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Are we at the verge of finding a new efficacious pharmacotherapy for obesity in the form of agonism at triple drug receptors: glucagon, Glucagon like peptide1 (GLP1), glucose dependent insulin tropic peptide (GIP)

Abstract

Obesity is becoming a worldwide pandemic, and it calls for concerted efforts to act in view of preventing it from becoming a menace. Since lifestyle interventions and exercise have proven to be not of much use by themselves with the weight loss getting defended by the obese brain, with the regained weight set point gets defended. Currently most pharmacotherapy do not offer a sustained weight loss and don't have efficacy over 1-5kg loss for over 3-6mths.Till now the only drug having some promise are believed to be thylakoids. Although the most effective weight loss strategy remains bariatric surgery(BS),although its mechanism of action remains unclear though it is the most effective ,but indicated in limited cases with severe morbidly obese or those with BMI over 35kg with co morbidities. Further it has disadvantage of being costly and not available to all obese patients and is not without its inherent risks .Still it causes immediate remission of T2DM,and mediates sustained weight loss .Some proposed mechanism of action of BS is by acting through CNS and some other GIT hormones like GLP1, ghrelin PYY. Thus the new class of multiagonists drugs are trying to combine to form a single molecular drug which might try to close the gap, improving efficacy to improve the metabolism of the system. The drug constitutes a single drug in which agonism for the receptors of glucagon, glucagon like peptide1 (GLP1), glucose dependent insulunotropic polypeptide (GIP) is combined. In preclinical studies these multiagonists do better than their mono agonist counter parts. In clinical trials rigorous safety analysis are on the way and these drugs might be on the way in becoming the elusive pharmacotherapy for obesity. Currently the drugs offering most promise as medical therapies remain thylakoids, BAT directed therapies and with these drugs passing the test of time and human clinical trials might be the most superior multiagonists for the future hopefully.

Keywords: BS; Glp1;GIP, Glucagon Dual and Triple Agonists; obesity; weight loss

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Introduction

The incidence of obesity in developed countries has increased rapidly and a parallel increase is seen in developing countries like India and China, having the highest population.[1] An effective therapy is badly needed to control the pandemic in view of morbidities associated like metabolic syndrome (MS), type2 diabetes mellitus (T2DM), hyperlipidemia, along with associated cardiovascular morbidity and mortality, which may prove to be fatal. Thus need of the hour is to have some effective way by which not only loss of weight can be achieved but its maintenance is also required. Life style interventions and exercize have proven to be ineffective by themselves .Of the pharmacotherapy developed earlier drugs like sibutramine and rimonabant although showing great promise initially had to be withdrawn in view of serious side effects. Thus currently only Qsymia (topiramate/plentermine slow release), Contrave (bupropion/naltrexone) are some of the combinations available yet, even with qsymia some side effects of phentermine are not tolerable and might not be accepted by the patient .The only effective acceptable thaerapies which remain are Glucagon like peptide (GLP1) agonists like liraglutide, dulaglutide etc but there also limitations in that weight loss is limited to 1-5kg and one needs long term maintenance. Till date only FDA approved drug is orlistat for long term maintenance although it's gastrointestinal (GIT) side effects might not be acceptable. Thylakoids are another group of drugs which hold promise in future targeting at different sites responsible for mechanism of action of obesity.[2–7] The only effective weight loss strategy that immediately gives weight loss is bariatric surgery(BS) which remains the most effective method till date.[8] We have tried to analyze how BS acts to understand how it can be translated to pharmacotherapy but there mechanism of action remains elusive .Some of the highlighted mechanisms are a change in Central nervous system(CNS) circuitry, change in gut hormone secretion related to gut brain axis. Yet BS is costly and not without risk.[9] Also it is recommended only for few indications like morbid obesity with BMI >40KG/m2 or with BMI>35kg/m2 with associated co morbidities. Thus a sustainable pharmacotherapy is needed which might have least side effects and achieve the desired targeting of weight loss, control co morbidities like MS,T2DM ,non alcoholic liver steatohepatitis(NASH).In our earlier review we had touched on how glucagon GLP co agonists were in pipeline,[4] but here we further elaborate ,how these strategies might help in overcoming lot of hurdles that pharmacotherapy faces once human clinical trials are cleared, although currently they are in early phase I and II trials.

