Oxyntomodulin, Obestatin and Leptin Potential Weight Reducing Agents: a Review

Shriram Bairagi[1*], M.A. Hameed Sadiq[1], Mohammed Shoaib Patel[1], Rahul B. Ushir[1], Suraj V. Patil[1], Ramesh Choudhary[1]

1. Ideal College of Pharmacy and research, Kalyan (E), 421306, Maharashtra, India.

ABSTRACT

As obesity remains the center of concern from many decades but yet there is no exact treatment, mostly you have to prefer the surgical method such as gastric bypass, which remains the only therapeutic treatment and the anti-obesity pharmacotherapy remains very limited therefore the priority is to discover or develop more potent drugs. The only potential strategy is to achieve weight loss it can be done by either reducing energy intake or by stimulating anorexigenic signals or by blocking orexegenic signals and to increase energy expenditure. This can be achieved by stimulating the Oxm, peptide PYY, GLP, GLP-1 receptor, and fat cells derived hormone like Leptin and Obestatin these reduces obesity by reducing food intake as seen in mice and humans by stimulating satiety signals, and by regulating the glucose homeostasis, by secreting glucose dependent insulin.

Keywords: Oxyntomodulin, Obestatin, Leptin, anti-obesity

*Corresponding Author Email: shrirambairagi@gmail.com

INTRODUCTION

Oxyntomodulin (Oxm) is an intestinal peptide from the pre-proglucagon family, which inhibits gastric acid secretion[1, 2] and inhibits food intake[3]. Oxm can bind and activate the glucagon-like peptide (GLP)-1 receptor[3, 4, 5]. The anorectic effects of Oxm are blocked by the GLP-1 receptor antagonist extend [6–9] and are absent in the GLP-1 receptor knockout mouse, suggesting that they are mediated by the GLP-1 receptor. Oxm and GLP-1 may differ in terms of central nervous system penetration or tissue-specific modification of receptor function but appear likely to both act via the GLP-1 receptor for at least some functions. Rational modifications of peptide sequence or secondary structure may enhance bioactivity and half-life[8]. Oxm treated animals lose more weight than control animals that consume the same amount of calories, which suggests that Oxm increases energy expenditure, possibly via an effect on the thyroid axis. Oxm has been found to reduce energy intake in normal-weight volunteers when administered intravenously or subcutaneously before a single study meal[9-11]. Oxyntomodulin enhanced glucose clearance via stimulation of insulin secretion but had no independent effect on insulin action in mice[12], Levels of Oxm vary throughout the day. Highest levels are detected in the evening, which then gradually fall to very levels in the early hours of the morning[13]. Oxm and GLP-1 are products of the preproglucagon gene (PPGP) produced by the action of prohormone convertase enzymes 1 and 2[14, 15]. Oxm is also a product of post-translational processing of preproglucagon in the intestine and the CNS[16]. Satiety signals include a number of ascending neural inputs as vagal signals from the gut, as well as metabolic and hormonal changes, including plasma glucose, gastrointestinal release of anorexigenic hormones such as peptide YY (PYY), pancreatic polypeptide (PP), Oxm, glucagon like peptide-1 (GLP-1) and cholecystokinin (CCK), suppression of ghrelin, and synergism with the anorexigenic adipocyte derived leptin. PWS patients have delayed meal termination, earlier return of hunger after the previous meal with early meal initiation[17]. Oxyntomodulin was identified over two decades ago, when it was found to reduce stomach acid and delay emptying of stomach contents in rodents. However, the available data showed no effect on gastric emptying in humans and its role in the control of appetite has only recently emerged Oxm, consists of 37 amino acids, and contains the 29 amino acid structure of glucagon, followed by an octapeptide C-terminal extension[18]. Oxm is a candidate substrate for the enzyme DPP-IV[19]. Oxm is released from intestinal L-cells 5–10 min after meal initiation. Levels peak at 30 min and in proportion to caloric intake, remaining elevated for several hours[20]. Like GLP-1, Oxm is also secreted by L cells of the small Intestine in response to a meal. In both rodents [21, 22] and in humans, [23] Oxm inhibits energy

