



What are
Amylin
receptors?

START

BACK

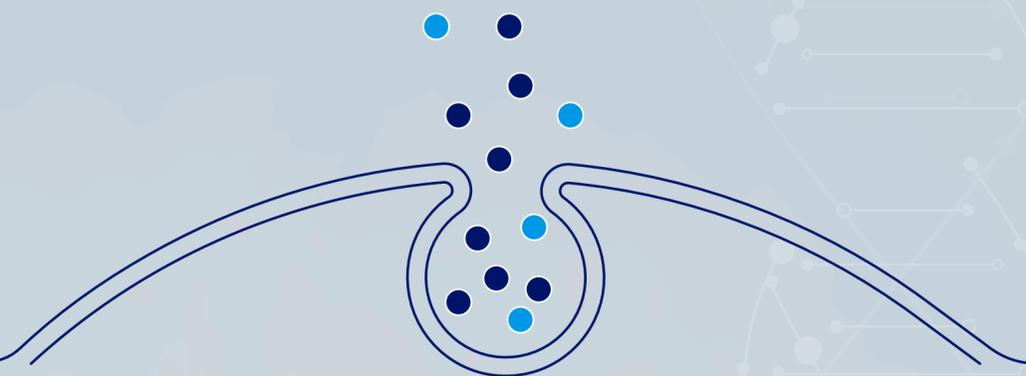


β cell

What is amylin?

Amylin is a nutrient-stimulated hormone that is co-secreted with insulin from pancreatic β cells after food intake^{1,2}

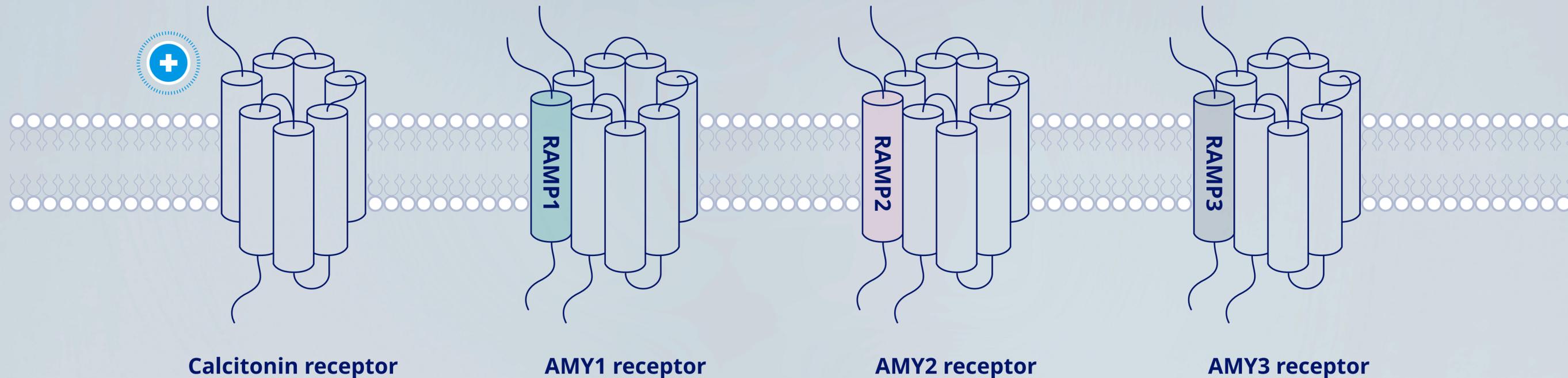
The metabolic actions of amylin are mediated through its binding to amylin receptors³



