Creating the amylin story

Lutz, Thomas A

DOI: https://doi.org/10.1016/j.appet.2022.105965

Appetite 172 (2022) 105965

Contents lists available at ScienceDirect

Appetite

journal homepage: www.elsevier.com/locate/appet

Creating the amylin story

Thomas A. Lutz

Institute of Veterinary Physiology Vetsuisse Faculty University of Zurich Winterthurerstrasse, 260 8057, Zurich, Switzerland

ARTICLE INFO

Keywords:
Amylin
Islet amyloid polypeptide (IAPP)
Satiation
Adiposity
CTR
RAMP
Leptin
Reward
Cagrilintide

ABSTRACT

This paper is based on a presentation given at the Annual Meeting of the Society for the Study of Ingestive Behavior in July 2021 and provides a personal view on some of the milestones in the discovery of amylin as a constituent of pancreatic islet amyloid deposits, as a pancreatic beta-cell hormone, and on its role in physiology and pathophysiology. Only selected effects of amylin are discussed here because we recently published extensive reviews on the physiology and pathophysiology of amylin. Amylin was discovered as the main constituent of islet amyloid that is predominantly found in pancreatic islets in type 2 diabetics. These deposits, and in particular small oligomer aggregates of amylin seem to contribute to the progressive beta-cell damage seen in type 2 diabetics. Amylin is also a physiologically relevant circulating hormone with diverse metabolic functions, e.g. inhibition of eating, of pancreatic glucagon secretion and of gastric emptying. Knowledge of these types of functions and amylin's mechanisms of action lead to the development of amylin analogues that are now among the most promising anti-obesity targets in clinical testing. With this review, I want to give a short overview of 35 exciting years of amylin research.

1. The dichotomy of amylin in physiology and pathophysiology

The mature 37 amino acid peptide amylin is derived from the *IAPP* (islet amyloid polypeptide) gene and is produced in pancreatic beta-cells and – in much lower amounts – in other tissues, like the stomach, spinal ganglia and in the brain (Cooper, 1994; Hay, Chen, Lutz, Parkes, & Roth, 2015). Amylin is characterized by an interesting *dichotomy* because this peptide, on one hand, contributes significantly to the development of type 2 diabetes (T2D) by its propensity to aggregate into fibrils (Westermark, Andersson, & Westermark, 2011), but on the other hand also to the physiological control of metabolism (Le Foll & Lutz, 2020). These dichotomous roles seem to be "functionally independent" in that some amylin forms aggregate into oligomers and eventually mature amyloid fibrils; this process likely involves multiple mechanisms and is independent of the cell membrane bound amylin receptor because aggregation is initiated intracellularly (Lorenzo, Razzaboni, Weir, & Yankner, 1994; Westermark et al., 2011). On the other hand, the soluble monomeric form of mature amylin activates the amylin receptor (AMY) in the brain to produce hormonal effects on glucose metabolism (inhibition of glucagon secretion, control of gastric emptying) and nutrient intake (induction of satiation), hence beneficial weight-lowering and anti-diabetic effects.

2. Time axis in amylin discovery

The first description of amylin-derived deposits in pancreatic islets dates back to 1900 when "hyaline appearance" was reported within islets from diabetic patients (Opie, 1901). In 1943 (Ahronheim, 1943) (and then confirmed in 1961 (Ehrlich & Ratner, 1961)), this extracellular material was histologically characterized as amyloid; similar deposits were described in diabetic cats in 1981 (Yano, Hayden, & Johnson, 1981a; 1981b). A milestone was the characterization of the partial sequence of the main constituent of pancreatic islet amyloid in 1986; the underlying peptide was originally called insulinoma amyloid peptide (IAP), and was renamed later as islet amyloid polypeptide (IAPP) (Westermark, Wernstedt, Wilander, & Sletten, 1986). About at the same time, Cooper and co-workers (Clark et al., 1987; Cooper et al., 1987) identified the sequence of the full 37 amino acid peptide from the pancreas of type 2 diabetics which was originally called diabetes-associated peptide (DAP) but soon renamed as amylin because it was realized that the presence of amylin is not restricted to T2D. I will use the term "amylin" for the rest of the article, realizing that some authors prefer the term "IAPP", in particular when a specific chemical structure is meant (Young, 2005d, 2005f).

Several groups identified the amylin gene (Mosselman, Höppener, Lips, & Jansz, 1989; Roberts et al., 1989; Sanke, Bell, Sample, Rubenstein, & Steiner, 1988) and it soon became clear that amylin is a beta-cell

E-mail address: tomlutz@vetphys.uzh.ch.

https://doi.org/10.1016/j.appet.2022.105965
Received 24 December 2021; Received in revised form 28 January 2022; Accepted 4 February 2022
Available online 17 February 2022

product, just as insulin, and is in fact co-packed and co-released with insulin (Asai et al., 1990; Johnson et al., 1988; Nakazato, Asai, Kangawa, Matsukura, & Matsuo, 1989; Nakazato et al., 1990; O'Brien, Westermark, & Johnson, 1991). The discovery of amylin as a "normal" beta-cell hormone was soon followed by the first reports on amylin's eating inhibitory effect (Balasubramaniam, Renugopalakrishnan, Stein, Fischer, & Chance, 1991; Chance, Balasubramaniam, Chen, & Fischer, 1992; Chance, Balasubramaniam, Stallion, & Fischer, 1993; Chance, Balasubramaniam, Zhang, Wimalawansa, & Fischer, 1991; Morley, Flood, Horowitz, Morley, & Walter, 1994). Based on amylin's metabolic actions, the first full-length amylin analogue, pramlintide, was developed in 1995/1996 (Kong et al., 1997; Thompson, Pearson, & Kolterman, 1997) and still today is the only approved amylin-based drug (Symlin^{R}) for the treatment of T1D and T2D (Weyer, Maggs, Young, & Kolterman, 2001). Another key event in amylin discovery was the characterization of the structure of the receptors of the calcitonin family of peptides which, next to calcitonin, includes amylin, calcitonin gene-related peptide (CGRP), adrenomedullin and adrenomedullin 2, also called intermedin (Christopoulos et al., 1999; McLatchie et al., 1998; Muff, Buhlmann, Fischer, & Born, 1999). Since then, we know that the AMY consists of the calcitonin receptor core (CTR) which heterodimerizes with receptor-activity modifying proteins (RAMP) 1, 2 or 3 to form the AMY 1–3 receptors (Hay, Christopoulos, Christopoulos, Poyner, & Sexton, 2005; Hay, Garelja, Poyner, & Walker, 2018). About at the same time, it became clear that amylin's metabolic actions are mediated by direct activation of the central nervous system, in particular the area postrema (AP) which is characterized by an open blood brain barrier (Lutz, Mollet, Rushing, Riediger, & Scharrer, 2001; Lutz, Senn, Althaus, Del Prete, Ehrensperger, & Scharrer, 1998).

Our own laboratory actively contributed to the increase in knowledge about amylin's physiological and pathophysiological role in metabolism. To give some examples, we were the first to quantify amylin-derived amyloid deposition in diabetic cats (Lutz & Rand, 1993, 1997), showed for the first time that amylin is a satiating hormone and reduces eating by a meal size effect (Lutz, Geary, Szabady, Del Prete, & Scharrer, 1995), that this effect is of physiological relevance (Mollet, Gilg, Riediger, & Lutz, 2004), and that amylin's effect does not seem to depend on afferent nerve signalling to the brain but rather a direct brain effect (Lutz, Althaus, Rossi, & Scharrer, 1998; Lutz, Del Prete, & Scharrer, 1994, 1995). Our studies which were then confirmed by other laboratories (Braegger, Asarian, Dahl, Lutz, & Boyle, 2014; Edwards et al., 1998; Mack et al., 2010; Smith et al., 2016) indicated that the AP plays a predominant role in mediating amylin's effect in the homeostatic control of eating (Le Foll & Lutz, 2020; Lutz, Mollet, et al., 2001; Lutz, Althaus, et al., 1998; Lutz, Senn, et al., 1998). Based on our findings that amylin also has characteristics of an adiposity signal (Rushing et al., 2001; Rushing, Hagan, Seeley, Lutz, & Woods, 2000), we subsequently showed that amylin synergizes with insulin and leptin (Osto, Wielinga, Alder, Walser, & Lutz, 2007); in particular the latter effect led to a large number of studies indicating that amylin seems to act as a sensitizer to leptin action, most likely via interaction in the hypothalamus (Trevaskis, Parkes, & Roth, 2010). We were also able to define neurotransmitters in the caudal hindbrain which are critical to mediate amylin's effect (Boccia, Le Foll, & Lutz, 2020; Braegger et al., 2014; Lutz, Del Prete, Walzer, & Scharrer, 1996; Lutz, Tschudy, Mollet, Geary, & Scharrer, 2001; Mollet et al., 2001; Potes, Turek, et al., 2010), and early on identified the lateral parabrachial nucleus (LPBN) as an important projection site of amylin activated AP neurons (Becskei, Grabler, Edwards, Riediger, & Lutz, 2007; Riediger, Zuend, Becskei, & Lutz, 2004). Interestingly, the primary AP dependent pathway activated by amylin seems to differ from pathways activated by other eating inhibitory stimuli (Zuger, Forster, Lutz, & Riediger, 2013), hence there seems to be a differentiation of processing of various incoming signals already at the level of the AP. Even though the structure of the AMY had been known for many years, it was not until 2016 that all necessary AMY components were co-localized in single neurons in native brain tissue (Liberini, Boyle, et al., 2016). Finally, we gave the first indications of AMY subtype specific actions of amylin, with the AMY3 receptor most likely mediating amylin's effect on eating and glucose metabolism, and the AMY1 being involved in the control of adiposity (Coester, Pence, et al., 2020).

3. Amylin, amyloidogenesis and type 2 diabetes mellitus

In certain species and under certain pathological conditions such as T2D or in insulinoma, amylin can self-aggregate and eventually form insoluble amylin amyloid plaques. This property is mainly seen in amylin from humans, other primates and cats, but not in rodent forms of amylin (Westermark et al., 2011).

3.1. Mechanisms of amyloidogenesis

The amino acid sequence of amylin is highly conserved among mammalian species. Formation of amylin derived amyloid is favored by differences in the amino acid sequence in an amyloidogenic region of the molecule that is essential for amyloid formation and toxicity (Betsholtz, Johnson, & Westermark, 1989; Hoppener et al., 1993; Matveyenko & Butler, 2006a, 2006b; Moriarty & Raleigh, 1999); this heterogeneity mainly depends on the amino acid residues 20–29 of the amylin sequence and influences the formation of ordered secondary structures such as the β-sheet conformation as an essential prerequisite for amyloidogenesis.