Role of Glucagon like peptide(GLP1)- Glucagon like peptide(GLP1) is secreted by the large intestinal L cells ,a response to nutrients reaching there.GLP1 has a direct action on the β cells and stimulates glucose secreted insulin secretion along with acting via central nervous system(CNS) for decreasing food intake.[10] The native GLP-1 rapidly gets destroyed by the enzyme dipeptidyl peptidase IV(DPPIV),that cleaves it at the N-terminal Alanine at the second position=>the formation of the inactive GLP-19-36amide orGLP-19-37.[11,12] Thus GLP1 has a half life of 1.5-5.[13,14] This limitation gets overcome by substituting a d-Serine or aminoisobutyric acid(AIB)residues at position 2,which increases resistance to destruction by DPP-IV. Another modification done is by extending the peptide that includes the nine amino acids along with C terminal extension(CEX)of extendin -4,that can stabilize the secondary structure and depending on the structure of the peptide improve the glucagon receptor agonism.[15–18] Further modifications like site specific acylation/conjugation with large biomolecules have=>development of different GLP-1 analogs that are commercially available, having different efficacies.[17,18] Despite so many possible changes ,GLP1 analogs possess only modest weight decreasing capacity that is based on dose, duration of therapy that ranges from 1-5kg.[19,20] Higher dosing is not possible in view of side effects like nausea, gastrointestinal(GI) distress, to get more weight loss. Although GLP1 is effective in controlling glycaemia effects only developing GLP1 receptor agonists has limitations regarding weight loss strategies.

It has been observed that the native GLP1 has high structural similarity to glucagon and the glucose dependent insulinotropic peptide (GIP).Similarly very similar sequence homology is shared by receptors for GLP1, glucagon and GIP, hence one can use sequence hybridization to activate these receptors at the same time with a single molecule. It had been known that glucagon might reduce body weight by inhibiting food intake as well as increase in energy expenditure.[10] Thus it was thought that developing a single molecule having dual agonism at the receptors of glucagon and GLP1 might cause complementary, possibly synergistic pharmacological action, which would help to achieve greater weight loss and glucose lowering effects via no redundant signalling pathways. Whatever benefit is seen would help in reducing dose of GLP1 which help in decreasing side effects. Giving two independent peptides alone means there will be different pharmacokinetics /peptide for each peptide. Thus a loose combination of these peptides means they act by variation of absorption for each peptide, along with distribution and how they get metabolized and cleared. Advantage of unimolecular formulation is that they have only one pharmacokinetic profile that was hypothesized to result in superior metabolic benefits .Moreover it is easier to get food and drug authority (FDA) approval with a single molecule polygamist.

Coagonism of GLP1/Glucagon

Initially combining GLP-1R and glucagon receptor (GCGR) agonist looks contradictory. This is in view of glucagon increasing blood glucose levels by neogluconeogenesis along with glycogenolysis.[10] This would be a negative effect in an obese patient who is prone to acquire diabetes mellitus(DM).It has been seen that glucagon actually causes development of DM,[21] while patients having T2DM do have postprandial hyperglucagonemia due to improper glucose inhibition of glucagon secretion.[22–24] But one positive effect of glucagon is that it increases satiety following food intake along with increasing energy expenditure in rodents as well as humans.[10] Hence the basis of developing a dual agonist that targets receptors for glucagon and GLP1 was that the insulinotropic effect would balance any hyperglycaemic effect of glucagon ,and at same time the anorexia promoting effects of GLP1would act in concert with the anorectic along with atherogenic effects of glucagon that ultimately would initiate loss of weight(Figure 1).Some arguments are there that naturally in human body first such GLP1/glucagon dual agonist was built by god in the form of oxyntomodulin(OXM).But problem is that in spite of having activity at both receptors ,OXM mostly favours GLP1R over the GCGR as shown by pocai2014.[25]

