ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Can GPR120 and CD36 Antagonists Have an Anti-Obesity Action?

Gado Dramane[1,2]*, Rock Aïkpon[1,2], Adam Gbankoto[2], Virgil Ahyi[3] and Simon A Akpona[4]

[1]*Department of Life Sciences, Normal Higher School of Natitingou, UNSTIM 03PB212 Parakou, Benin*

[2]*Laboratory of Molecular Physiopathology and Toxicology, Abomey-Calavi, Benin*

[3]*Regional University of Industrial Engineering, Biotechnology and applied sciences (IRGIB-Africa), Cotonou, Benin*

[4]*Laboratory of Biochemistry, Faculty of Medicine, University of Parakou, Benin*

***Corresponding Author:** Gado Dramane, Department of Life Sciences, Normal Higher School of Natitingou, UNSTIM 03PB212 Parakou, Benin.

Received: May 29, 2019; **Published:** August 29, 2019

Abstract

In this review, we highlight a receptor, CD36 and one of its associates, GPR 120, both involved in the perception of dietary fatty acids. We have shown in our previous work and also found in literature, that the mechanisms involved in the taste of fat signaling pathway are known for the most part, involving a process of preference for dietary lipids.

Here we are questioning the opportunity of the known inhibitors of this signaling pathway to fight the attraction of dietary lipids. Our elements of analysis initiate the questioning in order to find mechanisms of control of the energy supply by the food.

From the known role of GPR120 agonists involved in the treatment of plethora diseases and the role of glucagon antagonists involved in the management of type 2 diabetes, we chosen for the track of substances that inhibit the fixation of oxidized substrates on the CD36 glycoprotein.

Keywords: *CD36; GPR120; GPR40; Ingestive Signal; Fatty Acid; Obesity; Metabolic Diseases*

Background

For centuries, humans have been fueling themselves for energy and survival. We live in a time of food abundance, especially in developed countries. This abundance is associated with an energy enrichment of meals and unfortunately leads to the appearance of metabolic diseases called plethora diseases, such as obesity, type II diabetes and cardiovascular diseases.

Dietary fatty acids perception has traditionally been considered to be dependent on texture and olfaction, but recent findings suggest that taste may also play a role in the detection of long chain fatty acids. We have done a lot of work on the existence of a sixth modality of taste in addition to sweet, salty, bitter, acid and Umami. In this process, we have improved the understanding of all the mechanisms involved in perception of the "taste of fat". We have tried to improve the understanding of the mechanisms involved in this signaling [1-4].

It has previously been approved that CD36 glycoprotein, expressed by mouse circumvallate papillae, is involved in the oro-gustatory perception of dietary lipids. We demonstrated that linoleic acid (LA) by activating phospholipases, produces arachidonic acid (AA), lysophosphatidylcholine (lyso-PC) and triggers calcium influx, in cells expressing CD36 in mice. We have thus elucidated all the machinery responsible for the taste perception of food fatty acids by the brain and showed at the same time that there was a feeding behavior and then a genetic profile dependent on the development of obesity [5-9].

The whole question then was to know the interest in human health. We therefore asked about the possibility that knowledge of the perception of fatty acids will have a certain impact on public health. We can imagine pharmacological molecules that would allow us to consume fatty foods without the risk of having a health impact. We can think of a kind of aspartame for fat. Fat would be consumed without excess caloric intake. It would be possible to desensitize subjects to fatty foods, creating a repugnance among them.

The track we are discussing here is that of the use of inhibitors of fatty acid receptors to have a limiting action on their detection.

The G Proteins Receptors

Fred Riksson., *et al.* [11] have identified a 120 kDa orphan protein-coupled receptor G, GPR120. G protein-coupled receptors (GPCRs) are integral membrane proteins with seven transmembrane helices. The GPCR super-family is one of the largest and most diverse families of mammalian proteins [12,13]. The functions of GPCRs are highly variable because they play an important role in the physiology of all major peripheral organ systems and also in the brains of higher vertebrates. GPCRs are located on the cell surface and are responsible for the translation of an endogenous signal into an intracellular response by heterotrimeric G proteins that target other proteins, often enzymes that influence the level of intracellular messengers [11]. There would be seven members of the superfamily of human GPCRs, GPR100, GPR119, GPR120, GPR135, GPR136, GPR141 and GPR142 [11].