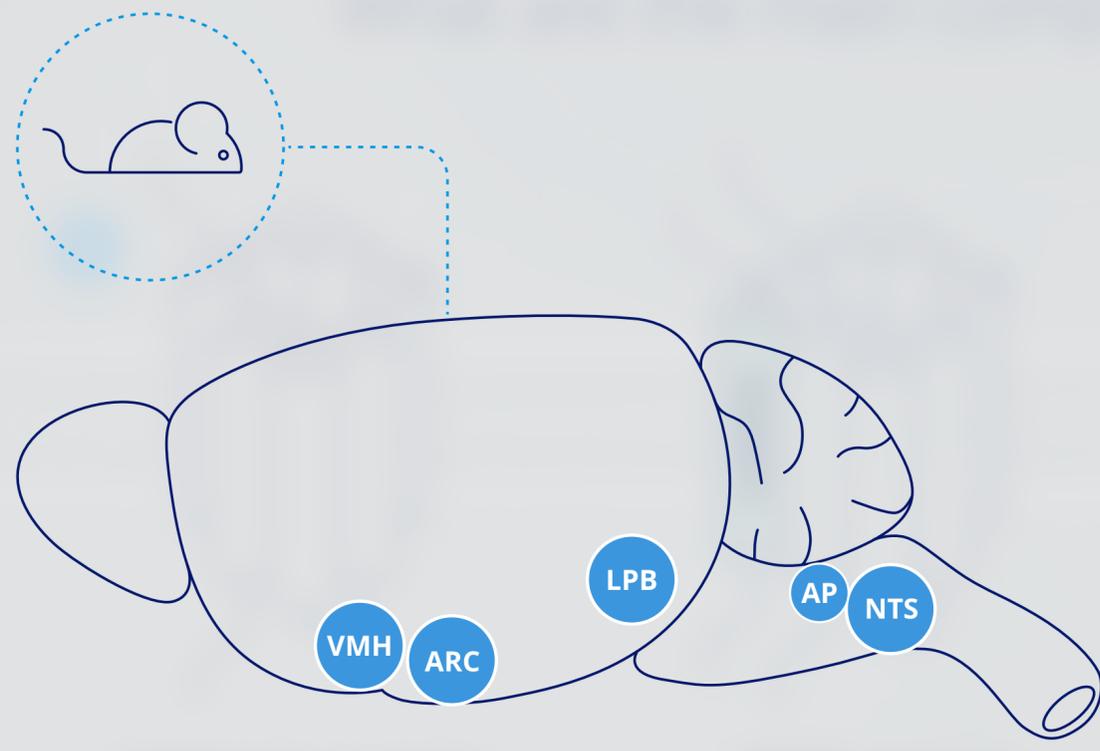
NEXT

REFERENCES

What are the main components of amylin receptors?



The amylin receptor is composed of multi-subunits of the calcitonin receptor (CTR), which heterodimerize to an associated receptor-activity modifying protein (RAMP) 1, 2, or 3, leading to the formation of AMY1, AMY2, and AMY3^{2,3}

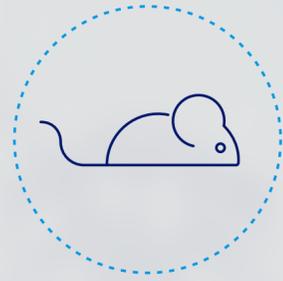


AP = Area postrema
ARC = Arcuate nucleus
LPB = Lateral parabrachial nucleus
NTS = Nucleus of the solitary tract
VMH = Ventromedial hypothalamus

The CTR belongs to a subfamily of the seven-transmembrane surface G protein-coupled receptors; it has different allosteric binding sites, which allows the receptor to modulate its affinity to different ligands²

Numerous splice variants of the CTR have been identified in different species.² In humans, the CTR is subject to an additional 16 amino acid insertion in the intracellular loop of the receptor, resulting in the most common splice variant, CTR_(b).^{2,4,5} The receptor that does not include this amino acid insertion is termed CTR_(a).²

Rodent studies have located CTRs throughout the body, including neurons in the area postrema and the hypothalamus¹



