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The story of amylin: from physiology to therapy

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Amylin is a glucoregulatory peptide hormone discovered in 1986. Almost 20 years later, pramlintide, a human amylin analogue, emerged as the first amylin-based drug, approved as an adjunct treatment to insulin for type 1 diabetes (T1D) and type 2 diabetes (T2D). Despite its effects on multiple organ systems, the therapeutic potential of amylin has remained relatively underexplored until recently, when growing interest in amylin has prompted advancement of several amylin-based therapies towards clinical use. This Review contextualizes the evolving therapeutic potential of amylin, focusing on recent preclinical and clinical data, amylin receptor pharmacology and its broader biological effects. We discuss the potential and challenges of developing amylin-based treatments for cardiometabolic disease, including milestones in drug development of amylin, and its combination with additional molecules as part of the future landscape of therapies for patients with diabetes or obesity.

Amylin-based therapies represent a promising option for obesity and associated comorbidities, offering a potentially more tolerable alternative to current glucagon-like peptide 1 (GLP1)-based treatments, possibly because of different receptor expression profiles in the hindbrain. Endogenous human amylin resembles a two-faced Dr Jekyll and Mr Hyde character, acting as a physiological regulator but potentially becoming pathological when aggregating into oligomers and fibrils in pancreatic islets[1–3]. This dual nature has complicated research into its mechanism of action and potential therapeutic role. However, there is increased understanding of many potential benefits of non-fibrillating amylin analogues (Fig. 1).

This Review introduces opportunities and challenges in developing amylin receptor (AMYR) agonists as treatments for cardiometabolic diseases, focusing mainly on receptor interaction and specificity, inherent characteristics of native amylin and potential effects beyond mere weight loss.

Introduction to endogenous amylin

Regulation of amylin gene expression and amylin secretion

Amylin, originally named diabetes-associated peptide and later islet amyloid polypeptide (IAPP), was first isolated from pancreatic amyloid deposits found in humans and cats with T2D[2,4]. 'Amylin' commonly denotes the circulating mature (monomeric) form of the 37-amino-acid peptide, whereas 'IAPP' refers to the fibrillating forms of the peptide.

Amylin, encoded by the *IAPP* gene on human chromosome 12, is synthesized as a precursor protein consisting of 89 residues and post-translationally modified to yield mature amylin protein[5].

Amylin and insulin are co-expressed and co-secreted from the same secretory granules of pancreatic β-cells[6,7], and regulation occurs in response to metabolic factors, including food intake, nutrient availability and hormonal signals, such as GLP1 (ref. 8). Glucose is the primary regulator of amylin synthesis and secretion[9,10]. Promoters of insulin and amylin genes act through partly shared key transcription factors, such as homeodomain factor pancreatic/duodenal homeobox 1 (PDX1), which binds to several sites within insulin and *IAPP* gene promoter regions; regulation of the amylin gene promoter in response to glucose depends on PDX1 activity[11,12].

Secretion and circulation patterns of amylin typically mirror those of insulin, with lower fasting and increasing postprandial levels in healthy individuals[3]. This co-secretion elicits a coordinated and synergistic physiological response to maintain glucose homeostasis[13]. Both hormones suppress glucagon secretion from pancreatic α-cells, although the role of amylin herein is debated[14–16]. Amylin slows gastric emptying and induces satiation[17–19], whereas insulin promotes glucose uptake in tissues, thereby preventing postprandial spikes in blood glucose levels[20]. Amylin and insulin have different secretion dynamics and plasma level dynamics, despite sharing common promotors, as amylin clears more slowly than insulin, with peripheral amylin accounting

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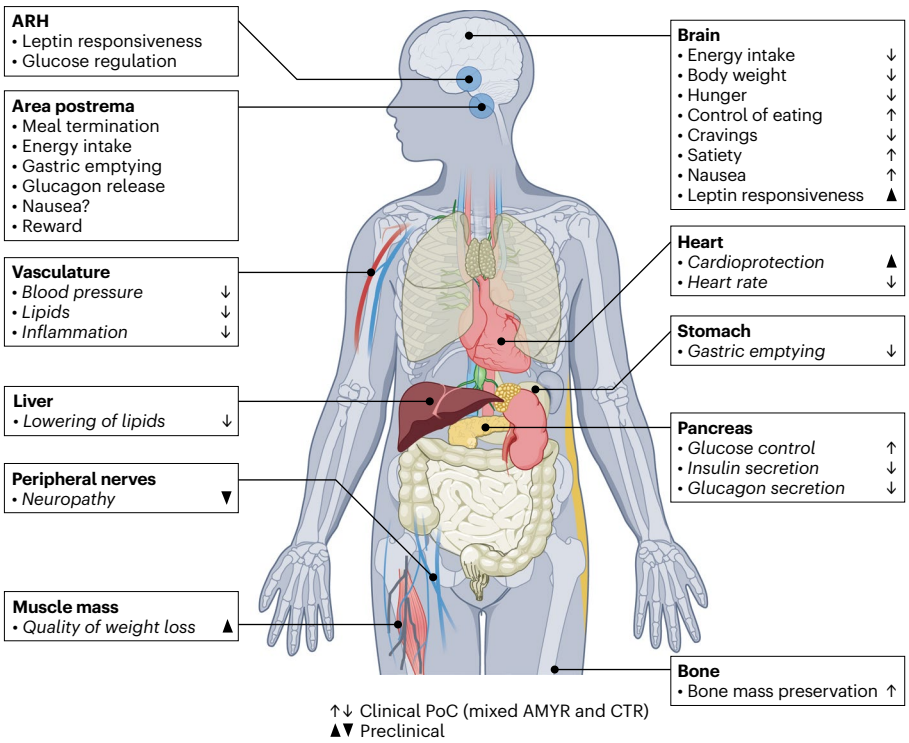

Fig. 1 | Physiological effects of amylin on different organs. Amylin has a physiological effect on many different organs. Thin arrows indicate demonstrated clinical effects with mixed AMYR and CTR agonists. Arrowheads indicate demonstrated preclinical effects. Text in italics indicates an indirect or unresolved mechanism of action. Bolded terms indicate organs and bullet points indicate physiological processes in which amylin is thought to exert a specific or direct effect. In muscle, the expression of CTR on satellite cells is hypothesized to improve function by augmenting regeneration. In the liver, pancreas, vasculature and heart, the effects of amylin are probably indirect as no evidence exists for *CALCR* gene expression in these compartments. In the bone, the effects of amylin are probably through the CTR. Note that several organs may be affected by endogenous amyloid aggregation, and prevention of this may resolve additional organ pathologies. ARH, arcuate nucleus of the hypothalamus; PoC, proof of concept.

for 10% of the insulin levels in fasting conditions, which is higher than stimulated levels[9,21].

