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Xenin, a hormone of satiety

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ABSTRACT

This review summarizes the physiological effects of xenin-25, a regulatory peptide secreted by K cells of the gastrointestinal mucosa. These same cells also secrete glucose-dependent insulinotropic polypeptide (GIP). Based on its primary structure, xenin is classified as a member of the neurotensin family of peptides, which also includes motilin, neuromedin N, and ghrelin. A specific xenin receptor has not yet been identified, but xenin is known to bind to neurotensin receptors type 1. After a meal, xenin plasma levels increase. Xenin inhibits gastric emptying and reduces small intestinal motility. Acting through numerous peripheral and central mechanisms, xenin enhances the feeling of satiety and reduces food intake. Xenin stimulates insulin secretion and protects beta cells of the islets of Langerhans from damaging factors. In adipose tissue, xenin reduces lipogenesis and enhances lipolysis. Xenin is one of the most ancient, and possibly the most ancient, regulatory peptides: the xenin motif is present in the primary structure of proteins in all taxa, from prokaryotes to humans. The peptide's absolute conservatism attests to its high biological significance. Long-acting artificial hybrid peptides based on xenin hold clinical promise for the development of new drugs for the treatment of obesity and type 2 diabetes.

Keywords: xenin, satiety, obesity, insulin, diabetes mellitus

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Ксенин, гормон сытости

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АННОТАЦИЯ

В обзоре обобщены сведения о физиологических эффектах ксенина-25, регуляторного пептида, который секретируется K-клетками слизистой оболочки желудочно-кишечного тракта. Те же клетки секретируют и глюкозозависимый инсулинотропный полипептид (ГИП, GIP). В соответствии с первичной структурой ксенина его относят к пептидному семейству нейротензина, в которое входят также мотилин, нейромедин N и грелин. Специфический ксениновый рецептор до настоящего времени не обнаружен, но известно, что ксенин способен связываться с нейротензиновыми рецепторами первого типа. После приема пищи уровень ксенина в плазме крови возрастает. Ксенин затормаживает эвакуацию пищи из желудка и снижает моторику тонкой кишки. Действуя через многочисленные периферические и центральные механизмы, ксенин усиливает ощущение сытости и снижает потребление пищи. Ксенин стимулирует секрецию инсулина и защищает бета-клетки островков Лангерганса от воздействия повреждающих факторов. В жировой ткани ксенин снижает липогенез и усиливает липолиз. Ксенин — один из самых древних, а, возможно, и самый древний из регуляторных пептидов: ксениновый мотив присутствует в первичной структуре белков у представителей всех таксонов — от прокариот до человека. Абсолютная консервативность пептида свидетельствует о его высокой биологической значимости. Созданные на основе ксенина длительно действующие искусственные гибридные пептиды имеют клинические перспективы при создании новых препаратов для лечения ожирения и сахарного диабета 2-го типа.

Ключевые слова: ксенин, сытость, ожирение, инсулин, сахарный диабет

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Obesity-related diseases are recognized as the main medical problem in developed countries in the XXI century [1]. In this regard, substances (both endogenous and drugs derived from them) that can normalize this process are attracting increased interest in the scientific community. Particular attention is paid to substances that are potentially suitable for treating diabetes mellitus.

Regulatory peptides as a basis for creating drugs have numerous fundamental advantages and few (technological) disadvantages.

HISTORY OF THE DISCOVERY

In 1992, a physiologically active pentacosapeptide was isolated from the mucous membrane of the human gastrointestinal tract in Germany [2] and its primary structure was established (see below). The C-terminal pentamer of this molecule (KRPWIL) turned out to be homologous to xenopsin, a protein of the smooth-spined frog Xenopus laevis, which was already known at that time, and the authors gave the new regulatory peptide a similar name — xenin.

The C-terminal fragments of xenin and neuro-tensin (NT) have some structural similarities:

MLTKFETKSARVKGLSFHPKRPWIL xenin-25
QLYENKPRRPYIL neurotensin-13

On this basis, xenin is classified as belonging to the neuro-tensin [3, 4] or ghrelin/neurotensin peptide family, which, in addition to xenin, neuro-tensin, and ghrelin, includes motilin and neuromedin N [5].

Xenin production

Xenin is present not only in the mucous membrane of the human stomach, but also in other parts of the gastrointestinal tract, as well as outside it, where a pepsin-like protease generates xenin-25 from its precursor [6].