Aggregation of amylin and formation of fibrils initiates intracellularly and some data indicate that the process already starts with pro-amylin and its intermediates rather than the mature 37 amino acid peptide (Moriarty & Raleigh, 1999; Oskarsson et al., 2015; Paulsson, Andersson, Westermark, & Westermark, 2006; Paulsson & Westermark, 2005; Westermark et al., 2011). Prolonged hyperglycemia may continuously stimulate beta-cells and lead to a higher concentration of pro-amylin within the β-cells which may form the core for further amylin aggregation (Paulsson & Westermark, 2005; Westermark et al., 2011).

Clear data about the first intracellular localizations of the aggregates are still missing but our own unpublished data indicate that amylin oligomer aggregates can be found just outside of secretory granules in the cytoplasma of beta-cells in diabetic cats; such aggregates were not seen in healthy control cats. Similarly, amyloid deposits in baboons were observed in the cytoplasm of β-cells as well as bound to the outer β-cell membrane (Guardado-Mendoza et al., 2009). However, amylin-derived amyloid is also observed in the endoplasmic reticulum (ER), Golgi apparatus and secretory vesicles (Westermark et al., 2011).

3.2. Pathological effects of amylin deposits on pancreatic β-cells

There is consensus in that abnormalities in the processing of amylin and its deposition as amyloid in the islets contribute to the progressive loss of pancreatic β-cells in T2D and feline diabetes (Clark et al., 1987; Henson & O'Brien, 2006; Jurgens et al., 2011; Westermark et al., 2011). The toxic effects induced by amylin amyloid deposits depend on a combination of mechanisms that act both intra- and extracellulary, and are in fact mechanistically similar to the intracellular processes that lead to neuronal damage by protein aggregates in Alzheimer disease (Lorenzo et al., 1994; Lutz & Meyer, 2015; Westermark et al., 2011).

Amylin-derived beta-cell toxicity is associated with ER stress and the unfolded protein response (UPR) (Preston, Gurisik, Bartley, Laybutt, & Biden, 2009). When degradation of misfolded proteins fails, protein aggregation and amyloidogenesis may eventually lead to the induction of cell apoptosis (Westermark et al., 2011). These processes may be operational especially during the early phase of T2D, during which amylin and insulin syntheses are markedly increased as a consequence of insulin resistance.

Once fibrillar material is formed, this may lead to a disruption of the

vesicles and result in the release of fibrillar material into the cytosol. Such aggregates can be dissolved by autophagy but in the early phase of T2D, the formation of autophagolysosomes seems to be attenuated, which in turn causes the accumulation of material in autophagic vacuoles, inducing a cascade of intracellular toxic effects (Westermark et al., 2011). Finally, toxic oligomers consisting of pro-amylin or amylin during the early phases of T2D may disrupt mitochondrial function, increased cellular oxidative stress and the formation of reactive oxygen species (ROS) and ultimately damage to cell structures and cause cell loss (Chen, Taylor, & Verchere, 2018; Marzban et al., 2004; Westermark et al., 2011). All these processes can also activate the inflammasome eventually contributing to beta-cell death (Donath, 2013; Donath, Dalmas, Sauter, & Boni-Schnetzler, 2013).

Overall, these abnormalities in the processing of amylin and its deposition as amyloid deposits in the islets contribute to the progressive loss of pancreatic beta-cells in T2D (Johnson, Hayden, O'Brien, & Westermark, 1986; O'Brien, Butler, Westermark, & Johnson, 1993; O'Brien, Hayden, Johnson, & Stevens, 1985; Westermark et al., 2011) and possibly also in diabetic cats (Henson & O'Brien, 2006; Lutz & Rand, 1993, 1995, 1997; Zini et al., 2016).

4. Amylin aggregates as a target for T2D therapy

Based on the important role of amylin aggregates in damaging pancreatic beta-cells in T2D, several strategies have been developed that aim at reducing the pathological consequences of these aggregates. As one strategy, recent studies indicated that antibodies targeting aggregated but not monomeric amylin may produce beneficial metabolic effects and maintain functional beta-cell mass. One such approach was based on the generation of an active vaccination against amylin aggregates which was induced by coupling such peptides to virus-like particles. This vaccination lead to the generation of specific antibodies which reduced the deposition of islet amyloid in human-amylin transgenic mice and delayed the onset of hyperglycemia, associated with a reduced pro-inflammatory response in pancreatic islets (Roesti et al., 2020). In a different approach, passive vaccination with antibodies targeting pathologic oligomer amylin aggregates (but not monomeric amylin) showed similar effects, in that normal beta-cell function was better maintained and the occurrence of diabetes symptoms was reduced (https://www.neurimmune.com/research-development/type-2-diabetes).

5. Amylin and insulin co-secretion from the pancreatic beta-cell, and other sources of peripheral amylin

Early after the discovery of amylin, it became clear that the pancreatic beta-cells are the main source of circulating amylin (Cooper, 1994). Amylin is co-packaged with insulin into the same secretory vesicles, and the same physiological stimuli lead to their co-release. Hence, circulating plasma amylin which ranges from 3 to 5 pM in the fasting state, increases post-prandially to concentrations of approx. 15–25 pM in rats (Boyle, Rossier, & Lutz, 2010, 2011). Further, the incretin glucagon-like peptide-1 (GLP-1) not only increases insulin but also amylin levels (Inoue, Hisatomi, Umeda, & Nawata, 1991). Other sources of peripheral amylin are e.g. neuroendocrine cells along the gastrointestinal tract and dorsal root ganglia, but the release of amylin from these cells and their physiological relevance has been poorly studied (Ferrier et al., 1989; Mulder et al., 1995; Nicholl, Bhatavdekar, Mak, Girgis, & Legon, 1992).

6. Amylin receptor pharmacology

Amylin receptors are heterodimers of the CTR which is a G-protein coupled receptor, and one (or several) RAMPs being co-expressed in the same cell (Bower & Hay, 2016; Hay et al., 2015; Hay et al., 2016; Morfis et al., 2008; Poyner et al., 2002; Tilakaratne, Christopoulos, Zumpe, Foord, & Sexton, 2000). The CTR has various spice variants, the variant $CT_{(a)}$ is the best characterized. The CTR core receptor changes its specificity and affinity for amylin depending on the co-expression of one of the three RAMPs in the same cell (Christopoulos et al., 1999; Fischer, Muff, & Born, 2002; McLatchie et al., 1998; Muff et al., 1999); in other words, RAMPs change CTR pharmacology from calcitonin-preferring to amylin-preferring receptors by affecting receptor specificity and affinity, and RAMPs may regulate CTR transport to the cell surface (Hay et al., 2015).

Three RAMPs have been defined so far, resulting in the known AMY 1–3 receptors. In a study showing for the first time the presence of CTR and RAMPs in single cells of native brain tissue, we also demonstrated that many AP neurons seem to express more than one RAMPs, at least at the level of mRNA (Liberini, Boyle, et al., 2016). Theoretically, this could result in even more AMY subtypes with different RAMPs associating with CTR in the same cell, but the potential pharmacology of such putative receptors is currently unknown.

The close relationship of AMY to the CTR and the calcitonin-like receptor (CLR (Hay et al., 2016)) makes it imperative to interpret data on amylin pharmacology with caution. Currently, no receptor-subtype specific antagonists exist, and no reliable RAMP antibodies are available that could e.g. be used for immunohistochemical double labeling studies in specific brain areas to demonstrate the co-expression of amylin receptor components in single cells at the protein level.

Various amylin agonists that are under development for the treatment of obesity seem to be less specific for AMY than the only approved amylin-based anti-diabetes drug pramlintide which has a similar AMY specificity and pharmacodynamic as native amylin (Weyer et al., 2001). Most newer agonists seem to qualify as dual receptor (CTR and AMY) agonists (Andreassen et al., 2014; Andreassen et al., 2021; Fletcher et al., 2021; Gydesen et al., 2017; Thomas Kruse et al., 2020). I believe that it is not yet clear whether these characteristics are necessary for improved body weight lowering activities; interestingly, human and rat calcitonin which activate the CTR but not AMYs, have little efficacy to reduce eating (Le Foll & Lutz, 2020; Lutz, 2010a).

7. Brain action of amylin

7.1. Caudal hindbrain with the AP and the nucleus of the solitary tract (NTS)

The caudal hindbrain, and in particular the AP seem to play a critical role for the direct mediation of peripheral amylin's effects. The AP which can be directly targeted by circulating amylin (Potes & Lutz, 2010; Shapiro & Miselis, 1985; van der Kooy & Koda, 1983), has a high density of amylin receptors (Sexton, Paxinos, Kenney, Wookey, & Beaumont, 1994) and the presence of the core receptor plus RAMPs provides the structural basis for a direct action of amylin on AP neurons (Potes & Lutz, 2010). Functional evidence from different laboratories support the idea that the AP is critically implicated in mediating amylin's satiating effect, its effect to reduce glucagon secretion and to slow gastric emptying (Edwards et al., 1998; Lutz, Althaus, et al., 1998; Lutz et al., 1994; Lutz, Del Prete, & Scharrer, 1995; Lutz, Senn, et al., 1998; Mack et al., 2010). A recent study suggested that amylin receptors may also be located on presynaptic terminals of AP neurons, and that their activation may trigger glutamate release acting on other AP neurons (Fukuda, Hirai, Maezawa, Kitagawa, & Funahashi, 2013). It is however not clear how the effects of presynaptic terminals may be linked to postsynaptic mechanisms that have been demonstrated convincingly (Riediger, Schmid, Lutz, & Simon, 2002), and whether they are physiologically relevant.

Several recent studies using modern state-of-the-art technology characterized caudal hindbrain neurons and defined specific clusters of cell populations (Dowsett et al., 2021; Ludwig et al., 2021; C.; Zhang et al., 2021). Interestingly, these studies confirmed previous findings that amylin responsive neurons may be a rather specific population that does not co-express receptors for GLP-1 and GDF-15. The latter two

peptides (Baraboi, St-Pierre, Shooner, Timofeeva, & Richard, 2011; Borner et al., 2020; Thiele et al., 1997), but not amylin (L. B. Boccia, T; Ghidewon, M.Y.; Kulka, P; Piffaretti, C; Doebley, S.A.; De Jonghe, B.C.; Grill, H.J.; Lutz, T.A.; Le Foll, C., 2022; Lutz, Geary, et al., 1995; Rushing, Seeley, Air, Lutz, & Woods, 2002), are known to induce aversive responses. These studies may therefore provide the explanation why stimuli targeting the AP may induce – at least in part – non-overlapping effects. Interestingly and different from the AP, neurons carrying both the CTR and the GLP-1 receptor seem to overlap in the NTS (Ludwig et al., 2021). In some of our own studies, we observed however that the total expression of CTR seems to be low compared to AP neurons (Coester, Foll, & Lutz, 2020); because NTS receptors are not as easily accessible as AP receptors, the relevance of these receptors was therefore not clear to us.

