthesis via HES-1 repression [38]

Undecanoic acid

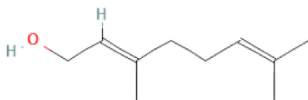


OR1A1/OLFR43

(-)-Carvone

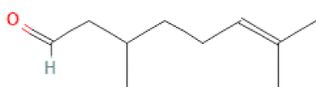


Geraniol

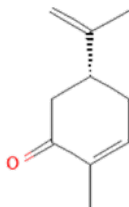


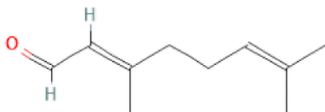
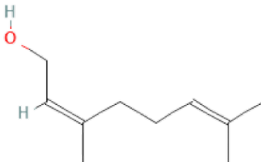
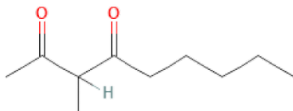
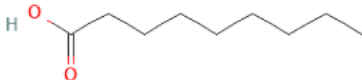
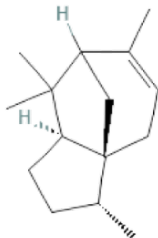
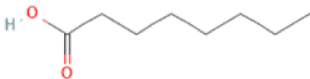
cAMP/Ca++
GLP-1 and Ca++-dependent glucagon secretion [59], [60]

Citronellal



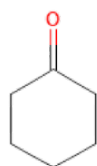
(-)-Carvone



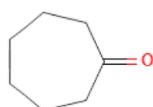
	<div>Citral</div> <div></div>	cAMP/CREB	PPARα-induced FAO and inhibition of triglycerides synthesis via HES-1 repression [35], [61]–[63]
	<div>Nerol</div> <div></div>		
	<div>3-Methyl-2,4-nonanedione</div> <div></div>		
OR51E1	<div>Nonanoic acid</div> <div></div>	cAMP/Ca++	Ca++-dependent GLP-1 secretion [43]
OR10J5/OLFR16		cAMP-CREB	PPARα-induced FAO and inhibition of triglycerides synthesis via HES-1 repression, hepatic steatosis improvement [36], [64], [65]
	<div>α-cedrene</div> <div></div>	cAMP-HSL	HSL-induced triglycerides breakdown, hepatic steatosis improvement [36], [64]
		cAMP-AMPK	LXRα and SREBP-1c repression, inhibition of lipogenic genes (ACC, FAS, SCD-1, hepatic steatosis improvement [36], [64], [65]
OLFR15, OLFR821	<div>Octanoic acid</div> <div></div>	PLC/IP3	Increased expression of GK, potentiation of glucose absorption and GSIS [27], [28]
OLFR734	<div>Asprosin (endogenous)</div>	cAMP/CREB	Increased expression of G6PC and PCK1, gluconeogenesis stimulation [34]

OLFR1393

Cyclohexanone



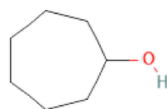
Cycloheptanone



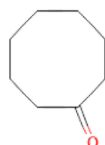
cAMP-?

Glucose reabsorption at renal tubules
level via increasing expression of
SGLT1 and SGLT2 [40]

Cycloheptanol



Cyclooctanone



2.1 ORs in glucose homeostasis

2.1.1 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 β - 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) breakdown of the previously stored glycogen (glycogenolysis) and, (iii) *de novo* glucose synthesis (gluconeogenesis) [76]–[78].

2.1.2 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 β -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. *Olf43* (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 lithocholic acid (LCA) and deoxycholic acid (DCA), generated from the intestinal microbiota [90]. These array of receptors are mostly known for their ability to sense microbial product, and, in addition to ORs provide an intricate network of chemical signaling that integrate nutrients, intestinal microbiota and host metabolism and immune system, that could be exploited for therapeutic purposes [91]–[93].

To further highlight these interactions, *Olfr15* and *Olfr821*, detected in β -pancreatic islets and β -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/IP₃ pathway, inducing glucokinase (GK) expression and potentiating glucose absorption and glucose-stimulated insulin 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: in fact, 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 hyperphosphorylation guided by insulin via PKA and PKC [98], [99]. Conversely, SGLT2 genetic mutations and/or deletions have been associated to familial renal glycosuria (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 *Olf1393* thus preventing SGLT2 expression offers novel therapeutic possibilities in this setting. *Olf134*, that is expressed by hepatocytes, is activated by asprosin, an endogenous fasting-induced hormone produced by adipose tissues [106], that in its turn increases 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 hypothalamic level [34]. The expression of *Olf1543*, *Olf1544*, *Olf1545* and *Olf1349* has been detected also in the pancreatic α -cells, but only the stimulation of *Olf1544* by azelaic acid results in Ca^{++} -dependant glucagon secretion [42] (Fig.2).

2.2 ORs and lipid metabolism

2.2.1 Lipid homeostasis

Lipids are an heterogeneous 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 biosynthesis of hormones such as progesterone, aldosterone, cortisol and testosterone, other than be a fundamental constituent 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 intestinal 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 triglycerides [116]. After TGs release, what remains of chylomicrons is absorbed by hepatocytes to form very low-density lipoproteins (VLDLs, constituted up to 60% by TGs), to bring lipids from the liver to peripheral 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 steroidogenesis cells for hormones production [117]. Role of HDLs is 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 represent the primary source of energy for [120]: via the mitochondrial β -oxidation pathway, fatty acids are converted in Acetyl CoA, which enters tricarboxylic acid cycle (TCA, also known as Krebs cycle) to finally obtain NADH and FADH₂ molecules, used as final electron acceptor for ATP production [121]. At the same time, reduction of the ATP/ADP ratio induces phosphorylation 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 PPAR α transcription factor [125].

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

2.2.2 ORs and NAFLD/NASH

In pathological conditions, the balance between *de novo* lipogenesis and fatty acids β -oxidation can be altered, resulting in dyslipidemia, excessive lipid accumulation and an increased 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 β -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 PPAR α nuclear receptors could be used, thanks to their ability to induce mitochondrial β -oxidation and reduce lipogenesis, finally resulting in decreased liver steatosis [127], [141], [142]. Liver-x-receptor α (LXR α), 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 LXR α 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] (*Fig.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.