Food intake stimulates the release of xenin from enteroendocrine cells located in the proximal small intestine [4, 7]. These cells secrete both xenin-25 and GIP (glucose-dependent insulinotropic polypeptide; formerly known as gastric inhibitory polypeptide) [8, 9].

Phylogeny of xenin

Xenin is the N-terminal fragment of the *coatomer* subunit alpha protein. This motif (sequence of amino acid residues) was initially traced in the evolutionary tree back to the level of yeast [10], i.e., over a period of approximately 1.1 billion years. The anorexigenic effect of xenin (see below) has been traced back to the level of bony fish (435 million years ago) [11].

The coatomer complex is involved in intracellular protein transport and consists of an assembly of seven polypeptide subunits, one of which is designated alpha-COP and is characterized by extreme conservatism of its primary structure [12].

Using the open-access MEDLINE protein database (33 million molecules; 11 billion amino acid residues) and an original computer program, we searched for the xenin motif in the primary structure of proteins and found this motif at *all stages of evolution.* A matif with 40% homology to human xenin is already present in prokaryotes as part of the reverse transcriptase enzyme and the endospore coat-associated protein YheD, which forms the wall of intracellular vesicles. Homology reaches 84–96% in single-celled algae and plants, becoming complete by the time bony fish appeared. Perhaps xenin is the most conservative of all regulatory peptides, or it shares this place with insulin [13].

Below are examples and the divergence time (in millions of years) from the evolutionary branch leading to humans [14, 15].

MLTKFETKSARVKGLSFHPKRPWIL *Homo sapiens* (human, 0) Xenin / Coatomer subunit alpha
MLTKFESKSNRVKGLAFHPTQPLLA *Coprinopsis cinerea* (yeast, 1150) Coatomer subunit alpha-2
MLTKFETKSNRVKGLAFHPRRPWIL *Hordeum vulgare* (barley, 1496) Coatomer alpha subunit
FLTKFETKSNRVKGLSFHPRRPWIV *Guillardia theta* (flagellate), 1780) Coatomer subunit alpha
TPLDISPGSLLVKGLSFHPKSGQWN *Bacillus licheniformis* (bacteria, 4290) Reverse transcriptase
TWSTPETKSEAVLSLRRHGYRPRPL *Achromobacter xylosoxidans* (bacteria, 4290) Reverse transcriptase

Our statistical analysis of the data showed that the probability of a random coincidence for these amino acid sequences is extremely low ($p << 0.001$).

It turns out that the motif, which later became the regulatory peptide xenin, had already formed at the dawn of life, i.e., more than 4 billion years ago. Initially, it was part of the most conservative proteins — *reverse transcriptases* (syn.: reversases), then it was used in *coatomers* — also very conservative protein complexes of transport vesicle membranes associated with cell membranes and cell organelles. The moment when the motif turned into a *regulatory peptide* has not yet been determined, and may not be determined anytime soon due to the difficulty in assessing the evolutionary age of specific receptors capable of binding regulatory peptides. The motif has been preserved in the structure of transcriptases and coatomer proteins, where it is also present in humans.

The cleavage of xenin-25 from the N-terminus of the cytosolic protein of the alpha-COP membrane [16] is carried out by aspartic proteases such as pepsin and cathepsin E [17].

MAIN PHYSIOLOGICAL EFFECTS OF XENIN

The physiological effects of xenin (both endogenous and systemically administered) have been summarized [18]. The main ones are listed below:

- acting on the gastrointestinal tract, xenin inhibits the evacuation of food from the stomach and reduces small intestine motility;
- the effect of xenin on the pancreas is to activate the beta cells of the islets of Langerhans and increase insulin release;
- in adipose tissue, xenin reduces lipogenesis and enhances lipolysis.
- the CNS-mediated effect of xenin is a feeling of satiety and reduced food consumption.

Let's take a closer look at these and other effects of xenin.

Xenine and the regulation of gastrointestinal motility

Xenine delays gastric emptying [19, 20], as demonstrated in both healthy individuals and patients with type 2 diabetes [21]. In volunteers, it has been shown that after a meal, systemic administration of xenin increased the frequency of duodenal contractions [22].

Xenin affects the smooth muscle of the rat ileum [23]. Food-stimulated release of xenin-25 can activate noncholinergic [24] VIP-ergic (vasoactive intestinal polypeptide) [25] neurons in the intestine.

Xenine modulates the activity of smooth muscles in the colon [26], especially in its distal section [7].