However, a specific role of CTR activation in the NTS in the control of energy balance has been suggested in a recent study (Cheng et al., 2020); the results suggested a direct NTS – LPBN pathway, leading to the activation of a population of LPBN neurons that mediate a decrease in eating. The potential interaction between these neurons and AP target neurons, and their respective projections to the LPBN needs to be defined in future studies. In addition, the network of CTR-positive neurons throughout the brain (Becskei, Riediger, Zund, Wookey, & Lutz, 2004; Cheng et al., 2020; Gonzalez et al., 2021; Pan et al., 2018a) and their respective role in eating control needs to be defined in the future. In other words, it will be important to understand whether and how the different neuronal populations with CTR interact in the control of eating and other metabolic actions of amylin and its related peptides, and whether peripheral ligands can directly access neurons outside of the circumventricular organs.

7.2. Lateral parabrachial nucleus

We had shown early on that an intact LPBN is necessary for peripheral amylin to reduce eating (Becskei et al., 2007), and our follow-up studies indicated an important role for direct projections from amylin activated AP neurons bypassing the NTS to the LPBN(Potes, Lutz, & Riediger, 2010). We recently started to elaborate on the different neuronal populations in the LPBN in mediating amylin's effect on eating. It had been reported that a large proportion of the amylin activated LPBN neurons are CGRP positive, and the large overlap of CGRP neurons with amylin-induced Fos in the LPBN indicated a potential functional role of these neurons (Carter, Soden, Zweifel, & Palmiter, 2013). Despite the role of CGRP neurons to control meal ending satiation (Campos, Bowen, Schwartz, & Palmiter, 2016) and meal size control under normal conditions (Campos et al., 2016) but also e.g. following bariatric surgery (Mumphrey et al., 2016) or in certain disease states (Campos et al., 2017; Carter, Han, & Palmiter, 2015), these neurons seem to play a minor role in mediating amylin's effect to reduce eating. Using various approaches, we recently showed that the silencing of CGRP neurons in the LPBN did not impair the effect of amylin to reduce eating. Interestingly, at least part of the eating inhibitory effect of the amylin agonist salmon calcitonin (sCT) appeared to be mediated by these neurons. Further, specifically knocking down the expression of CGRP in these LPBN neurons did not reduce amylin's or sCT's ability to decrease eating. Finally, the same studies also indicated an important difference between amylin and sCT in that sCT, but not amylin, induced conditioned taste avoidance in rats and induced a vomiting response in the musk shrew. Hence, overall the LPBN plays an important role in mediating the effect of amylin and sCT on eating but the critical neurotransmitter of LPBN neurons needs to be characterized; it has been hypothesized that glutamatergic neurotransmission may be involved but there are no functional data yet supporting this hypothesis. Further, at least part of sCT's effect on eating may be associated with an illness producing response (L. B. Boccia, T; Ghidewon, M.Y.; Kulka, P; Piffaretti, C; Doebley, S.A.; De Jonghe, B.C.; Grill, H.J.; Lutz, T.A.; Le Foll, C., 2022).

7.3. Other brain areas mediating the actions of amylin

Several other brain areas have been investigated for specific actions of amylin. Despite the widespread expression of an amylin induced cFos signal, the wide distribution of amylin binding sites throughout the brain (Sexton et al., 1994) and the expression of all critical amylin receptor components in many brain areas (Becskei et al., 2004; Ueda, Ugawa, Saishin, & Shimada, 2001), it is in most cases not clear whether peripheral amylin may directly reach these sites to induce biological effects.

7.3.1. Amylin action on specific neuronal populations in the hypothalamus

Based on numerous experiments, we developed a working model of amylin action in the hypothalamus, indicating a direct action of amylin on proopiomelanocortin (POMC) neurons and an indirect effect on neuropeptide Y/Agouti related peptide (NPY; AgRP) neurons in the hypothalamic arcuate nucleus (ARC), the latter effect possibly being mediated by interleukin-6 (IL-6) (Levin & Lutz, 2017; Lutz et al., 2018). Interestingly, other studies indicated that CTR positive and hence amylin sensitive neurons seem to co-localize with NPY rather than POMC in the ARC (Pan et al., 2018b), and some of our own data also indicated that sCT may bind and actually be taken up by NPY/AgRP, but not POMC neurons in the ARC (Zakariassen, John, & Lutz, 2020; Zakariassen, John, Lykkesfeldt, et al., 2020). Finally, amylin has recently been shown to directly suppress AgRP neurons based on a reduction of intracellular calcium signaling (Su, Alhadeff, & Betley, 2017). Hence, while the principal involvement of hypothalamic signaling via POMC and NPY/AgRP neurons in mediating amylin's effects on eating and energy expenditure has been supported by various studies, the exact pathways still need to be defined in future experiments.

7.3.2. Central reward areas including the ventral tegmental area (VTA) and the nucleus accumbens (NAc)

Various groups studied effects of amylin and its agonists on reward mediated actions. These studies have been elegantly summarized in recent reviews (Kern & Mietlicki-Baase, 2020; E.G.; Mietlicki-Baase & Hayes, 2014). Briefly, amylin activation of the VTA and the NAc seems to be linked to a decrease in the rewarding effect of food (Mietlicki-Baase et al., 2013) but also of alcohol intake (Kalafateli, Vallof, & Jerlhag, 2019). The exact pathway how these centers are activated is still a matter of debate because both direct actions (Mietlicki-Baase et al., 2017) and an indirect effect subsequent to AP activation (Whiting, McCutcheon, Boyle, Roitman, & Lutz, 2017) have been claimed.

7.4. Amylin-leptin interactions in the regulation of energy homeostasis

The interest of the scientific community in amylin research was boostered by the finding of a sensitizing effect of amylin towards the action of leptin. Early studies indicated a functionally relevant interaction between amylin and leptin because animals with defective leptin signaling (e.g., ob/ob mice, Zucker fa/fa rats) reacted less to the eating inhibitory effect of sCT (Eiden, Daniel, Steinbrueck, Schmidt, & Simon, 2002). We subsequently showed that central leptin administration increased the effect of peripheral amylin to acutely reduce eating (Osto et al., 2007). A large series of experiments then investigated the type of interaction, mode of interaction and potential site(s) of interaction between amylin and leptin (Chan, Roth, & Weyer, 2009; Roth et al., 2008a; Roth, Trevaskis, Turek, & Parkes, 2010; Trevaskis et al., 2008; Trevaskis, Lei, et al., 2010; Trevaskis, Parkes, & Roth, 2010; Trevaskis et al., 2016; Turek et al., 2010). The relevant findings have recently been reviewed extensively (Hay et al., 2015; Levin & Lutz, 2017). Briefly, an interaction between amylin and leptin seems to occur at several levels, i.e. in the caudal hindbrain (Liberini, Boyle, et al., 2016; Smith et al., 2016), the hypothalamus (Turek et al., 2010) and the VTA (Mietlicki-Baase, Olivos, Jeffrey, & Hayes, 2015). In the caudal hindbrain, mice and rats with a

defect in the leptin signaling pathway (i.e. leptin receptor deficient db/db mice and Zucker fa/fa rats) had less amylin induced c-Fos and CTR expression in the AP (Duffy, Lutz, & Boyle, 2018). In the mediobasal hypothalamus, the effect of chronic amylin administration to reduce food intake and increase energy expenditure in leptin resistant DIO rats was associated with an increased expression of the POMC gene in the ARC (Roth et al., 2010; Turek et al., 2010). The enhanced response to leptin by amylin was paralleled by increased leptin receptor activation in the ventromedial nucleus of the hypothalamus (VMN) and the ARC, and increased leptin receptor binding in the ARC and VMN (Turek et al., 2010). Using diet-induced obese rats, we showed that the amylin-leptin interaction in the ARC/VMN is probably mediated by IL-6, increasing LepRb expression and potentially also its transport to the cell membrane (Le Foll et al., 2015). Similar synergizing effects on eating and weight loss were reported in overweight humans receiving amylin and leptin analogues, respectively (Roth et al., 2008b).

7.5. Role of amylin in pathway development in the caudal hindbrain and the hypothalamus

Two important findings triggered research on a potential role of amylin in the development of neuronal pathways. First, amylin itself was shown to be a growth factor for the development of various organs, including the kidneys (Wookey, Lutz, & Andrikopoulos, 2006). Second, the similarities between amylin and leptin and their synergizing effect in the control of eating raised the question whether amylin, similar to leptin (Bouret, Draper, & Simerly, 2004a, 2004b; Bouret & Simerly, 2006), may also influence brain development.

In fact, we showed that amylin and amylin signaling are involved in the pathway development between the AP and the NTS (Abegg et al., 2017), and also in the development of projections from the hypothalamic ARC to the PVN (Coester, Koester-Hegmann, Lutz, & Le Foll, 2020; Lutz et al., 2018). Our studies suggested that the effect on the AgRPergic pathway may be indirect, and both this indirect and the direct effect on POMC neurons are mediated by specific AMY(Coester, Koester-Hegmann et al., 2020).

Several studies also suggested that amylin promotes neurogenesis in the hippocampus (Trevaskis, Turek, et al., 2010) and the caudal hindbrain (Liberini, Borner, Boyle, & Lutz, 2016). Interestingly, while amylin was also shown to promote cell proliferation during embryogenesis, the effect appeared to be rather specific on microglia than on neuronal cells (Lutz & Le Foll, 2019). These interesting findings left many questions open. E.g., about the exact timing of the effect (i.e. the critical period pre- or postnatally to influence these effects), the nature and the origin of the endogenous ligand mediating the effects, and potential differences between the action of endogenous versus exogenous amylin that need to be elaborated. In the same context, it needs to be studied whether some of the defects caused by the lack of endogenous amylin, such as e.g. in the caudal hindbrain (Abegg et al., 2017), can be rescued by amylin administration.

7.6. Central amylin synthesis

In recent years, progress has been made in respect to the presence of brain-derived amylin and its potential metabolic role. Peptides with similarity to amylin had been described a long time ago in the brain (Fischer, Tobler, Henke, & Tschopp, 1983) but it was not until about 10 years ago that the first convincing findings about central amylin expression were published (Dobolyi, 2009; Szabo, Cservenak, & Dobolyi, 2012). This was supported by a recent study with an extensive characterization of neurons in various hypothalamic areas (Li, Kelly, Heiman, Greengard, & Friedman, 2015). Pertinent findings have been summarized recently (Boccia, Gamakharia, et al., 2020).