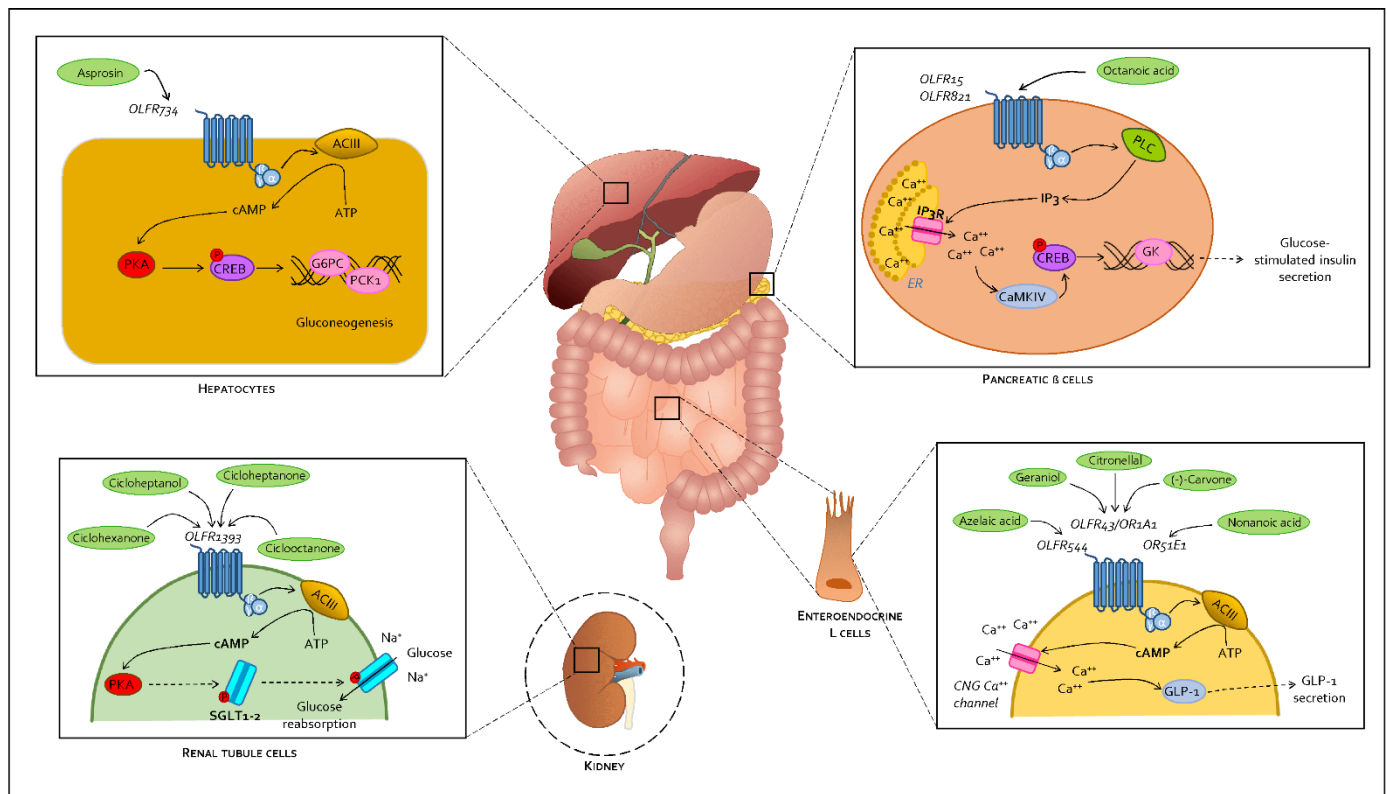


Figure 3

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.

Stimulation and activation of mouse OLF16 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], [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-1 α) 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* LXR α 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 SREBP-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 lylal 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 present 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].

Interestingly, three new olfactory receptors (i.e., OR_{4C11}, OR_{4P4} and OR_{4S2}) 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 (fig 4).

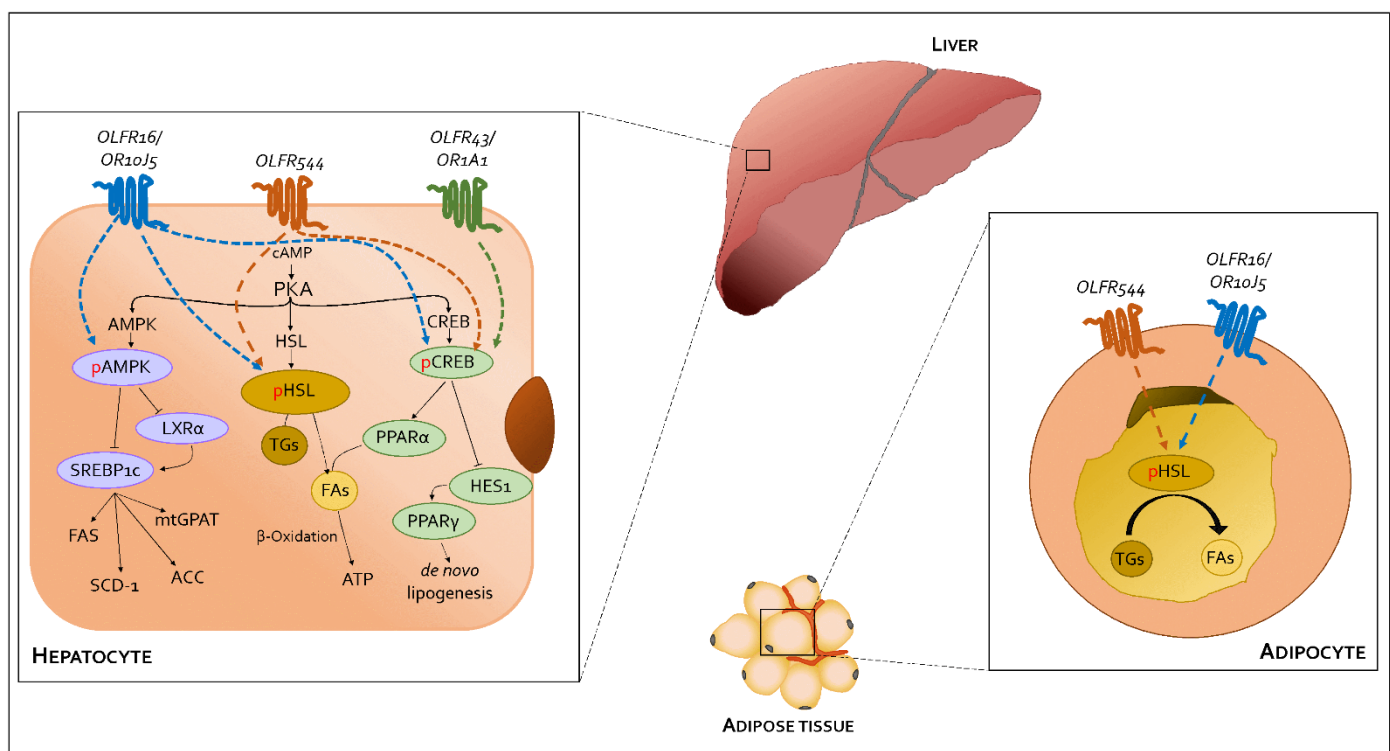


Figure 4

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 PPAR γ via HES1 inhibition thus reducing triglycerides synthesis on the one hand and inducing PPAR α expression and, thus, stimulating fatty acids β -oxidation, on the other hand. In the latter case, active p-AMPK down-

regulates LXR α 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.

3. 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.

Table of abbreviations

Abbreviation	Complete name
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
C subunit	Catalytic subunit

Ca ⁺⁺	Calcium
CAC channel	Calcium activated chloride channel
CaMKIV	Calcium /calmodulin-dependent protein kinase IV
cAMP	Cycling adenosine monophosphate
CNG channel	Cyclic nucleotide gated channel
CNS	Central nervous system
CNVR	Copy number variation region
CREBP	cAMP response element binding protein
CVDs	Cardiovascular diseases
DAG	1,2-diacylglycerol
ECL	Extracellular loop
ER	Endoplasmic reticulum
FAO	Fatty acids oxidation
FAS	Fatty acid synthase
G protein	GTP-binding protein
G6PC	Glucose-6-phosphatase
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
ICL	Intracellular loop
IP ₃	Inositol 1,4,5-triphosphate
IP ₃ R	Inositol 1,4,5-triphosphate receptor
IR	Insulin resistance
LXR α	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
PCK ₁	Phospho-enolpyruvate carboxykinase
PGC-1 α	Peroxisome proliferator-activated receptor γ coactivator 1 α
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
R subunit	Regulatory subunit
RF	Risk factor
SCD ₁	Stearoyl-CoA desaturase 1

SCFA	Short-chain fatty acid
SGLT	Sodium-glucose transporter
SREBP-1a	Sterol regulatory element-binding protein 1a
SREBP-1c	Sterol regulatory element-binding protein 1c
T2DM	Type 2 diabetes mellitus
TCA	Tricarboxylic acid
TM	Transmembrane
UCP1	Uncoupling protein 1

References

[1] L. Buck and R. Axel, "A novel multigene family may encode odorant receptors: a molecular basis for odor recognition.," *Cell*, vol. 65, no. 1, pp. 175–187, Apr. 1991, doi: 10.1016/0092-8674(91)90418-x.

[2] A. Sharma, R. Kumar, I. Aier, R. Semwal, P. Tyagi, and P. Varadwaj, "Sense of Smell: Structural, Functional, Mechanistic Advancements and Challenges in Human Olfactory Research.," *Curr. Neuroparmacol.*, vol. 17, no. 9, pp. 891–911, 2019, doi: 10.2174/1570159X17666181206095626.

[3] L. B. Buck, "The olfactory multigene family.," *Curr. Opin. Genet. Dev.*, vol. 2, no. 3, pp. 467–473, Jun. 1992, doi: 10.1016/s0959-437x(05)80159-5.

[4] S. M. de Munnik, M. J. Smit, R. Leurs, and H. F. Vischer, "Modulation of cellular signaling by herpesvirus-encoded G protein-coupled receptors.," *Front. Pharmacol.*, vol. 6, p. 40, 2015, doi: 10.3389/fphar.2015.00040.

[5] M. Beigi and A. Zell, "A Novel Method for Classifying Subfamilies and Sub-subfamilies of G-Protein Coupled Receptors BT - Biological and Medical Data Analysis," 2006, pp. 25–36.