Three RAMPs have been defined in humans: RAMP1, RAMP2, and RAMP3³

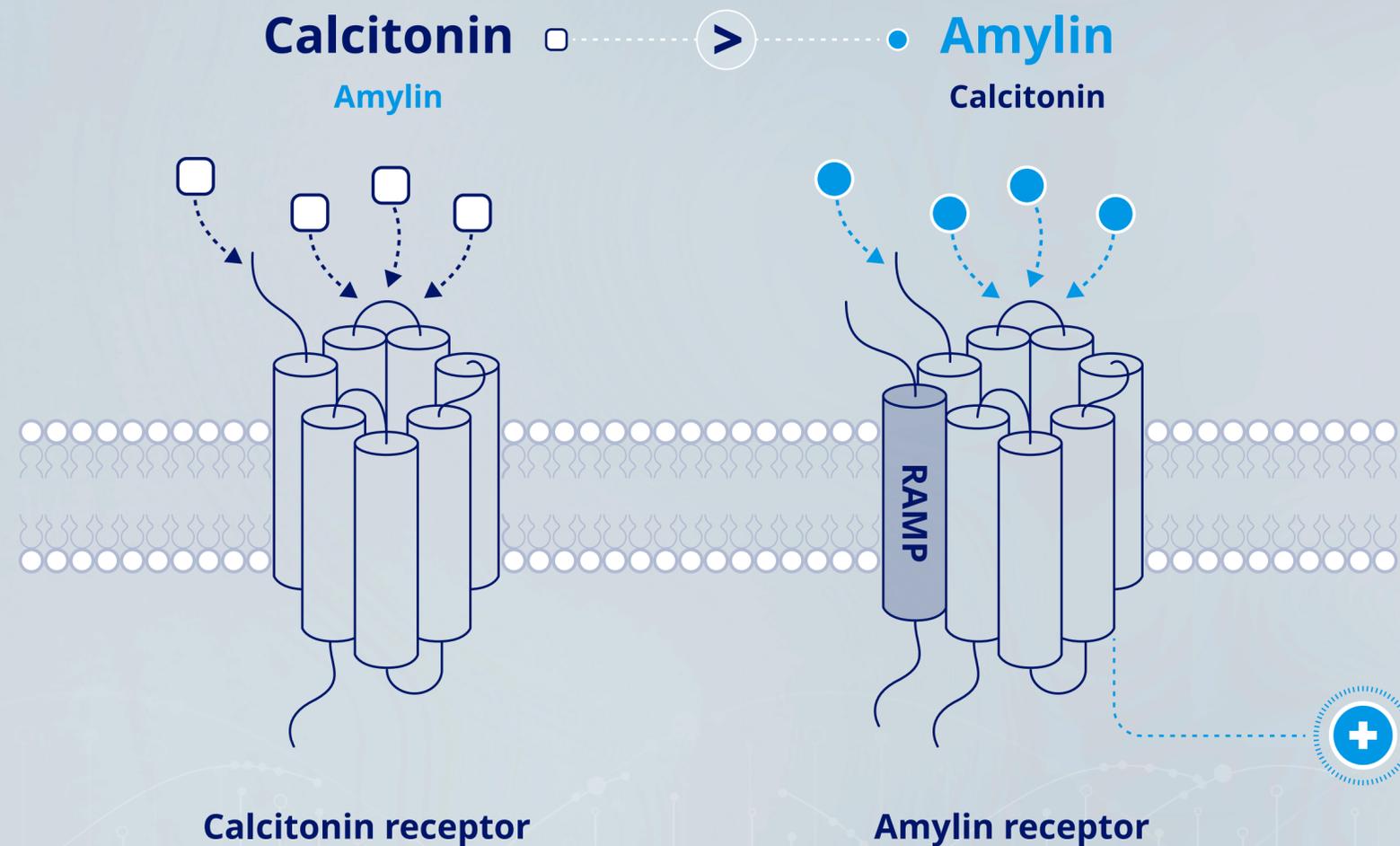
mRNA expression of RAMP1 has been detected in the lungs, muscle, and brain in rat models.² RAMP2 mRNA expression was also detected in the lungs, heart, skeletal muscle, endothelial tissue, and brain of rats.² Rat studies have shown that RAMP3 is mostly expressed in the brain and to a lesser amount in peripheral tissues such as the gut, lungs, heart, and kidneys²