In 1990, a 1:100 amylin-to-insulin ratio was reported when stimulating β-cells, independent of glucose levels[22]. This ratio followed a biphasic secretion pattern similar to insulin irrespective of the presence of insulin secretagogues[23,24], and remained stable regardless of age, obesity levels and weight loss[25,26]. However, some studies suggested that early stages of T1D and T2D could affect this ratio, leading to relative hyperamylinaemia[24,25,27,28]; however, assay limitations might produce variable (1–10%) amylin-to-insulin secretion ratios in humans[24,29], and differences in blood kinetics and clearing pathways—hepatic for insulin, renal for amylin—add to this variability[1]. Serum amylin concentrations are reduced in progressed T1D and insulin-deficient T2D, indicating pancreatic β-cells as a main source of overall circulating amylin and underscoring the importance of preserving β-cell integrity in cardiometabolic disease[1,8].

In summary, amylin and insulin are co-regulated, but the ratio is suggested to vary with specific disease states and is complicated by methodological limitations.

Amylin fibrillation

In 1901, deposits of an unknown material in the islet of Langerhans in people with T2D were originally described as 'hyaline material' and associated with β-cell deterioration[30]. Sixty years later, the hyaline material was identified as amyloid deposits consisting of a β-cell-produced peptide named 'diabetes-associated peptide' and then 'IAPP'[31]. This initiated research focusing on amyloid fibril formation, with only IAPP from primates and felines fibrillating owing to a specific amino acid sequence in a specific part of the peptide, as a pathological (and driving) factor of T2D[32].

The name amylin was first proposed in 1988 (ref. 3) and originates from the Greek word for starch (ámylon), referring to the sticky nature and toxic aggregates of the peptide[3]. Elevated amylin levels, probably the result of an oversecretion in insulin-resistant states, promote amylin oligomer and fibril formation, contributing to β-cell dysfunction and diabetes progression[27,32–35] (Fig. 2). Cross-seeding effects of amylin aggregates on additional amyloids[36,37] may also cause amyloid deposition in other organs susceptible to fibril accumulation, exacerbating chronic kidney disease, cardiovascular complications and neurodegenerative diseases[36–42].

When developing AMYR agonists to leverage the regulatory effects of amylin on metabolism, preventing fibrillation is essential[43,44]. Additional strategies include interfering with amylin fibrillation to preserve (or restore) functional β-cell mass in T2D[34,45]; however, no drug candidates have reached clinical development.

In conclusion, the strong fibrillation tendency of human amylin associates this peptide with several pathologies and challenges the development of non-fibrillating amylin molecules. By contrast, lowering endogenous, fibrillating amylin levels by non-fibrillating amylin analogues may offer therapeutic potential across metabolic comorbidities.

The CTR family

AMYRs

Amylin binds to three AMYRs belonging to the seven-transmembrane domain G-protein-coupled receptors, specifically the calcitonin receptor (CTR) family[46,47] (Fig. 3). AMYRs are heterodimers consisting of a CTR and a receptor activity-modifying protein (RAMP)[46,48]. The calcitonin receptor-like receptor (CRLR, also called CLR), related to CTR and AMYR, also forms complexes with RAMPs for calcitonin gene-related peptide (CGRP) and adrenomedullin[49].

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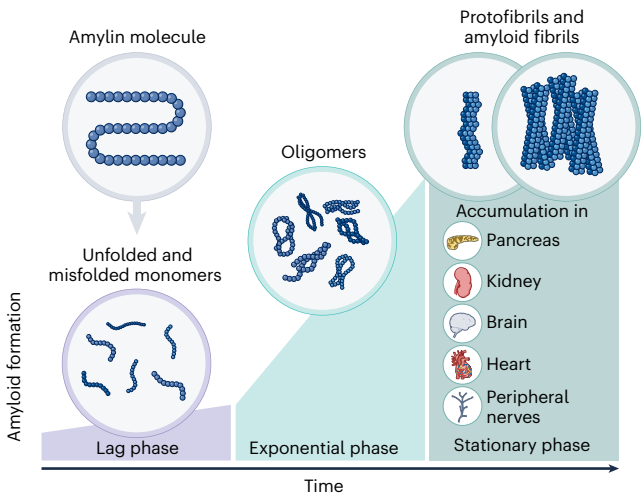

Fig. 2 | The process of amyloid formation. Schematic illustration of the progression of amyloid fibril precursor proteins over time. Initially, native amylin undergoes conformational destabilization to form unfolded and misfolded monomers. During the lag phase, these monomers accumulate and nucleate into early aggregation seeds. The subsequent exponential phase is characterized by assembly of oligomers, which turn into protofibrils and amyloid fibrils in the stationary phase. Accumulation of mature amyloid fibrils in several organs may lead to various pathologies. Originally created in BioRender. Vandekerckhove, L. https://biorender.com/0tal3w7 (2026).

The biological roles of AMY1R and AMY3R, primarily associated with inhibition of food intake and glucose regulation, are better defined[50] than for AMY2R, whose function remains less clear. Amylin also binds the CTR without a RAMP component with low affinity[51] and transiently lowers calcium levels in rodents at high concentrations[52], probably through activation of the CTR, which is involved in calcium homeostasis[53]. However, the physiological relevance for the metabolic effects of amylin through CTR activation alone remains unclear.

Endogenous ligands within the calcitonin family (calcitonin, amylin, CGRP and adrenomedullin) are not completely selective towards their main receptor, with AMY1R regarded as the second CGRP receptor[49].

Genetically modified mouse models provided insight into the role and relevance of specific AMYRs. Mice lacking RAMP1 and RAMP3 develop obesity when exposed to a high-fat diet, associated with impaired nutrient metabolism, including glucose tolerance[50]. Yet, mice overexpressing RAMP1 are more sensitive to amylin and demonstrate a greater increase in energy expenditure than wild-type mice[54,55].

