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Review

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Amylin as a Future Obesity Treatment

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Obesity is defined as abnormal or excessive fat accumulation that contributes to detrimental health impacts. One-third of the population suffers from obesity, and it is important to consider obesity as a chronic disease requiring chronic treatment. Amylin is co-secreted with insulin from β pancreatic cells upon nutrient delivery to the small intestine as a satiety signal, acts upon sub-cortical homeostatic and hedonic brain regions, slows gastric emptying, and suppresses post-prandial glucagon responses to meals. Therefore, new pharmacological amylin analogues can be used as potential anti-obesity medications in individuals who are overweight or obese. In this narrative review, we analyse the efficacy, potency, and safety of amylin analogues. The synthetic amylin analogue pramlintide is an approved treatment for diabetes mellitus which promotes better glycaemic control and small but significant weight loss. AM833 (cagrilintide), an investigational novel long-acting acylated amylin analogue, acts as a non-selective amylin receptor. This calcitonin G protein-coupled receptor agonist can serve as an attractive novel treatment for obesity, resulting in reduction of food intake and significant weight loss in a dose-dependent manner.

Key words: Obesity, Treatment, Satiety, Analogue, Weight loss

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INTRODUCTION

Fundamentally, obesity is caused by dysregulation of appetite control which then results in excess adipose tissue causing deterioration in health. One-third of the population suffers from obesity (body mass index, ≥30 kg/m^2).[1] Previously, the disease was not fully understood, and this resulted in a stigmatisation of people living with obesity.[1] Homeostatic centres in the brain play a key regulatory role in hunger and satiety. Only recently, however, have we gained an appreciable understanding surrounding the potential for dysfunctional gut-brain communications and obesity.[2] Importantly, gaining a better understanding of how dysfunctional homeostasis causes obesity will allow for both treatment of obesity as a disease and decrease of societal stigma.

The gastrointestinal system releases a plethora of satiety hormones in response to food intake.[3] Hormones such as glucagon-like peptide 1 (GLP-1), oxyntomodulin, and islet amyloid polypeptide (amylin) relay signals to hypothalamic nuclei and other areas of the subcortical areas of the brain, resulting in feelings of increased fullness and satisfaction.[4] Amylin receptors are located on specific nuclei of the dorsal-vagal-complex located within the hindbrain–the nucleus tractus solitarius (NTS), area postrema (AP), and dorsal motor nucleus of the vagus nerve.[4] Amylin and the amylin receptors (AMYRs) have been identified as potential targets for treatment of obesity. Released from β pancreatic cells, amylin is a 37-amino-acid polypeptide co-secreted with insulin, playing a primary role in glucose homeostasis by slowing gastric emptying, suppressing glucagon secretion, and initiating an anorectic signal post-prandially (Fig. 1).[5-11] The synthetic amylin analogue pramlintide is an approved treatment for diabetes mellitus which promotes better glycaemic control and small but significant weight loss. However, this small amount of wight loss is not sufficient to reverse the complications of obesity, which highlights the importance of developing new amylin analogues.[12]