RAMPs have several other G protein-coupled receptor partners, so their expression is only indicative of a potential interaction with the CTR¹

RAMPs affect receptor specificity and affinity, and they may regulate the transport of receptor complexes to the cell surface; however, the relevance of this effect for the CTR is unclear⁵



How does RAMP expression impact CTR activity?



The CTR changes its specificity and affinity for amylin depending on the co-expression of one of the three RAMPs¹

RAMPs alter the CTR pharmacology, conferring an increase in the affinity of CTR for amylin and inducing an amylin receptor phenotype¹

The AMY1 and AMY3 receptor complexes demonstrate a high affinity for amylin, whereas AMY2 demonstrates variable affinity for amylin⁴



Calcitonin and amylin receptor pharmacology¹

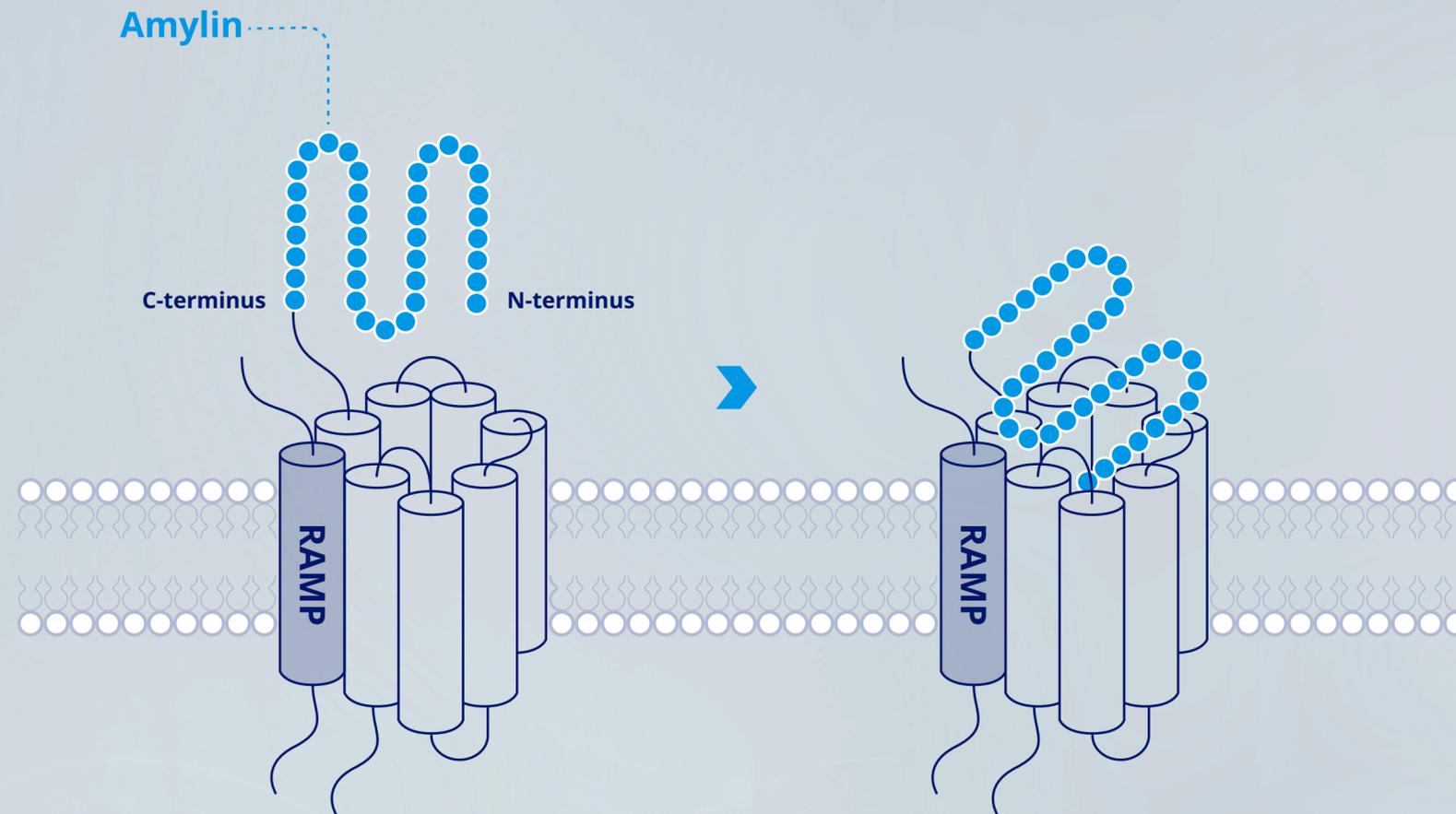
GPCR	RAMP	Receptor	Native ligand
CTR	-	CTR	sCT > hCT > AMY, CGRP
	RAMP1	AMY1	sCT > AMY > CGRP > AM2 > hCT
	RAMP2	AMY2	Cell-type dependent
	RAMP3	AMY3	sCT > AMY > CGRP > hCT

