Medical Science

To Cite:
Woźniak K, Stasiak M, Woźniak A, Glapiński F, Żyro W, Żyro K. Pharmacotherapy of obesity - Amylin Analogs and Dual Amylin-Calcitonin Receptor Agonists. A literature review. *Medical Science* 2025; 29: e62ms3558
doi: https://doi.org/10.54905/disssi.v29i158.e62ms3558

Authors' Affiliation:
[1]St. Anne's Trauma Surgery Hospital, Barska Str. 16/20, 02-315 Warsaw, Poland
[2] Central Clinical Hospital, 1a Banacha Str. 02-097 Warsaw, Poland
[3]Independent Public Health Care Facilities in Pruszków, al. Armii Krajowej 2/4, 05-800 Pruszków, Poland

[*]**Corresponding author**
Karolina Woźniak
St. Anne's Trauma Surgery Hospital, Barska Str. 16/20, 02-315 Warsaw, Poland
Email: karolinaa.karbownikk62@gmail.com

Peer-Review History
Received: 16 December 2024
Reviewed & Revised: 25/December/2024 to 21/April/2025
Accepted: 29 April 2025
Published: 03 May 2025

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

Pharmacotherapy of obesity - Amylin Analogs and Dual Amylin-Calcitonin Receptor Agonists. A literature review

Karolina Woźniak[1*], Michał Stasiak[2], Adam Woźniak[1], Franciszek Glapiński[2], Wiktor Żyro[1], Katarzyna Żyro[3]

ABSTRACT

Obesity has become one of the biggest challenges in medicine. Hundreds of millions of people struggle with this disease. It has a significant impact on mortality rates. Therefore, the search for new therapies is essential. This review aims to analyze Amylin Analogs and Dual Amylin-Calcitonin Receptor Agonists (DACRAs). These are new drugs tested for the treatment of diabetes and excess body weight. We will focus on their use in the treatment of obesity. Recent advances in gut hormone-modulating medications have implicated a possible mechanism by which the amylin-calcitonin pathway may help control body weight. Amylin Analogs, pramlintide, and cagrilintide exhibit encouraging efficacy in clinical studies. In preclinical studies, DACRAs KBP-066, KBP-088, and KBP-089 caused significant weight loss and metabolic effects. Mechanistic accounts reveal the complex neural networks and receptor dynamics that the therapies utilize. Amylin Analogs and DACRAs represent a novel platform for obesity treatment, but we need to translate preclinical evidence into everyday practice with patients. Conducting further studies to establish the dosage and possibly reduce side effects is essential.

Keywords: Obesity, Amylin, Calcitonin, Weight Management, Gastrointestinal Hormones

1. INTRODUCTION

In 2022, the problem of being overweight affected 2.5 billion adults, and over 890 million of them struggled with obesity. It contributes to millions of deaths due to cardiovascular diseases, diabetes, cancers, and digestive diseases. Nowadays, the influence of obesity on public health is a dominant problem. Older age, residing in metropolitan cities, and more recent periods have all been considered contributors to the growing occurrence of central obesity, highlighting the urgent need for intervention (Wong et al., 2020). For many years, our knowledge about being overweight was limited. It drove negative stereotypes correlated with

people struggling with this disease (Puhl & Heuer, 2010). Many hormones from the gastrointestinal system control satiety. These hormones include Glucagon-like Peptide-1 (GLP-1), oxyntomodulin, and islet amyloid polypeptide (amylin). They act in certain brain parts to enhance the feeling of fullness and reduce appetite (Züger et al., 2013).

Research shows imbalance or reduced sensitivity to these signals can disrupt hunger control. That said, it promotes overeating and contributes to obesity (Alhabeeb et al., 2021). Semaglutide, a long-acting GLP-1 analog, proved to be a breakthrough in treating obesity. These conclusions have contributed to research on further methods using enteropancreatic hormones. Our review aims to analyze Amylin Analogs and Dual Amylin-Calcitonin Receptor Agonists (DACRAs) from the perspective of their possible therapeutic application in obesity pharmacotherapy.

