Emerging Pharmacotherapies to Fight Obesity and Related Disorders

**Teodora Handjieva-Darlenska**, **Nadka Boyadjieva** and **Kaloyan Takov**

1Department of Pharmacology and Toxicology, Medical Faculty, Medical University – Sofia, Bulgaria
2School of Biomedical Sciences, College of Medicine and Veterinary Medicine, The University of Edinburgh, UK

**Abstract**

Obesity is a chronic disease, characterized by an accumulation of excess adipose tissue and associated with an increased risk for cardio-vascular diseases and mortality. Weight loss of a 5-10% prevents or tempers the severity of many obesity-related morbidities. The current therapy of obesity comprises diet, increased physical activity, and pharmacotherapy. At the moment, the only approved drug for treatment of obesity in the European Union is Orlistat. This paper covers the latest research in the field with emphasis on the modulation of the different physiological systems and peptides in the regulation of appetite and metabolism through drugs as well as new drugs to treat diabetes type 2 and obesity. Furthermore, the authors show own data and results on the treatment of obesity in animal models and humans.

**Keywords:** Pharmacotherapies; Obesity disorders; Body mass index; Weight loss

**Introduction**

Obesity is a growing problem among all ages and populations, regardless their income or social status. A report published recently with data collected six years ago showed that there are around 1.5 billion people worldwide which fall into overweight or obese categories (BMI ≥25kg/m²) representing 34% of the adult population on the planet [1] (Figure 1). The problems associated with obesity are not related only to aesthetic issues but more importantly to the complementary disorders such as hypertension, diabetes mellitus type II, dyslipidemia etc. Obese people are more susceptible to these disorders which progress rapidly and often irreversibly in these individuals. Overweight problems are difficult to be overcome by diets only as normal physiological mechanisms counteract any reduced food intake by increasing the appetite of the patients. Thus pharmacological treatments are needed to resolve this problem. Not many obesity-targeted drugs are marketed currently but extensive research leads to discovery of new small molecules and larger peptides which can potentially reduce obesity and associated health problems.

**Drugs Acting on Adrenergic and Serotonergic Systems**

Pharmacological approach might be taken to combat overweight states and obesity. Targets for antiobesity therapies are mainly in the central nervous system interfering with peptide receptors or adrenergic/serotonergic systems and also in the periphery by reducing absorption of nutrients. Among centrally-acting catecholamine-interfering drugs phentermine is a drug that suppresses appetite and is used in short-term treatments [2]. It increases the release of noradrenaline centrally and this is thought to be its main mechanism of action to reduce the appetite [3]. Recently a combination of phentermine with topiramate has been designed and showed good results from Phase III clinical trials [3-6]. Topiramate is an antiepilepsy drug with not entirely clear mechanism of action but thought to act synergistically with phentermine [7]. The Phase III study showed lower blood pressure, triglycerides, and glucose levels in the patient on phentermine/topiramate therapy compared with the placebo group and more than 50% of the treated obese people lost ≥10% of their body mass [3,4].

From the drugs which act on serotonergic systems lorcaserin has been approved for long-term treatment [2]. It is a selective 5-hydroxytryptamine (5-HT, serotonin) 2C receptor agonist and also showed good results in trials for sustained weight loss [8].

Recently a study compared five drugs that interfere with adrenergic and/or serotonergic system [9]. They either block selectively noradrenalin reuptake (mazindol) or serotonin reuptake (fluoxetine) or both (sibutramine) [9]. Some of the drugs act as noradrenalin releasers (diethylpropion) or to increase catecholamine action through various mechanisms including amphetamine-like action (fenproporex) [9]. The study was conducted in women and lasted one year and the drugs were administered along with lifestyle changes such as increased physical activity and reduced food intake. The results indicated a significant weight loss compared to placebo of all groups except women who were on fluoxetine. The biggest weight loss were with diethylpropion (mean weight loss=10kg) followed by sibutramine (mean weight loss=9.5kg). There were no significant differences found between women who used diethylpropion, sibutramine, mazindol or fenproporex at ≥5% and ≥10% weight loss suggesting they might be interchangeably taken [9].