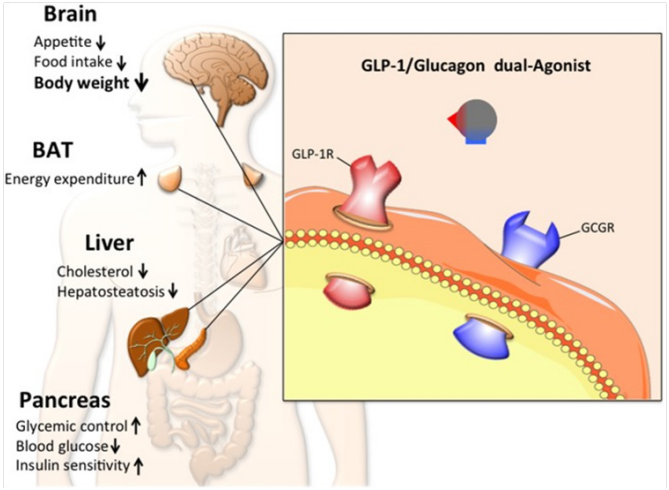

Figure 1 Courtesy ref no. 43 Schematic demonstrating the working principle, metabolic effects and key target tissues of the GLP-1/glucagon dual agonist, with the size of the text weighted to indicate the magnitude of the observed effect. Arrows pointing upwards indicate an increase or improvement, while arrows pointing downwards indicate a decrease. This dual agonist most prominently affects body weight.

The1st preclinically examined GLP1/Glucagon dual agonist got developed by DiMarchi and Tschop's group that was patented. It was based on the sequence which glucagon possesses having important GLP1 residues added to give it GLP1R agonism.[26] It also included an AIB residue at position number 2 for giving it protection against cleavage from DPPIV.A 40kda PEGylation got added to cysteine 24 for prolonging its *in vivo* action ,besides a lactam bridge introduced between Glu 16 and Lys 20 for stabilizing the secondary structure of this new molecule, and furher increase the GCGR action.[26] A single injection of 325nmol/kg given to DIO mice that was watched for 7days caused a reduction in food intake and body weight by 25%,mainly that was fat mass.[26] In a more chronic setup where weekly coagonist was administered at70nmol/kg ,for1mth =>28% loss in body weight ,mainly fat mass ,along with improved glucose tolerance with improved glucose tolerance, and increase in energy expenditure as well as increase in utilization of lipids as energy substrates.[26] Same dose showed that the coagonist decreases plasma triglycerides, lower density lipoprprotein(LDL) cholesterol and total cholesterol in a 27day study, along with reducing circulating leptin and normalized liver lipid content.[26] These observations show that this coagonist has multiple actions by which it corrects obesity along with improving metabolism simultaneously .

A 2nd example of a GLP1/GCGR coagonist was developed by the group of Merck. This was based on modifying the natural hormone OXM. To enhance the activity of OXM, d-Serine was substituted at 2nd position with a cholesterol residue addition at the C terminus of the peptide.[27] The resulting Dual AG peptides showed almost balanced

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potency at the receptors for GLP1 and glucagon.[27] When this Dual AG was given subcutaneous(s/c) every alternate day at a dose of 1.9pmol/kg x14 days which caused a decrease in food intake along with 25% body weight loss, mainly because of fat mass loss. Also this Dual AG=>markedly improved glucose tolerance associated with normal glucose levels, both beneficial effects following weight loss.[27] Same effects got reduced if either GLP1R-/- or GCGR-/-mice got used,[27] showing that both receptors were adding to the metabolic effects and thus importance of synergistic effects of both receptors.

3rdly GLP1/GCGR coagonist is developed by Sanigi, based on the extendin -4structure along with addition of glucagon residues added to increase activity of GCGR.[28] They found that by adding d-Serine at 2nd position like other dual agonists decreased degradation by peptides along with adding a palmitic acid at a Lys 14 for extending half life ,measured as 3.2h in healthy mice.[28] Giving a twice/day s/c injection of 50µg/kg of the dual agonist over32 days in DIO mice =>a lower HbA1c levels as compared to control animals.[28]