The heterodimer composition of the AMYR structure, and the lack of specific antibodies or antagonists for the AMYR complexes, challenge in vitro interpretation of ligand–receptor interaction and receptor distribution[46,47,56]. In most assays exploring ligand interaction, CTR and RAMPs are co-expressed at high concentrations to increase the likelihood of AMYR conformation[47,56]. However, distinguishing between ligand engagement with the AMYR complex or CTR alone remains challenging because the same downstream intracellular signalling pathways are activated[47,56]. Thus, reliable differentiation of AMYR versus CTR activation is only possible by testing ligands with receptor selectivity or by use of genetically modified mouse models[57,58].

Salmon calcitonin (sCT), a 32-amino-acid peptide, was discovered in the late 1960s as a potent CTR analogue[59], and was later found to be a potent activator of AMYRs[48]. This was surprising because it meant a calcium-lowering hormone also influenced glucose metabolism, satiation and energy regulation. This inspired the development of shorter AMYR agonists containing features of more potent non-fibrillating sCT analogues[60]. sCT and the majority of the shorter sCT-inspired analogues are reported to have a similar binding and activation profile to AMYRs and CTR[61–64]. Whether only the CTR is activated in these in vitro assays is unknown, necessitating verification of dual receptor action by other methods not currently available. Emerging assays that allow selective functional assessment of individual AMYR subtypes and provide unique insights into the pharmacology of potential therapeutic ligands are emerging and could aid better understanding of the interaction between amylin and calcitonin analogues and the complex AMYR family[65].

In summary, the receptors targeted by amylin and AMYR agonists are multifaceted and challenge the understanding of individual receptor contributions to pharmacology, with limited available assays to enhance knowledge. In the development of AMYR-based drugs, avoiding activation of receptor complexes within the calcitonin family such as the CRLR is important to avoid off-target effects.

Distribution of the CTR and RAMPs

Co-expression of both the CTR and a RAMP within the same cell is necessary for a functional AMYR complex, and this needs to be considered in evaluating AMYR expression. The current understanding of AMYR distribution is derived from studies in rats utilizing radioligand binding with labelled amylin and from gene expression analyses of CTR (encoded by the *CALCR* gene) and RAMPs within the same tissues rather than single cells[66,67]. Few studies examined the co-expression in single neurons, at least in the case of the RAMPs at the level of mRNA[68–70].

The brain is considered the main site of AMYR expression, with AMY1R, AMY2R and AMY3R being distributed in a region-specific and cell-type-specific manner, particularly regions implicated in homeostatic and hedonic regulation of energy intake, such as the area postrema and the nucleus of the solitary tract in the hindbrain, the arcuate nucleus of the hypothalamus, the ventromedial hypothalamic nucleus, the dorsomedial hypothalamic nucleus and the nucleus accumbens. AMYRs are also located in the medial preoptic area and in the dorsal raphe[66,68–70]. However, access of peripheral amylin is restricted to the hypothalamus and hindbrain, making other brain regions less relevant for potential AMYR activation in drug development[71].

Studies characterizing the co-expression of AMYR components in specific brain areas have shown that neurons often express the *CALCR* and more than one *RAMP*; this indicates the possibility for the presence of more than one AMYR in the same cell[69]. However, because RAMPs can associate with a number of receptors outside the calcitonin family, this remains speculative[72].

All the above studies are from rodents, and information on the translation to humans is still sparse; however, emerging human expression datasets will further enable exploration of translational aspects between preclinical models and humans. Recent transcriptional datasets with cellular resolution are available in some human brain regions[73,74], confirming co-expression of *CALCR* and *RAMP*s in the hypothalamus[73]. Among *CALCR*-positive neurons in the human hypothalamus, the largest proportion co-expressed *RAMP1*, suggesting that AMY1R is predominantly expressed[73]. This could indicate that the AMY1R may have a leading role in energy intake; however, according to most rodent studies, the area postrema in the brainstem is critical for mediating amylin action on energy intake, and co-expression of CTR and RAMPs at the protein level rather than mRNA in the brainstem, as well as additional regions, is yet to be explored[75–78].

Immunohistochemistry and in situ hybridization of CALCR, RAMPs and GLP1 receptors (GLP1Rs) in the human brain has demonstrated that the majority of CALCRs are expressed in distinct neurons from those expressing GLP1Rs, highlighting the clinical relevance in targeting both biological pathways in parallel[79].

The expression of AMYR is less well described in peripheral tissues than in the brain; in fact, we are not aware of specific studies investigating the presence of all AMYR components in single cells in

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GPCR	RAMP	Receptor	Biological function
CTR (*CALCR*)	-	Calcitonin receptor	Calcium and bone metabolism
	RAMP1	Amylin receptor AMY1R	Inhibition of food intake; glucose regulation; fat metabolism
	RAMP2	Amylin receptor AMY2R	??
	RAMP3	Amylin receptor AMY3R	Inhibition of food intake; glucose metabolism
CRLR	RAMP1	CGRP receptor	Vasodilation
	RAMP2	Adrenomedullin receptor AM1	Vasodilation
	RAMP3	Intermedin receptor AM2	Vasodilation