Xenine in the regulation of carbohydrate metabolism

Beta cells are sensors of multiple stimuli that are integrated to determine the degree of glucose-induced insulin release, and one such stimulus is the level of xenin in blood plasma [27].

Xenin enhances the proliferation of beta cells in the islets of Langerhans in rodents and humans [28].

Xenine stimulates insulin secretion by enhancing the insulinotropic effect of GIP [18, 29, 30], which is considered to play a *key role in glucose homeostasis*. Xenine retains some of its activity even after GIP receptors are knocked out [9]. Xenin reduces the release of GLP-1 itself [4, 20]. The direct effect of xenin on beta and alpha cells of the pancreas has also been proven [31]. The effect of xenin on the islets of Langerhans may also be mediated by a cholinergic mechanism [32].

Xenine increases plasma concentrations of glucagon, pancreatic polypeptide (PP), and VIP [33].

High plasma xenine levels enhance the action of some antidiabetic drugs [34]. Simultaneous activation of signaling cells producing xenin, gastrin, and GLP-1 produces an antidiabetic effect [35].

Xenin and lipid metabolism regulation

Adolescents with obesity had significantly higher plasma xenin concentrations than their normally developing peers. Contrary to expectations, xenin levels did not differ between healthy individuals and patients with nonalcoholic fatty liver disease (NAFLD; more modern name: metabolic dysfunction-associated steatotic liver disease, MASLD) [36].)

Central administration of xenin to obese mice reduces food intake and weight gain, and also alters the expression of genes and proteins associated with lipid metabolism in white adipose tissue (WAT) [37]. Centrally administered xenin causes metabolic changes that lead to increased lipolysis [38]. Repeated injections of the stable synthetic analogue xenin-25[Lys_{13}PAL] produce beneficial metabolic effects in high-fat mice [9].

Xenine in food intake regulation

The level of xenine in human blood plasma increases after eating [39]. Xenine reduces food intake, and this effect is at least partly due to delayed gastric emptying [40].

Xenine suppresses the secretion of hydrochloric acid in the stomach [19, 39], and the acidity of gastric contents affects the concentration of xenine in plasma. Gastrin does not affect xenine levels [41].

Obese people have elevated blood xenin levels, but they decrease after gastric bypass surgery [42].

Blood plasma xenin levels also increase with modified sham feeding, meaning that xenin release is (at least partially) a CNS-dependent effect. Brain xenin can also significantly reduce food intake [43].

The concentration of xenin in cerebrospinal fluid correlates linearly with that in blood plasma, regardless of body weight. The authors seek an answer to the question: either (a) there is transport through the blood-brain barrier, and this system is not saturated in the concentration range found in their study, or (b) there is coordinated release of xenin in the periphery and in the CNS [42].

The hypothalamus participates in xenin anorexigenic effects. However, it does so through signaling pathways that are independent of those used by leptin or melanocortins [44]. Intraperitoneal administration of xenin increases the level of hypothalamic interleukin-1 beta (IL-1beta) mRNA and significantly reduces food intake in wild-type mice; however, this effect is absent in mice deficient in IL-1 receptors [45].

When administered into the cerebrospinal fluid, xenin activates expression in non-spatinergic neurons of the brain and thereby suppresses food intake [46].

The central effects of xenin and GLP-1 reinforce each other: the combined administration of two peptides (both in ineffective doses) into the brain reduces food intake by almost half [47].

In a previously published work, we summarized data on the pathways of peripheral xenin's effect on brain regulatory mechanisms [5]:

1. Xenin is produced by cells of the gastric and duodenal mucosa. Its level in blood plasma increases during all phases of digestion, starting with the cerebral phase. Peripheral xenin participates in endocrine regulation: it stimulates the exocrine function of the pancreas.
2. Acting on the hypothalamic centers (by a mechanism that is still unknown), peripheral xenin suppresses appetite.
3. Cerebral xenin reduces food consumption through type 1 neurotensin receptors.
4. Since the effects of peripheral and cerebral xenins coincide, there must be receptors capable of binding this peptide on the vagus afferents and/or the outer side of the blood-brain barrier.

It is also possible that xenin has an anorexigenic effect mediated by behavioral changes: central administration of the peptide stimulates chickens to explore new environments, which may distract them from their feeders [48].