2.MATERIALS AND METHODS

To conduct this review, we searched the PubMed and Google Scholar databases for articles related to pharmacologic treatment of overweight and obesity with Amylin Analogs and DACRAs. We used keywords such as 'amylin,' 'dual amylin-calcitonin receptor agonists,' 'obesity pharmacotherapy,' and 'weight loss.' Our focus was on papers published between January 2020 and November 2024. We assessed the articles by titles, abstracts, and full texts. Articles were included in the review if they raised the problem of obesity pharmacotherapy with Amylin Analogs or with DACRAs. The research team excluded other papers.

3. RESULTS & DISCUSSION

Amylin – mechanism of action

Amylin demonstrates selective, moderate-affinity binding to the amylin receptor (AMYR)—a heterodimeric complex formed by a Class B G protein-coupled calcitonin receptor (CTR-A/B) paired with one of three receptor activity-modifying proteins (RAMP1-3), creating distinct AMYR1-3 subtypes. In contrast, salmon calcitonin (sCT) acts as a natural dual agonist, binding with high affinity to AMYR and CTR receptors. This unique polypharmacological profile classifies sCT as a DACRA (Hankir & Le Foll, 2024). These receptors are pivotal in mediating amylin's ability to slow gastric emptying, suppress postprandial glucagon, and enhance leptin sensitivity (Züger et al., 2013). These actions modulate metabolic activity and energy homeostasis (Zakariassen et al., 2020). Emerging research reveals that while the caudal hindbrain (particularly the dorsal vagal complex) was considered initially amylin's primary site of action, contemporary studies demonstrate a more complex neurocircuitry underlying its effects. Amylin operates on distributed networks of the central nervous system's neural networks to regulate feeding behavior through varied mechanisms (Hankir & Le Foll, 2024).

Therapeutic Breakthroughs

1. Amylin Analogs:

Amylin Analogs with better pharmacokinetics and a lower tendency to aggregate may help treat obesity. Pramlintide was the first approved Amylin Analog. It provided a basis for further developing this treatment strategy (Safaeian et al., 2022). ADO09, a co-formulation of pramlintide and insulin A21G, demonstrates benefits in managing obesity: Participants using ADO09 significantly reduced their body weight, attributed to pramlintide's appetite-suppressing effects. They experienced more frequent episodes of hypoglycemia and nausea (Andersen et al., 2023, 2024). Pramlintide was added to continuous subcutaneous insulin therapy in patients with type 1 diabetes. It improved glycemic control and reduced body weight. The safety profile was acceptable. Monitoring for adverse events is required during initiation of therapy (Herrmann et al., 2013).

AM833 (cagrilintide), a novel lipidated Amylin Analog, is a non-selective agonist targeting CTR and AMYRs. Its unique pharmacological profile differentiates it from selective agonists like pramlintide (AMYR-selective) and sCT, showing transient receptor binding (~3–6 minutes) akin to human calcitonin (hCT) but shorter than sCT or AM1784 (>1 hour), potentially mitigating cancer risks associated with prolonged receptor activation. In a 26-week phase 2 trial, once-weekly AM833 achieved 10.8% weight loss vs. 3.0% with placebo. Paired with semaglutide, AM833 induced 15.4–17.1% weight loss over 20 weeks. It worked better than semaglutide alone. These results indicate the potential of the AM833 (Fletcher et al., 2021). A long-acting selective amylin receptor agonist (AM1213) reduced food intake and body weight in both sexes of rats, but the effect was longer in males. These results support the role of amylin signaling in body weight regulation. It also suggests different mechanisms of action in males and females (Kalafateli et al., 2021).