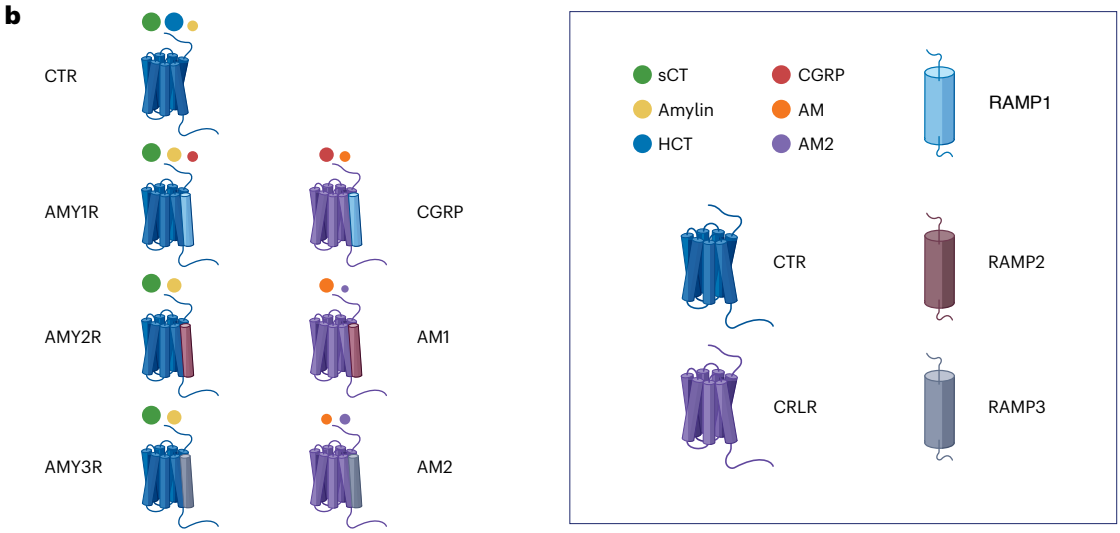

Fig. 3 | The CTR family. a, The seven members of the CTR family, each with diverse physiology. The most prevalent physiological function associated with each of these receptors is mentioned in the right column. **b**, The subunit composition and current classification of human calcitonin family receptors. The CTR (coloured in blue) with RAMP1, RAMP2 or RAMP3 (coloured in light blue, brown or grey) generates AMY1R, AMY2R or AMY3R, respectively. Ligands are shown as spheres with sizes showing their relative potency at each receptor (larger sphere indicates higher potency). AM, adrenomedullin; GPCR, G-protein-coupled receptor; HCT, human calcitonin. Icons originally created in BioRender. Vandekerckhove, L. https://biorender.com/3rv518o (2026). Panel **b** adapted from ref. 219, Elsevier.

the periphery since the first descriptions of the nature of the AMYR as a heterodimer[80]. Compared with the brain, AMYR expression is lower in the periphery because *CALCR* expression is lower. With recent emergence of more precise sequencing methods resulting in large-scale human databases, such as the CellxGene Census, the limited co-expression of *CALCR* and *RAMP*s becomes evident[81]. Exploring this resource reveals positive expression of *CALCR* in some tissues such as in the distal convoluted tubule epithelial cells and the thick ascending limb epithelial cells in the kidney and very sparsely in myeloid cells. *RAMP*s are not detected in these cells, indicating a *CALCR*-specific profile. The limitation to these databases is the lack of bone expression, although *CALCR*/CTR expression in osteoclasts is known to be abundant and has an important role in anti-resorptive effects[82]. *RAMP2* has also been reported to be expressed in osteoclasts, suggesting potential expression of AMY2R in these cells[83], yet there is no solid evidence of *CALCR* expression in osteoblasts. Finally, high expression of *CALCR* has been observed on human muscle satellite cells[84]. The functional consequence is currently unknown but is suggested to be associated with the maintained quiescent state of the satellite cells, and muscle regeneration and function[85–87].

Taken together, AMYR expression in the periphery and the brain is still underexplored, and more evidence in humans will enhance the translational insight into AMYR biology.

Receptor–ligand dynamics and kinetics

Differences in receptor affinity and the structural interaction of ligands with the different receptors are not well understood and add to the complexity of amylin-based drug development. As there are no completely specific ligands available, especially not for the CTR, it complicates the exploration of the different receptor interactions.

Recent studies using cryogenic electron microscopy have shown that different AMYR and CTR agonists interact differently with AMYR and CTRs, in terms of both receptor engagement and binding kinetics. In general, amylin and full-length amylin-based ligands, such as cagrilintide and pramlintide, associated with RAMPs more effectively when interacting with AMYR complexes, in comparison to shorter calcitonin-based ligands, such as calcitonin and sCT, which kept the receptor complex in a CTR-biased conformation irrespective of the presence of RAMPs[56]. Hence, even though sCT and cagrilintide share many in vitro characteristics of receptor activation[47], their in vivo effects may differ[58]. In addition, amino acid substitutions contribute to the degree of stability in ligand–receptor engagement in the individual molecules[88]. Together, this implies that the ligand structure determines whether receptor activation yields an amylin-dominant or calcitonin-dominant signalling profile[56], which could result in the activation of different physiological processes and may not be evident from classical receptor binding or potency assays.

sCT and derivatives have often been incorrectly referred to as amylin analogues; however, these have a strong affinity for CTR in addition to AMYR and receptor kinetics that are different from amylin backbone derivatives with almost irreversible binding[47]. In addition, AMYR antagonists such as shorter, truncated sCT 8–32 and AC187, used as tool molecules for exploring physiological responses of amylin, are not specific to AMYRs or AMYR subtypes and can also antagonize the CTR, leaving the same dogmata as for the agonists[89].

The physiological consequences of the difference in receptor engagement, receptor selectivity and the dissociation rates remain unclear, and a better understanding of these topics is essential in optimizing development of the best amylin analogues with high efficacy and limited side effects and off-target effects.

Intracellular signalling cascades elicited by amylin binding

Activation of the CTR and AMYR has been shown to engage multiple intracellular signalling cascades, such as cyclic adenosine monophosphate-activated protein kinase (the most common intracellular messaging system in in vitro assessments), extracellular signal-related kinases 1 and 2, protein kinase A, calcium, and β-arrestin (the latter with divergent reports)[47,90,91]. The relevance of these pathways is not well understood but could contribute to diverse biological responses, including energy homeostasis, appetite control and metabolic processes[70,71]. Assigning specific biological responses to different AMYR intracellular pathways poses a challenge due to the lack of selective pharmacological tools distinguishing between these AMYR pathways, and the translation of in vitro findings of pathway activation into biological effects remains unexplored.

Genetic support for the *CALCR* gene in cardiometabolic disease

An increasing number of online portals are available for evaluation of genetic associations with phenotypes, such as Open Targets (https://www.opentargets.org/) and the Common Metabolic Diseases Knowledge Portal (https://hugeamp.org/). In these, the *CALCR* gene encoding the CTR is associated with increased susceptibility to higher body mass index, body weight, hip circumference and T2D. A whole-exome sequencing study substantiated this evidence, reporting that potential loss of function of the *CALCR* gene was associated with higher adiposity and obesity risk in humans[92]. Thus, genetic evidence of the *CALCR* gene substantiates its potential relevance as a target for treatments related to these cardiometabolic diseases.

Amylin physiology and implications for drug development

Translation from rodents to humans

Use of rodent models in the study of obesity raises challenges about which model translates best to humans, and none of them may show all effects being quantitatively translatable for the parameters tested. In the case of amylin and its analogues, the short-term effects on food intake show similar patterns in rats and mice[93]. However, with subchronic treatment in obese animals, weight loss induced in rats quantitatively exceeds that of mice[58,94], where GLP1 analogues induce a more comparable relative weight loss in both species[95]. The reasons for these potential differences are unknown but may relate to the interaction of amylin with the leptin system[96,97]. Diet-induced obese (DIO) mice may exhibit a more severe type of adiposity and are more leptin resistant compared with DIO rats, and hence may be metabolically more compromised and react less to the amylin–leptin synergy[98]. An interesting observation in DIO mice is the differential response to full-length amylin analogues compared with sCT analogues, with the latter apparently giving rise to a very strong counter-regulatory response, resulting in weight gain following subchronic treatment[57,58]. DIO mice and DIO rats each represent underperformance and overperformance on amylin-induced body weight loss compared with humans, complicating recommendations on the use of one rodent model over the other, and effects in each model should be evaluated with this in mind. Despite the limited understanding of mouse body weight responses, genetically modified mouse models are available that allow insight into the mechanisms underlying amylin action at its diverse receptors.