Other effects of xenin

Xenin modulates ion transport in the intestinal wall [26]. After eating, xenin binds to NTR1 receptors on afferent fibers innervating the duodenum, causing the release of substance P and serotonin, which enhance duodenal secretion of HCO_3^- and Cl^- [49].

Xenine causes gallbladder contractions and enhances external secretion of the pancreas [19, 39].

Experiments with systemic administration of xenine to non-anesthetized dogs have shown that the induction of gallbladder contractions is the result of the direct action of xenine on the motility of the gastrointestinal tract. The authors believe that in this case, the nerve pathway mediating the action of xenin is cholinergic, not vagal [50].

RECEPTORS CAPABLE OF BINDING XENIN

It is unknown whether there is a specific xenin receptor. Xenine exerts its action by binding to neurotensin receptors [3, 26], but only to the first type, NTR1 [24, 51, 52], which are found on the membranes of beta cells of Langerhans islets in the pancreas [53] and neurons [4]. The structure of NTR1 has been described in detail [54]. Xeninin acts on the smooth muscle of the rat ileum through the muscle NT receptor, which is sensitive to apamin [23]. Some effects of xeninin may be mediated by myenteric neurons [19].

The KR_W motif at the C-terminus of the peptide molecule is essential for xenin binding to intestinal smooth muscle receptors [55].

XENIN FRAGMENTS — NATURAL AND SUBSTITUTED ONES

The C-terminal octapeptide $xenin_{18-25}$ [56], and the minimal fragment (in particular, for enhancing Cl^-/HCO_3^- secretion in the ileum) is the C-terminal pentapeptide $xenin_{21-25}$ [26].

Replacing the C-terminal peptide bond Lys-Arg (KR) in xenin-6 with a restored pseudopeptide bond increased the affinity of the peptide with receptors of isolated smooth muscle cell membranes in the wall of the small and large intestine by 7.7 and 21.0 times, respectively [55]. Such Psi-xenin-6 significantly enhanced the proliferation of clonal beta cells in humans and rodents, as well as completely protected beta cells from the action of cytokines, i.e., it acted more effectively than the natural peptides xenin-25 and xenin-6 [57]. The C-terminal hexapeptide of neurotensin NT_{8-13} was combined with a double-substituted C-terminal octapeptide of xenin:

Acetyl-NT_{8-13} + Xenin-8-Gln = Ac-NT/XN-8-Gln
RRPYIL + HPQQPWIL = RRPYILHPQQPWIL

This resulted in pronounced antidiabetic efficacy when administered together with exendin-4, a clinically approved GLP-1 receptor agonist [30].

Palmitate derivatives of xenin-25 are proposed as a new class of GIP secretion stimulants for the treatment of type 2 diabetes mellitus [58]. Xenin-25[Lys_{13}PAL] reduces neuroinflammation [59].

Xenin-25 is rapidly degraded in the bloodstream. It has been suggested that replacing all Lys (K) and Arg (R) with Gln (Q) would increase protease resistance and, accordingly, biological efficacy:

MLTKFETKSARVKGLSFHPKRPWIL xenin-25
MLTQFETQSAQVQGLSFHPQQPWIL xenin-25(Gln)

The resulting six-substituted xenin-25(Gln) was resistant to plasma degradation and had a beneficial metabolic effect on mice fed a high-fat diet, as well as on ob/ob mice. It significantly stimulated insulin secretion [60].

The Hybrid ($DAla_2$)GIP/xenin-8-Gln has the ability to stably activate GLP-1 receptors in diabetes mellitus [61].

PROSPECTS FOR THE PRACTICAL USE OF XENIN

The effect of K cells on GIP production (in which xenin is involved) may become a strategy for reducing obesity [62].

Long-acting hybrid peptides based on xenin have clinical prospects for the creation of new drugs for treating type 2 diabetes. The reader can find the formulas of specific potential drugs in sources [18, 30, 56, 58, 63–66].

CONCLUSION

1. Xenin-25 is a peptide secreted by K cells in the gastrointestinal mucosa. The level of xenin in human blood plasma increases after eating.

2. Xenin enhances the feeling of satiety and reduces food intake by acting through numerous peripheral and central mechanisms.

3. Xenin stimulates insulin secretion and protects the beta cells of Langerhans islets from damaging factors.

4. Xenin is one of the oldest, and possibly the oldest, regulatory peptides: the xenin motif is present in proteins of all taxa, from prokaryotes to humans. The absolute conservatism of the peptide indicates its high biological significance.