2. Dual Amylin-Calcitonin Receptor Agonists (DACRAs):

The first DACRAs, KBPs (KeyBiosciencePeptide), showed encouraging results in animal models. One study of DACRA called KBP-066 tested doses of 5, 50, and 500 μg/kg in rats fed a high-fat diet (HFD) and in diabetic rats (ZDF). The maximal weight loss was achieved at the 5 μg/kg dose in rats fed an HFD. There was no additional benefit at higher doses. However, in ZDF rats, higher doses better-preserved insulin secretion. These findings suggest that the lower doses of KBP-066 are sufficient for weight loss, and higher doses are more beneficial in diabetes. However, the study did not include a long-term assessment of the safety and efficacy of KBP-066, which is important before potential clinical use. The benefits observed at high doses in ZDF rats may be caused by their genetic background, specifically leptin receptor deficiency (Sonne et al., 2020). The effect of DACRA acylation was studied, and it was noted that KBP-066 acylation significantly prolonged the half-life and time to peak plasma concentration. KBP-066A (acylated) administered every 3 days (equivalent to weekly dosing in humans) was superior to daily dosing of KBP-066 in reducing body weight in obese rats and in improving glycemic control in obese and obese diabetic rats, but further clinical studies are needed to confirm the efficacy and safety of KBP-066A in humans (Andreassen et al., 2021).

The KBP-088 study revealed promising results for obesity and type 2 diabetes treatment. Administering KBP-088 every other day proved more effective than daily dosing in several key areas: more significant weight loss, improved food preferences, with subjects consuming more low-calorie foods, and enhanced glucose tolerance. While these findings are encouraging, some concerns were noted: potential muscle mass loss with every-other-day dosing, though not conclusively demonstrated, fluctuations in food intake and body weight, which may affect long-term treatment tolerance, uncertainty about translating rat study results to humans, particularly regarding nausea and taste aversion (Larsen et al., 2020). In obese rats fed a high-fat diet, the combination of DACRA (KBP-089) with the GLP-1 analog (liraglutide) achieved better effects in reducing body weight than monotherapy (Larsen et al., 2021). The effect of KBP on metabolism was also assessed in a model of postmenopausal obesity in rats.

The model combined a high-fat diet with ovariectomy. It led to an increase in body weight and adipose tissue. KBP treatment for 6 months caused a decrease in body weight and reduced food intake. Furthermore, KBP improved glucose tolerance, regardless of the dose used, indicating the potential of KBP as a promising candidate for treating obesity and metabolic disorders in older postmenopausal women (Katri et al., 2021).

In a 2024 study, KPB-336 significantly reduced osteoarthritis (OA) pain in obese rats regardless of weight loss. At larger dosages, KBP-336 also reduced body fat and induced weight loss. With its analgesic, antiresorptive, and metabolic properties, KBP-336 may be a potential option for a disease-modifying medication in OA (Mohamed et al., 2024).

ZP5461, a novel long-acting amylin/calcitonin receptor agonist, was investigated on food intake and body weight regulation in male rats. Systemic ZP5461 dose-dependently suppressed food intake and body weight in chow-fed and HFD-fed rats for 72 hours. Repeated ZP5461 administration failed to sustain long-term weight loss or feeding suppression, suggesting potential tolerance development. While not directly tested here, nausea—common with Amylin Analogs like pramlintide—remains a potential concern for clinical translation (Stein et al., 2021). The summary of clinical and preclinical findings on Amylin Analogs and DACRAs is presented in table 1.

Table 1. Clinical and preclinical findings on Amylin Analogs and DACRAs

Agent/Compound	Type	Key Findings	Study Type	Additional Notes
Pramlintide	Amylin Analog	Reduces appetite and body weight; improved glycemic control	Clinical & Preclinical	Risk of nausea and hypoglycemia
ADO09	Pramlintide + Insulin A21G	Significant weight loss, improved glucose control	Clinical	More hypoglycemia than control
AM833 (Cagrilintide)	Amylin Analog (lipidated)	Up to 17.1% weight loss with semaglutide; better than semaglutide alone	Preclinical	Shorter receptor binding time may reduce cancer risk
AM1213	Selective AMY receptor agonist	Reduced food intake and weight; longer effects in males	Preclinical	Suggests sex-based differences in response
KBP-066	DACRA	Maximal weight loss at 5 μg/kg; higher doses	Preclinical	Dose-response depends on