Many fatty acids are ligands of GPR40, another 41 kDa orphan receptor coupled to G protein [14]. GPR40 is expressed in the pancreas and modulates insulin secretion by fatty acid transport. GPR40 is also expressed in the entero- endocrine cells of the intestine and modulates the incretin stimulation by the fatty acid [10]. GPR40 has been localized in circumvallate and foliate papillae. Matsumura., *et al.* [15] showed the expression of GPR 40/120 in the papillae of rats**,** but they are not associated with α-gustducin [16].

Signaling via GPCR

GPCRs activate heterotrimeric G proteins, such as Gas, Gai, and Gaq. The ligands bind specifically to GPCRs to stimulate and induce several types of cellular responses via different second messenger pathways, such as those of cAMP, PLC, via ion channels, and MAPKs [17]. The cellular signaling mechanisms of GPR120 and GPR40 have not yet been elucidated. There are some studies that have addressed GPR120/40 signaling in different cell types.

Hirasawa., *et al.* [18] showed that stimulation of GPR120 by free fatty acids leads to elevation of intracellular calcium and activation of MAPK cascade, including ERK. Oh., *et al*. [19] reported that GPR120 functions as an n-3 fatty acid sensor and its stimulation inhibits both inflammatory responses of TLR4-and TNF-α. TNF-α and TLR2/3 can also stimulate TAK1 by activating IKKβ and JNK [20]. β-arrestins can serve as scaffolds or adapter proteins for a wide range of GPCRs [21] The C-terminal region of GPR120 contains several (S/T) X4-5 (S/T) characteristics of β-arrestins [22]. After binding of the ligand, β-arrestins can associate with the cytoplasmic domains of GPCR and to couple to the receptor downstream of specific signaling pathways [23].

In pancreatic cells, linoleic acid reduces the voltage-gated potassium current via GPR40 (Feng et al., 2006). The signaling pathways downstream of GPR40 and GPR120 remain to be determined. GPR120 and GPR40 are unlikely to couple to gustducin because α-gustducin knockout mice have a normal reaction to soybean oil [24].

Role of GPCR in lipid perception

Both GPCRs play a role in the mechanism of fat transduction and are widely expressed in taste buds. The taste selectivity would be determined by the co-expression of GPR40 or GPR120 with CD36 and downstream regulation of DRK. Alternatively, it would be possible for all cells to express GPR40 and GPR120 and activation would be by the fatty acid or neuromodulators that encode the fat signal. DRK (delayed rectification potassium channels) are inhibited by polyunsaturated fatty acids *in vitro* [25]. These channels may contribute to the fat taste response. Either independently of the GPCRs or by partially involving the transduction cascade initiated by the activation of GPR40 or GPR120 [10].

Hirasawa., *et al*. [18] showed that GPR120 acts as a receptor for polyunsaturated fatty acids (PUFAs). GPR120 participates in the secretion of fatty acids induced by glucagon-like peptide-1 [18] and cholecystokinin (CCK) in SC-1 cells [26]. GPR40 has been reported as a long and medium chain fatty acid receptor [26]. GPR120 and GPR40 are respectively expressed in type I and type II taste cells [10]. Circumvallate and fungiform papillae express GPR120, but not GPR40 mRNA in the rat tongue [15]. Cartoni., *et al.* [10] recently demonstrated in mice the expression of GPR40 in circumvallate papillae. We do not know why there is this difference in. However, it could be due to differences between rat and mouse species.

These researchers [10] also conducted experiments on knockout mice and observed that GPR40 KO animals had a lower preference for linoleic acid and oleic acid and GPR120 KO for linoleic acid. They studied the responses of glossopharyngeal nerve, which supplies the dorsum of the tongue; GPR40 KO GPR120 KO mice showed lower responses for oleic acid, linoleic acid stimulations. GPR40 or GPR120 must play an important role in the ability of mice to detect fatty acids. GPR120 is very expressed in mouse and human intestines and should have a role as a receptor for unsaturated long chain fatty acid [18]. The responses to the nerve of the tympanic cord and the glossopharyngeal nerve were blunted in GPR120 KO mice [10].

Is there a link between CD36 and GPCR?

To date, there is no highlighted coupling between CD36 and GPR. In STC-1 cells, an endocrine cell line, the Fatty Acids Induce GPR120 Calcium Mobilization and GLP-1 Release (glucagon-like peptide-1) [18]. GPR120 and CD36 would use lanes different to promote the transcription of stimuli related to the perception of fatty acids. The role of CD36 in the transduction mechanism would probably be to transfer the fatty acid molecules with GPR120. A carrier would be required to transfer the molecules to the receptor from saliva where there is association through binding proteins. It has already been shown that CD36 is a co-receptor or facilitator of the activation of Toll-like receptors TLR2 and TLR6 by diacyl-glyceride [27] and that SNMP, CD36 homologous protein in Drosophila, is essential for the detection of pheromones, which are also fatty acids [28]. In both cases CD36 acts as a ligand transporter to the receptor.