[6] G. L. Bowman, "Biomarkers for early detection of Parkinson disease: A scent of consistency with olfactory dysfunction.," *Neurology*, vol. 89, no. 14. United States, pp. 1432–1434, Oct. 2017. doi: 10.1212/WNL.0000000000004383.

[7] N. Kang and J. Koo, "Olfactory receptors in non-chemosensory tissues.," *BMB Rep.*, vol. 45, no. 11, pp. 612–622, Nov. 2012, doi: 10.5483/bmbrep.2012.45.11.232.

[8] B. Malnic, P. A. Godfrey, and L. B. Buck, "The human olfactory receptor gene family," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 101, no. 8, pp. 2584 LP – 2589, Feb. 2004, doi: 10.1073/pnas.0307882100.

[9] D. Maßberg and H. Hatt, "Human Olfactory Receptors: Novel Cellular Functions Outside of the Nose.," *Physiol. Rev.*, vol. 98, no. 3, pp. 1739–1763, Jul. 2018, doi: 10.1152/physrev.00013.2017.

[10] M. Parmentier *et al.*, "Expression of members of the putative olfactory receptor gene family in mammalian germ cells.," *Nature*, vol. 355, no. 6359, pp. 453–455, Jan. 1992, doi: 10.1038/355453ao.

[11] G. Drutel, J. M. Arrang, J. Diaz, C. Wisnewsky, K. Schwartz, and J. C. Schwartz, "Cloning of OL1, a putative olfactory receptor and its expression in the developing rat heart.," *Receptors Channels*, vol. 3, no. 1, pp. 33–40, 1995.

[12] S. Itakura, K. Ohno, T. Ueki, K. Sato, and N. Kanayama, "Expression of Golf in the rat placenta: Possible implication in olfactory receptor transduction.," *Placenta*, vol. 27, no. 1, pp. 103–108, Jan.

- 2006, doi: 10.1016/j.placenta.2004.12.006.
- [13] J. L. Pluznick *et al.*, "Functional expression of the olfactory signaling system in the kidney.," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 106, no. 6, pp. 2059–2064, Feb. 2009, doi: 10.1073/pnas.0812859106.
- [14] J. L. Pluznick *et al.*, "Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation.," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 110, no. 11, pp. 4410–4415, Mar. 2013, doi: 10.1073/pnas.1215927110.
- [15] T. Braun, P. Volland, L. Kunz, C. Prinz, and M. Gratzl, "Enterochromaffin cells of the human gut: sensors for spices and odorants.," *Gastroenterology*, vol. 132, no. 5, pp. 1890–1901, May 2007, doi: 10.1053/j.gastro.2007.02.036.
- [16] R. Kurtz, L. G. Steinberg, M. Betcher, D. Fowler, and B. D. Shepard, "The Sensing Liver: Localization and Ligands for Hepatic Murine Olfactory and Taste Receptors.," *Front. Physiol.*, vol. 11, p. 574082, 2020, doi: 10.3389/fphys.2020.574082.
- [17] T. Tong, Y. Wang, S.-G. Kang, and K. Huang, "Ectopic Odorant Receptor Responding to Flavor Compounds: Versatile Roles in Health and Disease.," *Pharmaceutics*, vol. 13, no. 8, 2021, doi: 10.3390/pharmaceutics13081314.
- [18] M. Spehr *et al.*, "Identification of a testicular odorant receptor mediating human sperm chemotaxis.," *Science*, vol. 299, no. 5615, pp. 2054–2058, Mar. 2003, doi: 10.1126/science.1080376.
- [19] C. Flegel *et al.*, "Characterization of the Olfactory Receptors Expressed in Human Spermatozoa.," *Front. Mol. Biosci.*, vol. 2, 2016, doi: 10.3389/fmolb.2015.00073.
- [20] N. Fukuda and K. Touhara, "Developmental expression patterns of testicular olfactory receptor genes during mouse spermatogenesis.," *Genes Cells*, vol. 11, no. 1, pp. 71–81, Jan. 2006, doi: 10.1111/j.1365-2443.2005.00915.x.
- [21] N. Fukuda, K. Yomogida, M. Okabe, and K. Touhara, "Functional characterization of a mouse testicular olfactory receptor and its role in chemosensing and in regulation of sperm motility.," *J. Cell Sci.*, vol. 117, no. Pt 24, pp. 5835–5845, Nov. 2004, doi: 10.1242/jcs.01507.
- [22] J.-C. Gaudin, L. Breuils, and T. Haertlé, "New GPCRs from a Human Lingual cDNA Library.," *Chem. Senses*, vol. 26, no. 9, pp. 1157–1166, 2001, doi: 10.1093/chemse/26.9.1157.
- [23] L. Durzyński, J.-C. Gaudin, M. Myga, J. Szydlowski, A. Goździcka-Józefiak, and T. Haertlé, "Olfactory-like receptor cDNAs are present in human lingual cDNA libraries.," *Biochem. Biophys. Res. Commun.*, vol. 333, no. 1, pp. 264–272, Jul. 2005, doi: 10.1016/j.bbrc.2005.05.085.
- [24] N. Jovancevic *et al.*, "Medium-chain fatty acids modulate myocardial function via a cardiac odorant receptor.," *Basic Res. Cardiol.*, vol. 112, no. 2, p. 13, 2017, doi: 10.1007/s00395-017-0600-y.
- [25] M. Weber, U. Pehl, H. Breer, and J. Strotmann, "Olfactory receptor expressed in ganglia of the autonomic nervous system.," *J. Neurosci. Res.*, vol. 68, no. 2, pp. 176–184, Apr. 2002, doi: 10.1002/jnr.10164.
- [26] P. Blache, L. Gros, G. Salazar, and D. Bataille, "Cloning and tissue distribution of a new rat olfactory receptor-like (OL2).," *Biochem. Biophys. Res. Commun.*, vol. 242, no. 3, pp. 669–672, Jan. 1998, doi: 10.1006/bbrc.1997.8041.
- [27] J. Leem, H.-M. Shim, H. Cho, and J.-H. Park, "Octanoic acid potentiates glucose-stimulated insulin secretion and expression of glucokinase through the olfactory receptor in pancreatic β -cells.," *Biochem. Biophys. Res. Commun.*, vol. 503, no. 1, pp. 278–284, Sep. 2018, doi: 10.1016/j.bbrc.2018.06.015.