These data indicate that amylin is expressed in various nuclei and that there may be a marked sexual dimorphism (Li et al., 2015). Amylin expression seems to be particularly strong in the medial preoptic area (MPOA) in lactating rat dams (Dobolyi, 2009). This was recently confirmed in our own studies. The physiological role of centrally synthesized amylin in general and of amylin in the MPOA is only partly understood (Dobolyi, 2009; Szabo et al., 2012; Szabó et al., 2015). Some studies indicate that CTR signaling in the MPOA influences maternal behavior (Yoshihara et al., 2021), but it is unclear whether this effect is based on an autocrine effect within this brain area. Future experiments will have to define how central amylin expression is regulated, whether central amylin is secreted to act as a neurotransmitter, where the pertinent neurons project to, and what their role in physiology or pathophysiology is.

8. AMY subtypes

All AMY components are expressed in numerous brain regions. However, the heterodimeric nature of the AMY, the lack of receptor subtype specific antibodies and the lack of specific RAMP antibodies are some hurdles which may explain why the exact cellular mediation of amylin-induced effects is still rather unclear. A further complicating factor is the fact that RAMPs can bind other peptides when combined with other GPCR (Barbash, Lorenzen, Persson, Huber, & Sakmar, 2017; Barbash et al., 2019), in addition to the CTR and the calcitonin receptor-like receptor (CLR). Finally, the expression of some receptor components seems to be rather dynamic. In the AP, e.g. exogenous amylin reduced the expression of RAMP1 and RAMP3 mRNA, but not CTR, and increased RAMP2 expression (Liberini, Boyle, et al., 2016). Hence, it cannot be excluded that the relevance for specific AMY subtypes may vary depending on the experimental conditions.

Nonetheless, some progress has been made recently and the data support previous assumptions that the AMY3 receptor may be particularly relevant for amylin's effects on eating. Using RAMP knockout animals, we recently provided evidence that the AMY3 receptor seems to be mainly responsible for the eating inhibitory and glucose regulatory effects of amylin, and that the AMY1 may be particularly relevant for the control of fat utilization (Coester, Pence, et al., 2020). The latter findings add to previous reports that RAMP1 overexpression – presumably by increasing endogenous amylin action at the AMY1 receptor – increases energy expenditure in mice (Fernandes-Santos et al., 2013; Zhang et al., 2011).

9. Pre-clinical studies with amylin as an anti-obesity target

Various amylin analogues have been developed and tested in preclinical models for their effect on body weight and the control of glucose metabolism (Andreassen et al., 2014; Andreassen et al., 2021; Baggio & Drucker, 2020; Fletcher et al., 2021; Gydesen et al., 2016; Gydesen et al., 2017; Hay et al., 2015; Henriksen et al., 2021; Jorsal, Rungby, Knop, & Vilsboll, 2016; Thomas Kruse et al., 2020). Many of the compounds tested can be classified as dual agonists at the calcitonin and the amylin receptors because their in vitro characteristics imply the potential to activate both receptors. This is interesting because CTR activation by mammalian (human or rat) calcitonin per se seem to have a minor effect on eating. This is in contrast to fish (salmon or eel) calcitonin which inhibit eating and which strongly activate the AMY(Le Foll & Lutz, 2020; Lutz, 2010b). How exactly, i.e. by which cellular mechanisms, CTR plus AMY activation by the dual receptor agonists leads to a strong eating and weight reducing effect is currently unknown. It is also unknown whether the effects of the dual receptor agonists on eating depend on the activation of CTR plus AMY in the same target cells or whether CTR and AMY in different brain areas need to be activated simultaneously to achieve the strong biological effects.

Some of the most recent studies tested the involvement of AMY receptor subtypes in the mediation of long acting amylin analogues. These studies indicated that the relatively AMY specific agonist NN1213 also requires the AMY3 for its eating inhibitory and weight reducing effect, similar to native amylin (Arrigoni et al., 2021). Interestingly, the same

study showed the CTR and AMY agonist sCT did not lead to sustained weight loss in mice, which is different from rats. Hence, in addition to the unknown cellular mechanisms and interactions that contribute to the effects of dual CTR and AMY agonists, species differences may also need to be considered and need to be elaborated in future studies.

10. Clinical studies using amylin agonists in obesity therapy

The only approved amylin-based drug is the amylin analogue pramlintide which has similar characteristics and a similar pharmacodynamic and pharmacokinetic profile than (rat) amylin. Early studies had indicated a weight lowering profile of pramlintide but the absolute effect was modest (Aronne et al., 2007; Chapman et al., 2005; Fineman, Weyer, Maggs, Strobel, & Kolterman, 2002; Fineman, Koda, et al., 2002; Hollander et al., 2004). However, pramlintide given together with the leptin analogue metreleptin produced a very strong decrease in body weight, presumably by enhancing leptin sensitivity similar to what had been observed in preclinical studies (Ravussin et al., 2009).

More recent studies indicated that several amylin-based drugs are safe and highly effective in people. The rather unspecific CTR and AMY agonist AM833 (cagrilintide) was shown to produce sustained and marked weight loss, and that its effect when combined with the GLP-1 agonist semaglutide was even stronger and bypassed the effect of most other pharmacotherapies (Becerril & Frühbeck, 2021; David et al., 2020; Enebo et al., 2021; Thomas Kruse et al., 2020). Amylin analogues are therefore considered an interesting strategy for the further development of highly effect weight lowering agents.

11. Summary

Most research focused on amylin's effect on eating, glucagon secretion and gastric emptying. Based on these findings, amylin-based drugs are in clinical use or in clinical testing and have shown promise to be a new generation of weight lowering compounds. Interestingly, some biological effects of amylin described early after its discovery (inhibition of insulin secretion, reduction of insulin sensitivity) have attracted very little attention in the last 20 years, even though antagonist studies had suggested effects of potential physiological relevance (Young, 2005a; 2005b; 2005c, 2005e). However, it needs to be mentioned that the role of the AMY, as we know it since the discovery of the heterodimers CTR/RAMPs, has never been tested for these effects so that it is unclear whether such effects are truly amylin mediated.

Next to these metabolic effects, amylin in primates and cats has a second "face" in that it can aggregate and form insoluble oligomers and fibrils that contribute to beta-cell loss in T2D and feline diabetes. Recent research efforts tried to diminish the load of amylin aggregates in an attempt to reverse this factor that causes beta-cell dysfunction in T2D (Roesti et al., 2020).

In summary, this review gave an admittedly personal view on the amylin story which started in 1986 with its (partial) sequence analysis. Since then, we tremendously increased our knowledge on the physiology and pathophysiology of amylin.

Acknowledgement

I gratefully acknowledge many of my colleagues and friends who helped me perform my research on the physiology and pathophysiology of amylin. I also gratefully acknowledge the financial support from many funding sources that helped me perform my research, in particular the Swiss National Science Foundation, the National Institutes of Health, the EU Frame Program 7, and the University of Zurich. And finally, my sincere gratitude to the Society for the Study of Ingestive Behavior for awarding me the Hoebel Prize of Creativity in 2021.

References

Abegg, K., Hermann, A., Boyle, C. N., Bouret, S. G., Lutz, T. A., & Riediger, T. (2017). Involvement of amylin and leptin in the development of projections from the area postrema to the nucleus of the solitary tract. *Frontiers in Endocrinology, 8*, 324.

Ahronheim, J. H. (1943). The nature of the hyaline material in the pancreatic islands in diabetes mellitus. *American Journal Of Pathology, 19*, 873–882.

Andreassen, K. V., Feigh, M., Hjuler, S. T., Gydesen, S., Henriksen, J. E., Beck-Nielsen, H., et al. (2014). A novel oral dual amylin and calcitonin receptor agonist (KBP-042) exerts antiobesity and antidiabetic effects in rats. *American Journal of Physiology. Endocrinology and Metabolism, 307*, E24–E33.

Andreassen, K. V., Larsen, A. T., Sonne, N., Mohamed, K. E., Karsdal, M. A., & Henriksen, K. (2021). KBP-066A, a long-acting dual amylin and calcitonin receptor agonist, induces weight loss and improves glycemic control in obese and diabetic rats. *Molecular Metabolism, 53*, 101282.

Aronne, L., Fujioka, K., Aroda, V., Chen, K., Halseth, A., Kesty, N. C., et al. (2007). Progressive reduction in body weight after treatment with the amylin analog pramlintide in obese subjects: A phase 2, randomized, placebo-controlled, dose-escalation study. *The Journal of Cinical Endocrinology and Metabolism, 92*, 2977–2983.

Arrigoni, S., Foll, C. L., Cabak, A., Lundh, S., Raun, K., John, L. M., et al. (2021). Selective role of RAMP in the sub-chronic action of the amylin selective receptor agonist NN1213 compared to salmon calcitonin on body weight and food intake in male mice. *European Journal of Neuroscience, 54*, 4863–4876.

Asai, J., Nakazato, M., Miyazato, M., Kangawa, K., Matsuo, H., & Matsukura, S. (1990). Regional distribution and molecular forms of rat islet amyloid polypeptide. *Biochemical and Biophysical Research Communications, 169*, 788–795.

Baggio, L. L., & Drucker, D. J. (2020). Glucagon-like peptide-1 receptor co-agonists for treating metabolic disease. *Molecular Metabolism*, 101090.

Balasubramaniam, A., Renugopalakrishnan, V., Stein, M., Fischer, J. E., & Chance, W. T. (1991). Syntheses, structures and anorectic effects of human and rat amylin. *Peptides, 12*, 919–924.

Baraboi, E. D., St-Pierre, D. H., Shooner, J., Timofeeva, E., & Richard, D. (2011). Brain activation following peripheral administration of the GLP-1 receptor agonist exendin-4. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 301*, R1011–R1024.

Barbash, S., Lorenzen, E., Persson, T., Huber, T., & Sakmar, T. P. (2017). GPCRs globally coevolved with receptor activity-modifying proteins, RAMPs. *Proceedings of the National Academy of Sciences of the U S A, 114*, 12015–12020.

Barbash, S., Persson, T., Lorenzen, E., Kazmi, M. A., Huber, T., & Sakmar, T. P. (2019). Detection of concordance between transcriptional levels of GPCRs and receptor-activity-modifying proteins. *iScience, 11*, 366–374.

Becerril, S., & Frühbeck, G. (2021). Cagrilintide plus semaglutide for obesity management. *Lancet, 397*, 1687–1689.

Becskei, C., Grabler, V., Edwards, G. L., Riediger, T., & Lutz, T. A. (2007). Lesion of the lateral parabrachial nucleus attenuates the anorectic effect of peripheral amylin and CCK. *Brain Research, 1162*, 76–84.

Becskei, C., Riediger, T., Zund, D., Wookey, P., & Lutz, T. A. (2004). Immunohistochemical mapping of calcitonin receptors in the adult rat brain. *Brain Research, 1030*, 221–233.