CD36 proteins and GPCRs are potential candidates for lipid taste perception. Knowing how two receptor proteins might be involved in an identical task is an enigma. GPR120/40 and CD36 may cooperate in the cell signaling mechanism. It is very likely that CD36 acts as a co-receiver of GPR120/40. A transporter may be required for translocation of fatty acids to the receptor or they may be associated with binding proteins or formation micelles, since most of the fatty acid concentrations that have been used up to then are above of their critical micellar concentration.

Taste preference for fatty acids is mediated by GPR40 and GPR120

The structure of CD36 is very interesting because this glycoprotein has a hairpin structure with a large extracellular hydrophobic pocket located between two short cytoplasmic tails [29,30] which justifies its role in as an oral lipid sensor. It was a research team from the University of Burgundy that provided the first evidence that CD36-positive taste cells play an important role in the perception of dietary lipids in mice. Indeed, inactivation of the CD36 gene completely abolishes the spontaneous preference for long chain fatty acids (AGLC), observed in wild mice [4,5]. It is noteworthy that this effect on dietary behavior is lipid-specific since the preference for sweet foods and the aversion to bitter foods are unaffected in these transgenic mice [4,31].

This spontaneous preference for fatty acids is associated with the mechanism of depolarization of the taste receptor membrane. The exact mechanisms of depolarization are not known. However, TRPM5 (transient receptor potential melastatin-5) may be involved in AGLC-induced plasma membrane depolarization. Liu and Liman [32] have shown that the initial increase in intracellular calcium concentration, activates the TRPM5 channels, thus promoting the influx of Na^+ responsible for the depolarization of the cell. Recently, Sclafani., *et al.* [33] reported that the invalidation of the TRPM5 gene abolishes the preference for fat in mice Although TRPM5 is a calcium-activated channel, direct regulation by arachidonic acid (AA) has been reported in mouse taste cells [34]. Furthermore, TRPM5-positive cells also express lipase mono-glyceride and phospholipase A2-IIA (PLA2-IIA), responsible for the release of free fatty acids (mainly AA) from mem-

brane phospholipids [34]. Using RT-qPCR and confocal microscopy techniques, we observed that CD36-positive lipid taste cells express the different subtypes of sPLA2, iPLA2, and cPLA2 (results published in the second publication). These different isoforms of PLA2 appear to be involved in the regulation of calcium homeostasis in these cells [5].

Spontaneous preference for lipid enriched solutions was investigated by means of the 2-bottle preference test. The wild-type, Stim1–/–, or CdCl2-injected mice were first accustomed to water drinking in 2 bottles for a period of 24 hours. Then, the individually caged mice were allowed to choose between 0.1% colza oil emulsified in 0.3% xanthan gum in water or water with vehicle alone (0.3% xanthan gum) over a period of 12 hours. The water intake was determined by weighing the feeders. So, we demonstrate that stromal interaction molecule 1 (STIM1), a sensor of Ca^{2+} depletion in the endoplasmic reticulum, mediates fatty acid-induced Ca^{2+} signaling in the mouse tongue and fat preference [5].

The two G-protein coupled receptors GPR40 (Ffar1) and GPR120 are activated by medium and long chain fatty acids. Cartoni., *et al.* [10] have showed that GPR120 and GPR40 are expressed in the taste buds, mainly in type II and type I cells, respectively. They also compared wild-type mice, male and female GPR120 knock-out and GPR40 knock-out mice. They found a diminished preference for linoleic acid and oleic acid, and diminished taste nerve responses to several fatty acids. Preference for food-borne molecules may result from many cues, including gustatory, olfactory, trigeminal and post-ingestive signals, and this is particularly true for fat. Expression of GPR40 and GPR120 in taste cells, and diminished taste nerve responses in the knock-out mice show that these two GPCRs contribute to preference for fatty acids through the gustatory system. However, Cartoni., *et al.* [10] data do not exclude a contribution of GPR120 and/or GPR40-dependent post-ingestive signals to fat preference, although the short access test shows that post-ingestive cues are not the only driver of preference. They think that flavor preference can be conditioned in rodents by intra-gastric infusion of lipids, and repeated exposures to linoleic acid emulsions lead to increased preference, suggesting an important role for post-ingestive signals in the preference for fat [33]. GPR120 could be expressed in the gut and mediates GLP-1 and CCK release in response to fatty acids [18,26]. GPR40 is expressed in the pancreas and mediates the modulation of insulin secretion by circulating fatty acids [14]. GPR40 is also expressed in entero-endocrine cells of the intestine and mediates free fatty acid stimulation of incretin secretion [35].