- [28] Y. Munakata *et al.*, "Olfactory receptors are expressed in pancreatic β -cells and promote glucose-stimulated insulin secretion," *Sci. Rep.*, vol. 8, no. 1, p. 1499, 2018, doi: 10.1038/s41598-018-19765-5.
- [29] E. A. Feingold, L. A. Penny, A. W. Nienhuis, and B. G. Forget, "An olfactory receptor gene is located in the extended human beta-globin gene cluster and is expressed in erythroid cells," *Genomics*, vol. 61, no. 1, pp. 15–23, Oct. 1999, doi: 10.1006/geno.1999.5935.
- [30] L. L. Xu *et al.*, "PSGR, a novel prostate-specific gene with homology to a G protein-coupled receptor, is overexpressed in prostate cancer," *Cancer Res.*, vol. 60, no. 23, pp. 6568–6572, Dec. 2000.
- [31] E. M. Neuhaus, W. Zhang, L. Gelis, Y. Deng, J. Noldus, and H. Hatt, "Activation of an olfactory receptor inhibits proliferation of prostate cancer cells," *J. Biol. Chem.*, vol. 284, no. 24, pp. 16218–16225, Jun. 2009, doi: 10.1074/jbc.M109.012096.
- [32] C. A. Griffin, K. A. Kafadar, and G. K. Pavlath, "MOR23 promotes muscle regeneration and regulates cell adhesion and migration," *Dev. Cell*, vol. 17, no. 5, pp. 649–661, Nov. 2009, doi: 10.1016/j.devcel.2009.09.004.
- [33] T. T. Yuan, P. Toy, J. A. McClary, R. J. Lin, N. G. Miyamoto, and P. J. Kretschmer, "Cloning and genetic characterization of an evolutionarily conserved human olfactory receptor that is differentially expressed across species," *Gene*, vol. 278, no. 1–2, pp. 41–51, Oct. 2001, doi: 10.1016/S0378-1119(01)00709-0.
- [34] E. Li *et al.*, "OLFR734 Mediates Glucose Metabolism as a Receptor of Asprosin," *Cell Metab.*, vol. 30, no. 2, pp. 319–328.e8, Aug. 2019, doi: 10.1016/j.cmet.2019.05.022.
- [35] C. Wu *et al.*, "Activation of OR1A1 suppresses PPAR- γ expression by inducing HES-1 in cultured hepatocytes," *Int. J. Biochem. Cell Biol.*, vol. 64, pp. 75–80, Jul. 2015, doi: 10.1016/j.biocel.2015.03.008.
- [36] T. Tong *et al.*, "Olfactory receptor 10J5 responding to α -cedrene regulates hepatic steatosis via the cAMP–PKA pathway," *Sci. Rep.*, vol. 7, no. 1, p. 9471, 2017, doi: 10.1038/s41598-017-10379-x.
- [37] D. Maßberg *et al.*, "Monoterpene (-)-citronellal affects hepatocarcinoma cell signaling via an olfactory receptor," *Arch. Biochem. Biophys.*, vol. 566, pp. 100–109, 2015.
- [38] C. Wu *et al.*, "Olfactory receptor 544 reduces adiposity by steering fuel preference toward fats," *J. Clin. Invest.*, vol. 127, no. 11, pp. 4118–4123, Nov. 2017, doi: 10.1172/JCI89344.
- [39] S. Crunkhorn, "Ectopic olfactory receptor activation reverses obesity," *Nat. Rev. Drug Discov.*, vol. 16, no. 12, pp. 826–827, 2017, doi: 10.1038/nrd.2017.230.
- [40] B. D. Shepard *et al.*, "A Renal Olfactory Receptor Aids in Kidney Glucose Handling," *Sci. Rep.*, vol. 6, no. 1, p. 35215, 2016, doi: 10.1038/srep35215.
- [41] P. Rajkumar, W. H. Aisenberg, O. W. Acres, R. J. Protzko, and J. L. Pluznick, "Identification and characterization of novel renal sensory receptors," *PLoS One*, vol. 9, no. 10, p. e111053, 2014, doi: 10.1371/journal.pone.0111053.
- [42] N. Kang *et al.*, "Olfactory receptor Olfr544 responding to azelaic acid regulates glucagon secretion in α -cells of mouse pancreatic islets," *Biochem. Biophys. Res. Commun.*, vol. 460, no. 3, pp. 616–621, May 2015, doi: 10.1016/j.bbrc.2015.03.078.
- [43] Y. E. Han *et al.*, "Olfactory Receptor OR51E1 Mediates GLP-1 Secretion in Human and Rodent Enteroendocrine L Cells," *J. Endocr. Soc.*, vol. 2, no. 11, pp. 1251–1258, Nov. 2018, doi: 10.1210/je.2018-00165.
- [44] X. Zhang, A. V Bedigian, W. Wang, and U. S. Eggert, "G protein-coupled receptors participate in cytokinesis," *Cytoskeleton (Hoboken)*, vol. 69, no. 10, pp. 810–818, Oct. 2012, doi: 10.1002/cm.21055.

-
- [45] J. M. Otaki, H. Yamamoto, and S. Firestein, "Odorant receptor expression in the mouse cerebral cortex.," *J. Neurobiol.*, vol. 58, no. 3, pp. 315–327, Feb. 2004, doi: 10.1002/neu.10272.
- [46] F. Gaudel, D. Stephan, V. Landel, G. Sicard, F. Féron, and G. Guiraudie-Capraz, "Expression of the Cerebral Olfactory Receptors Olfr110/111 and Olfr544 Is Altered During Aging and in Alzheimer's Disease-Like Mice.," *Mol. Neurobiol.*, vol. 56, no. 3, pp. 2057–2072, Mar. 2019, doi: 10.1007/s12035-018-1196-4.
- [47] P. Garcia-Esparcia *et al.*, "Functional Genomics Reveals Dysregulation of Cortical Olfactory Receptors in Parkinson Disease: Novel Putative Chemoreceptors in the Human Brain," *J. Neuropathol. Exp. Neurol.*, vol. 72, no. 6, pp. 524–539, 2013, doi: 10.1097/NEN.ob013e318294fd76.
- [48] I. Ferrer *et al.*, "Olfactory Receptors in Non-Chemosensory Organs: The Nervous System in Health and Disease.," *Front. Aging Neurosci.*, vol. 8, p. 163, 2016, doi: 10.3389/fnagi.2016.00163.
- [49] W. H. Aisenberg *et al.*, "Defining an olfactory receptor function in airway smooth muscle cells.," *Sci. Rep.*, vol. 6, p. 38231, Dec. 2016, doi: 10.1038/srep38231.
- [50] B. Kalbe *et al.*, "Olfactory Receptors Modulate Physiological Processes in Human Airway Smooth Muscle Cells.," *Front. Physiol.*, vol. 7, p. 339, 2016, doi: 10.3389/fphys.2016.00339.
- [51] M. J. Marinissen and J. S. Gutkind, "G-protein-coupled receptors and signaling networks: emerging paradigms.," *Trends Pharmacol. Sci.*, vol. 22, no. 7, pp. 368–376, Jul. 2001, doi: 10.1016/s0165-6147(00)01678-3.
- [52] P. Sassone-Corsi, "The cyclic AMP pathway.," *Cold Spring Harb. Perspect. Biol.*, vol. 4, no. 12, Dec. 2012, doi: 10.1101/cshperspect.a011148.
- [53] F. Sekiya, "Phospholipase C," W. J. Lennarz and M. D. B. T.-E. of B. C. (Second E. Lane, Eds. Waltham: Academic Press, 2013, pp. 467–471. doi: <https://doi.org/10.1016/B978-0-12-378630-2.00346-7>.
- [54] K. Ravnskjaer, A. Madiraju, and M. Montminy, "Role of the cAMP Pathway in Glucose and Lipid Metabolism.," *Handb. Exp. Pharmacol.*, vol. 233, pp. 29–49, 2016, doi: 10.1007/164_2015_32.
- [55] R. H. Eckel, S. M. Grundy, and P. Z. Zimmet, "The metabolic syndrome," *Lancet*, vol. 365, no. 9468, pp. 1415–1428, 2005, doi: [https://doi.org/10.1016/S0140-6736\(05\)66378-7](https://doi.org/10.1016/S0140-6736(05)66378-7).
- [56] M. G. Saklayen, "The Global Epidemic of the Metabolic Syndrome.," *Curr. Hypertens. Rep.*, vol. 20, no. 2, p. 12, Feb. 2018, doi: 10.1007/s11906-018-0812-z.
- [57] S. L. Samson and A. J. Garber, "Metabolic syndrome.," *Endocrinol. Metab. Clin. North Am.*, vol. 43, no. 1, pp. 1–23, Mar. 2014, doi: 10.1016/j.ecl.2013.09.009.
- [58] A. Lonardo, S. Ballestri, G. Marchesini, P. Angulo, and P. Loria, "Nonalcoholic fatty liver disease: a precursor of the metabolic syndrome.," *Dig. liver Dis. Off. J. Ital. Soc. Gastroenterol. Ital. Assoc. Study Liver*, vol. 47, no. 3, pp. 181–190, Mar. 2015, doi: 10.1016/j.dld.2014.09.020.
- [59] K.-S. Kim *et al.*, "Activation of intestinal olfactory receptor stimulates glucagon-like peptide-1 secretion in enteroendocrine cells and attenuates hyperglycemia in type 2 diabetic mice.," *Sci. Rep.*, vol. 7, no. 1, p. 13978, 2017, doi: 10.1038/s41598-017-14086-5.
- [60] B. Jones, S. R. Bloom, T. Buenaventura, A. Tomas, and G. A. Rutter, "Control of insulin secretion by GLP-1.," *Peptides*, vol. 100, pp. 75–84, Feb. 2018, doi: 10.1016/j.peptides.2017.12.013.
- [61] C. Wu, T. T. Thach, Y.-J. Kim, and S.-J. Lee, "Olfactory receptor 43 reduces hepatic lipid accumulation and adiposity in mice.," *Biochim. Biophys. acta. Mol. cell Biol. lipids*, vol. 1864, no. 4, pp. 489–499, Apr. 2019, doi: 10.1016/j.bbali.2019.01.004.
- [62] S. Alsanea and D. Liu, "BITC and S-Carvone Restrain High-Fat Diet-Induced Obesity and Ameliorate