Betsholtz, C., Johnson, K. H., & Westermark, P. (1989). Amylin' hormone. *Nature, 338*, 211.

Boccia, L., Gamakharia, S., Coester, B., Whiting, L., Lutz, T. A., & Le Foll, C. (2020). Amylin brain circuitry. *Peptides, 132*, 170366.

Boccia, L., Ghidewon, M. Y., Kulka, P., Piffaretti, C., Doebley, S. A., De Jonghe, B. C., et al. (2022). Hypophagia induced by salmon calcitonin, but not by amylin, is partially driven by malaise and is mediated by CGRP neurons. *Molecular Metabolism*. https://doi.org/10.1016/j.molmet.2022.101444

Boccia, L., Le Foll, C., & Lutz, T. A. (2020). Noradrenaline signaling in the LPBN mediates amylin's and salmon calcitonin's hypophagic effect in male rats. *The FASEB Journal, 34*, 15448–15461.

Borner, T., Shaulson, E. D., Ghidewon, M. Y., Barnett, A. B., Horn, C. C., Doyle, R. P., et al. (2020). GDF15 induces anorexia through nausea and emesis. *Cell Metabolism, 31*, 351–362. e355.

Bouret, S. G., Draper, S. J., & Simerly, R. B. (2004a). Formation of projection pathways from the arcuate nucleus of the hypothalamus to hypothalamic regions implicated in the neural control of feeding behavior in mice. *Journal of Neuroscience, 24*, 2797–2805.

Bouret, S. G., Draper, S. J., & Simerly, R. B. (2004b). Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science, 304*, 108–110.

Bouret, S. G., & Simerly, R. B. (2006). Developmental programming of hypothalamic feeding circuits. *Clinical Genetics, 70*, 295–301.

Bower, R. L., & Hay, D. L. (2016). Amylin structure-function relationships and receptor pharmacology: Implications for amylin mimetic drug development. *British Journal of Pharmacology, 173*, 1883–1898.

Boyle, C. N., Rossier, M. M., & Lutz, T. A. (2010). Diet-induced obesity, hyperamylinemia and amylin sensitivity. *Appetite, 54*, 636.

Boyle, C. N., Rossier, M. M., & Lutz, T. A. (2011). Influence of high-fat feeding, diet-induced obesity, and hyperamylinemia on the sensitivity to acute amylin. *Physiology & Behavior, 104*, 20–28.

Braegger, F. E., Asarian, L., Dahl, K., Lutz, T. A., & Boyle, C. N. (2014). The role of the area postrema in the anorectic effects of amylin and salmon calcitonin: Behavioral and neuronal phenotyping. *European Journal of Neuroscience, 40*, 3055–3066.

Campos, C. A., Bowen, A. J., Han, S., Wisse, B. E., Palmiter, R. D., & Schwartz, M. W. (2017). Cancer-induced anorexia and malaise are mediated by CGRP neurons in the parabrachial nucleus. *Nature Neuroscience, 20*, 934–942.

Campos, C. A., Bowen, A. J., Schwartz, M. W., & Palmiter, R. D. (2016). Parabrachial CGRP neurons control meal termination. *Cell Metabolism, 23*, 811–820.
Carter, M. E., Han, S., & Palmiter, R. D. (2015). Parabrachial calcitonin gene-related peptide neurons mediate conditioned taste aversion. *Journal of Neuroscience, 35*, 4582–4586.
Carter, M. E., Soden, M. E., Zweifel, L. S., & Palmiter, R. D. (2013). Genetic identification of a neural circuit that suppresses appetite. *Nature, 503*, 111–114.
Chance, W. T., Balasubramaniam, A., Chen, X., & Fischer, J. E. (1992). Tests of adipsia and conditioned taste aversion following the intrahypothalamic injection of amylin. *Peptides, 13*, 961–964.
Chance, W. T., Balasubramaniam, A., Stallion, A., & Fischer, J. E. (1993). Anorexia following the systemic injection of amylin. *Brain Research, 607*, 185–188.
Chance, W. T., Balasubramaniam, A., Zhang, F. S., Wimalawansa, S. J., & Fischer, J. E. (1991). Anorexia following the intrahypothalamic administration of amylin. *Brain Research, 539*, 352–354.
Chan, J. L., Roth, J. D., & Weyer, C. (2009). It takes two to tango: Combined amylin/leptin agonism as a potential approach to obesity drug development. *Journal of Investigative Medicine, 57*, 777–783.
Chapman, I., Parker, B., Doran, S., Feinle-Bisset, C., Wishart, J., Strobel, S., et al. (2005). Effect of pramlintide on satiety and food intake in obese subjects and subjects with type 2 diabetes. *Diabetologia, 48*, 838–848.
Cheng, W., Gonzalez, I., Pan, W., Tsang, A. H., Adams, J., Ndoka, E., et al. (2020). Calcitonin receptor neurons in the mouse nucleus tractus solitarius control energy balance via the non-aversive suppression of feeding. *Cell Metabolism, 31*, 301–312. e305.
Chen, Y. C., Taylor, A. J., & Verchere, C. B. (2018). Islet prohormone processing in health and disease. *Diabetes, Obesity and Metabolism, 20*(Suppl 2), 64–76.
Christopoulos, G., Perry, K. J., Morfis, M., Tilakaratne, N., Gao, Y., Fraser, N. J., et al. (1999). Multiple amylin receptors arise from receptor activity-modifying protein interaction with the calcitonin receptor gene product. *Molecular Pharmacology, 56*, 235–242.
Clark, A., Cooper, G. J., Lewis, C. E., Morris, J. F., Willis, A. C., Reid, K. B., et al. (1987). Islet amyloid formed from diabetes-associated peptide may be pathogenic in type-2 diabetes. *Lancet, 2*, 231–234.
Coester, B., Foll, C. L., & Lutz, T. A. (2020). Viral depletion of calcitonin receptors in the area postrema: A proof-of-concept study. *Physiology & Behavior, 223*, 112992.
Coester, B., Koester-Hegmann, C., Lutz, T. A., & Le Foll, C. (2020). Amylin/calcitonin receptor-mediated signaling in POMC neurons influences energy balance and locomotor activity in chow-fed male mice. *Diabetes, 69*, 1110–1125.
Coester, B., Pence, S. W., Arrigoni, S., Boyle, C. N., Le Foll, C., & Lutz, T. A. (2020). RAMP1 and RAMP3 differentially control amylin's effects on food intake, glucose and energy balance in male and female mice. *Neuroscience, 447*, 74–93.
Cooper, G. J. (1994). Amylin compared with calcitonin gene-related peptide: Structure, biology, and relevance to metabolic disease. *Endocrine Reviews, 15*, 163–201.
Cooper, G. J., Willis, A. C., Clark, A., Turner, R. C., Sim, R. B., & Reid, K. B. (1987). Purification and characterization of a peptide from amyloid-rich pancreases of type 2 diabetic patients. *Proceedings of the National Academy of Sciences of the U S A, 84*, 8628–8632.
David, J. M., Lau, C. W., Erichsen, L., Francisco, A. M., Le Roux, C., McGowan, B., … Batterham, R. L. (2020). Efficacy and safety of AM833 for weight loss: A dose-finding trial in adults with overweight/obesity. *Proceedings, the Obesity Week, oral presentation*, 043.
Dobolyi, A. (2009). Central amylin expression and its induction in rat dams. *Journal of Neurochemistry, 111*, 1490–1500.
Donath, M. Y. (2013). When metabolism met immunology. *Nature Immunology, 14*, 421–422.
Donath, M. Y., Dalmas, E., Sauter, N. S., & Boni-Schnetzler, M. (2013). Inflammation in obesity and diabetes: Islet dysfunction and therapeutic opportunity. *Cell Metabolism, 17*, 860–872.
Dowsett, G. K. C., Lam, B. Y. H., Tadross, J. A., Cimino, I., Rimmington, D., Coll, A. P., et al. (2021). A survey of the mouse hindbrain in the fed and fasted states using single-nucleus RNA sequencing. *Molecular Metabolism, 53*, 101240.
Duffy, S., Lutz, T. A., & Boyle, C. N. (2018). Rodent models of leptin receptor deficiency are less sensitive to amylin. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 315*, R856–r865.
Edwards, G. L., Gedulin, B. R., C, J., Dilts, R. P., Miller, C. C., & Young, A. (1998). Area postrem (AP)-lesions block the regulation of gastric emptying by amylin. *Neuro-Gastroenterology and Motility, 10*.