Central actions

Because amylin was demonstrated to lower food intake in rodents, one of the most explored, and probably the most relevant, areas of amylin biology is the regulation of energy intake and satiation[18,99–101]. There are detailed reviews of the central actions of amylin on the regulation of metabolism, beyond the scope of the current Review[49,102–104]; the following section will only briefly describe some of the key discoveries and conclusions.

The area postrema located in the dorsal vagal complex of the brainstem is the best-explored brain region and is considered critical for mediating the acute anorectic effects of amylin and body weight regulation[60,76–78,105–107]. Several biological functions such as gastric emptying, food intake and regulation of body weight are largely abolished in area postrema-lesioned rats[76,108]. Peripheral amylin has been shown to activate neurons in the area postrema, which further communicates to key appetite-regulating brain regions such as the lateral parabrachial nucleus, the central nucleus of the amygdala and the bed nucleus of the stria terminalis[109–112]. These pathways have been associated not only with regulation of energy intake but also with aversive stimuli, and activation of neurons containing CGRP in the parabrachial nucleus contributes to these behaviours[110,111,113,114]. Several studies have shown that amylin also activates the CGRP neurons in the parabrachial nucleus[110,115]; however, follow-up studies indicate that this activation and CGRP as a neurotransmitter in the parabrachial nucleus are not necessary for the effect of amylin on eating[116].

In comparison to other hormones such as GLP1 that also activate the parabrachial nucleus[95], the distribution of AMYRs in the area postrema is specifically located to the ventricular zone, which is different from the more scattered location of the GLP1Rs, suggesting different pathways[79]. Furthermore, data indicate that amylin-receptive and GLP1-receptive neurons differ in the area postrema[117]. In support of this, clinical data of the GLP1 analogue semaglutide and the amylin analogue cagrilintide showed they both lower body weight but demonstrated distinct differences in gastrointestinal-related adverse events, with fewer gastrointestinal adverse events reported with cagrilintide[118] and the amylin analogue eloralintide[119].

Recent studies suggest that the hypothalamus potentially contributes to the effect on body weight regulation, because amylin has direct access to the hypothalamus from the periphery and has been reported to engage proopiomelanocortin neurons in this area[70,71]. Deletion of CTR on proopiomelanocortin neurons did not affect the acute response to peripheral amylin on food intake, but did increase body weight and adiposity, and decreased glucose tolerance in high-fat-fed male mice[70]. Thus, the engagement of the hypothalamus may be more important in long-term body weight homeostasis, including leptin responsiveness and glucose regulation[70].

Additional brain regions have been reported to be involved in the regulation of energy intake by amylin; however, in many of these reports, AMYR agonists are directly injected into specific brain regions where peripheral amylin and AMYR agonists may not reach biologically relevant concentrations in vivo[71,120–125].

Beyond its anorectic effects, amylin and amylin analogues may modulate energy expenditure by counteracting compensatory metabolic adaptations that typically reduce energy utilization following weight loss[94,126]. The mechanism behind this is currently unknown but it has been suggested to occur through activation of the sympathetic nervous system[55] via enhanced activity of brown adipose tissue, which is probably more relevant in rodents. More relevant to humans, energy expenditure could be affected through increased mitochondrial

respiration in skeletal muscle[127]. As with most of the studies discussed, these findings are primarily based on rodent studies and require further clinical validation.

Owing to the co-secretion of amylin and insulin from pancreatic β-cells, amylin levels are typically elevated in individuals with obesity due to insulin hypersecretion subsequent to insulin resistance[1]. However, unlike several appetite-regulating hormones that demonstrate a reduced efficacy with excess body weight, amylin and amylin analogues in relevant doses appear to retain their anorectic potential in obese rats and also in people with obesity[118,128,129]. Only states of extreme obesity seem to lower the effectiveness of amylin to reduce eating and body weight[130]. The underlying mechanisms of these findings are still unknown but could be associated with lowered leptin responsiveness.

Somewhat counterintuitive to the body weight-lowering effect of amylin and AMYR agonists, transgenic mice overexpressing amylin in very high levels gained more body weight than wild-type mice[131]. A similar phenomenon has been observed in DIO mice dosed with an amylin analogue, where a dose–response study demonstrated a bell-shaped curve with the highest doses being less effective on reducing body weight[132], and may be a similar phenomenon to the chronic effect of sCT in mice[58]. These findings suggest the development of amylin resistance under extreme conditions, at least in mice[58].

Leptin responsiveness. Leptin is a hormone produced by adipose tissue involved in metabolic regulation, including body weight control and energy homeostasis[133]. Interestingly, body weight lost with leptin treatment seems to be exclusively loss of fat mass[134]. In healthy conditions, leptin is believed to signal energy status to the hypothalamus, suppressing appetite and increasing energy expenditure[135]. However, in people with obesity, leptin levels are high and ineffective in reducing appetite—a phenomenon that is referred to as leptin resistance, and is associated with increased food intake and reduced energy expenditure[135].

Leptin seems to be important for the effect of amylin on energy intake: amylin administration in leptin-compromised rodent models led to an attenuated response;[136] conversely, leptin is less effective in the absence of amylin[137]. In addition, a substantial series of experiments suggests synergistic action of amylin and leptin[97,138–141]. Some of these findings indicate that amylin may directly enhance leptin receptor signalling and responsiveness in the brain, particularly in the context of obesity and metabolic regulation, and increase the expression of leptin receptors in the hypothalamus[70,138,141]. Improving leptin responsiveness and restoring leptin balance in cardiometabolic disease has been associated with enhanced insulin sensitivity, favourable changes in body composition and improved weight maintenance—all therapeutically relevant in the management of obesity and related conditions[142–145].