- Hepatic Steatosis and Insulin Resistance.," *Pharm. Res.*, vol. 34, no. 11, pp. 2241–2249, Nov. 2017, doi: 10.1007/s11095-017-2230-3.
- [63] C. Geithe, F. Noe, J. Kreissl, and D. Krautwurst, "The Broadly Tuned Odorant Receptor OR1A1 is Highly Selective for 3-Methyl-2,4-nonanedione, a Key Food Odorant in Aged Wines, Tea, and Other Foods.," *Chem. Senses*, vol. 42, no. 3, pp. 181–193, Mar. 2017, doi: 10.1093/chemse/bjw117.
- [64] T. Tong, R. Yu, and T. Park, "α-Cedrene protects rodents from high-fat diet-induced adiposity via adenylyl cyclase 3.," *Int. J. Obes. (Lond.)*, vol. 43, no. 1, pp. 202–216, Jan. 2019, doi: 10.1038/s41366-018-0176-0.
- [65] T. Tong, J. Park, C. Moon, and T. Park, "Regulation of Adipogenesis and Thermogenesis through Mouse Olfactory Receptor 23 Stimulated by α-Cedrene in 3T3-L1 Cells.," *Nutrients*, vol. 10, no. 11, Nov. 2018, doi: 10.3390/nu10111781.
- [66] P. Gurung and I. Jialal, "Plasma Glucose.," Treasure Island (FL), 2022.
- [67] A. M. Navale and A. N. Paranjape, "Glucose transporters: physiological and pathological roles.," *Biophys. Rev.*, vol. 8, no. 1, pp. 5–9, Mar. 2016, doi: 10.1007/s12551-015-0186-2.
- [68] M. S. Desai *et al.*, "Hypertrophic cardiomyopathy and dysregulation of cardiac energetics in a mouse model of biliary fibrosis," *Hepatology*, vol. 51, no. 6, pp. 2097–2107, 2010, doi: 10.1002/hep.23585.
- [69] M. M. Adeva-Andany, M. González-Lucán, C. Donapetry-García, C. Fernández-Fernández, and E. Ameneiros-Rodríguez, "Glycogen metabolism in humans.," *BBA Clin.*, vol. 5, pp. 85–100, Jun. 2016, doi: 10.1016/j.bbacli.2016.02.001.
- [70] S. Panda, "Circadian physiology of metabolism.," *Science*, vol. 354, no. 6315, pp. 1008–1015, Nov. 2016, doi: 10.1126/science.aah4967.
- [71] H.-S. Han, G. Kang, J. S. Kim, B. H. Choi, and S.-H. Koo, "Regulation of glucose metabolism from a liver-centric perspective.," *Exp. Mol. Med.*, vol. 48, no. 3, p. e218, Mar. 2016, doi: 10.1038/emm.2015.122.
- [72] L. M. Furtado, R. Somwar, G. Sweeney, W. Niu, and A. Klip, "Activation of the glucose transporter GLUT4 by insulin.," *Biochem. Cell Biol.*, vol. 80, no. 5, pp. 569–578, 2002, doi: 10.1139/002-156.
- [73] C. R. Kahn, "The molecular mechanism of insulin action.," *Annu. Rev. Med.*, vol. 36, pp. 429–451, 1985, doi: 10.1146/annurev.me.36.020185.002241.
- [74] D. J. Drucker, "Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1.," *Cell Metab.*, vol. 27, no. 4, pp. 740–756, Apr. 2018, doi: 10.1016/j.cmet.2018.03.001.
- [75] C. J. Ramnanan, D. S. Edgerton, G. Kraft, and A. D. Cherrington, "Physiologic action of glucagon on liver glucose metabolism.," *Diabetes. Obes. Metab.*, vol. 13 Suppl 1, no. Suppl 1, pp. 118–125, Oct. 2011, doi: 10.1111/j.1463-1326.2011.01454.x.
- [76] R. C. Nordlie, J. D. Foster, and A. J. Lange, "Regulation of glucose production by the liver.," *Annu. Rev. Nutr.*, vol. 19, pp. 379–406, 1999, doi: 10.1146/annurev.nutr.19.1.379.
- [77] L. Janah *et al.*, "Glucagon Receptor Signaling and Glucagon Resistance.," *Int. J. Mol. Sci.*, vol. 20, no. 13, Jul. 2019, doi: 10.3390/ijms20133314.
- [78] G. Jiang and B. B. Zhang, "Glucagon and regulation of glucose metabolism.," *Am. J. Physiol. Endocrinol. Metab.*, vol. 284, no. 4, pp. E671-8, Apr. 2003, doi: 10.1152/ajpendo.00492.2002.
- [79] S. Chatterjee, K. Khunti, and M. J. Davies, "Type 2 diabetes.," *Lancet (London, England)*, vol. 389, no. 10085, pp. 2239–2251, Jun. 2017, doi: 10.1016/S0140-6736(17)30058-2.
- [80] G. Lomberg and R. Urrutia, "Primers on Molecular Pathways—The Insulin Pathway," *Pancreatology*,

- vol. 9, no. 3, pp. 203–205, 2009, doi: <https://doi.org/10.1159/000200021>.
- [81] U. Galicia-Garcia *et al.*, "Pathophysiology of Type 2 Diabetes Mellitus," *Int. J. Mol. Sci.*, vol. 21, no. 17, Aug. 2020, doi: [10.3390/ijms21176275](https://doi.org/10.3390/ijms21176275).
- [82] R. A. DeFronzo *et al.*, "Type 2 diabetes mellitus," *Nat. Rev. Dis. Prim.*, vol. 1, p. 15019, Jul. 2015, doi: [10.1038/nrdp.2015.19](https://doi.org/10.1038/nrdp.2015.19).
- [83] K. D. Niswender, "Basal insulin: physiology, pharmacology, and clinical implications," *Postgrad. Med.*, vol. 123, no. 4, pp. 17–26, Jul. 2011, doi: [10.3810/pgm.2011.07.2300](https://doi.org/10.3810/pgm.2011.07.2300).
- [84] F. Pivari, A. Mingione, C. Brasacchio, and L. Soldati, "Curcumin and Type 2 Diabetes Mellitus: Prevention and Treatment," *Nutrients*, vol. 11, no. 8, Aug. 2019, doi: [10.3390/nu11081837](https://doi.org/10.3390/nu11081837).
- [85] C. Corcoran and T. F. Jacobs, "Metformin," Treasure Island (FL), 2022.
- [86] "Standards of Medical Care in Diabetes-2019 Abridged for Primary Care Providers," *Clin. Diabetes*, vol. 37, no. 1, pp. 11–34, Jan. 2019, doi: [10.2337/cd18-0105](https://doi.org/10.2337/cd18-0105).
- [87] C. Tang *et al.*, "Loss of FFA2 and FFA3 increases insulin secretion and improves glucose tolerance in type 2 diabetes," *Nat. Med.*, vol. 21, no. 2, pp. 173–177, Feb. 2015, doi: [10.1038/nm.3779](https://doi.org/10.1038/nm.3779).
- [88] M. Grundmann, E. Bender, J. Schamberger, and F. Eitner, "Pharmacology of Free Fatty Acid Receptors and Their Allosteric Modulators," *Int. J. Mol. Sci.*, vol. 22, no. 4, Feb. 2021, doi: [10.3390/ijms22041763](https://doi.org/10.3390/ijms22041763).
- [89] C. Chimere, E. Emery, D. K. Summers, U. Keyser, F. M. Gribble, and F. Reimann, "Bacterial metabolite indole modulates incretin secretion from intestinal enteroendocrine L cells," *Cell Rep.*, vol. 9, no. 4, pp. 1202–1208, Nov. 2014, doi: [10.1016/j.celrep.2014.10.032](https://doi.org/10.1016/j.celrep.2014.10.032).
- [90] S. Fiorucci, E. Distrutti, A. Carino, A. Zampella, and M. Biagioli, "Bile acids and their receptors in metabolic disorders," *Prog Lipid Res*, vol. 82, p. 101094, 2021, doi: [10.1016/j.plipres.2021.101094](https://doi.org/10.1016/j.plipres.2021.101094).
- [91] S. Fiorucci and E. Distrutti, "Linking liver metabolic and vascular disease via bile acid signaling," *Trends Mol. Med.*, Nov. 2021, doi: [10.1016/j.molmed.2021.10.005](https://doi.org/10.1016/j.molmed.2021.10.005).
- [92] M. H. Kim, S. G. Kang, J. H. Park, M. Yanagisawa, and C. H. Kim, "Short-chain fatty acids activate GPR41 and GPR43 on intestinal epithelial cells to promote inflammatory responses in mice," *Gastroenterology*, vol. 145, no. 2, pp. 310–396, Aug. 2013, doi: [10.1053/j.gastro.2013.04.056](https://doi.org/10.1053/j.gastro.2013.04.056).
- [93] S. Fiorucci *et al.*, "Bile Acid Signaling in Inflammatory Bowel Diseases," *Dig Dis Sci*, vol. 66, no. 3, pp. 674–693, Mar. 2021, doi: [10.1007/s10620-020-06715-3](https://doi.org/10.1007/s10620-020-06715-3).
- [94] F. Lemarié, E. Beauchamp, P. Legrand, and V. Rioux, "Revisiting the metabolism and physiological functions of caprylic acid (C8:0) with special focus on ghrelin octanoylation," *Biochimie*, vol. 120, pp. 40–48, Jan. 2016, doi: [10.1016/j.biochi.2015.08.002](https://doi.org/10.1016/j.biochi.2015.08.002).
- [95] B. D. Shepard, H. Koepsell, and J. L. Pluznick, "Renal olfactory receptor 1393 contributes to the progression of type 2 diabetes in a diet-induced obesity model," *Am. J. Physiol. Renal Physiol.*, vol. 316, no. 2, pp. F372–F381, Feb. 2019, doi: [10.1152/ajprenal.00069.2018](https://doi.org/10.1152/ajprenal.00069.2018).
- [96] A. R. Schiazza, E. G. Considine, M. Betcher, and B. D. Shepard, "Loss of renal olfactory receptor 1393 leads to improved glucose homeostasis in a type 1 diabetic mouse model," *Physiol. Rep.*, vol. 9, no. 23, p. e15007, Dec. 2021, doi: [10.14814/phy2.15007](https://doi.org/10.14814/phy2.15007).
- [97] H. Rahmoune, P. W. Thompson, J. M. Ward, C. D. Smith, G. Hong, and J. Brown, "Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes," *Diabetes*, vol. 54, no. 12, pp. 3427–3434, Dec. 2005, doi: [10.2337/diabetes.54.12.3427](https://doi.org/10.2337/diabetes.54.12.3427).