Ehrlich, J. C., & Ratner, I. M. (1961). Amyloidosis of the islets of Langerhans. A restudy of islet hyalin in diabetic and non-diabetic individuals. *American Journal Of Pathology, 38*, 49–59.
Eiden, S., Daniel, C., Steinbrueck, A., Schmidt, I., & Simon, E. (2002). Salmon calcitonin - a potent inhibitor of food intake in states of impaired leptin signalling in laboratory rodents. *The Journal of Physiology, 541*, 1041–1048.
Enebo, L. B., Berthelsen, K. K., Kankam, M., Lund, M. T., Rubino, D. M., Satylganova, A., et al. (2021). Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2·4 mg for weight management: A randomised, controlled, phase 1b trial. *Lancet, 397*, 1736–1748.
Fernandes-Santos, C., Zhang, Z., Morgan, D. A., Guo, D. F., Russo, A. F., & Rahmouni, K. (2013). Amylin acts in the central nervous system to increase sympathetic nerve activity. *Endocrinology, 154*, 2481–2488.
Ferrier, G. J., Pierson, A. M., Jones, P. M., Bloom, S. R., Girgis, S. I., & Legon, S. (1989). Expression of the rat amylin (IAPP/DAP) gene. *Journal of Molecular Endocrinology, 3*, R1–R4.
Fineman, M. S., Koda, J. E., Shen, L. Z., Strobel, S. A., Maggs, D. G., Weyer, C., et al. (2002). The human amylin analog, pramlintide, corrects postprandial hyperglucagonemia in patients with type 1 diabetes. *Metabolism, 51*, 636–641.
Fineman, M., Weyer, C., Maggs, D. G., Strobel, S., & Kolterman, O. G. (2002). The human amylin analog, pramlintide, reduces postprandial hyperglucagonemia in patients with type 2 diabetes mellitus. *Hormone and Metabolic Research, 34*, 504–508.
Fischer, J. A., Muff, R., & Born, W. (2002). Functional relevance of G-protein-coupled-receptor-associated proteins, exemplified by receptor-activity-modifying proteins (RAMPs). *Biochemical Society Transactions, 30*, 455–460.
Fischer, J. A., Tobler, P. H., Henke, H., & Tschopp, F. A. (1983). Salmon and human calcitonin-like peptides coexist in the human thyroid and brain. *The Journal of Cinical Endocrinology and Metabolism, 57*, 1314–1316.
Fletcher, M. M., Keov, P., Truong, T. T., Mennen, G., Hick, C. A., Zhao, P., et al. (2021). AM833 is a novel agonist of calcitonin family G protein-coupled receptors: Pharmacological comparison with six selective and nonselective agonists. *Journal of Pharmacology and Experimental Therapeutics, 377*, 417–440.
Fukuda, T., Hirai, Y., Maezawa, H., Kitagawa, Y., & Funahashi, M. (2013). Electrophysiologically identified presynaptic mechanisms underlying amylinergic modulation of area postrema neuronal excitability in rat brain slices. *Brain Research, 1494*, 9–16.
Gonzalez, I. E., Ramirez-Matias, J., Lu, C., Pan, W., Zhu, A., Myers, M. G., et al. (2021). Paraventricular calcitonin receptor-expressing neurons modulate energy homeostasis in male mice. *Endocrinology, 162*.
Guardado-Mendoza, R., Davalli, A. M., Chavez, A. O., Hubbard, G. B., Dick, E. J., Majluf-Cruz, A., et al. (2009). Pancreatic islet amyloidosis, beta-cell apoptosis, and alpha-cell proliferation are determinants of islet remodeling in type-2 diabetic baboons. *Proceedings of the National Academy of Sciences of the U S A, 106*, 13992–13997.
Gydesen, S., Andreassen, K. V., Hjuler, S. T., Christensen, J. M., Karsdal, M. A., & Henriksen, K. (2016). KBP-088, a novel DACRA with prolonged receptor activation, is superior to davalintide in terms of efficacy on body weight. *American Journal of Physiology. Endocrinology and Metabolism, 310*, E821–E827.
Gydesen, S., Hjuler, S. T., Freving, Z., Andreassen, K. V., Sonne, N., Hellgren, L. I., et al. (2017). A novel dual amylin and calcitonin receptor agonist, KBP-089, induces weight loss through a reduction in fat, but not lean mass, while improving food preference. *British Journal of Pharmacology, 174*, 591–602.
Hay, D. L., Chen, S., Lutz, T. A., Parkes, D. G., & Roth, J. D. (2015). Amylin: Pharmacology, physiology, and clinical potential. *Pharmacological Reviews, 67*, 564–600.
Hay, D. L., Christopoulos, G., Christopoulos, A., Poyner, D. R., & Sexton, P. M. (2005). Pharmacological discrimination of calcitonin receptor: Receptor activity-modifying protein complexes. *Molecular Pharmacology, 67*, 1655–1665.
Hay, D. L., Garelja, M. L., Poyner, D. R., & Walker, C. S. (2018). Update on the pharmacology of calcitonin/CGRP family of peptides: IUPHAR review 25. *British Journal of Pharmacology, 175*, 3–17.
Hay, D. L., Walker, C. S., Gingell, J. J., Ladds, G., Reynolds, C. A., & Poyner, D. R. (2016). Receptor activity-modifying proteins; multifunctional G protein-coupled receptor accessory proteins. *Biochemical Society Transactions, 44*, 568–573.
Henriksen, K., Broekhuizen, K., de Boon, W. M. I., Karsdal, M. A., Bihlet, A. R., Christiansen, C., et al. (2021). Safety, tolerability and pharmacokinetic characterisation of DACRA KBP-042 in healthy male subjects. *British Journal of Clinical Pharmacology, 87*, 4786–4796.
Henson, M. S., & O'Brien, T. D. (2006). Feline models of type 2 diabetes mellitus. *ILAR Journal, 47*, 234–242.
Hollander, P., Maggs, D. G., Ruggles, J. A., Fineman, M., Shen, L., Kolterman, O. G., et al. (2004). Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. *Obesity Research, 12*, 661–668.
Hoppener, J. W., Verbeek, J. S., de Koning, E. J., Oosterwijk, C., van Hulst, K. L., Visser-Vernooy, H. J., et al. (1993). Chronic overproduction of islet amyloid polypeptide/amylin in transgenic mice: Lysosomal localization of human islet amyloid polypeptide and lack of marked hyperglycaemia or hyperinsulinaemia. *Diabetologia, 36*, 1258–1265.
Inoue, K., Hisatomi, A., Umeda, F., & Nawata, H. (1991). Effects of glucagon-like peptide 1 (7-36) amide and glucagon on amylin release from perfused rat pancreas. *Hormone and Metabolic Research, 23*, 407–409.
Johnson, K. H., Hayden, D. W., O'Brien, T. D., & Westermark, P. (1986). Spontaneous diabetes mellitus-islet amyloid complex in adult cats. *American Journal Of Pathology, 125*, 416–419.
Johnson, K. H., O'Brien, T. D., Hayden, D. W., Jordan, K., Ghobrial, H. K., Mahoney, W. C., et al. (1988). Immunolocalization of islet amyloid polypeptide (IAPP) in pancreatic beta cells by means of peroxidase-antiperoxidase (PAP) and protein A-gold techniques. *American Journal Of Pathology, 130*, 1–8.
Jorsal, T., Rungby, J., Knop, F. K., & Vilsboll, T. (2016). GLP-1 and amylin in the treatment of obesity. *Current Diabetes Reports, 16*, 1.
Jurgens, C. A., Toukatly, M. N., Fligner, C. L., Udayasankar, J., Subramanian, S. L., Zraika, S., et al. (2011). beta-cell loss and beta-cell apoptosis in human type 2 diabetes are related to islet amyloid deposition. *American Journal Of Pathology, 178*, 2632–2640.
Kalafateli, A. L., Vallof, D., & Jerlhag, E. (2019). Activation of amylin receptors attenuates alcohol-mediated behaviours in rodents. *Addiction Biology, 24*, 388–402.
Kern, K. A., & Mietlicki-Baase, E. G. (2020). Distributed amylin receptor signaling and its influence on motivated behavior. *Physiology & Behavior, 222*, 112958.
Kong, M. F., King, P., Macdonald, I. A., Stubbs, T. A., Perkins, A. C., Blackshaw, P. E., et al. (1997). Infusion of pramlintide, a human amylin analogue, delays gastric emptying in men with IDDM. *Diabetologia, 40*, 82–88.