		preserved insulin in diabetic rats		metabolic context
KBP-066A	Acylated DACRA	Superior to KBP-066 in weight and glucose control; weekly dosing effective	Preclinical	Supports long-acting formulation
KBP-088	DACRA	Better effects with alternate-day dosing; improved food choices	Preclinical	Risk of muscle loss and fluctuating food intake
KBP-089 + Liraglutide	DACRA + GLP-1 RA	Combination therapy more effective than monotherapy	Preclinical	Suggests synergistic effects
KBP (menopause model)	DACRA	Reduced body weight and improved glucose tolerance in ovariectomized rats	Preclinical	Potential in postmenopausal obesity
KBP-336	DACRA	Weight loss and osteoarthritis pain relief	Preclinical	Disease-modifying potential in OA
ZP5461	DACRA	Short-term weight reduction; possible tolerance with repeated use	Preclinical	Tolerance may limit clinical potential

3. Mechanistic insights - neural circuitry, receptor dynamics, and structural engineering:

Recently, it has been observed that noradrenergic (NA) signaling in the lateral parabrachial nucleus (LPBN) is essential for mediating the hypophagic effects of amylin and sCT in male rats. Depleting NA in the LPBN via 6-hydroxydopamine (6-OHDA) abolished the anorectic responses to both peptides, confirming the necessity of the AP → LPBN pathway for transmitting satiety signals. Amylin activated CGRP-expressing neurons in the LPBN, but NA depletion reduced this activation by 40–58%, suggesting NA indirectly facilitates CGRP neuron excitation. Notably, 60% of amylin-activated LPBN neurons were non-CGRP, raising unresolved questions about their functional role and potential mechanistic distinctions between amylin and sCT. The findings highlight NA-dependent and independent pathways in appetite regulation, with implications for understanding energy homeostasis and potential obesity therapies.

The function of receptor activity-modifying proteins (RAMPs) in the action of DACRA-sCT and selective amylin receptor agonist (NN1213) in mice was highlighted. In wild-type (WT) mice, NN1213 (selective amylin receptor agonist) decreased body weight; however, sCT had no impact. RAMP3's absence increased sCT's effectiveness while decreasing NN1213's. The effects in RAMP1/3 KO mice were comparable to those in RAMP3 KO mice. The AMY3 receptor (CTR + RAMP3) is necessary for NN1213 to impact food intake and body weight significantly. Although in opposing directions, AMY3 is crucial in regulating the actions of both substances (Arrigoni et al., 2021). In another investigation in wild-type and RAMP1/3 KO mice, a long-acting Amylin Analog (LAAMA) inhibited body weight increase, demonstrating that RAMP1/3 is unnecessary for LAAMA's activities. Unlike amylin, research has shown that LAAMA does not always require RAMP to reduce body weight. The neuronal CTR primarily mediates LAAMA's effects (Gamakharia et al., 2021). One study aimed to create high-affinity calcitonin fragment analogs that target the extracellular domains (ECD) of calcitonin family receptors. When three mutations were added to the sCT fragment, its affinity for the calcitonin receptor's ECD was 21 times higher than that of the wild-type fragment. Moreover, these changes enhanced the fragment's affinity for the ECD of all three kinds of amylin receptors.

Structural studies indicated that San45 (DACRA), via a conjugated lipid at position 21, has two binding modes: a persistent alternative mode at CTR and a bypass mode at AMY3R. This dual mechanism allows for wide receptor binding, while lipid conjugation improves stability and duration of action. These findings emphasize lipid alteration as a strategic method for creating long-acting DACRAs, which could simultaneously provide new anti-obesity therapeutics by targeting numerous energy control mechanisms (Cao et al., 2024).

4. CONCLUSION

Gastrointestinal hormones play a major role in regulating appetite. Recently, we have seen significant progress in the pharmacology of gastrointestinal hormones, especially those targeting the amylin and calcitonin pathways. The DACRAs reduce body weight, improve glucose control, and attenuate hyperglucagonemia. Dual therapies, especially DACRAs with GLP-1 agonists, show better weight loss than monotherapies. Longer studies are necessary to assess sustained weight loss and cardiovascular benefits. Perhaps targeting LPBN pathways could help reduce adverse effects like nausea. It seems important to identify biomarkers to predict sex- or age-specific responses, which could help in personalizing treatment. Amylin Analogs and DACRAs have great potential. However, further studies are needed to implement them in everyday practice.