Another 4th GLP1/GCGR coagonist (MED 10382) is being developed by Med Immune. This peptide possesses equal activity at both receptors and has greater stability, not getting peptide degradation.[29] Its half life gets further increased by palmitoylation at lys 10, that increases binding to albumin. Giving acute injection in dose of 10nmol/kg in DIO mice decreased food intake along with improving glucose tolerance, the effects absent in GLP-1R knockout mice.[29] Giving it at a chronic rate of 30nmol/kg of this MED10382 caused a 30% reduction of food intake over 4weeks.[29] In another study giving 10nmol/kg over 3weeks => more weight loss in comparison to pair fed controls ,along with greater O2consumption and a decrease in the respiration exchange ratio as compared to vehicle controls, and this was not accompanied by any change in locomotor activity, which suggests that energy expenditure is an important part of weight loss. These weight loss effects were also seen in cynomolgous monkeys .These monkeys were given a dose between 8-27nmol/kg over 29days where they lost between 5 and 13%of their body weight,[29] which was associated with decrease in food intake. Following stoppage of therapy, monkeys who had received treatment with MED10382 maintained a lower body weight as compared to control monkeys that suggests probably MED10382 caused a lower set point for body weight regulation. In another study giving 4-27nmol/kg for 29days in cynomolgus mokeys had no effect on blood glucose.[29]

Above are few of the GLP1/GCGR coagonist under development right now of which various have progressed to phase me and phase II clinical tests. Gradually more information will be gained regarding the drugs clinical effects.

Coagonism of GLP/GIP

In response to nutrient intake with food, the protein GIP gets secreted by the enter endocrine K cells of the proximal small intestine, and it is made up of 42 aminoacids.[30] Being an incretin hormone, its main role is to stimulate insulin secretion. Also treatment with GIP has been shown to normalize blood glucose along with having a better glucose tolerance,[31–33] an effect which has been seen to be reduced in some patients having T2DM.[34] Initially GIP was not considered for any ant obesity targets despite it having its effects on glucose tolerance, in view of some studies showing it had showed that giving GIP chronically in rodents might reduce weight.[35] Mice which over express GIP express better glycaemic control in addition to resistance to diet induced obesity(DIO).[33] GIPR agonism chronically improves glucose metabolism further in DIO mice ,without any evidence of increased weight gain.[36] Transgenic pigs that express a dominant negative GIP receptor in the pancreas also have delayed insulinotropic action ,which is approximately 60% decreased β cell proliferation and a decrease in islet mass by upto 58% by the age of 1yr.[37] Combining GLP1and GIP as a single molecule was on the thinking that a dual incretin hormone action would give the best glycaemic effects and the anorexigenic potential of GLP-1 would counter any obesity promoting effect of GIP(Figure 2). Coadministration of GLP1and GIP improved glycemia and body weight loss in DIO that confirmed the above hypothesis.[16]

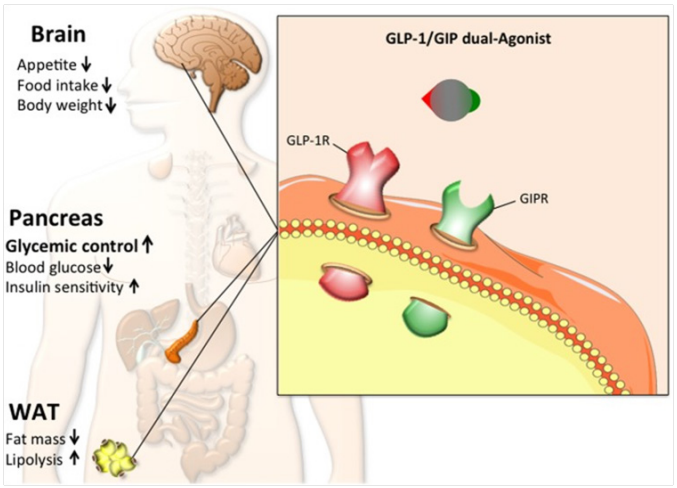

Figure 2 Courtesy ref no. 43-Schematic demonstrating the working principle, metabolic effects and key target tissues of the GLP-1/GIP dual agonist. Arrows pointing upwards indicate an increase or improvement, while arrows pointing downwards indicate a decrease. The emphasis on glycemic control indicates the relative magnitude of the effect.