- [98] C. Ghezzi and E. M. Wright, "Regulation of the human Na⁺-dependent glucose cotransporter hSGLT2.," *Am. J. Physiol. Cell Physiol.*, vol. 303, no. 3, pp. C348-54, Aug. 2012, doi: 10.1152/ajpcell.00115.2012.
- [99] C. Ghezzi, D. D. F. Loo, and E. M. Wright, "Physiology of renal glucose handling via SGLT1, SGLT2 and GLUT2.," *Diabetologia*, vol. 61, no. 10, pp. 2087-2097, Oct. 2018, doi: 10.1007/s00125-018-4656-5.
- [100] R. Santer and J. Calado, "Familial renal glucosuria and SGLT2: from a mendelian trait to a therapeutic target.," *Clin. J. Am. Soc. Nephrol.*, vol. 5, no. 1, pp. 133-141, Jan. 2010, doi: 10.2215/CJN.04010609.
- [101] C. M. Khoo, "Diabetes Mellitus Treatment.," in *International Encyclopedia of Public Health (Second Edition)*, Second Edi., S. R. Quah, Ed. Oxford: Academic Press, 2017, pp. 288-293. doi: <https://doi.org/10.1016/B978-0-12-803678-5.00108-9>.
- [102] A. S. Nair, D. Bagchi, T. E. Lehmann, and S. Nair, "Chapter 16 - Renal Sodium-Glucose Transporter-2 Inhibitors as Antidiabetic Agents.," in *Nutritional and Therapeutic Interventions for Diabetes and Metabolic Syndrome (Second Edition)*, Second Edi., D. Bagchi and S. Nair, Eds. Academic Press, 2018, pp. 207-214. doi: <https://doi.org/10.1016/B978-0-12-812019-4.00016-7>.
- [103] K. S. Polonsky and C. F. Burant, "Chapter 31 - Type 2 Diabetes Mellitus.," in *Williams Textbook of Endocrinology (Thirteenth Edition)*, Thirteenth., S. Melmed, K. S. Polonsky, P. R. Larsen, and H. M. Kronenberg, Eds. Philadelphia: Elsevier, 2016, pp. 1385-1450. doi: <https://doi.org/10.1016/B978-0-323-29738-7.00031-9>.
- [104] O. Marsenic, "Glucose control by the kidney: an emerging target in diabetes.," *Am. J. kidney Dis. Off. J. Natl. Kidney Found.*, vol. 53, no. 5, pp. 875-883, May 2009, doi: 10.1053/j.ajkd.2008.12.031.
- [105] L. De Nicola, F. B. Gabbai, M. E. Liberti, A. Sogliocca, G. Conte, and R. Minutolo, "Sodium/glucose cotransporter 2 inhibitors and prevention of diabetic nephropathy: targeting the renal tubule in diabetes.," *Am. J. kidney Dis. Off. J. Natl. Kidney Found.*, vol. 64, no. 1, pp. 16-24, Jul. 2014, doi: 10.1053/j.ajkd.2014.02.010.
- [106] C. Romere et al., "Asprosin, a Fasting-Induced Glucogenic Protein Hormone.," *Cell*, vol. 165, no. 3, pp. 566-579, Apr. 2016, doi: 10.1016/j.cell.2016.02.063.
- [107] E. Fahy, D. Cotter, M. Sud, and S. Subramaniam, "Lipid classification, structures and tools.," *Biochim. Biophys. Acta*, vol. 1811, no. 11, pp. 637-647, Nov. 2011, doi: 10.1016/j.bbalip.2011.06.009.
- [108] I. Tabas, "Cholesterol in health and disease.," *J. Clin. Invest.*, vol. 110, no. 5, pp. 583-590, Sep. 2002, doi: 10.1172/JCI16381.
- [109] D. W. Russell, "Cholesterol biosynthesis and metabolism.," *Cardiovascular drugs and therapy*, vol. 6, no. 2. United States, pp. 103-110, Apr. 1992. doi: 10.1007/BF00054556.
- [110] W. Dowhan, "The role of phospholipids in cell function.," vol. 2, R. W. Gross, Ed. JAI, 1997, pp. 79-107. doi: [https://doi.org/10.1016/S1874-5245\(97\)80006-7](https://doi.org/10.1016/S1874-5245(97)80006-7).
- [111] J. Luo, H. Yang, and B.-L. Song, "Mechanisms and regulation of cholesterol homeostasis.," *Nat. Rev. Mol. Cell Biol.*, vol. 21, no. 4, pp. 225-245, 2020, doi: 10.1038/s41580-019-0190-7.
- [112] C. Kirschbaum et al., "Unravelling the structural complexity of glycolipids with cryogenic infrared spectroscopy.," *Nat. Commun.*, vol. 12, no. 1, p. 1201, 2021, doi: 10.1038/s41467-021-21480-1.
- [113] K. Hanafusa, T. Hotta, and K. Iwabuchi, "Glycolipids: Linchpins in the Organization and Function of Membrane Microdomains.," *Front. Cell Dev. Biol.*, vol. 8, 2020, doi: 10.3389/fcell.2020.589799.
- [114] E. J. Masoro, "Lipids and lipid metabolism.," *Annu. Rev. Physiol.*, vol. 39, pp. 301-321, 1977, doi:

- 10.1146/annurev.ph.39.030177.001505.
- [115] J. Iqbal and M. M. Hussain, "Intestinal lipid absorption," *Am. J. Physiol. Endocrinol. Metab.*, vol. 296, no. 6, pp. E1183-94, Jun. 2009, doi: 10.1152/ajpendo.90899.2008.
- [116] D. G. Waller and A. P. Sampson, "48 - Lipid disorders," in *Medical Pharmacology and Therapeutics (Fifth Edition)*, Fifth Edit., D. G. Waller and A. P. Sampson, Eds. Elsevier, 2018, pp. 547-557. doi: <https://doi.org/10.1016/B978-0-7020-7167-6.00048-8>.
- [117] P. Nguyen et al., "Liver lipid metabolism," *J Anim Physiol Anim Nutr*, vol. 92, no. 3, pp. 272-283, 2008, doi: 10.1111/j.1439-0396.2007.00752.x.
- [118] B. Hewing, K. J. Moore, and E. A. Fisher, "HDL and cardiovascular risk: time to call the plumber?," *Circ. Res.*, vol. 111, no. 9, pp. 1117-1120, Oct. 2012, doi: 10.1161/CIRCRESAHA.112.280958.
- [119] K. Mahdy Ali, A. Wonnerth, K. Huber, and J. Wojta, "Cardiovascular disease risk reduction by raising HDL cholesterol--current therapies and future opportunities," *Br. J. Pharmacol.*, vol. 167, no. 6, pp. 1177-1194, Nov. 2012, doi: 10.1111/j.1476-5381.2012.02081.x.
- [120] S. Bhatt and R. N. Kulkarni, "Chapter 17 - Significance of Organ Crosstalk in Insulin Resistance and Type 2 Diabetes," in *Translational Endocrinology of Bone*, G. Karsenty, Ed. San Diego: Academic Press, 2013, pp. 199-219. doi: <https://doi.org/10.1016/B978-0-12-415784-2.00017-8>.
- [121] N. Fillmore, J. Mori, and G. D. Lopaschuk, "Mitochondrial fatty acid oxidation alterations in heart failure, ischaemic heart disease and diabetic cardiomyopathy," *Br. J. Pharmacol.*, vol. 171, no. 8, pp. 2080-2090, Apr. 2014, doi: 10.1111/bph.12475.
- [122] M. M. Mihaylova and R. J. Shaw, "The AMPK signalling pathway coordinates cell growth, autophagy and metabolism," *Nat. Cell Biol.*, vol. 13, no. 9, pp. 1016-1023, Sep. 2011, doi: 10.1038/ncb2329.
- [123] B. Viollet et al., "Activation of AMP-activated protein kinase in the liver: a new strategy for the management of metabolic hepatic disorders," *J. Physiol.*, vol. 574, no. Pt 1, pp. 41-53, Jul. 2006, doi: 10.1113/jphysiol.2006.108506.
- [124] L. Chen, X.-W. Chen, X. Huang, B.-L. Song, Y. Wang, and Y. Wang, "Regulation of glucose and lipid metabolism in health and disease," *Sci. China. Life Sci.*, vol. 62, no. 11, pp. 1420-1458, Nov. 2019, doi: 10.1007/s11427-019-1563-3.
- [125] M. Yoon, "The role of PPARalpha in lipid metabolism and obesity: focusing on the effects of estrogen on PPARalpha actions," *Pharmacol. Res.*, vol. 60, no. 3, pp. 151-159, Sep. 2009, doi: 10.1016/j.phrs.2009.02.004.
- [126] F. R. Ponziani, S. Pecere, A. Gasbarrini, and V. Ojetti, "Physiology and pathophysiology of liver lipid metabolism," *Expert Rev. Gastroenterol. Hepatol.*, vol. 9, no. 8, pp. 1055-1067, 2015, doi: 10.1586/17474124.2015.1056156.
- [127] V. Souza-Mello, "Peroxisome proliferator-activated receptors as targets to treat non-alcoholic fatty liver disease," *World J. Hepatol.*, vol. 7, no. 8, pp. 1012-1019, May 2015, doi: 10.4254/wjh.v7.i8.1012.
- [128] S. Koba and T. Hirano, "[Dyslipidemia and atherosclerosis]," *Nihon Rinsho.*, vol. 69, no. 1, pp. 138-143, Jan. 2011.
- [129] C. D. Byrne and G. Targher, "NAFLD: a multisystem disease," *J. Hepatol.*, vol. 62, no. 1 Suppl, pp. S47-64, Apr. 2015, doi: 10.1016/j.jhep.2014.12.012.
- [130] L. Kořínková et al., "Pathophysiology of NAFLD and NASH in Experimental Models: The Role of Food Intake Regulating Peptides," *Front. Endocrinol. (Lausanne).*, vol. 11, p. 597583, 2020, doi: 10.3389/fendo.2020.597583.

-
- [131] M. Swain *et al.*, "Biochemical Profile of Nonalcoholic Fatty Liver Disease Patients in Eastern India with Histopathological Correlation.," *Indian J. Clin. Biochem.*, vol. 32, no. 3, pp. 306–314, Jul. 2017, doi: 10.1007/s12291-016-0612-7.
- [132] D. E. Cohen and E. A. Fisher, "Lipoprotein metabolism, dyslipidemia, and nonalcoholic fatty liver disease.," *Semin. Liver Dis.*, vol. 33, no. 4, pp. 380–388, Nov. 2013, doi: 10.1055/s-0033-1358519.
- [133] K. Pei *et al.*, "An Overview of Lipid Metabolism and Nonalcoholic Fatty Liver Disease.," *Biomed Res. Int.*, vol. 2020, p. 4020249, 2020, doi: 10.1155/2020/4020249.
- [134] Y. Okada *et al.*, "Rosuvastatin ameliorates high-fat and high-cholesterol diet-induced nonalcoholic steatohepatitis in rats.," *Liver Int. Off. J. Int. Assoc. Study Liver*, vol. 33, no. 2, pp. 301–311, Feb. 2013, doi: 10.1111/liv.12033.
- [135] G. Ji, X. Zhao, L. Leng, P. Liu, and Z. Jiang, "Comparison of dietary control and atorvastatin on high fat diet induced hepatic steatosis and hyperlipidemia in rats.," *Lipids Health Dis.*, vol. 10, p. 23, Jan. 2011, doi: 10.1186/1476-511X-10-23.
- [136] L.-W. Chong *et al.*, "Fluvastatin attenuates hepatic steatosis-induced fibrogenesis in rats through inhibiting paracrine effect of hepatocyte on hepatic stellate cells.," *BMC Gastroenterol.*, vol. 15, p. 22, Feb. 2015, doi: 10.1186/s12876-015-0248-8.
- [137] V. G. Athyros *et al.*, "Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study.," *Curr. Med. Res. Opin.*, vol. 22, no. 5, pp. 873–883, May 2006, doi: 10.1185/030079906X104696.
- [138] A. Lonardo, S. Sookoian, C. J. Pirola, and G. Targher, "Non-alcoholic fatty liver disease and risk of cardiovascular disease.," *Metabolism.*, vol. 65, no. 8, pp. 1136–1150, Aug. 2016, doi: 10.1016/j.metabol.2015.09.017.
- [139] H. Hyogo *et al.*, "Efficacy of atorvastatin for the treatment of nonalcoholic steatohepatitis with dyslipidemia.," *Metabolism.*, vol. 57, no. 12, pp. 1711–1718, Dec. 2008, doi: 10.1016/j.metabol.2008.07.030.
- [140] S. Singh, P. P. Singh, A. G. Singh, M. H. Murad, and W. Sanchez, "Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis.," *Gastroenterology*, vol. 144, no. 2, pp. 323–332, Feb. 2013, doi: 10.1053/j.gastro.2012.10.005.
- [141] V. Ratzu *et al.*, "Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor- α and - δ , Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening.," *Gastroenterology*, vol. 150, no. 5, pp. 1147–1159.e5, May 2016, doi: 10.1053/j.gastro.2016.01.038.
- [142] M. Pawlak, P. Lefebvre, and B. Staels, "Molecular mechanism of PPAR α action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease.," *J. Hepatol.*, vol. 62, no. 3, pp. 720–733, Mar. 2015, doi: 10.1016/j.jhep.2014.10.039.
- [143] S. Fiorucci, E. Distrutti, A. Carino, A. Zampella, and M. Biagioli, "Bile acids and their receptors in metabolic disorders.," *Prog Lipid Res*, vol. 82, p. 101094, 2021, doi: 10.1016/j.plipres.2021.101094.
- [144] M. Ni *et al.*, "Biological mechanisms and related natural modulators of liver X receptor in nonalcoholic fatty liver disease.," *Biomed. Pharmacother.*, vol. 113, p. 108778, 2019, doi: <https://doi.org/10.1016/j.biopha.2019.108778>.
- [145] D. S. Akerib *et al.*, "A role for proteinase-activated receptor-1 in inflammatory bowel diseases.," *Gastroenterology*, vol. 10, no. 2, p. 21303, 2012, doi: 10.1021/jm500889f.
- [146] M. Wang *et al.*, "Inhibition of LXR α /SREBP-1c-Mediated Hepatic Steatosis by Jiang-Zhi Granule.,"