Can GPR120 and CD36 antagonists have an anti-obesity action?

In the future, it may be possible to synthesize selective lipid taste receptor antagonists to decrease the sensitivity of fat taste in normal or obese subjects. In the past, sulfo-N-succinimidyl derivatives of long-chain fatty acids, such as oleic acid and myristic acid, have been synthesized [36]. Therefore, SSO (sulfo-N-succinimidyl oleate) which specifically binds to CD36, has been shown to be an inhibitor of CD36 signaling. Recently, Sun., *et al.* [37] have synthesized several GPR120 antagonists and agonists based on structure-activity relationships, but their potential as anti-obesity agents is unknown. The best approach would be to synthesize agents that not only have high specificity for receptor binding, but also possess an intrinsic value of "lipid taste". An example of molecules that have no caloric value, such as aspartame or alitame, which have, respectively, a sweetening power of 200 and 2000 times higher than glucose and can therefore be taken to avoid consumption of conventional sweeteners that are very caloric. We still do not know if people who prefer fast food foods have overexpression of CD36 and GPR120/40 in their taste buds. If so, the antagonists of these receptors will certainly help to modulate human eating behavior. Extraordinarily, human taste cells express CD36 in goblet and follicle papillae [38]. Some results [37] suggest that CD36 expression in goblet papillae of obese rats may be associated with decreased taste sensitivity of fat. CD36 gene polymorphism induced a decrease in the gene's expression and is responsible for an increase in the oral detection threshold of dietary lipids in obese subjects. Obese women with the CD36 AA genotype (rs1761667) possess higher thresholds for lipid taste sensitivity than do those with GG genotypes [31,39]. The oro-sensorial perception of fat taste is transformed in some obese subjects. These authors have shown that the A allele of CD36 rs1761667 polymorphism in obese women, which was previously associated with decreased expression of the CD36 protein, is associated with a high oro-gustatory threshold detection for oleic acid [31].

Obese patients have a greater preference for fatty foods than those with low body mass index [40,41] showed a positive correlation between overall fat preference and body fat in humans. Stewart., *et al.* [42] found that people who were orally sensitive to oleic acid, consumed more energy and fat and had a higher body mass index (BMI) than those defined as hypersensitive. These observations indicate that lowering the taste sensitivity of fat may contribute to a resolution of the increased preference for foods. Overeating and sustained gain in body weight can be eradicated.

Conclusions

GPR120 agonists are provided. These compounds are useful for the treatment of metabolic diseases, including Type II diabetes and diseases associated with poor glycemic control. This invention relates to novel isothiazole and thiophene derivatives which are GPR120 agonists and are useful for the treatment of disorders that are affected by the modulation of the GPR120 receptor. The invention also relates to pharmaceutical compositions for the treatment of various diseases, syndromes and disorders, including obesity, related disorders, impaired oral glucose tolerance, insulin resistance, Type II diabetes mellitus, metabolic syndrome, dyslipidemia and cardiovascular disorders [43]. Since we knew that Glucagon receptor antagonist compounds are disclosed and that, the compounds are useful for treating type 2 diabetes and related conditions [44], we are hopeful for the role of GPR120 antagonists in association with CD36 antagonist to reduce the impact of dietary lipids intake. As far as CD36 is concerned, it exists the track of the substances which inhibits the binding of oxidized proteins to CD36 or inhibit its functions induced by their interaction [45]. The expression of CD36 gene is ligand-binding dependent and can either be up or down regulated. For instance, ox-LDL-CD36 interaction up regulates a PPARγ-dependent CD36 gene expression in monocytes-macrophages [46] whereas interaction with fatty acid down regulates gene expression and protein synthesis in enterocytes [47], but can up regulate the gene in adipocytes [48].

Competing Interests

The authors declare no conflicts of interest.

Authors' Contributions

Authors play the same part during the writing.