5. Long-acting artificial hybrid peptides based on xenin have clinical potential in the development of new drugs for treating type 2 diabetes and obesity.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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ЛИТЕРАТУРА / REFERENCES

1. Okunogbe A., Nugent R., Spencer G., Powis J., Ralston J., Wilding J. Economic impacts of overweight and obesity: current and future estimates for 161 countries. *BMJ Glob Health*. 2022;7(9):e009773. https://doi.org/10.1136/bmjgh-2022-009773.
2. Feurle G.E., Hamscher G., Kusiek R., Meyer H.E., Metzger J.W. Identification of xenin, a xenopsin-related peptide, in the human gastric mucosa and its effect on exocrine pancreatic secretion. *J Biol Chem*. 1992;267(31):22305–9. PMID: 1429581.
3. Kim E.R., Mizuno T.M. Role of neurotensin receptor 1 in the regulation of food intake by neuromedins and neuromedin-related peptides. *Neurosci Lett*. 2010;468(1):64–67. https://doi.org/10.1016/j.neulet.2009.10.064.
4. Sterl K., Wang S., Oestricker L., Wallendorf M.J., Patterson B.W., Reeds D.N., Wice B.M. Metabolic responses to xenin-25 are altered in humans with Roux-en-Y gastric bypass surgery. *Peptides*. 2016;82:76–84. https://doi.org/10.1016/j.peptides.2016.06.001.
5. Maryanovich A.T. Foundations of Peptide Regulation of the Physiological Functions: Blood-Brain Barrier and Evolution of Viscera-to-Brain Communications. Saint Petersburg: Publishing House of the North-Western State Medical University named after I.I. Mechnikov; 2014: 578.
6. Hamscher G., Meyer H.E., Metzger J.W., Feurle G.E. Distribution, formation, and molecular forms of the peptide xenin in various mammals. *Peptides*. 1995;16(5):791–797. https://doi.org/10.1016/0196-9781(95)00053-m.
7. Kuwahara Y., Kato I., Inui T., Marunaka Y., Kuwahara A. The effect of Xenin25 on spontaneous circular muscle contractions of rat distal colon in vitro. *Physiol Rep*. 2021;9(4):e14752. https://doi.org/10.14814/phy2.14752.
8. Althage M.C., Ford E.L., Wang S., Tso P., Polonsky K.S., Wice B.M. Targeted ablation of glucose-dependent insulinotropic polypeptide-producing cells in transgenic mice reduces obesity and insulin resistance induced by a high fat diet. *J Biol Chem*. 2008;283(26):18365–76. https://doi.org/10.1074/jbc.M710466200.
9. Gault V.A., Martin C.M., Flatt P.R., Parthsarathy V., Irwin N. Xenin-25[Lys_{13}PAL]: a novel long-acting acylated analogue of xenin-25 with promising antidiabetic potential. *Acta Diabetol*. 2015;52(3):461–471. https://doi.org/10.1007/s00592-014-0681-0.
10. Hamscher G., Meyer H.E., Feurle G.E. Identification of proxenin as a precursor of the peptide xenin with sequence homology to yeast and mammalian coat protein alpha. *Peptides*. 1996;17(6):889–893. https://doi.org/10.1016/0196-9781(96)00150-7.
11. Kerbel B., Badal K., Sundarrajan L., Blanco A., Unniappan S. Xenin is a novel anorexigen in goldfish (Carassius auratus). *PLoS One*. 2018;13(5):e0197817. https://doi.org/10.1371/journal.pone.0197817.
12. Chow V.T., Sakharkar M.K., Lim D.P., Yeo W.M. Phylogenetic relationships of the seven coat protein subunits of the coatomer complex, and comparative sequence analysis of murine xenin and proxenin. *Biochem Genet*. 2001;39(5-6):201–211. https://doi.org/10.1023/a:1010245409552.
13. Maryanovich A.T., Kormilets D.Y., Polyanovsky A.D. Xenin: the oldest after insulin? *Mol Biol Rep*. 2018;45(2):143–150. https://doi.org/10.1007/s11033-018-4147-2.
14. Hedges S.B., Dudley J., Kumar S. TimeTree: a public knowledge-base of divergence times among organisms. *Bioinformatics*. 2006 ;22(23):2971–2972. https://doi.org/10.1093/bioinformatics/btl505.
15. Hedges S.B. (ed.), Kumar S (ed.) The Timetree of Life. Oxford University Press; 2009. https://doi.org/10.1093/oso/9780199535033.001.0001.
16. Chow V.T., Quek H.H. Alpha coat protein COPA (HEP-COP): presence of an Alu repeat in cDNA and identity of the amino terminus