intake. These effects are thought to be mediated via the GLP-1 Receptor and its effects are inhibited by the GLP-1 Receptor antagonist exendin-9-39[24]. The downstream anorectic effects of Oxm appear to be mediated by the GLP-1 receptor since these effects were abolished in GLP-1 receptor null mice[25]. Although Oxm has a 50-fold lower affinity for binding at this receptor and less potent incretin activity, it has an equal potency for inhibiting food intake[26, 27, 28]. It is not clear how differential potency is mediated by acting on the same receptor. Studies have demonstrated that the two hormones produce different patterns of neuronal activation in the hypothalamus.[27.29, 30] Oxm cross-reacting with other receptors, an independent Oxm receptor, ligand-specific interactions at the GLP-1 receptor or a combination of all three.[31] Oxm is an alternative cleavage product of proglucagon that is co-secreted with GLP-1 from the L cells of the distal small bowel[32]. Oxm acts as a dual agonist of the GLP-1 receptor and the glucagon receptor. However, it is a less potent ligand at these receptors than the canonical peptides by 1 and 2 orders of magnitude, respectively[33]. Nevertheless; Oxm can combine the effects of GLP-1 and glucagon to act as a potentially more effective treatment for obesity than GLP-1 receptor agonists. GLP-1 and glucagon are known to suppress food intake. In addition, glucagon can increase energy expenditure[34]. The combination of decreased intake of food and increased expenditure of energy would be expected to enhance weight loss compared with decreasing intake of food alone (as with GLP-1). Activation of glucagon receptors is classically associated with an elevation in glucose levels, which would be deleterious in patients with T2DM[35], but GLP-1 receptor agonism would be expected to counteract this effect. Indeed, Oxm administration to high fat-fed mice improved glucose tolerance, enhanced glucose disposal in a hyperinsulinaemic clamp study and inhibited endogenous production of glucose[36]. Some reports indicate that sustained glucagon receptor (GCGR) activation not only decreases food intake, but also promotes lipolysis and weight loss. Chronic investigation of glucagon's metabolic effects are challenging since the native hormone is rapidly degraded and has poor solubility and stability in physiological buffers. Glucagon and GLP-1 have distinct receptors that are also structurally related.[37] Central and peripheral administration of Oxm inhibits food intake in rodents and humans. Some of the anorectic effects of peripherally administered Oxm may be effected through a reduction in circulating levels of ghrelin.[38, 39] Similar to GLP-1 Oxm also simulates the release of insulin[40]; Oxm is a potent inhibitor of food intake when administered intraperitoneally[41] intra cerebroventricular in rats. [42] Oxm anorectic actions are blocked by co-administration of the GLP-1 receptor antagonist, exen-din-9–39[42]. Oxm also augmented postprandial insulin secretion, inhibited gastric acid secretion and reduced gastric motility. [42] It is known to delay gastric emptying and to reduce gastric acid secretion. It also reduces feeding in the

rat, an action which is blocked following co-administration of a GLP-1 antagonist[43]. Two studies in obese humans have suggested that Oxm, or related peptides, might have utility in the treatment of obesity. In a four week trial with obese participants, sc administration of Oxm three times daily led to a reduction in body weight that was 1.8 kg greater than observed with placebo,[44] subsequently it was shown that Oxm administration was associated with increased energy expenditure in addition to a reduced food intake[45]. The effects of Oxm on food intake may be caused by a reduction in plasma ghrelin level s and/or an increase in the release of a MSH in the ARC[46, 47]. Oxm increases core body temperature and heart rate in rodents [48] while in humans it has been shown to increase energy expenditure and voluntary physical activity[49]. Oxm reduces bodyweight in animal and human studies due possibly to suppression of pre-prandial released ghrelin[48, 50].