Studies have shown that co-administration of amylin and leptin in rodents, and co-administration of pramlintide and metreleptin in humans, lowered body weight to a larger extent than either hormone alone[146,147]. The synergistic effect in rodents involved hypothalamic pathways, potentially through modulation of receptor sensitivity and signalling[97,137–140,146,147]. Translation to humans seems plausible but is unproven.

It is difficult to measure leptin responsiveness in humans directly, but increased soluble leptin receptor (sLepR) levels in plasma have been suggested as a biomarker[148–150]. An increase in sLepR was observed in a clinical trial in participants with T2D following administration of cagrilintide but not semaglutide, emphasizing the potential association of leptin responsiveness with amylin-related improvements in glycaemic regulation[151].

Reward and addiction. In addition to regulation of energy intake, several studies have indicated that amylin may also affect the rewarding effect of food items[121,125,152–154]. Further substantiating these observations, amylin reduces the preference for high-fat diet intake in animal models[98], and was also observed in rodents and humans with the AMYR agonists KBP-089 and petrelintide[155,156]. As more indirect evidence in humans, pramlintide was shown to reduce binge-eating episodes[157] and cagrilintide improved the control of eating[158]. Some of these effects may be through regulation of dopamine levels, which has been demonstrated following peripheral administration with sCT and seemed to depend on area postrema engagement[159]. Although much literature points to the ventral tegmental area–nucleus accumbens axis[121–123] as well as the lateral dorsal tegmental nucleus and the medial prefrontal cortex[124,125] as important for reward-related eating behaviour, it is uncertain whether these studies mimic amylin in circulation because they all explored the effect of AMYR/CTR activation by direct brain injections. Although the exact brain pathways engaged in this modulation of reward remain to be clarified, the effect on dopamine and the effects on reward-related eating suggest that AMYR/CTR engagement may extend to inhibition of reward/addiction in a broader context. In support of this, several AMYR agonists have been shown to reduce alcohol and nicotine intake in rats[160–162].

In summary, the brain has an essential role as a direct target of amylin in many of the physiologies, including homeostatic and hedonic food intake. The area postrema seems especially important, although the hypothalamus may contribute. These two regions express AMYRs and are directly engaged by amylin from the periphery. Finally, leptin and amylin seem to interact, although the exact nature of this is not well understood.

Peripheral actions

Direct peripheral actions of amylin are less well explored than its central actions. Several of the early studies of amylin focused on potential direct effects in skeletal muscle, adipose tissue and the liver, which could potentially drive changes in insulin sensitivity[3,52,163–165]. It has long since been acknowledged that the effects on adipose tissue and liver were indirect due to lack of direct effects on adipocytes and hepatocytes; however, using ex vivo techniques on isolated skeletal muscle indicated direct effects of amylin in this tissue[3,52,163,166–169]. This observation is surprising, as no expression data indicate the presence of *CALCR* in either rat or human myocytes[85]. Even though *CALCRs* are expressed on quiescent satellite cells, it is difficult to understand how amylin could cause direct metabolic effects on ex vivo muscle preparations. By contrast, some studies explored the effects of amylin on muscle insulin sensitivity, reporting negative outcomes[166–169]. Many of these investigations utilized human amylin[166–168], which tends to fibrillate immediately after dissolution, and these fibrils may have detrimental effects on their own, which could explain some of the results obtained. Studies using non-fibrillating selective analogues will be important to understand amylin's potential direct and indirect effects in muscle tissue.

By contrast, circulating, pharmacological activators of AMYRs and CTRs seem to exert a positive influence on insulin sensitivity in rodents[170–172]. Direct evidence is missing, but it is believed that the same is true in humans. Pramlintide is used as an adjunct to insulin therapy to reduce the required insulin dose in people with T1D and T2D[173]; to improve glucose control potentially through the inhibition of glucagon release, lowering hepatic glucose production; and through the inhibition of gastric emptying[173]. It has not yet been formally tested, but the ability of pramlintide to increase insulin sensitivity could also be associated with an improvement in leptin sensitivity[174–176].

The majority of studies today indicate that the peripheral metabolic effects of amylin are indirectly mediated via neuronal pathways originating from primary activation of the caudal hindbrain, or via modulation of hormones, such as insulin, glucose and glucagon. Studies suggested that interruption of vagal or non-vagal afferents from the periphery to the brain did not influence the metabolic effects of amylin[177–179], while ablation of central AMYR, particularly in the area postrema, blocked the effects of peripherally administered amylin or amylin analogues[60,76,180].

Amylin in obesity and metabolic comorbidities

Bone health

Although amylin's role in bone metabolism has not been extensively explored, research indicates that amylin may influence bone remodelling processes, modulating the balance between bone resorption and formation[181,182]. As mentioned, expression of the CTR is well described in osteoclasts as a target for sCT, which has been used for decades for the treatment of osteoporosis[183]. The expression of AMY2R has also been described in osteoclasts, indicating potential effects of amylin in bone homeostasis[82,83]. Several amylin analogues in development exhibit affinity for both CTRs and AMYRs, implying that these agents may also protect bone during weight loss[47,56], with pramlintide recently reported to lower the bone resorption biomarker CTX-1 during infusion[15]. Although direct clinical evidence is lacking, as low bone density can increase the risk of fractures particularly in the context of weight loss and diabetes, this potential effect of amylin in bone health is relevant when considering treatment options[184].

Muscle health

The preservation of lean body mass during weight loss has become an increasingly important consideration[184–186], and has been extensively debated with the use of pharmacological weight-loss treatment. The debate entails several assumptions such as lean mass representing muscle mass, while it represents everything but fat tissue, and often lacks inclusion of additional parameters such as age, adiposity and physical activity[187], in addition to muscle functional outcomes. Following this, some amylin analogues have been suggested to preserve muscle mass during weight loss, as observed in animal studies[188–191]. These studies are typically conducted in growing rats, which potentially masks the effect on both lean and fat mass loss when presented as a percentage of the total body weight loss[126,189,191]. Thus, body composition effects are better studied in mature DIO animal models or even more importantly in clinical trials using techniques suitable for quantifications of lean body mass and muscle function.

In a recently published clinical study with dual-energy X-ray absorptiometry (DEXA) scanning, both cagrilintide and semaglutide, and the combination, demonstrated a greater reduction of fat mass relative to lean mass[118] but without indication of differential effects between the amylin and GLP1 component[118]. Similar effects on fat mass and lean mass loss using DEXA scanning were observed in another clinical study with eloralintide[119]. These findings support that the narrative based on preservation of lean mass observed in rodent models might not robustly translate to humans. Noteworthy, the studies did have shortcomings such as low sample size in the DEXA subgroup, and further studies including better methods for discriminating muscle mass from lean mass, such as magnetic resonance imaging and methods to assess muscle function, will improve the understanding of muscle effects by amylin.