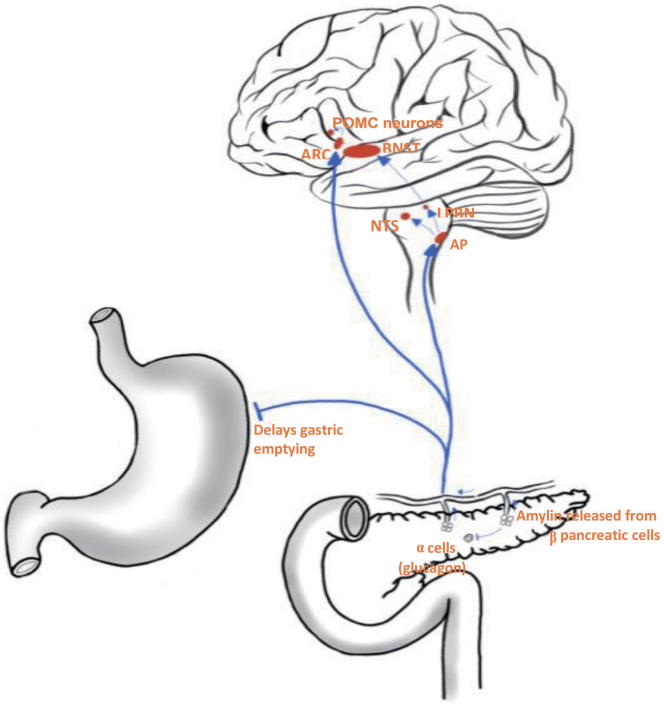

Figure 1. Amylin functions as a satiety hormone. Released into the bloodstream by β pancreatic cells, amylin activates various homeostatic and reward centres in the brain to suppress appetite and reduce food intake. In addition, amylin acts as an inhibitory signal to delay gastric emptying and suppress the release of glucagon from α pancreatic cells. POMC, proopiomelanocortin; ARC, arcuate nucleus; BNST, bed nucleus of the stria terminalis; NTS, nucleus tractus solitarius; LPBN, lateral parabrachial nucleus; AP, area postrema.

Therefore, newer pharmacological amylin analogues such as AM833 (cagrilintide), an investigational novel long-acting acylated amylin analogue, acts as a non-selective AMYR. This calcitonin G protein-coupled receptor (CTR) agonist can serve as an attractive novel treatment for obesity which can result in reduction of food intake and weight loss in a dose-dependent manner.[13-15]

AMYLIN AS A SATIETY HORMONE

Hunger and satiety are regulated by negative feedback mechanisms to maintain caloric intake appropriate to the body's energy requirements.[2,3] Ghrelin is the only known orexigenic gut hormone, although a complex interplay of satiety gut hormones stimulates the subcortical areas of the brain.[2-4] Failure to regulate these processes can result in hypophagia or hyperphagia, leading to weight loss or weight gain, respectively.[2-4] Gut hormones, such as amylin, play a key role in regulating satiety postprandially. Amylin is co-secreted with insulin from β pancreatic cells upon nutrient delivery to the small intestine. AMYRs are located in the of the brainstem.[16] As a circumventricular organ, the AP detects amylin through CTRs propagating signals to the NTS and lateral parabrachial nucleus and then onto the amygdala and the bed nucleus of the stria terminalis of the forebrain, a key centre in regulating energy metabolism (Fig. 1).[17,18] Chronically elevated doses of amylin fail to induce hypophagia in rats with lesions in the AP.[19] Similarly, when the amylin receptor antagonist AC 187 is infused directly into the AP of rats, food intake is increased.[18,20]

However, higher than normal doses of amylin can induce hypophagia in rats with AP lesions by activating other regions of the central nervous system. In addition to the AP, amylin also binds to receptors located in the arcuate nucleus (ARC) of the hypothalamus to synergise with leptin to phosphorylate STAT3 pathways in the ARC and ventromedial hypothalamic nuclei.[21] Independent of leptin, amylin also activates proopiomelanocortin neurons, a critical regulator of neurons, through extracellular-signal regulated kinases signalling.[16,21]

SYNTHETIC AMYLIN ANALOGUES

Amylin appears to be an attractive target for inducing weight loss and glucose stabilisation. However, this is challenging due to the short acting nature of amylin as well as its tendency to self-aggregate.[22] To overcome this, pramlintide, a long acting synthetic analogue, was developed with proline substitutions at positions 25, 28, and 29 to prevent aggregation.[23,24] As amylin is an incretin hormone, pramlintide was developed to treat hyperglycaemia in both type 1 and type 2 diabetes mellitus (T2DM) patients.[25] As such, the use of pramlintide in this context is associated with a reduction in glycosylated hemoglobin (HbA1c) as well as modest weight loss.[26-28] To this end, early clinical trials demonstrated a decrease in body weight in people with obesity when treated with pramlintide (Table 1).[12,29,30] In individuals with suboptimal glycaemic control in the setting of type 1 diabetes mellitus, pramlintide successfully lowered HbA1c through inhibition of glucagon secretion (a native hormone that liberates glucose from glycogen stores in the body). When administered in combination with basal insulin, pramlintide lowers HbA1c to a significantly greater extent than does basal insulin alone.[28]