van der Kooy, D., & Koda, L. Y. (1983). Organization of the projections of a circumventricular organ: The area postrema in the rat. *Journal of Comparative Neurology, 219*, 328–338.
Le Foll, C., Johnson, M. D., Dunn-Meynell, A. A., Boyle, C. N., Lutz, T. A., & Levin, B. E. (2015). Amylin-induced central IL-6 production enhances ventromedial hypothalamic leptin signaling. *Diabetes, 64*, 1621–1631.
Le Foll, C., & Lutz, T. A. (2020). Systemic and central amylin, amylin receptor signaling, and their physiological and pathophysiological roles in metabolism. *Comprehensive Physiology, 10*, 811–837.
Levin, B. E., & Lutz, T. A. (2017). Amylin and leptin: Co-regulators of energy homeostasis and neuronal development. *Trends in Endocrinology and Metabolism, 28*, 153–164.
Liberini, C. G., Borner, T., Boyle, C. N., & Lutz, T. A. (2016). The satiating hormone amylin enhances neurogenesis in the area postrema of adult rats. *Molecular Metabolism, 5*, 834–843.
Liberini, C. G., Boyle, C. N., Cifani, C., Venniro, M., Hope, B. T., & Lutz, T. A. (2016). Amylin receptor components and the leptin receptor are co-expressed in single rat area postrema neurons. *European Journal of Neuroscience, 43*, 653–661.
Li, Z., Kelly, L., Heiman, M., Greengard, P., & Friedman, J. M. (2015). Hypothalamic amylin acts in concert with leptin to regulate food intake. *Cell Metabolism, 22*, 1059–1067.
Lorenzo, A., Razzaboni, B., Weir, G. C., & Yankner, B. A. (1994). Pancreatic islet cell toxicity of amylin associated with type-2 diabetes mellitus. *Nature, 368*, 756–760.
Ludwig, M. Q., Cheng, W., Gordian, D., Lee, J., Paulsen, S. J., Hansen, S. N., et al. (2021). A genetic map of the mouse dorsal vagal complex and its role in obesity. *Nat Metab, 3*, 530–545.
Lutz, T. A. (2010a). The role of amylin in the control of energy homeostasis. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 298*, R1475–R1484.
Lutz, T. A. (2010b). Roles of amylin in satiation, adiposity and brain development. *Forum of nutrition, 63*, 64–74.
Lutz, T. A., Althaus, J., Rossi, R., & Scharrer, E. (1998). Anorectic effect of amylin is not transmitted by capsaicin-sensitive nerve fibers. *American Journal of Physiology, 274*, R1777–R1782.
Lutz, T. A., Coester, B., Whiting, L., Dunn-Meynell, A. A., Boyle, C. N., Bouret, S. G., et al. (2018). Amylin selectively signals onto POMC neurons in the arcuate nucleus of the hypothalamus. *Diabetes, 67*, 805–817.
Lutz, T. A., Del Prete, E., & Scharrer, E. (1994). Reduction of food intake in rats by intraperitoneal injection of low doses of amylin. *Physiology & Behavior, 55*, 891–895.
Lutz, T. A., Del Prete, E., & Scharrer, E. (1995). Subdiaphragmatic vagotomy does not influence the anorectic effect of amylin. *Peptides, 16*, 457–462.
Lutz, T. A., Del Prete, E., Walzer, B., & Scharrer, E. (1996). The histaminergic, but not the serotoninergic, system mediates amylin's anorectic effect. *Peptides, 17*, 1317–1322.
Lutz, T. A., Geary, N., Szabady, M. M., Del Prete, E., & Scharrer, E. (1995). Amylin decreases meal size in rats. *Physiology & Behavior, 58*, 1197–1202.
Lutz, T. A., & Le Foll, C. (2019). Endogenous amylin contributes to birth of microglial cells in arcuate nucleus of hypothalamus and area postrema during fetal development. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 316*, R791–r801.
Lutz, T. A., & Meyer, U. (2015). Amylin at the interface between metabolic and neurodegenerative disorders. *Frontiers in Neuroscience, 9*, 216.
Lutz, T. A., Mollet, A., Rushing, P. A., Riediger, T., & Scharrer, E. (2001). The anorectic effect of a chronic peripheral infusion of amylin is abolished in area postrema/nucleus of the solitary tract (AP/NTS) lesioned rats. *International Journal of Obesity and Related Metabolic Disorders, 25*, 1005–1011.
Lutz, T. A., & Rand, J. S. (1993). A review of new developments in type 2 diabetes in human beings and cats. *British Veterinary Journal, 149*, 527–536.
Lutz, T. A., & Rand, J. S. (1995). Pathogenesis of feline diabetes mellitus. *Vet Clin North Am Small Anim Pract, 25*, 527–552.
Lutz, T. A., & Rand, J. S. (1997). Detection of amyloid deposition in various regions of the feline pancreas by different staining techniques. *Journal of Comparative Pathology, 116*, 157–170.
Lutz, T. A., Senn, M., Althaus, J., Del Prete, E., Ehrensperger, F., & Scharrer, E. (1998). Lesion of the area postrema/nucleus of the solitary tract (AP/NTS) attenuates the anorectic effects of amylin and calcitonin gene-related peptide (CGRP) in rats. *Peptides, 19*, 309–317.
Lutz, T. A., Tschudy, S., Mollet, A., Geary, N., & Scharrer, E. (2001). Dopamine D(2) receptors mediate amylin's acute satiety effect. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 280*, R1697–R1703.
Mack, C. M., Soares, C. J., Wilson, J. K., Athanacio, J. R., Turek, V. F., Trevaskis, J. L., et al. (2010). Davalintide (AC2307), a novel amylin-mimetic peptide: Enhanced pharmacological properties over native amylin to reduce food intake and body weight. *International Journal of Obesity, 34*, 385–395.
Marzban, L., Trigo-Gonzalez, G., Zhu, X., Rhodes, C. J., Halban, P. A., Steiner, D. F., et al. (2004). Role of beta-cell prohormone convertase (PC)1/3 in processing of pro-islet amyloid polypeptide. *Diabetes, 53*, 141–148.
Matveyenko, A. V., & Butler, P. C. (2006a). Beta-cell deficit due to increased apoptosis in the human islet amyloid polypeptide transgenic (HIP) rat recapitulates the metabolic defects present in type 2 diabetes. *Diabetes, 55*, 2106–2114.
Matveyenko, A. V., & Butler, P. C. (2006b). Islet amyloid polypeptide (IAPP) transgenic rodents as models for type 2 diabetes. *ILAR Journal, 47*, 225–233.
McLatchie, L. M., Fraser, N. J., Main, M. J., Wise, A., Brown, J., Thompson, N., et al. (1998). RAMPs regulate the transport and ligand specificity of the calcitonin-receptor-like receptor. *Nature, 393*, 333–339.
Mietlicki-Baase, E. G., & Hayes, M. R. (2014). Amylin activates distributed CNS nuclei to control energy balance. *Physiology & Behavior, 136*, 39–46.
Mietlicki-Baase, E. G., McGrath, L. E., Koch-Laskowski, K., Krawczyk, J., Reiner, D. J., Pham, T., et al. (2017). Amylin receptor activation in the ventral tegmental area reduces motivated ingestive behavior. *Neuropharmacology, 123*, 67–79.
Mietlicki-Baase, E. G., Olivos, D. R., Jeffrey, B. A., & Hayes, M. R. (2015). Cooperative interaction between leptin and amylin signaling in the ventral tegmental area for the control of food intake. *American Journal of Physiology. Endocrinology and Metabolism, 308*, E1116–E1122.
Mietlicki-Baase, E. G., Rupprecht, L. E., Olivos, D. R., Zimmer, D. J., Alter, M. D., Pierce, R. C., et al. (2013). Amylin receptor signaling in the ventral tegmental area is physiologically relevant for the control of food intake. *Neuropsychopharmacology, 38*, 1685–1697.
Mollet, A., Gilg, S., Riediger, T., & Lutz, T. A. (2004). Infusion of the amylin antagonist AC 187 into the area postrema increases food intake in rats. *Physiology & Behavior, 81*, 149–155.
Mollet, A., Lutz, T. A., Meier, S., Riediger, T., Rushing, P. A., & Scharrer, E. (2001). Histamine H1 receptors mediate the anorectic action of the pancreatic hormone amylin. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 281*, R1442–R1448.
Morfis, M., Tilakaratne, N., Furness, S. G., Christopoulos, G., Werry, T. D., Christopoulos, A., et al. (2008). Receptor activity-modifying proteins differentially modulate the G protein-coupling efficiency of amylin receptors. *Endocrinology, 149*, 5423–5431.
Moriarty, D. F., & Raleigh, D. P. (1999). Effects of sequential proline substitutions on amyloid formation by human amylin20-29. *Biochemistry, 38*, 1811–1818.
Morley, J. E., Flood, J. F., Horowitz, M., Morley, P. M., & Walter, M. J. (1994). Modulation of food intake by peripherally administered amylin. *American Journal of Physiology, 267*, R178–R184.
Mosselman, S., Höppener, J. W., Lips, C. J., & Jansz, H. S. (1989). The complete islet amyloid polypeptide precursor is encoded by two exons. *FEBS Letters, 247*, 154–158.
Muff, R., Buhlmann, N., Fischer, J. A., & Born, W. (1999). An amylin receptor is revealed following co-transfection of a calcitonin receptor with receptor activity modifying proteins-1 or -3. *Endocrinology, 140*, 2924–2927.
Mulder, H., Leckstrom, A., Uddman, R., Ekblad, E., Westermark, P., & Sundler, F. (1995). Islet amyloid polypeptide (amylin) is expressed in sensory neurons. *Journal of Neuroscience, 15*, 7625–7632.
Mumphrey, M. B., Hao, Z., Townsend, R. L., Patterson, L. M., Munzberg, H., Morrison, C. D., et al. (2016). Eating in mice with gastric bypass surgery causes exaggerated activation of brainstem anorexia circuit. *International Journal of Obesity, 40*, 921–928.
Nakazato, M., Asai, J., Kangawa, K., Matsukura, S., & Matsuo, H. (1989). Establishment of radioimmunoassay for human islet amyloid polypeptide and its tissue content and plasma concentration. *Biochemical and Biophysical Research Communications, 164*, 394–399.
Nakazato, M., Miyazato, M., Asai, J., Mitsukawa, T., Kangawa, K., Matsuo, H., et al. (1990). Islet amyloid polypeptide, a novel pancreatic peptide, is a circulating hormone secreted under glucose stimulation. *Biochemical and Biophysical Research Communications, 169*, 713–718.
Nicholl, C. G., Bhatavdekar, J. M., Mak, J., Girgis, S. I., & Legon, S. (1992). Extra-pancreatic expression of the rat islet amyloid polypeptide (amylin) gene. *Journal of Molecular Endocrinology, 9*, 157–163.
O'Brien, T. D., Butler, P. C., Westermark, P., & Johnson, K. H. (1993). Islet amyloid polypeptide: A review of its biology and potential roles in the pathogenesis of diabetes mellitus. *Veterinary Pathology Online, 30*, 317–332.
O'Brien, T. D., Hayden, D. W., Johnson, K. H., & Stevens, J. B. (1985). High dose intravenous glucose tolerance test and serum insulin and glucagon levels in diabetic and non-diabetic cats: Relationships to insular amyloidosis. *Veterinary Pathology Online, 22*, 250–261.
O'Brien, T. D., Westermark, P., & Johnson, K. H. (1991). Islet amyloid polypeptide and insulin secretion from isolated perfused pancreas of fed, fasted, glucose-treated, and dexamethasone-treated rats. *Diabetes, 40*, 1701–1706.
Opie, E. L. (1901). The relation oe diabetes mellitus to lesions OF the pancreas. Hyaline degeneration OF the islands oe langerhans. *Journal of Experimental Medicine, 5*, 527–540.
Oskarsson, M. E., Paulsson, J. F., Schultz, S. W., Ingelsson, M., Westermark, P., & Westermark, G. T. (2015). In vivo seeding and cross-seeding of localized amyloidosis: A molecular link between type 2 diabetes and alzheimer disease. *American Journal Of Pathology, 185*, 834–846.
Osto, M., Wielinga, P. Y., Alder, B., Walser, N., & Lutz, T. A. (2007). Modulation of the satiating effect of amylin by central ghrelin, leptin and insulin. *Physiology & Behavior, 91*, 566–572.
Pan, W., Adams, J. M., Allison, M. B., Patterson, C., Flak, J. N., Jones, J., et al. (2018a). Essential role for hypothalamic calcitonin receptor–expressing neurons in the control of food intake by leptin. *Endocrinology, 159*, 1860–1872.
Pan, W., Adams, J. M., Allison, M. B., Patterson, C., Flak, J. N., Jones, J., et al. (2018b). Essential role for hypothalamic calcitonin ReceptorExpressing neurons in the control of food intake by leptin. *Endocrinology, 159*, 1860–1872.
Paulsson, J. F., Andersson, A., Westermark, P., & Westermark, G. T. (2006). Intracellular amyloid-like deposits contain unprocessed pro-islet amyloid polypeptide (proIAPP) in beta cells of transgenic mice overexpressing the gene for human IAPP and transplanted human islets. *Diabetologia, 49*, 1237–1246.
Paulsson, J. F., & Westermark, G. T. (2005). Aberrant processing of human proislet amyloid polypeptide results in increased amyloid formation. *Diabetes, 54*, 2117–2125.
Potes, C. S., & Lutz, T. A. (2010). Brainstem mechanisms of amylin-induced anorexia. *Physiology & Behavior, 100*, 511–518.