Bibliography

1. Gaillard D., *et al.* "The gustatory pathway is involved in CD36-mediated orosensory perception of long-chain fatty acids in the mouse". *The FASEB Journal* 22.5 (2008): 1458-1468.

2. Khan NA and Besnard P. "Oro-sensory perception of dietary lipids: New insights into the fat taste transduction". *Biochimica et Biophysica Acta* 1791.3 (2009): 149-155.

3. Khan NA., *et al.* "Unraveling the downstream signalling of gustatory perception of lipids". *Medical Sciences* 24.8-9 (2008): 692-693.

4. Laugerette F., *et al.* "CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions". *Journal of Clinical Investigation* 115.11 (2005): 3177-3184.

5. Dramane G., *et al.* "STIM1 regulates calcium signaling in taste budcells and preference for fat in mice". *Journal of Clinical Investigation* 122.6 (2012): 2267-2282.

6. Khan AS., *et al.* "ERK1 and ERK2 activation modulates diet-induced obesity in mice". *Biochimie* 137 (2017): 78-87.

7. Dramane G., *et al.* "Cell signaling mechanisms of gustatory perception of lipids: can the taste cells be the target of anti-obesity agents?". *Current Medicinal Chemistry* 18.22 (2011): 3417-3422.

8. Dramane G., *et al.* "The sensing of oro-gustatory dietary lipids: review of chemicals mechanisms". *Biochimie* 107 (2014): 11-14.

9. Dramane G., *et al.* "Docosahexaenoic Acid and Eicosapentaenoic Acid Modulate Calcium Signaling in Murine CD36-Positive Taste Buds Cells, via Phospholipase Pathways". *Journal of Chemistry and Chemical Engineering* 8 (2014): 570-579.

10. Cartoni C., *et al.* "Taste Preference for Fatty Acids Is Mediated by GPR40 and GPR120". *The Journal of Neuroscience* 30.25 (2010): 8376-8382.

11. Fredriksson R., *et al.* "Seven evolutionarily conserved human rhodopsin G protein-coupled receptors lacking close relatives". *FEBS Letters* 554.3 (2003): 381-388.

12. Lander ES., *et al.* "Initial sequencing and analysis of the human genome". *Nature* 409.6822 (2001): 860-821.

13. Venter JC., *et al*. "The Sequence of the Human Genome". *Science* 291.5507 (2001):1304-1351.

14. Itoh Y., *et al.* "Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40". *Nature* 422.6928 (2003):173-176.

15. Matsumura S., *et al.* "GPR expression in the rat taste bud relating to fatty acid sensing". *Biomedical Research* 28.1 (2007): 49-55.

16. Martin C., *et al.* "The lipid-sensor candidates CD36 and GPR120 are differentially regulated by dietary lipids in mouse taste buds: impact on spontaneous fat preference". *PLoS One* 6.8 (2011): e24014.

17. Schulte G and Fredholm BB. "Signaling from adenosine receptors to mitogen-activated protein kinases". *Cell Signaling* 15.9 (2003): 813-827.

18. Hirasawa A., *et al.* "Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120". *Nature Medicine* 11.1 (2005): 90-94.

19. Oh DY., *et al.* "GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects". *Cell* 142.5 (2010): 687-698.

20. Takaesu G., *et al.* "TAK1 is critical for IkappaB kinase-mediated activation of the NF-kappaB pathway". *Journal of Molecular Biology* 326.1 (2003): 105-115.

21. Miller WE and Lefkowitz RJ. "Expanding roles for beta-arrestins as scaffolds and adapters 1in GPCR signaling and trafficking". *Current Opinion in Cell Biology* 13.2 (2001): 139-145.

22. Cen B., *et al.* "Direct and differential interaction of beta-arrestins with the intracellular domains of different opioid receptors". *Molecular Pharmacology* 59.4 (2001): 758-764.

23. Luttrell LM and Lefkowitz RJ. "The role of beta-arrestins in the termination and transduction of G-protein-coupled receptor signals". *Journal of Cell Science* 115.3 (2002): 455-465.

24. Oike H., *et al.* "Group IIA phospholipase A (2) is coexpressed with SNAP-25 in mature taste receptor cells of rat circumvallate papillae". *Journal of Comparative Neurology* 494.6 (2006): 876-886.

25. Gilbertson TA., *et al.* "Fatty acid modulation of K+ channels in taste receptor cells: gustatory cues for dietary fat". *American Journal of Physiology* 272.4-1 (1997): C1203-C1210.