Table 1. Baseline characteristics of trials included in this review

Study	Study duration, Hawken et al. (2019)[17]	Blinding	Study arm	Number of patients randomized	BMI (kg/m^2)	Body weight (kg)	Age (yr), Hawken et al. (2019)[17]	Female (%)	Significant loss in body weight vs. placebo
Smith et al. (2008)[12]	16	Double-blind, placebo controlled	120 μg pramlintide bid	38	37.5±5.0	105.1±19.9	43.0±11.0	73	Yes
			240 μg pramlintide bid	38	37.7±5.1	105.6±18.0	46.0±12.0	71	Yes
			360 μg pramlintide bid	32	38.1±5.4	107.7±19.5	45.0±14.0	72	Yes
			120 μg pramlintide tid	45	37.2±4.9	104.7±19.2	44.0±14.0	75	Yes
			240 μg pramlintide tid	49	37.8±5.5	106.9±22.1	44.0±12.0	71	Yes
			360 μg pramlintide tid	42	37.7±4.6	108.1±17.2	46.0±13.0	73	Yes
			Placebo	36	37.2±4.4	104.0±17.8	47.0±12.0	73	NA
Enebo et al. (2021)[14]	20	Randomized, placebo controlled	0.16 mg cagrilintide+2.4 mg semaglutide	12	31.0±32.0	93.0±10.6	43.0±9.2	33	No
			0.30 mg cagrilintide+2.4 mg semaglutide	12	30.8±2.3	92.9±11.7	38.4±10.4	42	No
			0.60 mg cagrilintide+2.4 mg semaglutide	12	333±3.7	9.3±11.7	40.0±8.3	50	No
			1.20 mg cagrilintide+2.4 mg semaglutide	12	32.6±4.4	95.1±14.4	41.3±11.1	50	Yes
			2.40 mg cagrilintide+2.4 mg semaglutide	12	32.2±2.5	92.1±11.9	43.0±8.1	58	Yes
			4.50 mg cagrilintide+2.4 mg semaglutide	11	33.0±4.2	98.0±17.3	37.0±9.7	27	Yes
			Placebo+2.4 mg semaglutide	24	32.2±3.0	99.6±15.6	41.0±8.8	33	NA
Riddle et al. (2007)[28]	16	Double-blind, placebo controlled	120 μg pramlintide bid or tid	107	35.0±6.0	103.0±18.0	55.0±10.0	48	Yes
			Placebo	105	35.0±5.0	103.0±18.0	55.0±9.0	54	NA
Smith et al. (2007)[29]	6	Double-blind, placebo controlled	180 μg before meals	60	35.3±3.6	100.2±14.3	49.9±9.0	50	Yes
			Placebo	28	36.3±4.7	103.2±17.8	51.0±8.0	50	NA
Aronne et al. (2007)[30]	16	Double-blind, placebo controlled	240 μg tid	137	37.9±5.7	105.5±18.4	48.0±10.0	80	Yes
			Placebo	67	37.6±5.5	104.9±19.1	19.0±10.0	81	NA
Lau et al. (2021)[15]	26	Double-blind, placebo controlled	0.3 mg cagrilintide once weekly	101	38.4±7.5	109.8±25.1	53.5±10.3	55	Yes
			0.6 mg cagrilintide once weekly	100	37.2±6.9	106.2±23.8	53.2±11.0	62	Yes
			1.2 mg cagrilintide once weekly	102	37.1±6.2	104.4±21.5	52.1±8.7	63	Yes
			2.4 mg cagrilintide once weekly	102	37.9±7.6	106.8±24.1	52.7±9.8	75	Yes
			4.5 mg cagrilintide once weekly	101	38.4±7.7	111.0±28.6	51.5±12.7	56	Yes*
			3.0 mg liraglutide qd	99	38.4±7.4	107.8±24.1	51.5±59.3	65	NA
			Placebo	101	37.1±5.7	106.2±21.6	51.4±11.9	59	NA

Values are presented as mean±standard deviation.
*Significant weight loss was achieved versus placebo and liraglutide arms in the context of a comparable weight loss trial.
BMI, body mass index; bid, twice a day; tid, three times a day; qd, once a day.

AM833 (cagrilintide) is a new investigational drug that exhibited some promising results in a recently completed phase II clinical trial for treatment of obesity.[15] In this 26-week blinded phase 2 monotherapy trial, 706 people with obesity or overweight with at least one weight-related comorbidity and without history of diabetes were randomized to six active treatment arms including once-weekly cagrilintide at one of five doses (0.3, 0.6, 1.2, 2.4, or 4.5 mg; n=100–102 per arm), once-daily liraglutide 3.0 mg (n=99), or their volume-matched placebo arms (n=101). Cagrilintide resulted in more significant weight loss at all doses (0.3–4.5 mg, 6.0%–10.8% [6.4–11.5 kg]) versus placebo (3.0% [3.3 kg], $P<0.001$) and at 4.5 mg doses versus liraglutide 3.0 mg (10.8% [11.5 kg] vs. 9.0% [9.6 kg], $P=0.03$) over 26 weeks.[15] On the cagrilintide 4.5 mg arm, 88.7% of participants achieved ≥5% weight loss and 53.5% of patients achieved ≥10% weight loss over 26 weeks (Table 1).[15]