CTRs are expressed in muscle satellite cells, which are stem cells important for regeneration of muscle cells during injury, and have been reported to be downregulated with ageing[85]. Limited knowledge exists around the consequences of CTR activation in these cells, but it could have a role in their activation, differentiation and regulation of muscle regeneration processes, including preserving muscle function during weight loss-induced muscle loss[85].

The RAAS and cardiovascular risk factors

In an acute setting, amylin has been reported to activate the renin–angiotensin–aldosterone system (RAAS), a key regulator of blood pressure, electrolyte balance and fluid homeostasis[192]. Although activation of the RAAS is typically associated with detrimental cardiovascular effects, including increased blood pressure, the use of amylin analogues is not associated with an increased cardiovascular risk in people with T2D[158,193].

Understanding how, and to what extent, amylin engages with the RAAS and how this is counteracted by the diuretic and natriuretic effects of amylin[194] could help clarify its role in cardiovascular and renal physiology, and may inform the broader relevance of amylin-targeted therapies in cardiometabolic disease.

Cardiovascular health

Demonstrating the effect of amylin and AMYR agonists in preclinical models of cardiovascular disease is challenged by the rodent models available. Most models are developed in mice and, as previously mentioned, AMYR agonists have limited effects, at least on body weight, in mice. Despite this shortcoming, clinical evidence from treatment of people with obesity and/or T2D with the amylin analogue cagrilintide (phase III trial) or eloralintide (phase II trial) has been associated with reductions in circulating lipid levels and C-reactive protein, suggesting potential indirect benefits of amylin on cardiovascular risk factors[118,119,151,158]. Moreover, cagrilintide demonstrated a sustained reduction in heart rate, different from what is typically found with incretins[118,158]. The mode of action is not fully understood but it potentially sets amylin agonist treatment apart as a positive cardiovascular differentiator.

Although amylin at normal physiological levels is not associated with cardiovascular effects, hypersecretion of (human) amylin in cardiometabolic disease may lead to amylin aggregation in the coronary microvasculature and myocardial interstitium[42,195]. Overexpression of human amylin in rats reproduced the amylin-associated cardiac pathologies observed in humans, indicating a role for amylin aggregates in the development of diabetes-related heart failure[42]. It is currently unknown whether treatment with exogenous, non-fibrillating amylin molecules leads to downregulation of endogenous amylin. A decrease in endogenous amylin, and hence less fibril formation, is also possible following improvements in insulin sensitivity, where the endogenous insulin and amylin secretion is expected to decrease. In addition, improvements in cardiometabolic disease also associate with improvements in cardiovascular pathology[196].

To summarize, amylin acts primarily in the brain and modulates energy homeostasis and metabolic processes (Fig. 1). However, the development of amylin analogues targeting both the AMYR and the CTR extend the physiological effects of amylin beyond glucose metabolism, satiation and appetite control, potentially also maintaining bone mass during weight loss, affecting muscle function and improving cardiovascular risk-associated factors (Fig. 1). Furthermore, the potential for downregulation of endogenous fibrillating amylin with treatment of non-fibrillating analogues also gives a possibility to affect organ classes where these are involved in pathophysiology.

Development of amylin analogues

What does it take to make a 'good' amylin analogue?

Developing amylin analogues has been constrained by several structural and pharmacological challenges. As mentioned, native amylin has a strong propensity to aggregate into amyloid fibrils, complicating its formulation and stability[33,197], and overcoming this fibrillation tendency has been central to designing clinically viable analogues[43,198].

Another limitation is the short half-life of the peptide. Pramlintide, the first amylin analogue approved by the US Food and Drug Administration, requires multiple daily injections due to rapid clearance, resulting in a high treatment burden[199]. Extending the half-life through molecular engineering has been central to next-generation AMYR agonists, and drugs targeting the AMYRs and potentially the CTR have been formulated as longer-acting, weekly administered molecules[188]. Several of these are currently being evaluated in clinical trials[43,200].

Most AMYR agonists interact with both the CTR and AMYRs with varying activation selectivity across these different receptors[47,56]. Receptor selectivity and subsequent distinct biological effects should be considered in amylin analogue development besides efficacy and the gastrointestinal-related adverse events that are the most frequently observed side effects[151,158]. Different selectivity profiles and other

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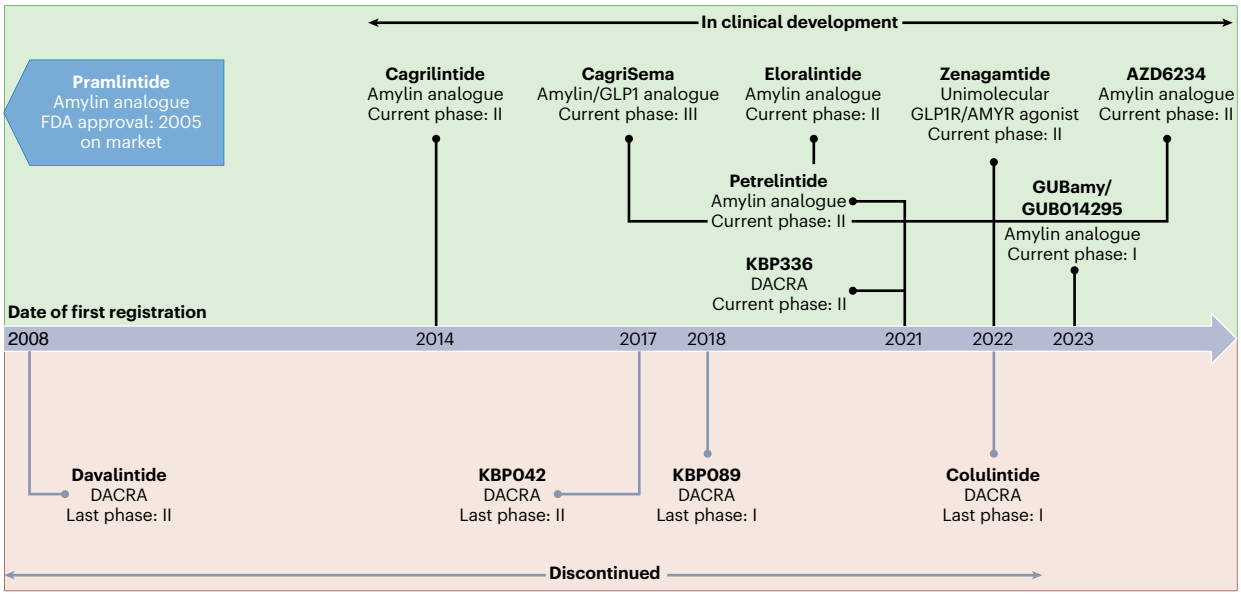