Together, the CTR and RAMP can bind multiple ligands with different affinities.² The CTR alone has the greatest affinity to calcitonin and its variant, salmon calcitonin²

Different specific agonists also act on the amylin receptors. RAMPs alter CTR pharmacology, transforming it into amylin-preferring¹

AM2, adrenomedullin 2; AMY, amylin; CGRP, calcitonin gene-related peptide; CTR, calcitonin receptor; GPCR, G protein-coupled receptor; hCT, human calcitonin; RAMP, receptor activity-modifying protein; sCT, salmon calcitonin.

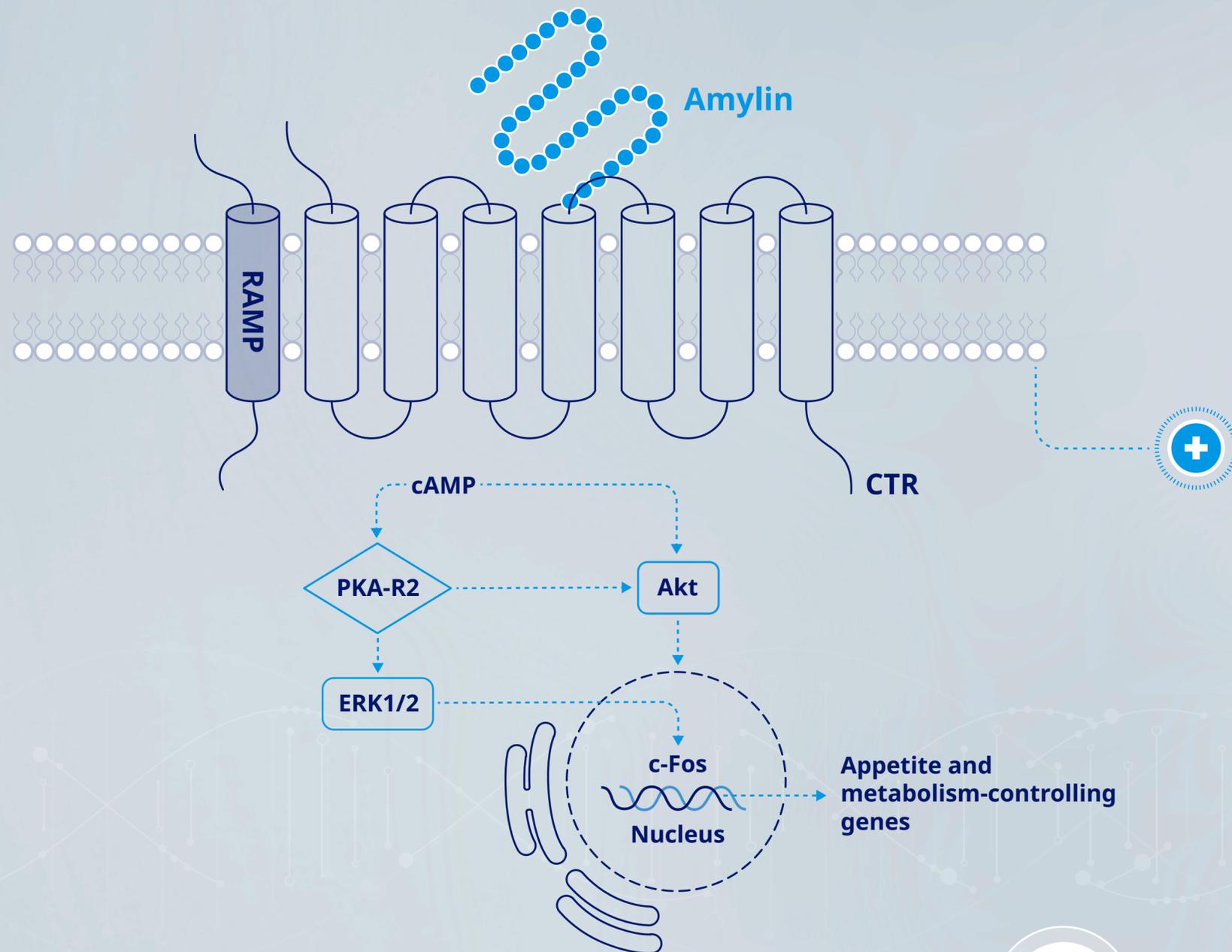
How does amylin bind to its receptor?