From a structural viewpoint, AM833 (cagrilintide) is very similar in sequence to pramlintide with differences in lipidation of the N-terminal lysine as well as substitutions of three amino acids (N14E, V17R, and P37Y) responsible for AM833 (cagrilintide), a non-selective AMYR and CTR agonist that can dually activate both class of receptors. This can promote greater weight loss in comparison with pramlintide.[13]

AMYLIN AND GLP-1 COMBINATION THERAPY

GLP-1 is a 37-amino acid peptide hormone released by enteroendocrine L cells of the distal small intestine in response to intralu-

minal contents.[31] Known for their incretin effects, synthetic GLP-1 analogues, namely liraglutide and semaglutide, have been developed for treatment of T2DM and obesity.[32,33] Like amylin, GLP-1 is a potent satiety hormone, acting on receptors in the ARC in the hypothalamus, the AP, and other appetite centres within the subcortical areas of the brain.[34] GLP-1- and amylin receptor analogue-dependent weight loss are mediated through both distinct and overlapping neural pathways. To this end, combined therapy might yield a synergistic effect with respect to both glycaemic control and weight loss. In rhesus monkeys, the GLP-1 and amylin analogues of exendin-4 and salmon calcitonin produced a synergistic reduction in food intake.[35]

An AM833 (cagrilintide) and semaglutide phase 1 combination trial over 20 weeks 14 tested six dosages of AM833 (cagrilintide; 0.16, 0.3, 0.6, 1.2, 2.4, and 4.5 mg) versus placebo, alone and in combination with once-weekly subcutaneous semaglutide 2.4 mg. The drugs were administered in 95 individuals who were obese or classified as overweight (0.16–2.4 mg group, n = 12; 4.5 mg group, n = 11) or placebo (n = 24). At week 20, participants given cagrilintide 0.16–2.4 mg in combination with semaglutide 2.4 mg had achieved weight loss from 8.3% to 17.1%. The greatest weight loss (17.1%) was achieved with cagrilintide 1.2 or 2.4 mg in combination with semaglutide 2.4 mg; pooled placebo in combination with semaglutide 2.4 mg led to 9.8% weight loss (Table 1).[14]

SAFETY AND SIDE EFFECTS OF AMYLIN ANALOGUES

Studies have shown that pramlintide therapy was generally well-tolerated and safe, with no associated cardiovascular, pulmonary, hepatic, or renal toxicity.[36,37] In terms of cardiovascular safety, the assessment of the frequency of major adverse cardiovascular events showed that pramlintide therapy is not associated with increased risk of cardiovascular adverse events.[38]

The most common adverse events associated with pramlintide are gastrointestinal side-effects, particularly mild to moderate nausea which typically is temporary, dose-dependent, and easily managed. Constipation can also result due to the amylin analogue effects on slowing gastric emptying.[36-38] The mentioned side effects are similar to those of GLP-1 agonists and can be managed by prolonging the dose escalation period, sufficient hydration, and reassurance.[36-38]

Clinical trials on AM833 (cagrilintide) have demonstrated its safe and well-tolerated profile. Serious adverse events were few and not dependent on cagrilintide dose.[14,15] The severity of gastrointestinal disorders observed for the combination of AM833 and semaglutide was comparable to that of GLP-1 in monotherapy.[14,15]

CONCLUSION

Amylin analogues can be considered as a potent, efficient, and safe treatment option for obesity. The preliminary results of recent clinical trials support the benefits of combination therapy of amylin analogues with GLP-1 agonists to achieve greater weight loss in comparison with mono-therapy. Therefore, our review highlights the importance of conducting more clinical trials with larger samples to demonstrate the efficacy and safety of these promising therapeutic agents in obesity management.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: all authors; acquisition of data: BD and NRSS; analysis and interpretation of data: BD and NRSS; drafting of the manuscript: all authors; critical revision of the manuscript: all authors; statistical analysis: BD and NRSS; obtained funding: CWLR; administrative, technical, or material support: BD and NRSS; and study supervision: CWLR.

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