**Peripheraly Acting Drugs**

Among the peripherally acting drugs which are designed for obesity treatment and interfere with nutrient absorption orlistat is the only one approved [10,11]. Orlistat is a derivative of lipstatin (an irreversible inhibitor of pancreatic lipase) and it inhibits gastric and pancreatic lipases [10,11]. Hence the drug reduces the hydrolysis of lipids and fatty acids and the amount of fat which is absorbed in the gut [12].

A very interesting new pancreatic lipase inhibitor was found in hen egg yolk [13]. It is an immunoglobulin G naturally stored in the hen eggs and called IgY which has the ability to inhibit pancreatic lipase and therefore to reduce the absorption of fat in the gut similarly to orlistat. It is administered by the enteral route (orally) and it has been shown to inhibit pancreatic lipase in the very low micromolar range [13]. However, it is important to note that this anti-lipase IgY did not...
induced weight loss in vivo but only reduced fat mass, adipose tissue, total lipids and cholesterol and increased the excretion of triglycerides from the body [13].

**Effects of Non-Hormonal Drugs on Metabolism**

We have previously published that various non-hormonal drugs may affect the metabolism. Our experimental studies on the atypical antipsychotic drug clozapine on male rats indicated that clozapine promoted obesity and insulin resistance. The long term treatment (30 and 60 days) of rats with clozapin presented changes in blood glucose after glucose challenge (by oral glucose tolerance test, OGTT). In addition, the rats on clozapin gained body weight. Our data correlate with the data of Ana Maria Volpato et al. about changes of leptin and ghrelin in the hypoglycemic state and 24 h after glucose challenge (by oral glucose tolerance test, OGTT). In our study shows that atypical antipsychotic drug clozapine may influence the glucose metabolism and develop both obesity and insulin resistance [14].

**The Effects of Alginates on the Appetite and Weight in Obese Rats**

Food supplements containing alginate acid is an approved pharmacological treatment of obesity. However, the effect of such supplements on the appetite regulation and metabolism is still unknown. Thus, the aim of our study was to investigate possible effect of alginates on appetite hormones such as ghrelin and leptin in obese male rats.

Male Wistar rats (n=30) were randomly assigned to two different groups: 1st group – control (on a chow food) and 2nd group – experimental (on a high-fat diet). The nutritional period consisted of 2 months. The high-fat group increased their body weight in comparison with the control group. Then, the obese rats (n=15) were put either on a food supplement with alginate acid or only on a high-fat diet. At the end of the study, rats were anaesthetized and killed. Blood specimens were taken for further biochemical analyses. Plasma ghrelin and leptin concentrations were examined by ELISA methodology.

High-fat diet led to the development of obesity in male Wistar rats. The group treated with alginate acid showed a significant reduction of body weight and adiposity. Moreover, there were changes in the blood levels of ghrelin and leptin between those treated with/without alginates. Thus, The beneficial effect of alginates on ghrelin could be possibly explained by its mechanical effect of the stomach mucosa, and thus on the ghrelin secretion [10].

Our studies on the effects of the alginate acid (Algigracil-instant) on the parameters of obesity show a significant reduction of body weight with 27.5% and decrease in plasma levels of glucose and triglycerides in our patients with overweight and obesity [15].

**Small Peptide Hormones as Potential Drug Targets**

Endocrine cells in stomach and gut secrete small peptide hormones (around 30 amino acid long) in response to food being ingested (e.g. pancreatic polypeptide, peptide YY, glucagon-like peptide-1, oxyntomodulin) or during fasting (e.g. ghrelin). These serve as a mechanism to signal the brain to reduce or increase the food intake by regulation of the appetite and also to reduce or increase peristalsis and gut blood supply [16]. The potential of these hormones to regulate appetite thus is exploited in order to generate new therapies to reduce the patient’s desire to eat and therefore to combat further weight gain.