Amylin binds to its receptor via a “two-domain model of binding” approach.⁴ The C-terminus of amylin binds to the extracellular N-terminus of the receptor, allowing amylin to dock^{1,4}

This optimally aligns the N-terminus of amylin to the upper transmembrane domain and extracellular loops of the receptor, ultimately causing receptor activation^{1,4}

What intracellular pathways are activated?

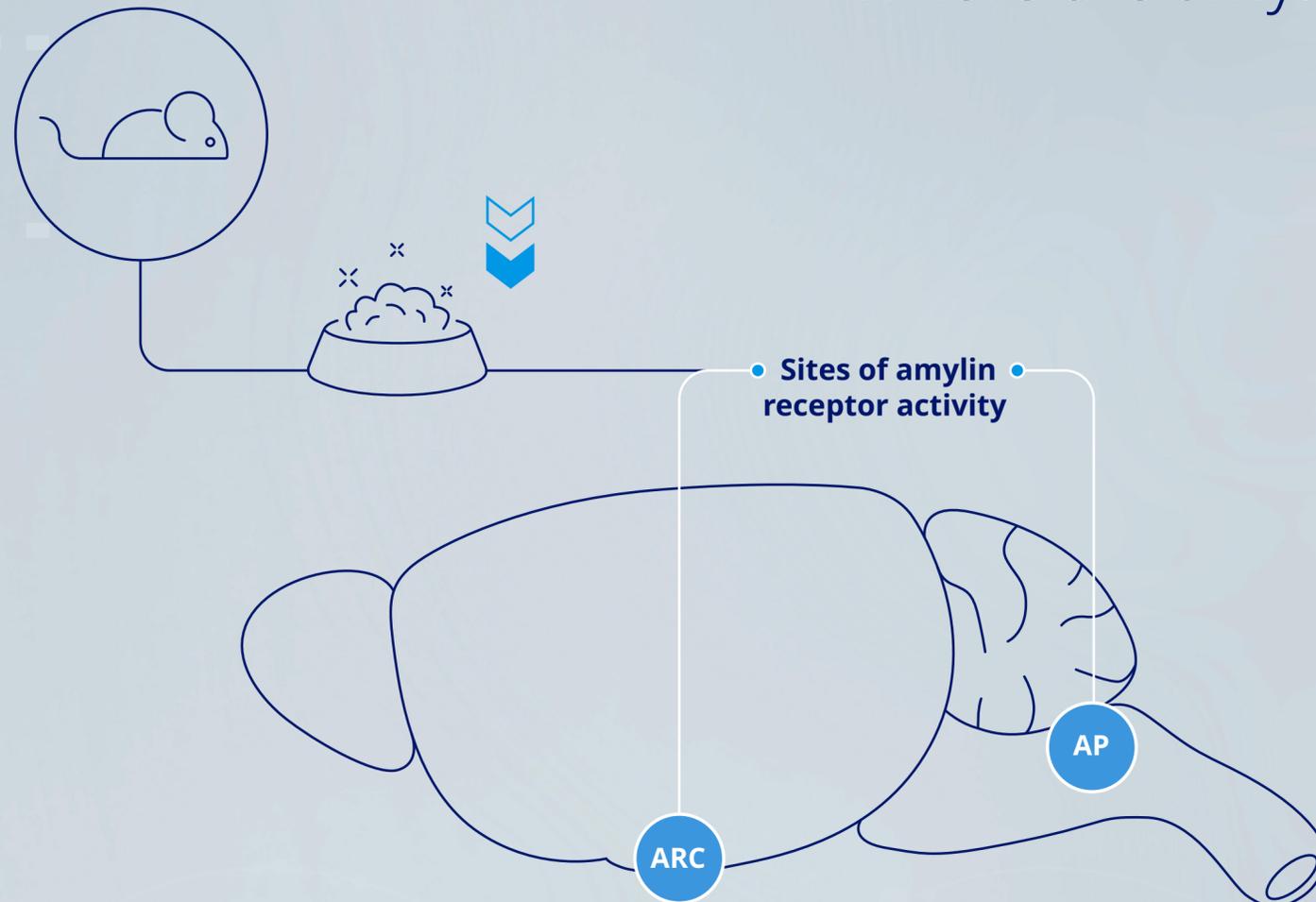


Activation of the amylin receptor triggers intracellular pathways.⁵ Amylin activates the Gs-coupled pathway, which results in elevated levels of cyclic adenosine monophosphate (cAMP)⁵. Elevated cAMP levels also lead to an acute phosphorylation of extracellular signal-related kinases and activation of Akt⁶. These intracellular pathways result in activation of appetite-regulating genes⁷.



Overall, intracellular events triggered by amylin receptor activation have only been partly resolved, and it is still unclear whether specific pathways are linked to specific amylin effects or specific amylin receptor subtypes¹

Where are amylin receptors located?



AP = Area postrema
ARC = Arcuate nucleus

All amylin receptors are expressed in numerous brain regions associated with satiety and appetite regulation^{3,8}

Rodent models have demonstrated that amylin receptor components are co-localized predominantly to the area postrema of the hindbrain, yet there is evidence that the amylin receptor is also present in various areas of the hypothalamus^{1,9}