26. Tanaka T., *et al.* "Free fatty acids induce cholecystokinin secretion through GPR120". *Naunyn-Schmiedeberg's archives of pharmacology* 377.4-6 (2008): 523-527.

27. Hoebe K., *et al.* "CD36 is a sensor of diacylglycerides". *Nature* 433.7025 (2005): 523-527.

28. Benton R., *et al.* "An essential role for a CD36-related receptor in pheromone detection in Drosophila". *Nature* 450.7167 (2007): 289-293.

29. Abumrad NA., *et al.* "Cloning of a rat adipocyte membrane protein implicated in binding or transport of long-chain fatty acids that is induced during preadipocyte differentiation. Homology with human CD36". *The Journal of Biological Chemistry* 268.24 (1993): 17665-17668.

30. Greenwalt., *et al.* "Membrane glycoprotein CD36: a review of its roles in adherence, signal transduction, and transfusion medicine". *Blood* 80.5 (1992): 1105-1115.

31. Mrizak I., *et al.* "The A allele of cluster of differentiation 36 (CD36) SNP 1761667 associates with decreased lipid taste perception in obese Tunisian women". *British Journal of Nutrition* 111.3 (2015): 1330-1337.

32. Liu D and Liman ER. "Intracellular Ca2+ and the phospholipid PIP2 regulate the taste transduction ion channel TRPM5". *Proceedings of the National Academy of Sciences of the United States of America* 100.25 (2003): 15160-15165.

33. Sclafani A., *et al.* "CD36 gene deletion reduces fat preference and intake but not post-oral fat conditioning in mice". *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 293.5 (2007): R1823-R1832.

34. Oike H., *et al.* "Arachidonic acid can function as a signaling modulator by activating the TRPM5 cation channel in taste receptor cells". *Biochimica et Biophysica Acta* 1761.9 (2006):1078-1084.

35. Edfalk S., *et al.* "Gpr40 is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion". *Diabetes* 57.9 (2008): 2280-2287.

36. Harmon CM., *et al.* "Labeling of adipocyte membranes by sulfo-N-succinimidyl derivatives of long-chain fatty acids: inhibition of fatty acid transport". *The Journal of Membrane Biology* 121.3 (1991): 261-268.

37. Sun Q., *et al.* "Structure-activity relationships of GPR120 agonists based on a docking simulation". *Molecular Pharmacology* 78.5 (2010): 804-810.

38. Simons PJ., *et al.* "Apical CD36 immunolocalization in human and porcine taste buds from circumvallate and foliate papillae". *Acta Histochemica* 10 (2010): 1016.

39. Pepino MY., *et al.* "The fatty acid translocase gene CD36 and lingual lipase influence oral sensitivity to fat in obese subjects". *Journal of Lipid Research* 53.3 (2012): 561-566.

40. Drewnowski A., *et al.* "Sweet tooth reconsidered: taste responsiveness in human obesity". *Physiology and Behavior* 35.4 (1985): 617-622.

41. Mela DJ and Sacchetti DA. "Sensory preferences for fats: relationships with diet and body composition". *The American Journal of Clinical Nutrition* 53.4 (1991): 908-915.

42. Stewart JE., *et al.* "Marked differences in gustatory and gastrointestinal sensitivity to oleic acid between lean and obese men". *The American Journal of Clinical Nutrition* 93.4 (2011): 703-711.

43. Janssen Pharmaceutica NV. "Gpr120 agonists for the treatment of type II diabetes". World Intellectual Property Organization WO2014/159054A (2014).

44. Ronald M., *et al.* "Glucagon receptor antagonist compounds, compositions containing such compounds and methods of use". United States Patent US 7,989.472 B2 (2007).

45. Kehrel Beate. "Inhibition of the interaction between oxidized proteins and cd36 or the active mechanism thereof". World Intellectual Property Organization WO02 32445 A2 (2001).

46. Tontonoz P., *et al.* "PPARγ promotes monocytes/macrophage differentiation and uptake of ox-LDL". *Cell* 93.2 (1998): 241-252.

47. Tran TTT., *et al.* "Luminal lipid regulates CD36 levels and downstream signaling to stimulate chylomicron synthesis". *Journal of Biological Chemistry* 286.28 (2011): 25201-25211.

48. Teboul L., *et al.* "Structural and functional characterization of the mouse fatty acid translocase promoter: activation during adipose differentiation". *Biochemical Journal* 360.2 (2001): 305-312.

Volume 18 Issue 9 September 2019