Therapy for Obesity

Oxm acts on the hypothalamus, an area of the brain known to be important for the control of energy balance. Oxm and other circulating signals are able to cross the barrier between the blood and the brain, via a specialized area next to the hypothalamus. The hypothalamus can then receive and integrate these signals. Neurotransmitters are released, which send messages from the hypothalamus to many different brain regions and result in changes in behavior. Thus, an increase in the circulating levels of Oxm results in a feeling of satiety and allows an increase of activity levels.[51]
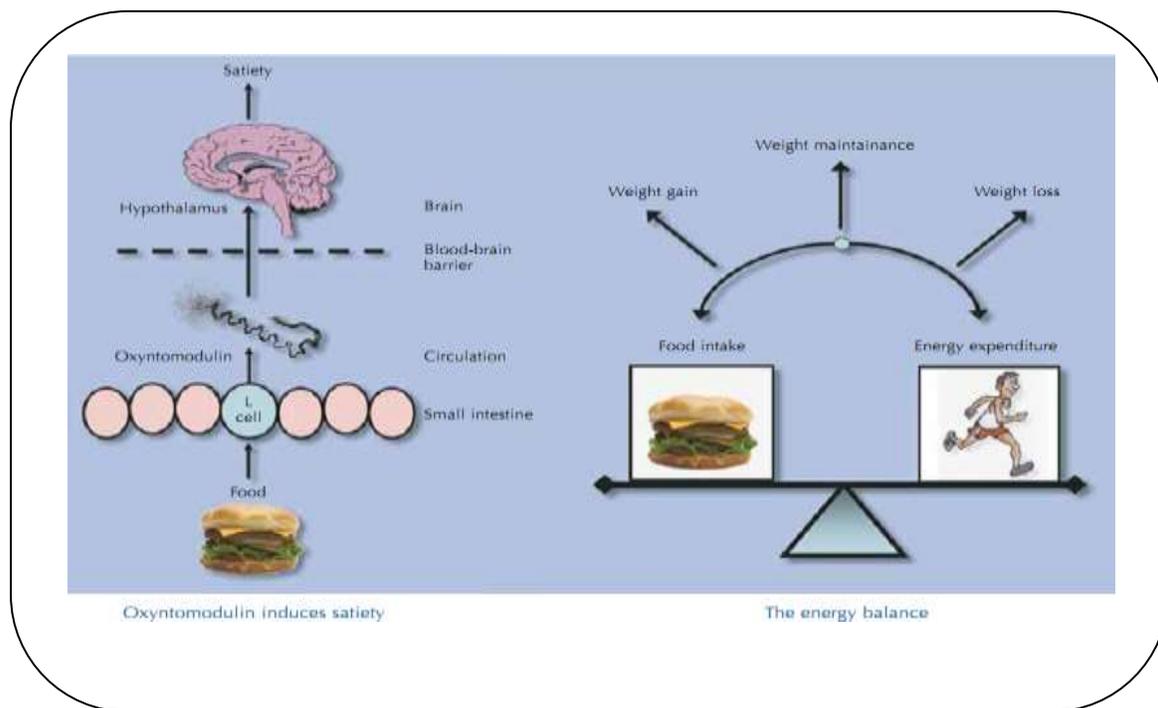
Chemistry

Oxm is a product of proglucagon processing in the intestine and central nervous system (CNS), released from intestinal L-cells with the putative satiety factor, glucagon-like peptide-1 (GLP-1)[52]. It is also produced in the neurons of the nucleus of the solitary tract (NTS) of the brain stem[53]. The structure of Oxm comprises the entire glucagon sequence with a C-terminal basic octapeptide extension named spacer peptide-1 (also known as KA-8) [54,55].

Recent Discoveries

The role of Oxm and peptide tyrosine-tyrosine (PYY) in appetite control has recently been review[56, 57]. Recent evidence has also suggested that Oxm may play a role in glucose homeostasis through long term bodyweight reduction, most probably due to the causal link between obesity and type-2 Diabetes[58] as well as enhancing glucose-dependent insulin Secretion[59]. Proglucagon peptides are rapidly degraded by the ubiquitous enzyme dipeptidyleptid as e-IV (DPP -IV) [60]. However, many studies have demonstrated greatly increased bioactivity of other DPP-IV susceptible gut hormones through Chemical modifications[61, 62]. Notably, substitution of the naturally occurring L-Ala at position 8 in GLP-1 or position 2 in GIP results in DPP-IV resistance[63, 64]. Furthermore terminal PEGylation and fatty acid derivatisation of GIP and GLP-1 results in long eracting and more potent analogues, due largely to reduced renal clearance through binding to plasma proteins.[65,66] Building on these observations and approaches to stabilize related gut hormones, we developed a novel Oxm analogue with D-Ser at position 2 and C-16 palmitic acid conjugated via a mini-PEG linker at the C-terminus, (D-Ser2) OXM [mPEG-PAL], and assessed its antihyperglycaemic, insulinotropic and anorexigenic properties. mPEG was used as a linker in view of previous reports that such linkers improve the actions of other acylated peptides such as GLP -1[65]. Oxm induces catabolic effects that favor weight loss through activation of the glucagon receptor while modulating glucose homeostasis through agonism of the GLP-1 receptor[67]. Indeed, the insulinotropic properties of GLP-1 and the regulation of metabolism in fasting through the glucagon receptor are well established[68, 69]. Oxm has been shown to activate both GLP-1 and glucagon receptors, albeit with a 10 to 100-fold reduced potency relative to GLP-1 and glucagon[70]. This may point to the possibility of a dual action Oxm based therapy aimed at both obesity and type-2 diabetes.[71] Studies have shown that Oxm reduces food intake in rodents[71, 72, 73]. Furthermore, chronic Oxm administration to rodents has been shown to reduce their weight-gain.[74] Similarly in humans, acute Oxm administration reduced food intake in lean volunteers[75] Chronic Oxm subcutaneous injections in obese individuals induced an average weight-loss of 2.3 kg after 4 weeks, compared to 0.5 kg in the control group [76] Work by Wynne et al. suggests that