Potes, C. S., Lutz, T. A., & Riediger, T. (2010). Identification of central projections from amylin-activated neurons to the lateral hypothalamus. *Brain Research, 1334*, 31–44.
Potes, C. S., Turek, V. F., Cole, R. L., Vu, C., Roland, B. L., Roth, J. D., et al. (2010). Noradrenergic neurons of the area postrema mediate amylin's hypophagic action. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 299*, R623–R631.
Poyner, D. R., Sexton, P. M., Marshall, I., Smith, D. M., Quirion, R., Born, W., et al. (2002). International Union of Pharmacology. XXXII. The mammalian calcitonin gene-related peptides, adrenomedullin, amylin, and calcitonin receptors. *Pharmacological Reviews, 54*, 233–246.
Preston, A. M., Gurisik, E., Bartley, C., Laybutt, D. R., & Biden, T. J. (2009). Reduced endoplasmic reticulum (ER)-to-Golgi protein trafficking contributes to ER stress in lipotoxic mouse beta cells by promoting protein overload. *Diabetologia, 52*, 2369–2373.
Ravussin, E., Smith, S. R., Mitchell, J. A., Shringarpure, R., Shan, K., Maier, H., et al. (2009). Enhanced weight loss with pramlintide/metreleptin: An integrated neurohormonal approach to obesity pharmacotherapy. *Obesity, 17*, 1736–1743.
Riediger, T., Schmid, H. A., Lutz, T. A., & Simon, E. (2002). Amylin and glucose co-activate area postrema neurons of the rat. *Neuroscience Letters, 328*, 121–124.
Riediger, T., Zuend, D., Becskei, C., & Lutz, T. A. (2004). The anorectic hormone amylin contributes to feeding-related changes of neuronal activity in key structures of the gut-brain axis. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 286*, R114–R122.
Roberts, A. N., Leighton, B., Todd, J. A., Cockburn, D., Schofield, P. N., Sutton, R., et al. (1989). Molecular and functional characterization of amylin, a peptide associated with type 2 diabetes mellitus. *Proceedings of the National Academy of Sciences of the U S A, 86*, 9662–9666.
Roesti, E. S., Boyle, C. N., Zeman, D. T., Sande-Melon, M., Storni, F., Cabral-Miranda, G., et al. (2020). *Vaccination against amyloidogenic aggregates in pancreatic islets prevents development of type 2 diabetes mellitus* (Vol. 8). Basel): Vaccines.
Roth, J. D., Roland, B. L., Cole, R. L., Trevaskis, J. L., Weyer, C., Koda, J. E., et al. (2008a). Leptin responsiveness restored by amylin agonism in diet-induced obesity: Evidence from nonclinical and clinical studies. *Proceedings of the National Academy of Sciences of the U S A, 105*, 7257–7262.
Roth, J. D., Roland, B. L., Cole, R. L., Trevaskis, J. L., Weyer, C., Koda, J. E., et al. (2008b). Leptin responsiveness restored by amylin agonism in diet-induced obesity: Evidence from nonclinical and clinical studies. *Proceedings of the National Academy of Sciences of the U S A, 105*, 7257–7262.
Roth, J. D., Trevaskis, J. L., Turek, V. F., & Parkes, D. G. (2010). Weighing in" on synergy: Preclinical research on neurohormonal anti-obesity combinations. *Brain Research, 1350*, 86–94.
Rushing, P. A., Hagan, M. M., Seeley, R. J., Lutz, T. A., D'Alessio, D. A., Air, E. L., et al. (2001). Inhibition of central amylin signaling increases food intake and body adiposity in rats. *Endocrinology, 142*, 5035.
Rushing, P. A., Hagan, M. M., Seeley, R. J., Lutz, T. A., & Woods, S. C. (2000). Amylin: A novel action in the brain to reduce body weight. *Endocrinology, 141*, 850–853.
Rushing, P. A., Seeley, R. J., Air, E. L., Lutz, T. A., & Woods, S. C. (2002). Acute 3rd-ventricular amylin infusion potently reduces food intake but does not produce aversive consequences. *Peptides, 23*, 985–988.
Sanke, T., Bell, G. I., Sample, C., Rubenstein, A. H., & Steiner, D. F. (1988). An islet amyloid peptide is derived from an 89-amino acid precursor by proteolytic processing. *Journal of Biological Chemistry, 263*, 17243–17246.
Sexton, P. M., Paxinos, G., Kenney, M. A., Wookey, P. J., & Beaumont, K. (1994). In vitro autoradiographic localization of amylin binding sites in rat brain. *Neuroscience, 62*, 553–567.
Shapiro, R. E., & Miselis, R. R. (1985). The central neural connections of the area postrema of the rat. *Journal of Comparative Neurology, 234*, 344–364.
Smith, P. M., Brzezinska, P., Hubert, F., Mimee, A., Maurice, D. H., & Ferguson, A. V. (2016). Leptin influences the excitability of area postrema neurons. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 310*, R440–R448.
Su, Z., Alhadeff, A. L., & Betley, J. N. (2017). Nutritive, post-ingestive signals are the primary regulators of AgRP neuron activity. *Cell Reports, 21*, 2724–2736.
Szabo, E. R., Cservenak, M., & Dobolyi, A. (2012). Amylin is a novel neuropeptide with potential maternal functions in the rat. *The FASEB Journal, 26*, 272–281.
Szabó, E. R., Cservenák, M., Lutz, T. A., Gévai, L., Endrényi, M., Simon, L., et al. (2015). Behavioral changes in mothers and maternally sensitized female mice. *Behaviour, 152*, 1801–1819.
Thiele, T. E., Van, D. G., Campfield, L. A., Smith, F. J., Burn, P., Woods, S. C., et al. (1997). Central infusion of GLP-1, but not leptin, produces conditioned taste aversions in rats. *American Journal of Physiology, 272*, R726–R730.
Thomas Kruse, K. D., Schäffer, L., Hansen, J. L., Poulsen, C., Kruse Hansen, A. M., Charlotta, D., et al. (2020). AM833 – development of a long-acting amylin analogue. In *Proceedings, the obesity week*. Poster 028.
Thompson, R. G., Pearson, L., & Kolterman, O. G. (1997). Effects of 4 weeks' administration of pramlintide, a human amylin analogue, on glycaemia control in patients with IDDM: Effects on plasma glucose profiles and serum fructosamine concentrations. *Diabetologia, 40*, 1278–1285.
Tilakaratne, N., Christopoulos, G., Zumpe, E. T., Foord, S. M., & Sexton, P. M. (2000). Amylin receptor phenotypes derived from human calcitonin receptor/RAMP coexpression exhibit pharmacological differences dependent on receptor isoform and host cell environment. *Journal of Pharmacology and Experimental Therapeutics, 294*, 61–72.
Trevaskis, J. L., Coffey, T., Cole, R., Lei, C., Wittmer, C., Walsh, B., et al. (2008). Amylin-mediated restoration of leptin responsiveness in diet-induced obesity: Magnitude and mechanisms. *Endocrinology, 149*, 5679–5687.
Trevaskis, J. L., Lei, C., Koda, J. E., Weyer, C., Parkes, D. G., & Roth, J. D. (2010). Interaction of leptin and amylin in the long-term maintenance of weight loss in diet-induced obese rats. *Obesity, 18*, 21–26.
Trevaskis, J. L., Parkes, D. G., & Roth, J. D. (2010). Insights into amylin-leptin synergy. *Trends in Endocrinology and Metabolism, 21*, 473–479.
Trevaskis, J. L., Wittmer, C., Athanacio, J. R., Griffin, P. S., Parkes, D. G., & Roth, J. D. (2016). Amylin/leptin synergy is absent in extreme obesity and not restored by calorie restriction-induced weight loss in rats. *Obesity Science & Practice, 2*, 385–391. http://onlinelibrary.wiley.com/doi/10.1002/osp4.62/pdf.
Turek, V. F., Trevaskis, J. L., Levin, B. E., Dunn-Meynell, A. A., Irani, B., Gu, G., et al. (2010). Mechanisms of amylin/leptin synergy in rodent models. *Endocrinology, 151*, 143–152.
Ueda, T., Ugawa, S., Saishin, Y., & Shimada, S. (2001). Expression of receptor-activity modifying protein (RAMP) mRNAs in the mouse brain. *Brain Res Mol Brain Res, 93*, 36–45.
Westermark, P., Andersson, A., & Westermark, G. T. (2011). Islet amyloid polypeptide, islet amyloid, and diabetes mellitus. *Physiological Reviews, 91*, 795–826.
Westermark, P., Wernstedt, C., Wilander, E., & Sletten, K. (1986). A novel peptide in the calcitonin gene related peptide family as an amyloid fibril protein in the endocrine pancreas. *Biochemical and Biophysical Research Communications, 140*, 827–831.
Weyer, C., Maggs, D. G., Young, A. A., & Kolterman, O. G. (2001). Amylin replacement with pramlintide as an adjunct to insulin therapy in type 1 and type 2 diabetes mellitus: A physiological approach toward improved metabolic control. *Current Pharmaceutical Design, 7*, 1353–1373.
Whiting, L., McCutcheon, J. E., Boyle, C. N., Roitman, M. F., & Lutz, T. A. (2017). The area postrema (AP) and the parabrachial nucleus (PBN) are important sites for salmon calcitonin (sCT) to decrease evoked phasic dopamine release in the nucleus accumbens (NAc). *Physiology & Behavior, 176*, 9–16.
Wookey, P. J., Lutz, T. A., & Andrikopoulos, S. (2006). Amylin in the periphery II: An updated mini-review. *The Scientific World Journal, 6*, 1642–1655.
Yano, B. L., Hayden, D. W., & Johnson, K. H. (1981a). Feline insular amyloid: Association with diabetes mellitus. *Veterinary Pathology Online, 18*, 621–627.
Yano, B. L., Hayden, D. W., & Johnson, K. H. (1981b). Feline insular amyloid: Incidence in adult cats with no clinicopathologic evidence of overt diabetes mellitus. *Veterinary Pathology Online, 18*, 310–315.
Yoshihara, C., Tokita, K., Maruyama, T., Kaneko, M., Tsuneoka, Y., Fukumitsu, K., et al. (2021). Calcitonin receptor signaling in the medial preoptic area enables risk-taking maternal care. *Cell Reports, 35*, 109204.
Young, A. (2005a). Effects in fat. *Advances in Pharmacology, 52*, 235–238.
Young, A. (2005b). Effects in liver. *Advances in Pharmacology, 52*, 229–234.
Young, A. (2005c). Effects in skeletal muscle. *Advances in Pharmacology, 52*, 209–228.
Young, A. (2005d). Historical background. *Advances in Pharmacology, 52*, 1–18.
Young, A. (2005e). Inhibition of insulin secretion. *Advances in Pharmacology, 52*, 173–192.
Young, A. (2005f). Tissue expression and secretion of amylin. *Advances in Pharmacology, 52*, 19–45.
Zakariassen, H. L., John, L. M., & Lutz, T. A. (2020). Central control of energy balance by amylin and calcitonin receptor agonists and their potential for treatment of metabolic diseases. *Basic and Clinical Pharmacology and Toxicology, 127*, 163–177.
Zakariassen, H. L., John, L. M., Lykkesfeldt, J., Raun, K., Glendorf, T., Schaffer, L., et al. (2020). Salmon calcitonin distributes into the arcuate nucleus to a subset of NPY neurons in mice. *Neuropharmacology, 167*, 107987.
Zhang, C., Kaye, J. A., Cai, Z., Wang, Y., Prescott, S. L., & Liberles, S. D. (2021). Area postrema cell types that mediate nausea-associated behaviors. *Neuron, 109*, 461–472. e465.
Zhang, Z., Liu, X., Morgan, D. A., Kuburas, A., Thedens, D. R., Russo, A. F., et al. (2011). Neuronal receptor activity modifying protein-1 promotes energy expenditure in mice. *Diabetes, 60*, 1063–1071.
Zini, E., Lunardi, F., Zanetti, R., Heller, R. S., Coppola, L. M., Ferro, S., et al. (2016). Endocrine pancreas in cats with diabetes mellitus. *Veterinary Pathology Online, 53*, 136–144.
Zuger, D., Forster, K., Lutz, T. A., & Riediger, T. (2013). Amylin and GLP-1 target different populations of area postrema neurons that are both modulated by nutrient stimuli. *Physiology & Behavior, 112–113*, 61–69.