**Targeting Ghrelin – A Peptide Which Increases Food Intake**

Ghrelin is a 28 amino-acid hormone secreted during fasting mainly by the stomach fundus but probably also by organs such as pancreas and lower gut [17]. It is posttranslationally modified with an acyl moiety on Ser3 position [18]. This serves to activate the ghrelin peptide which is physiologically inert in the non-acylated form [18]. Ghrelin acts on the hypothalamus in the brain to regulate the appetite mainly through GHS-R1A receptor which is a G-protein coupled receptor activating phospholipase C which in turn produces diacylglycerol (DAG) and inositoltrisphosphate (IP3) as second messengers and leads to elevated intracellular Ca2+ levels [18]. Ghrelin has rather complex actions on
 lobster endogenous GIP. They showed a significant difference in virus-like particles which induced an immune response and protected the animals [23]. Fulurija et al. [25] vaccinated mice by attaching GIP to its receptor and knockout studies appeared to be effective in reduction of weight gain of the animals [23]. Zorilla et al. [23] proposed a method using ghrelin fragments attached to haptens – molecules able to elicit immune response. This has been carried out [25]. Gastric inhibitory peptide (GIP) is reduced plasma ghrelin levels in Wistar rats and reduced the weight gain of the animals [23].

These features of the ghrelin system enables researchers to target it in order to reduce the appetite and therefore cause weight loss in patients who are overweight or obese. There are several approaches used: directly targeting ghrelin release, antagonism of ghrelin receptor or inhibition of ghrelin O-acyltransferase (GOAT) enzyme which produces activated acyl-ghrelin [20-23].

Inhibition of GOAT enzyme has been achieved by modification studies of its substrate – ghrelin [22,24]. Authors showed that a peptide with the first five amino acids of the ghrelin which is octanoylated on Ser3 and has two amide ends (Figure 2) can serve as an inhibitor. It was also shown that when Ser3 is replaced by diaminopropionic acid (Dap) the inhibitory effect is increased [22].

Another way to interfere with ghrelin is to antagonise its receptor and several studies with compounds acting as antagonists have been conducted [20]. However, there are still very few in vivo results for these drugs and they are still under development [20].

A very interesting recent approach is to sequester ghrelin peptide by use of an RNA molecule modified by polyethylene glycol to obtain the so called “RNA Spiegelmer” [21]. This RNA binds ghrelin and neutralises it thus blocking its action on GHS-R1A receptor. Authors proved that the RNA is stable in vivo and a treatment of obese mice showed weight loss and reduced food intake [21].

Furthermore, vaccination against ghrelin has also been suggested [23]. Zorilla et al. [23] proposed a method using ghrelin fragments attached to haptens – molecules able to elicit immune response. This reduced plasma ghrelin levels in Wistar rats and reduced the weight gain of the animals [23].

Experiments with vaccination against another gastrointestinal peptide has been carried out [25]. Gastric inhibitory peptide (GIP) is an incretin released from the small intestine which has been shown to have effects on glucose and lipid metabolism [25]. Since antagonists to its receptor and knockout studies appeared to be effective in reduction of weight gain Fulurija et al. [25] vaccinated mice by attaching GIP to virus-like particles which induced an immune response and protected against endogenous GIP. They showed a significant difference in vaccinated versus control mice weight 70 days after start of treatment and the fat tissue of vaccinated mice at day 142 was reduced significantly. Essential part of their experiments were the results showing that GIP does not impair normal glucose tolerance and metabolism which might have been expected as a side effect of such a therapy [25].

Our data shows the effect of Orlistat on take ghrelin secretion by the stomach mucosa in rats [15]. In our study we have demonstrated that Orlistat group has significantly lower plasma levels of ghrelin, compared to the control group. We speculate on the hypothesis that Orlistat as acting in the stomach inhibits the secretion of ghrelin. Most changes in ghrelin secretions could be as a result of interaction between the Orlistat molecules and the ghrelin receptors in the stomach. Further investigations are needed to examine the mechanism of actions between Orlistat and ghrelin.

Handjiev and Hadjieva-Darlenska et al. (2008) have demonstrated data for beneficial lifestyle changes (resp. reduced fat intake) in obese patients after 3-month treatment of Orlistat.

Peptides which Reduce Food Intake

Peptide tyrosine-tyrosine (PYY) and glucagon-like peptide-1 (GLP-1) are small gastrointestinal hormones secreted in response to food ingestion [16]. PYY acts presynaptically on a subtype of neuropeptide Y receptors and negatively regulates neuropeptide Y release which causes reduction in appetite and therefore food intake [26]. PYY has a short half-life due to being rapidly cleaved by dipeptidyl peptidase-4 (DPP-4) in blood [26].