Fig. 4 | Amylin and salmon calcitonin analogues in clinical development. Years represent the first time an analogue was registered in a clinical trial database (ClinicalTrials.gov or EudraCT), except for pramlintide, where 2005 indicates the year of US Food and Drug Administration approval. Analogues listed on top of the timeline are in clinical development, whereas analogues below the timeline are discontinued. DACRA, dual amylin and calcitonin receptor; FDA, US Food and Drug Administration.

factors affecting ligand–receptor interactions could affect several biologies, such as bone homeostasis-related outcomes.

Generally, amylin analogues seem to have a more benign gastrointestinal tolerability profile than GLP1 analogues, as demonstrated in the phase III REDEFINE1 clinical trial for CagriSema, a combination of the GLP1 analogue semaglutide and the non-selective amylin analogue cagrilintide[118]. Selectivity of AMYRs has been suggested to affect tolerability[201]. However, early clinical data from other non-selective amylin analogues, such as petrelintide, indicate adverse event profiles similar to those from more AMYR-selective analogues such as pramlintide and eloralintide[119,158,202–204], questioning the relevance of CTR versus AMYR selectivity as an important factor for tolerability[201,202,205]. In addition, escalation to full dose of these molecules may be relevant for tolerability, and direct comparisons of different titration regimens could improve this understanding.

Selectivity towards other CTR family receptors should also be considered. As such, the CGRP receptor has been associated with migraine[206], and adrenomedullin receptors have been associated with vascular homeostasis[207], and these receptors should be avoided when developing future therapies for metabolic diseases. Pramlintide, for example, has affinity towards the CGRP receptor and has been reported to induce migraine[208], which could be a CGRP receptor-driven effect[65]. The receptor engagement and receptor off-rates of the individual analogues may vary and present additional considerations[47,56], and finally, the scaffold for amylin analogues, for example in full-length amylin-based, calcitonin-based and adrenomedullin-based scaffolds, can differ. The physiological consequences of these scaffolds and receptor dynamics are currently not well understood, but opposing biological effects of amylin-based and sCT-based molecules have been demonstrated both in DIO mice and in RAMP1/RAMP3 knockout mice[57,58].

Amylin drugs in development and beyond

Since pramlintide's approval, amylin-based therapy development has evolved considerably, focusing on both single-agent amylin analogues and multi-acting compounds that target multiple pathways involved in metabolic regulation[43,188,209–214]. These include small molecules and engineered peptides with modified scaffolds for improved receptor engagement and differential selectivity for AMYR over CTRs[215]. Several of these are in clinical development[215] (Fig. 4). As many of these are based on scaffolds other than full-length amylin, the correct term for these is 'AMYR agonists'. Notably, all discontinued molecules in clinical development are based on scaffolds different from the amylin backbone, but it is not known if this is the crucial factor determining successful continuation. Limited knowledge of the structure–activity relationship and receptor selectivity complicates amylin-based therapy development, as was recently reported with the development of the dual AMYR and CTR agonist BGM1812 (ref. 216).

In clinical trials, AMYR agonists reduced body weight up to 20% in people living with obesity[118,119]. Additionally, in obesity both eloralintide and cagrilintide lowered fasting insulin levels, and in T2D cagrilintide showed a small improvement in glycaemia with simultaneous lowering of insulin levels, indicating an effect on insulin sensitivity[151]. Furthermore, additional improvements in lipid levels, blood pressure, C-reactive protein levels and leptin sensitivity as proposed by the leptin-to-sLepR ratio were observed[118,151].

In preclinical studies, several AMYR agonists have been demonstrated to reduce body weight—especially fat mass—and energy intake[60,132,201,217]. In addition, preclinical data show that cagrilintide may have beneficial effects on energy expenditure and insulin sensitivity[94,172,218].

There is a growing interest in combination therapies that target multiple hormonal pathways aiming to achieve greater efficacy through complementary mechanisms[151]. CagriSema, for example, is being developed for the treatment of people with obesity and T2D and demonstrated synergistic effects in weight loss and glycaemic control[118,151,200]. In addition, zenagamtide (formerly known as amycretin) is a unimolecular molecule that targets both the GLP1R and the AMYR/CTR, and demonstrated significant weight loss accompanied by reduction in fasting glucose in people with obesity[209].

In parallel, small-molecule modulators to regulate amylin signalling are being explored in preclinical studies.

Conclusions and outlook

Amylin has emerged as a promising therapeutic target for cardiometabolic disease, with effects extending beyond glycaemic control,

including appetite regulation and potentially broader metabolic health. Acting through distinct neuronal pathways, amylin complements other anorectic hormones, such as GLP1, and may further enhance leptin responsiveness and insulin sensitivity, while improving bone and muscle health. Furthermore, improved tolerability of amylin analogues compared with GLP1 analogues may be relevant for treatment selection.

The inherent fibrillation tendency of endogenous human amylin could potentially be mitigated by treatment with non-fibrillating drug candidates. Limited knowledge of preferred receptor profile (AMYR versus CTR) and uncertainties about which specific downstream signalling pathways are activated following receptor binding need more exploration before therapeutic development. Furthermore, in vitro and animal data limitations and correct interpretation should be considered for regulatory and translational guidance.

Looking ahead, amylin pharmacology offers a versatile and clinically relevant target as it lowers appetite though distinct neuronal pathways while potentially improving insulin sensitivity and endogenous leptin responsiveness and potentially maintaining bone health during weight loss.

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Author contributions

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Competing interests

A.S. and K.R. are employees of Novo Nordisk A/S, which is developing amylin-based drugs for the treatment of metabolic diseases. K.R. is listed as inventor on the patent covering CagriSema, a fixed-dose combination of an amylin analogue and a GLP1R analogue. T.A.L. has research collaborations with Novo Nordisk A/S, had a collaboration with Structure Therapeutics and has consulted for AbbVie, AstraZeneca, Eli Lilly, Roche and Zealand Pharma.

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