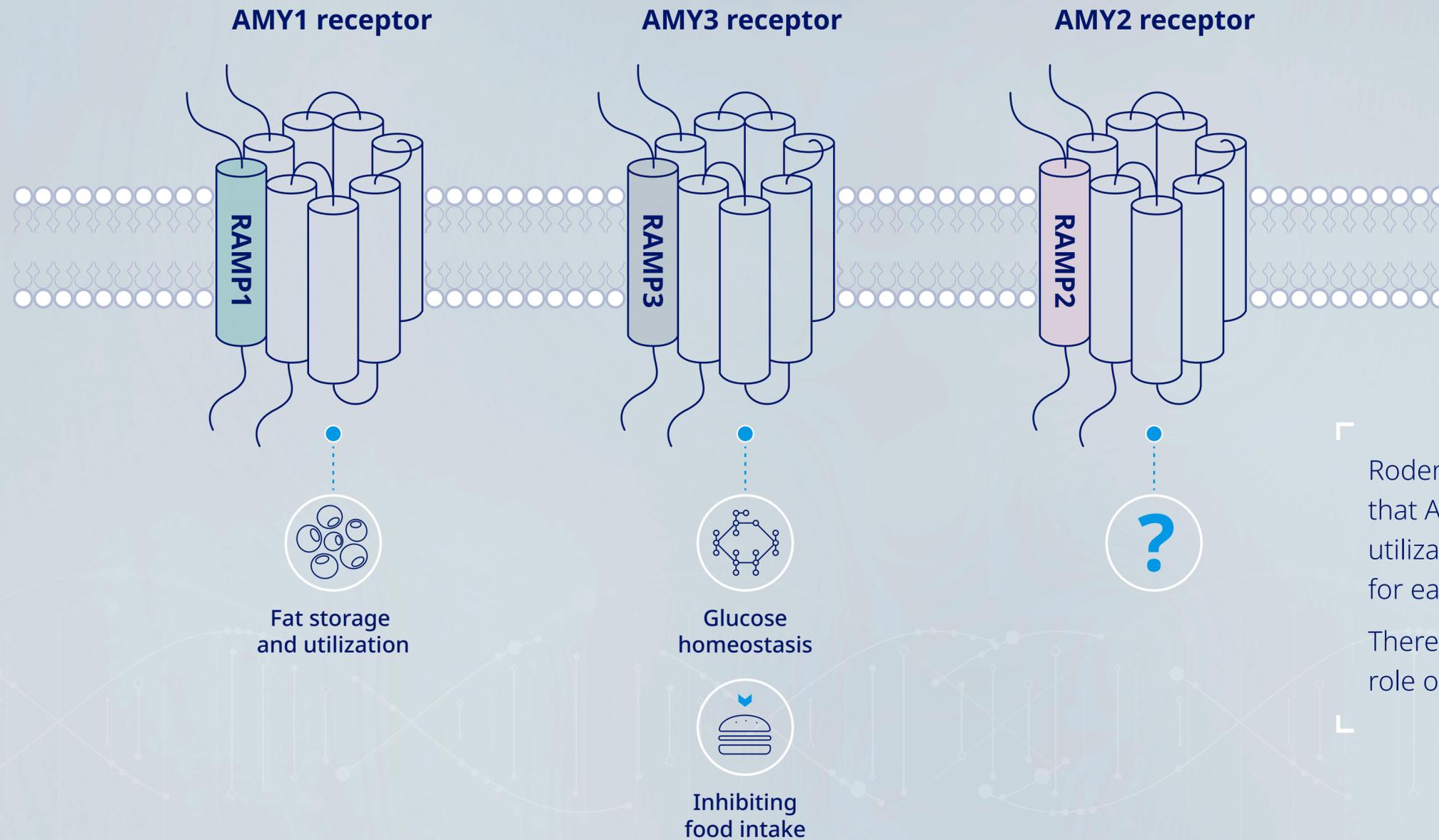


Functional studies using animal models have shown that the area postrema and nucleus of solitary tract have the primary role in mediating the effect of amylin on central appetite regulation^{2,8}

All key components of the amylin receptors have been identified as being expressed in the area postrema, the nucleus of the solitary tract, the lateral hypothalamic area and arcuate hypothalamic nuclei, and the ventral tegmental area^{7,8}

In the area postrema, the majority of calcitonin-positive neurons co-express one or more RAMP subunit⁸

Do specific amylin receptors exert specific physiological functions?



Rodent knockout studies have demonstrated that AMY1 may have a particular role in fat utilization and that AMY3 is mainly responsible for eating inhibition and glucose regulation^{1,9}

There is currently little evidence on the exact role of AMY2



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