Similarly to studies shown above for GOAT inhibitors, Tan et al. [27] modified naturally occurring PYY and synthesised a peptide with several amino acid changes, C-terminal amide group and an additional amino acid. Phase I clinical trials have been conducted with results showing increased half-life with respect to PYY and good tolerability [27]. However, there are still no outcomes of efficacy studies in humans which should show the ability of this compound to be used as a treatment for obesity.

Usually peptide hormones are not efficient when administered orally due to the presence of proteases in the stomach. Interestingly however, PYY was detected in the mice saliva and it appears to induce satiety by action on receptors in mouth [28]. This was exploited by authors and by targeted gene delivery of PYY to salivary glands they remarkably achieved 12.3% reduction in food intake and significant but not very convincing body weight reduction [28]. Another delivery methods examined PYY-vitamin B12 conjugate exploiting the route of
vitamin B\textsubscript{12} absorption in order to increase the bioavailability of the hormone [29]. Intranasal administration has also been investigated in humans but the experiment failed to give any positive outcomes [30].

GLP-1 is another peptide which is secreted from the gut and have anorexigenic and incretin properties [16,26]. It acts via G-protein coupled receptors in the gastrointestinal tract and in the brain (mainly hypothalamus) to decrease gut motility and appetite [16]. Similarly to the other peptides it has a short half-life in blood being degraded by DPP4 enzyme and therefore GLP-1 is not useful as a drug itself [16,26].

To overcome these problems drugs like exenatide were developed [31]. Being a homolog of the human GLP-1 it acts on the same receptor but it is more potent and in addition to that it is not subject to DPP-4 degradation [31]. This appeared to be a good approach as many clinical studies showed reductions in glucose and body weight of subjects on exenatide [31]. Lixisenatide is a derivative of the exenatide and have also been approved for human use [32].

The search for a GLP-1 analogue that would be even more stable in plasma but that would still act on its receptor continues. Laraglutide has been designed which is very similar to GLP-1 but it is conjugated to a fatty acid chain which allows it to bind to plasma albumin and therefore achieve a longer half-life [16]. Phase III clinical trial assessed the ability of liraglutide to sustain weight loss [33]. This was achieved by liraglutide treatment and even additional weight loss has been observed [33]. However, it has been noted that after the treatment stopped patients showed some weight gain even though it was less than the subjects previously on placebo [33].

Other studies in humans with oral administration of PYY with or without GLP-1 being co-administered gave a mean reduction of single-meal food intake of 12.0% for PYY alone up to 21.5% with GLP-1 co-administration but no long-term (24 hours) significant difference was detected which might imply a need for frequent administration [34].

Novel delivering technologies are also under investigation. This include slow-release formulation of exenatide or an osmotic pump device to deliver the same drug in a continuous manner subcutaneously [16].

Therapies exploiting other anorexigenic hormone pathways are also under development such exploiting systems of oxyntomodulin [16,35,36] and pancreatic polypeptide [16,27,37]. None of them have reached market yet but some substances can be regarded as potential drug candidates.

**Antidiabetic Drugs to Treat Obesity**

There is an increase in awareness that antidiabetic drugs might be used to treat obesity as well. Such examples are dapagliflozin and canagliflozin [38,39]. Both drugs selectively inhibit Na\textsuperscript{+}/glucose co-transporter 2 expressed in the proximal tubules in nephrons of the kidney which is responsible for reabsorption of glucose from tubular lumen back into the blood [40]. Blockage of this channel will result in a rise of the osmotic pressure of the tubular fluid which will increase the amount of urine excreted leading to increased energy expenditure and loss of body weight [38]. Two-year study in Europe in patients with diabetes mellitus type II assessed the long-term effects of dapagliflozin and found reductions in overall body mass, fat mass, waist circumference and blood glucose [38]. Similar results were obtained in a trial with canagliflozin [39].

The most widely used drug for treatment of diabetes mellitus type II is metformin. Its molecular mechanism is not entirely understood although it is thought to be an insulin sensitizer acting to lower blood glucose, increasing its uptake in muscle cells and reducing de novo production by gluconeogenesis in the liver [41]. It acts by inhibiting complex I of the respiratory chain in mitochondria [41] but also by other mechanisms including a recently discovered one which shows that metformin is able to reduce lipid accumulation in liver by activating AMP-activated protein kinase (AMPK) which phosphorylates and inactivates acetyl-coA carboxylases – rate-limiting enzymes in fatty acid synthesis [42]. Knockout studies demonstrated that AMPK is an essential regulator of lipid accumulation and insulin sensitivity which can have implications in obesity-diabetes treatments [42].