- Evid. Based. Complement. Alternat. Med.*, vol. 2013, p. 584634, 2013, doi: 10.1155/2013/584634.
- [147] R. Kurtz, M. F. Anderman, and B. D. Shepard, "GPCRs get fatty: the role of G protein-coupled receptor signaling in the development and progression of nonalcoholic fatty liver disease.," *Am. J. Physiol. Gastrointest. Liver Physiol.*, vol. 320, no. 3, pp. G304–G318, Mar. 2021, doi: 10.1152/ajpgi.00275.2020.
- [148] S. Zhang, L. Li, and H. Li, "Role of ectopic olfactory receptors in glucose and lipid metabolism," *Br. J. Pharmacol.*, vol. 178, no. 24, pp. 4792–4807, 2021, doi: <https://doi.org/10.1111/bph.15666>.
- [149] J. Y. Hong *et al.*, "GC-MS/MS method for the quantification of α -cedrene in rat plasma and its pharmacokinetic application.," *J. Sep. Sci.*, vol. 36, no. 21–22, pp. 3558–3562, Nov. 2013, doi: 10.1002/jssc.201300828.
- [150] T. Tong, M. Kim, and T. Park, " α -Cedrene, a Newly Identified Ligand of MOR23, Increases Skeletal Muscle Mass and Strength," *Mol. Nutr. & Food Res.*, vol. 62, no. 15, p. 1800173, 2018, doi: <https://doi.org/10.1002/mnfr.201800173>.
- [151] T. Iida *et al.*, "Discovery of potent liver-selective stearyl-CoA desaturase-1 (SCD1) inhibitors, thiazole-4-acetic acid derivatives, for the treatment of diabetes, hepatic steatosis, and obesity," *Eur. J. Med. Chem.*, vol. 158, pp. 832–852, 2018, doi: <https://doi.org/10.1016/j.ejmech.2018.09.003>.
- [152] D. Lindén, L. William-Olsson, M. Rhedin, A.-K. Asztély, J. C. Clapham, and S. Schreyer, "Overexpression of mitochondrial GPAT in rat hepatocytes leads to decreased fatty acid oxidation and increased glycerolipid biosynthesis," *J. Lipid Res.*, vol. 45, no. 7, pp. 1279–1288, 2004, doi: <https://doi.org/10.1194/jlr.M400010-JLR200>.
- [153] J. Himms-Hagen, "Role of thermogenesis in the regulation of energy balance in relation to obesity.," *Can. J. Physiol. Pharmacol.*, vol. 67, no. 4, pp. 394–401, Apr. 1989, doi: 10.1139/y89-063.
- [154] M. Alcalá, M. Calderon-Dominguez, D. Serra, L. Herrero, and M. Viana, "Mechanisms of Impaired Brown Adipose Tissue Recruitment in Obesity," *Front. Physiol.*, vol. 10, 2019, doi: 10.3389/fphys.2019.00094.
- [155] A. M. Cypess and C. R. Kahn, "Brown fat as a therapy for obesity and diabetes.," *Curr. Opin. Endocrinol. Diabetes. Obes.*, vol. 17, no. 2, pp. 143–149, Apr. 2010, doi: 10.1097/MED.0b013e328337a81f.
- [156] B. Knebel *et al.*, "Inactivation of SREBP-1a Phosphorylation Prevents Fatty Liver Disease in Mice: Identification of Related Signaling Pathways by Gene Expression Profiles in Liver and Proteomes of Peroxisomes.," *Int. J. Mol. Sci.*, vol. 19, no. 4, Mar. 2018, doi: 10.3390/ijms19040980.
- [157] D. Eberlé, B. Hegarty, P. Bossard, P. Ferré, and F. Foufelle, "SREBP transcription factors: master regulators of lipid homeostasis," *Biochimie*, vol. 86, no. 11, pp. 839–848, 2004, doi: 10.1016/j.biochi.2004.09.018.
- [158] X. Grosmaître, A. Vassalli, P. Mombaerts, G. M. Shepherd, and M. Ma, "Odorant responses of olfactory sensory neurons expressing the odorant receptor MOR23: a patch clamp analysis in gene-targeted mice.," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 103, no. 6, pp. 1970–1975, Feb. 2006, doi: 10.1073/pnas.0508491103.
- [159] S. Mehmood, I. Orhan, Z. Ahsan, S. Aslan, and M. Gulfray, "Fatty acid composition of seed oil of different Sorghum bicolor varieties.," *Food Chem.*, vol. 109, no. 4, pp. 855–859, Aug. 2008, doi: 10.1016/j.foodchem.2008.01.014.
- [160] S. Muthulakshmi and R. Saravanan, "Protective effects of azelaic acid against high-fat diet-induced oxidative stress in liver, kidney and heart of C57BL/6J mice.," *Mol. Cell. Biochem.*, vol. 377, no. 1–2,

- pp. 23–33, May 2013, doi: 10.1007/s11010-013-1566-1.
- [161] S. Muthulakshmi, A. K. Chakrabarti, and S. Mukherjee, "Gene expression profile of high-fat diet-fed C57BL/6J mice: in search of potential role of azelaic acid.," *J. Physiol. Biochem.*, vol. 71, no. 1, pp. 29–42, Mar. 2015, doi: 10.1007/s13105-014-0376-6.
- [162] T. Abaffy, H. Matsunami, and C. W. Luetje, "Functional analysis of a mammalian odorant receptor subfamily.," *J. Neurochem.*, vol. 97, no. 5, pp. 1506–1518, Jun. 2006, doi: 10.1111/j.1471-4159.2006.03859.x.
- [163] C. Morcia, G. Tumino, R. Ghizzoni, and V. Terzi, "Carvone (Mentha spicata L.) Oils," 2016, pp. 309–316. doi: 10.1016/B978-0-12-416641-7.00035-3.
- [164] C. Bushdid, C. A. de March, S. Fiorucci, H. Matsunami, and J. Golebiowski, "Agonists of G-Protein-Coupled Odorant Receptors Are Predicted from Chemical Features," *J Phys Chem Lett*, vol. 9, no. 9, pp. 2235–2240, 2018, doi: 10.1021/acs.jpcllett.8b00633.
- [165] S. Diels *et al.*, "Copy number variant analysis and expression profiling of the olfactory receptor-rich 11q11 region in obesity predisposition," *Mol. Genet. Metab. Reports*, vol. 25, p. 100656, 2020, doi: <https://doi.org/10.1016/j.ymgmr.2020.100656>.
- [166] M. E. Giusepponi *et al.*, "Gene expression profiling in adipose tissue of Sprague Dawley rats identifies olfactory receptor 984 as a potential obesity treatment target," *Biochem. Biophys. Res. Commun.*, vol. 505, no. 3, pp. 801–806, 2018, doi: <https://doi.org/10.1016/j.bbrc.2018.09.137>.
- [167] I. Jarick *et al.*, "Novel common copy number variation for early onset extreme obesity on chromosome 11q11 identified by a genome-wide analysis," *Hum. Mol. Genet.*, vol. 20, no. 4, pp. 840–852, 2010, doi: 10.1093/hmg/ddq518.
- [168] M. Dharmalingam and P. G. Yamasandhi, "Nonalcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus.," *Indian J. Endocrinol. Metab.*, vol. 22, no. 3, pp. 421–428, 2018, doi: 10.4103/ijem.IJEM_585_17.
- [169] M. Asrih and F. R. Jornayvaz, "Metabolic syndrome and nonalcoholic fatty liver disease: Is insulin resistance the link?," *Mol. Cell. Endocrinol.*, vol. 418 Pt 1, pp. 55–65, Dec. 2015, doi: 10.1016/j.mce.2015.02.018.
- [170] F. J. Zieve, "The metabolic syndrome: diagnosis and treatment.," *Clin. Cornerstone*, vol. 6 Suppl 3, pp. S5–13, 2004, doi: 10.1016/S1098-3597(04)80093-0.
- [171] M. Faour, C. Magnan, H. Gurden, and C. Martin, "Olfaction in the context of obesity and diabetes: Insights from animal models to humans," *Neuropharmacology*, vol. 206, p. 108923, 2022, doi: <https://doi.org/10.1016/j.neuropharm.2021.108923>.
- [172] R. L. Perlman, "Mouse models of human disease: An evolutionary perspective.," *Evol. Med. public Heal.*, vol. 2016, no. 1, pp. 170–176, 2016, doi: 10.1093/emph/eow014.