this effect could also be due to an increase in energy expenditure, since thrice daily subcutaneous administration of Oxm resulted in a 26.2 ± 9.9% increase in activity-related energy expenditure over a 4-day period in healthy, overweight or obese individuals[77].
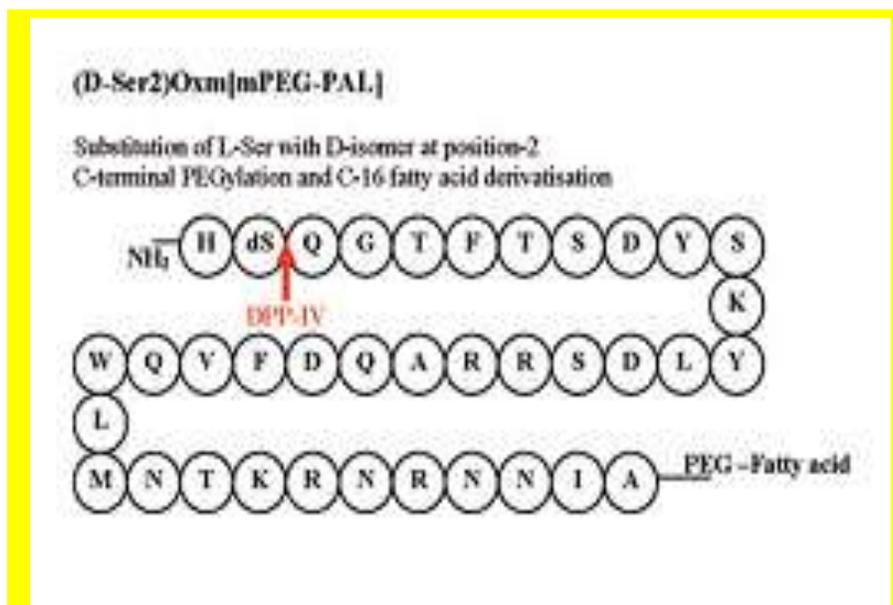
Oxm and Peptide Tyrosine–Tyrosine (PYY)

Oxyntomodulin and peptide tyrosine-tyrosine (PYY) are released from intestinal enteroendocrine cells in response to a meal. The weight loss that has been observed in animal models after repeated administration of Oxm and PYY has led to interest in developing these peptides as antiobesity therapies in humans. Preliminary studies have found that Oxm or PYY administration reduces food intake and body weight effectively in overweight human being. Oxm and PYY are synthesized within the gastrointestinal tract in specialized enteroendocrine cells, named L cells,[78] After a meal, Oxm and PYY are released synchronously[79]. The rapid rise of circulating hormone levels signals a change in energy status to the brain and also acts locally to enhance digestive processes. Within the gastrointestinal tract, Oxm delays gastric emptying and decreases gastric acid secretion,[80] PYY increases meal absorption, slows gastric emptying and delays gallbladder and pancreatic secretion[81, 82, 83]. Batterham *et al.*[84] observed that chronic administration of PYY led to reduced food intake and an accompanying reduction in weight gain after 2 days, suggesting that PYY could also be involved in body-weight homeostasis. This work was supported by data from Pittner *et al.*,[85] who found that peripheral administration of PYY reduced energy intake, body-weight gain and glycemic index in wild-type mice and in several rodent models of obesity and type 2 diabetes. Sileno *et al.*[86] reported in 2006 that rabbits treated with daily bolus intravenous injection of PYY have reduced average weight at the end of 2 weeks, and Koegler *et al.*[87] observed a 1.9% weight-

loss in rhesus macaques treated with twice-daily intravenous infusions of PYY over a 2-week period.