**Conclusion**

To sum up, the pharmacotherapy of obesity is a complex and difficult process because it includes an interplay between appetite-regulating hormones and several neuro-endocrinological systems. In the last decade two drugs were withdrawn from the market due to side effects on the cardio-vascular system and psychological problems. Several new drugs are arising at the US market affecting the noradrenaline system, and show a promising results. The only drug for treatment of obesity in Europe is Orlistat with its well-known beneficial effects on body weight and lipids but with no effect for a long-term use. The new stars on the horizon are the ghrelin antagonists and the incretin-based therapy widely used for the treatment of diabetes type 2. More research is needed to elucidate the mechanism of these drugs/ vaccine for the long-term therapy of obesity.

**References**

1. Keats S, Wiggins S (2014) Future diets: Implications for agriculture and food prices.
2. Monteiro MP (2014) Obesity vaccines. Human vaccines & immunotherapeutics 10: 1.
3. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, et al. (2011) Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. The Lancet 377: 1341–1352.
4. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, et al., (2012) Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. The American Journal of Clinical Nutrition 95: 297-308.
5. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwartz ML, et al. (2012) Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity (Silver Spring) 20: 330-342.
6. Winslow DH, Bowden CH, DDSonato KP, McCullough PA (2012) A randomized, double-blind, placebo-controlled study of an oral, extended-release formulation of phentermine/topiramate for the treatment of obstructive sleep apnea in obese adults. Sleep 35: 1529-1539.
7. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE (2000) An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia 41 Suppl 1: S3-9.
8. Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, et al. (2010) Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med 363: 245-256.
9. Suplicy H, Boguszewski CL, Dos Santos CM, do Destesto de Figueiredo M, Cunha DR, et al. (2014) A comparative study of five centrally acting drugs on the pharmacological treatment of obesity. Int J Obes (Lond) 38: 1097-1103.
10. Handjieva-Darlenska T, Boyadjieva N (2014) The effects of alginates on the appetite and weight in obese rats. Obesity Facts 7: 72-73.
11. Sjöström L, Rissanen A, Andersen T, Baldring M, Golay A, et al.(1998) Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. The Lancet 352:167–172.
12. Nakai K, Wada R, Iida S, Kawanishi T, Matsumoto Y (2014) Modeling and simulation of orlistat to predict weight loss and weight maintenance in obesity patients. Drug Metab Pharmacokinet 29: 278-282.
13. Hirose M, ANDo T, Sho&iq R, Umeda K, Kodama Y, et al. (2013) Anti-obesity activity of hen egg anti-lipase immunoglobulin yolk, a novel pancreatic lipase inhibitor. Nutr Metab (Lond) 10: 70.
14. Lazarov L, Boyadjieva N (2014) Effects of non-hormonal drugs on metabolism, Xth International Symposium on Obesity and Related Diseases. Albena, abstract: A3.
15. Handjieva-Darlenska T, Boyadjieva N (2007) VII. Pharmacotherapy of obesity. Obesity: pharmacotherapy and pharmacogenetics: 291–320.
16. Troke RC, Tan TM, Bloom SR (2014) The future role of gut hormones in the treatment of obesity. Ther Adv Chronic Dis 5: 4-14.
17. Wierup N, Sundler F, Heller RS (2013) The islet ghrelin cell. J Mol Endocrinol 52: R35-49.
18. Delporte C (2013) Structure and physiological actions of ghrelin. Scientifica (Cairo) 2013: 518909.
19. Williams DL, Grill HJ, Cummings DE, Kaplan JM (2003) Vagotomy dissociates short- and long-term controls of circulating ghrelin. Endocrinology 144: 5184-5187.