Thus the unimolecular dual incretins ('twin cretin') hormones ere thus created on the basis of primary glucagon sequence. These dual agonists had key GLP1 and GIP residues enabling them to activate both GLP1 and GIPR with equipotency '*in vitro*'.[16] Besides that other modifications done were having an AIB residue at position 2 for preventing degradation by DPPIV. Also it was acylated with a C16:O fatty acid (acylated version)at Lys 40or PEGylated with 40kda,PEG at Cys24 (PEGylated version)for prolonging *in vivo* action. Further modification was done at the C terminal peptides for carrying the CEX tail from extendin -4.Administering 30nmol/kg of the unacylated version of the dual agonist daily in DIO mice over7days=>a 14% decrease in body weight, which was more than comparable dose of extending -4.[16] Giving a single 30nmol/kg dose of the 16-carbon acylated form of the peptide =>18.8%decrease in body weight.[16] Thus both versions of the peptide reduced food intake and body weight mainly via loss of fat mass and lowering blood glucose levels.[16] Same results were obtained by the PEGylated peptide with less frequent dosages. Thus GLP1R/GIPR co agonists have potential for being an effective weight losing drug.

Further the acylated GLP1R/GIPR coagonist was studied in cynomolgous monkeys. The monkeys received a single dose of 10nmol/kg injection of the acylated coagonist, which was followed 24hlater by a dextrose injection, when glucose and insulin were measured as well. This coagonist reduced blood glucose and increased insulin, both much more than that with a matched dose of liraglutide.[16]

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Even in humans the PEGylated coagonist has been tested. A single injection of 4, 8 or 16mgof this coagonist followed by dextrose infusion 72h later was given to a cohort of healthy nondiabetic subjects. This coagonist reduced blood glucose and raised plasma insulin secretion.[16] In another chronic study 3 patients having T2DM were given weekly injections at a dose of 4, 12, 20 and 30mg of the PEGylated coagonist x 6weeks .This PEGylated coagonist reduced HbA1c in a dose dependent manner. It was well tolerated with only mild-moderate side effects.[16] In phase II study this compound in patients with T2DM, was compared with placebo and liraglutide treatment. As compared to placebo, treatment using s/c injections of 1.8mg of acylated coagonist caused a significant reduction in plasma HbA1c, significant decrease in both fasting and self reported plasma glucose along with reduction in body weight that was significant at week 8 but not at week 12.[38] Also treatment with acylated coagonist =>a marked decrease in total cholesterol, besides reduction of LDL, triglycerides, free fatty acids and Apolipoprotein B.[38] In the same study no change in cholesterol was seen with liraglutide.[38] There was also a decrease in plasma leptin(22%as compared to placebo) seen, that suggests an increase in leptin sensitivity. In a meal tolerance test, this formulation lowered blood glucose 2h postprandially. No serious side effects were seen related to treatment. Besides this many more GIPR-GLP1R co agonists are being developed. The promising preclinical results have to be further followed to see if =>any beneficial drug development.

Triple agonism of GLP1/GIP. Glucagon

Based on above one thought of combining all 3 peptides in a single molecule A hypothesis was given that combining GLP1and GIP would give dual insulinotropic effects, which would neutralize the diabetogenic effect of glucagon and having combined agonism at GLP1 and glucagon receptors would dampen any obesogenic effect of GIP. Ultimate goal of triple agonist was a huge ability to lower body weight along with improving glycemic control (Figure 3).