Leptin

The satiety hormone, Leptin is an anorexigenic adipokine with 167 amino acids[88]. It is made by fat cells which then regulates the amount of fat stored in the body, the following is done by suppressing the hunger and increasing the energy expenditure, When the amount of fats reaches a certain level the hunger is inhibited and the satiety hormone leptin is secreted, and primarily activating leptin receptors in the arcuate nuceus of the hypothalamus. The expenditure of energy is controlled by both via brain signals or by leptin receptors on peripheral targets[89]. The existence of a Hormone regulating hunger and energy expenditure was hypothesized based on studies of mutant obese mice colony at Jackson Laboratory in 1950. Mice homozygous for the ob mutation (ob/ob) ate voraciously and were massively obese[90]. In 1960s Douges Coleman identified a second mutation causing obesity and he named it diabetes (db/db)[91-93]. In 1990 the mapping of the ob gene was reported by Rudolph Leibel and Jeffrey M. Friedman[94-96]. The hypothesis of Leibel and Friedman was confirmed by other Labs too, that a novel hormone circulated in the blood and that could suppress food intake and body weight in ob and wild type mice, but not in the db type mice[97-100]. In 1994 Friedman isolated the ob gene and reported the discovery of the gene and he named it as Leptin. [V] Leptin was the first fat cell derived hormone[101]. Production sites are Adipose tissue and Non-adipose tissue includes stomach, placenta, skeletal muscle and mammary epithelium. The satiety is enhanced when the leptin combines with the Ob-R on afferent vagal nerves and directly to the ARC. The expression of orexegenic NPY/AgRP hypothalamic neurons is also inhibited. Also stimulates the anorexigenic POMC neurons in ARC. Leptin acts by Thermogenesis and decrease in Food intake. Thermogenesis stimulate the transcription of mitochondrial uncoupling protein (UCP) or thermogenin, which forms a channel in the inner mitochondrial membrane that allows protons to reenter the mitochondrial matrix without passing through the ATP synthase complex. This permits the continual oxidation of fuel (fatty acids in an adipocyte) without ATP synthesis, dissipating energy as heat and consuming dietary calories or stored fats in potentially very large amounts (Nelson and Cox 2005). Decrease in food intake occurs when the satiety is enhanced when the leptin combines with the Ob-R on afferent vagal nerves and directly to the ARC. The expression of orexegenic NPY/AgRP hypothalamic neurons is also inhibited. Also stimulates the anorexigenic POMC neurons in ARC[102]. Leptin insensitivity or resistance is also associated with obesity, rather than leptin deficiency. Obese and non-obese subjects have similar central leptin levels, which suggest that transport to CNS, rather than

intrinsic responsiveness to leptin, might be rate limiting for leptin activity in the obese state[103]. It would be necessary to develop a treatment that overcame leptin insensitivity or bypassed normal central leptin functioning, for example, by developing novel forms of leptin with stronger physiological properties[104].

Obestatin

Ghrelin, a circulating appetite-inducing hormone, is derived from a prohormone by post-translational processing. On the basis of the bioinformatic prediction that another peptide also derived from pro-ghrelin exists, they have isolated a hormone from rat stomach and named it Obestatin-a contraction of obese[105]. Obestatin is a hormone that is produced in specialized epithelial cells of the stomach and small intestine of several mammals including human[106]. Obestatin was originally identified as an anorectic peptide, but its effect on food intake remains controversial[107]. Obestatin was discovered using a bioinformatics approach, by computer search of the sequenced genomes of several organisms[108]. The functions of Obestatin is that it opposes the action of ghrelin[109]. Contrary to the appetite stimulating effects of Ghrelin, treatment of rats with Obestatin suppressed food intake, inhibited jejuna contraction, and decreased body-weight gain.[110] Studies on the Obestatin/Ghrelin ratio in the gastrointestinal tract and plasma are associated with obesity, [111] Prader-Willi syndrome, [112] and type-II diabetes mellitus[113, 114].

CONCLUSION

Oxm is an intestinal peptide from the pre-proglucagon family, which inhibits gastric acid secretion and food intake. Oxm can bind and activate the Glucagon like Peptide-1 (GLP-1) receptor. Preliminary studies have found that Oxm or Peptide tyrosine-tyrosine (PYY) administration reduces food intake and body weight effectively in overweight human being. Within the gastrointestinal tract, Oxm delays gastric emptying and decreases gastric acid secretion, PYY are released from intestinal enteroendocrine cells in response to a meal. PYY increases meal absorption, slows gastric emptying and delays gall bladder and pancreatic secretion, peripheral administration of PYY reduced energy intake, body-weight gain and glycemic index in wild-type mice and in several rodent models of obesity and type 2 diabetes. Leptin is an anorexigenic adipokine with 167 amino acids. It helps to regulate the fat stored in the body by inhibiting hunger and releasing the hormone leptin (which causes satiation), by binding to leptin receptors. Obestatin is mainly produced in the stomach and small intestine by specialized epithelial cells in several mammals. It can be said as anti-ghrelin as it opposes the actions of gherlin. So, Oxm along with leptin and obestin appears to be a potent and could be referred or considered as a choice of

treatment for obesity in near future as these possesses intrinsic ability of reducing food intake and even regulating the fats stored in the body.

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