Authors' contribution:

Conceptualization: Karolina Woźniak, Michał Stasiak
Methodology: Wiktor Żyro, Adam Woźniak
Formal analysis: Michał Stasiak, Katarzyna Żyro
Resources, data curation: Franciszek Glapiński
Investigation: Adam Woźniak, Wiktor Żyro
Writing – original draft: Karolina Woźniak, Katarzyna Żyro
Writing – review & editing: Franciszek Glapiński, Michał Stasiak
All authors have read and agreed with the present version of the manuscript.

Acknowledgement:

Not applicable.

Informed Consent

Not applicable.

Ethical approval

Not applicable.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

REFERENCES

1. Alhabeeb H, AlFaiz A, Kutbi E, AlShahrani D, Alsuhail A, AlRajhi S, Alotaibi N, Alotaibi K, AlAmri S, Alghamdi S, AlJohani N. Gut hormones in health and obesity: The upcoming role of short chain fatty acids. Nutrients 2021;13:481 doi: 10.3390/nu13020481.
2. Andersen G, Eloy R, Famulla S, Heise T, Meiffren G, Seroussi C, Gaudier M, Mégret C, Chan Y-P, Soula O, Riddle M. A co-formulation of pramlintide and insulin A21G (ADO09) improves postprandial glucose and short-term control of mean glucose, time in range, and body weight versus insulin aspart in adults with type 1 diabetes. Diabetes Obes Metab 2023;25:1241–8. doi: 10.1111/dom.14972.
3. Andersen G, Eloy R, Heise T, Gaudier M, Mégret C, Seroussi C, Chan Y-P, Soula O, Riddle M, DeVries JH. ADO09, a co-formulation of pramlintide and insulin A21G, lowers body weight versus insulin lispro in type 1 diabetes. Diabetes Obes Metab 2024;26:4639–45. doi: 10.1111/dom.15827.
4. Andreassen KV, Larsen AT, Sonne N, Mohamed KE, Karsdal MA, Henriksen K. KBP-066A, a long-acting dual amylin and calcitonin receptor agonist, induces weight loss and improves