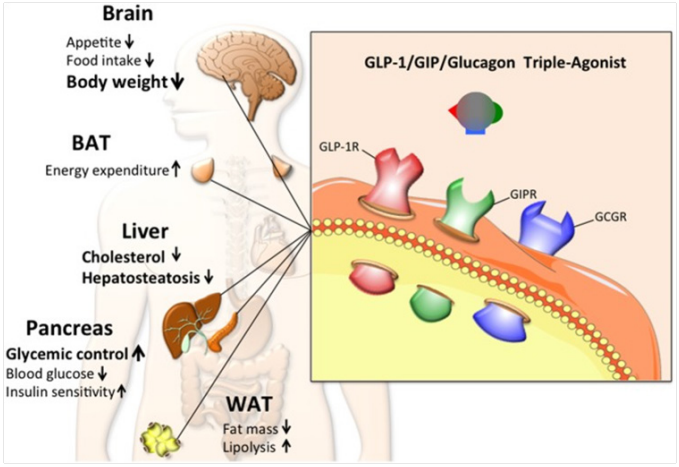

Figure 3 Courtesy ref no. 43-Schematic demonstrating the working principle, metabolic effects and key target tissues of the GLP-1/GIP/glucagon triple agonist, with the size of the text weighted to indicate the magnitude of the observed effect. Arrows pointing upwards indicate an increase or improvement, while arrows pointing downwards indicate a decrease. The triagonist most predominately affects body weight, glycemic control and liver cholesterol and hepatosteatosis.

Initially in the same GLP1/glucagon dual agonist structure GIP residues got added stepwise ,for formation of a peptide that had equal in vitro activity at all 3 receptors and action that was better than all 3 native peptides.[17,18] It also had an AIB residue added at position 2 for protecting it against degradation by DPPIV ,along with a C16:O palmitic acid at the Lys 10position for prolonging the in vitro action.[17,18] A daily s/c injection ,as low as 3nmol/kg of the triple agonist caused a 26.6% decrease in body weight in DIO mice ,in a 20day study ,a loss that was mainly because of fat mass loss.[17,18] Also this triple agonist decreased ad libitum blood glucose besides improving glucose tolerance and simultaneously reduced insulin levels, which gave a suggestion of increased insulin sensitivity. Further this triple agonist lowered hepatic lipid content,[17,18] that would help in a setting in patients having fatty liver disease and non-alcoholic steatohepatitis (NASH). One important factor is that these metabolic benefits are based on signalling at all 3 target receptors,[17,18] showing it is actually triple agonism causing these beneficial results. The efficiency of the triple agonist was also tested in female mice and it was found that it was equally effective in reducing body weight in DIO female mice as controlled to fat mass matched male mice.[39] Additionally giving a 10nmolkg dose daily x27days this triple agonist finished the hepatosteatosis which was seen in female mice.[39] As expected this triple agonist had just mild effects on glucose tolerance in female mice as the female mice are naturally protected against developing hyperglycemia and hyerinsulinemia. Still the mild hyerinsulinemia seen was resolved by the triple agonist in these female mice. Thus triagonist has potential for developing therapies in both sexes.

Other triple agonists are in development. A glucagon based triple agonist, HM15211, has been found to have equal efficiency in all 3 receptors *in vivo*.[40,41] This triple agonist reduces body weight ,more than liraglutide alone in DIO mice besides improving lipid metabolism along with hepatic steatosis.[40,41]

Another example of a triple agonist is Syn –GIP-ZP, that is formed by fusing a GLP1R/GCGR dual agonist along with a GIP analogy to the heavy and light chain of Synagis, which is an antibody having low immunogenicity in human beings.[42] This peptide possesses agonistic effect at all 3 receptors,[43] showing that multiagonistic properties is not only limited to peptides having structural similarity, but can be obtained by fusion to large biomolecules .Advantage of this approach are an increased flexibility for synthesizing and better pharmacokinetics, yet one needs to manufacture these molecules by careful engineering, to get stability and needs to be designed with care to get the ratio of agonism between components that has metabolic good effects.

Conclusion

As discussed earlier, the attention has been on developing single molecular targets or dual agonism like in Qsymia (topiramate/phentermine), bupropion/naltrexone combination (contrave) one has concentrated on loose combination of any combined mixtures. Earlier pharmacotherapies have an undesirable balance between efficiency and safety. Development of these new multiagonist drugs as a unimolecular drug perform better than any other drugs for treating obesity but one has to wait whether the promise shown is as expected from the preclinical phase I and II trials. These teals done in both animals, like rodents and monkeys will actually be seen in humans has to be observed .Hopefully longterm studies and clinical trials promise a new step forward with good efficacy and no side effects like the initial promise that was seen with rimonabant and later withdrawal due to side effects and possibly prove to be the most promising

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therapy ,one has to anticipate for future in terms of pharmacotherapy for obesity ,even if doesn't parallel BS, atleast one come close to it.

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None.

Conflicts of interest

The author declares no conflicts of interest.

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