20. Schellens H, Dinan TG, Cryan JF (2010) Lean mean fat reducing “ghrelin” machine: hypothalamic ghrelin and ghrelin receptors as therapeutic targets in obesity. Neuropeharmacology 58: 2-16.
21. Shearman LP, Wang SP, Heliming S, Stirblis DS, Mazur P, et al. (2006) Ghrelin neutralization by a ribonuclease acid-SPM ameliorates obesity in diet-induced obese mice. Endocrinology 147: 1517-1528.
22. Yang J, Zhao TJ, Goldstein JL, Brown MS (2008) Inhibition of ghrelin O-acetyltransferase (GOAT) by octanoylated pentapeptides. Proc Natl Acad Sci U S A 105: 10750-10755.
23. Zorrilla EP, Iwasaki S, Moss JA, Chang J, Otsuji J, et al. (2006) Vaccination against weight gain. Proc Natl Acad Sci U S A 103: 13226-13231.
24. Guallullo O, Lago F, Dieguez C (2008) Introducing GOAT: a target for obesity and anti-diabetic drugs? Trends Pharmacol Sci 29: 398-401.
25. Fulurija A, Lutz TA, Sladko K, Osto M, Wielinga PY, et al. (2008) Vaccination against GIP for the treatment of obesity. PLoS One 3: e3163.
26. Yu JH, Kim MS (2012) Molecular mechanisms of appetite regulation. Diabetes Metab J 36: 391-398.
27. Tan TM, Field BC, Minnion JS, Cuenco-Shillito J, Chambers ES, et al. (2012) Pharmacokinetics, adverse effects and tolerability of a novel analogue of human pancreatic polypeptide, PP 1420. Br J Clin Pharmacol 73: 232-239.
28. Acosta A, Hurtado MD, Gorbatyuk O, La Sala M, Duncan D, et al. (2011) Salivary PYY: a putative bypass to satiety. PLoS One 6: e26137.
29. Fazen CH, Valentin D, Fairchild TJ, Doyle RP (2011) Oral delivery of the appetite suppressing peptide HPYY(3-36) through the vitamin B12 uptake pathway. J Med Chem 54: 8707-8711.
30. Gantz I, Erondu N, Mallick M, Muser B, Krishna R, et al. (2007) Efficacy and safety of intranasal peptide YY3-36 for weight reduction in obese adults. J Clin Endocrinol Metab 92: 1754-1757.
31. Robles GI, Singh-Franco D (2009) A review of exenatide as adjunctive therapy in patients with type 2 diabetes. Drug Des Devel Ther 3: 219-240.
32. Bolli GB, Owens DR (2014) Lixisenatide, a novel GLP-1 receptor agonist: efficacy, safety and clinical implications for type 2 diabetes mellitus. Diabetes Obes Metab 16: 988-901.
33. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, et al. (2013) Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The Scale Maintenance randomized study. International Journal of Obesity: 1-9.
34. Steinert RE, Poller B, Castelli MC, Drewe J, Beglinger C (2010) Oral administration of glucagon-like peptide 1 or peptide YY 3-36 affects food intake in healthy male subjects. Am J Clin Nutr 92: 810-817.
35. Tan T, Bloom S (2013) Gut hormones as therapeutic agents in treatment of diabetes and obesity. Curr Opin Pharmacol 13: 996-1001.
36. Irwin N, Flatt PR (2013) Enteroeudocrine hormone mimetics for the treatment of obesity and diabetes. Curr Opin Pharmacol 13: 989-995.
37. Banerjee A, Onyukseh H (2012) Human pancreatic polypeptide in a phospholipid-based micellar formulation. Pharm Res 29: 1696-1711.
38. Bolinder J, Ljunggren O, Johansson L, Wilding J, Langkilde AM, et al. (2013) Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes, Obesity and Metabolism 15: 159-169.
39. Wilding JP, Charpentier G, Hollander P, Gonzalez-Galvez G, Mathieu C, et al. (2013) Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylureas: a randomised trial. Int J Clin Pract 67: 1287-1292.
40. Borghese M, Majowicz M (2009) Inhibitors of Sodium/Glucose Cotransport. Drugs of the Future 34: 297.
41. Shaw RJ (2013) Metformin trims fats to restore insulin sensitivity. Nat Med 19: 1570-1572.
42. Fullerton MD, Galic S, Marcinko K, Sikkema S, Pulinaikunn T, et al. (2013) Single phosphorylation sites in Ac1 and Ac2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. Nat Med 19: 1649-1654.