glycemic control in obese and diabetic rats. Mol Metab 2021;53:101282. doi: 10.1016/j.molmet.2021.101282.
5. Arrigoni S, Le Foll C, Cabak A, Lundh S, Raun K, John LM, Lutz TA. A selective role for receptor activity-modifying proteins in subchronic action of the amylin selective receptor agonist NN1213 compared with salmon calcitonin on body weight and food intake in male mice. Eur J Neurosci 2021;54:4863–76. doi: 10.1111/ejn.15376.
6. Cao J, Belousoff MJ, Gerrard E, Danev R, Fletcher MM, Dal Maso E, Schreuder H, Lorenz K, Evers A, Tiwari G, Besenius M, Li Z, Johnson RM, Wootten D, Sexton PM. Structural insight into selectivity of amylin and calcitonin receptor agonists. Nat Chem Biol 2024;20:162–9. doi: 10.1038/s41589-023-01393-4.
7. Fletcher MM, Keov P, Truong TT, Mennen G, Hick CA, Zhao P, Furness SGB, Kruse T, Clausen TR, Wootten D, Sexton PM. AM833 is a novel agonist of calcitonin family G protein-coupled receptors: Pharmacological comparison with six selective and nonselective agonists. J Pharmacol Exp Ther 2021;377:417–40. doi: 10.1124/jpet.121.000567.
8. Gamakharia S, Le Foll C, Rist W, Baader-Pagler T, Baljuls A, Lutz TA. The calcitonin receptor is the main mediator of LAAMA's body weight lowering effects in male mice. Eur J Pharmacol 2021;908:174352. doi: 10.1016/j.ejphar.2021.174352.
9. Hankir MK, Le Foll C. Central nervous system pathways targeted by amylin in the regulation of food intake. Biochimie 2024;229:95–104. doi: 10.1016/j.biochi.2024.10.012.
10. Herrmann K, Frias JP, Edelman SV, Lutz K, Shan K, Chen S, Maggs D, Kolterman OG. Pramlintide improved measures of glycemic control and body weight in patients with type 1 diabetes mellitus undergoing continuous subcutaneous insulin infusion therapy. Postgrad Med 2013;125:136–44. doi: 10.3810/pgm.2013.05.2635.
11. Kalafateli AL, Vestlund J, Raun K, Egecioglu E, Jerlhag E. Effects of a selective long-acting amylin receptor agonist on alcohol consumption, food intake and body weight in male and female rats. Addict Biol 2021;26:e12910. doi: 10.1111/adb.12910.
12. Katri A, Reker D, Karsdal MA, Bay-Jensen A-C, Henriksen K. Treatment with a dual amylin and calcitonin receptor agonist improves metabolic health in an old, obese, and ovariectomized rat model. Menopause 2021;28:423–30. doi: 10.1097/gme.0000000000001722.
13. Larsen AT, Gydesen S, Sonne N, Karsdal MA, Henriksen K. The dual amylin and calcitonin receptor agonist KBP-089 and the GLP-1 receptor agonist liraglutide act complimentarily on body weight reduction and metabolic profile. BMC Endocr Disord 2021;21:10. doi: 10.1186/s12902-020-00678-2.
14. Larsen AT, Sonne N, Andreassen KV, Karsdal MA, Henriksen K. Dose frequency optimization of the dual amylin and calcitonin receptor agonist KBP-088: Long-lasting improvement in food preference and body weight loss. J Pharmacol Exp Ther 2020;373:269–78. doi:10.1124/jpet.119.263400.
15. Mohamed KE, Larsen AT, Melander S, Andersen F, Kerrn EB, Karsdal MA, Henriksen K. The dual amylin and calcitonin receptor agonist KBP-336 elicits a unique combination of weight loss, antinociception and bone protection - a novel disease-modifying osteoarthritis drug. Arthritis Res Ther 2024;26:129. doi: 10.1186/s13075-024-03361-2.
16. Puhl RM, Heuer CA. Obesity stigma: important considerations for public health. Am J Public Health 2010;100:1019–28. doi: 10.2105/AJPH.2009.159491.
17. Safaeian L, Shafiee F, Naderi M. Pramlintide: An amylin analogue protects endothelial cells against oxidative stress through regulating oxidative markers and NF-κb expression. Int J Prev Med 2022;13:20. doi:10.4103/ijpvm.IJPVM_425_20.
18. Sonne N, Larsen AT, Andreassen KV, Karsdal MA, Henriksen K. The dual amylin and calcitonin receptor agonist, KBP-066, induces an equally potent weight loss across a broad dose range while higher doses may further improve insulin action. J Pharmacol Exp Ther 2020;373:92–102. doi: 10.1124/jpet.119.263723.
19. Stein LM, McGrath LE, Lhamo R, Koch-Laskowski K, Fortin SM, Skarbaliene J, Baader-Pagler T, Just R, Hayes MR, Mietlicki-Baase EG. The long-acting amylin/calcitonin receptor agonist ZP5461 suppresses food intake and body weight in male rats. Am J Physiol Regul Integr Comp Physiol 2021;321:R250–9. doi: 10.1152/ajpregu.00337.2020.
20. Wong MCS, Huang J, Wang J, Chan PSF, Lok V, Chen X, Leung C, Wang HHX, Lao XQ, Zheng Z-J. Global, regional and time-trend prevalence of central obesity: a systematic review and meta-analysis of 13.2 million subjects. Eur J Epidemiol 2020;35:673–83. doi: 10.1007/s10654-020-00650-3.
21. Zakariassen HL, John LM, Lutz TA. Central control of energy balance by amylin and calcitonin receptor agonists and their potential for treatment of metabolic diseases. Basic Clin Pharmacol Toxicol 2020;127:163–77. doi: 10.1111/bcpt.13427.
22. Züger D, Forster K, Lutz TA, Riediger T. Amylin and GLP-1 target different populations of area postrema neurons that are both modulated by nutrient stimuli. Physiol Behav 2013;112–113:61–9. doi: 10.1016/j.physbeh.2013.02.006.