to xenin. *Ann Hum Genet*. 1997;61(Pt 4):369–373. https://doi.org/10.1046/j.1469-1809.1997.6140369.x.
17. Feurle G.E.. Xenin — a review. *Peptides*. 1998;19(3):609–615. https://doi.org/10.1016/s0196-9781(97)00378-1.
18. Craig S.L., Irwin N., Gault V.A. Xenin and related peptides: potential therapeutic role in diabetes and related metabolic disorders. *Clin Med Insights Endocrinol Diabetes*. 2021;14:11795514211043868. https://doi.org/10.1177/11795514211043868.
19. Zhang S., Hyrc K., Wang S., Wice B.M. Xenin-25 increases cytosolic free calcium levels and acetylcholine release from a subset of myenteric neurons. *Am J Physiol Gastrointest Liver Physiol*. 2012;303(12):G1347–55. https://doi.org/10.1152/ajpgi.00116.2012.
20. Chowdhury S., Wang S., Dunai J., Kilpatrick R., Oestricker L.Z., Wallendorf M.J., Patterson B.W., Reeds D.N., Wice B.M. Hormonal responses to cholinergic input are different in humans with and without type 2 diabetes mellitus. *PLoS One*. 2016;11(6):e0156852. https://doi.org/10.1371/journal.pone.0156852.
21. Chowdhury S., Reeds D.N., Crimmins D.L., Patterson B.W., Laciny E., Wang S., Tran H.D., Griest T.A., Rometo D.A., Dunai J., Wallendorf M.J., Ladenson J.H., Polonsky K.S., Wice B.M. Xenin-25 delays gastric emptying and reduces postprandial glucose levels in humans with and without type 2 diabetes. *Am J Physiol Gastrointest Liver Physiol*. 2014;306(4):G301–9. https://doi.org/10.1152/ajpgi.00383.2013.
22. Feurle G.E., Pfeiffer A., Schmidt T., Dominguez-Munoz E., Malfertheiner P., Hamscher G. Phase III of the migrating motor complex: associated with endogenous xenin plasma peaks and induced by exogenous xenin. *Neurogastroenterol Motil*. 2001;13(3):237–246. https://doi.org/10.1046/j.1365-2982.2001.00263.x.
23. Clemens A., Katsoulis S., Nustede R., Seebeck J., Seyfarth K., Morys-Wortmann C., Feurle G.E., Fölsch U.R., Schmidt W.E. Relaxant effect of xenin on rat ileum is mediated by apamin-sensitive neurotensin-type receptors. *Am J Physiol*. 1997;272(1 Pt 1):G190–6. https://doi.org/10.1152/ajpgi.1997.272.1.G190.
24. Nustede R., Schmidt W.E., Horstmann O., Sikovec N., Schemminger R., Becker H. On the effect of xenin and xenin fragments on exocrine pancreas secretion in vivo. *Regul Pept*. 1999;81(1-3):61–66. https://doi.org/10.1016/s0167-0115(99)00019-1.
25. Kuwahara A., Kuwahara Y., Kato I., Kawaguchi K., Harata D., Asano S., Inui T., Marunaka Y. Xenin-25 induces anion secretion by activating noncholinergic secretomotor neurons in the rat ileum. *Am J Physiol Gastrointest Liver Physiol*. 2019;316(6):G785–G796. https://doi.org/10.1152/ajpgi.00333.2018.
26. Kuwahara Y., Takahashi K., Akai M., Kato I., Kozakai T., Asano S., Inui T., Marunaka Y., Kuwahara A. Minimum biological domain of xenin-25 required to induce anion secretion in the rat ileum. *Peptides*. 2022;147:170680. https://doi.org/10.1016/j.peptides.2021.170680.
27. Hussain M.A., Akalestou E., Song W.J. Inter-organ communication and regulation of beta cell function. *Diabetologia*. 2016;59(4):659–667. https://doi.org/10.1007/s00125-015-3862-7.
28. Khan D., Vasu S., Moffett R.C., Gault V.A., Flatt P.R., Irwin N. Locally produced xenin and the neurotensinergic system in pancreatic islet function and β-cell survival. *Biol Chem*. 2017;399(1):79–92. https://doi.org/10.1515/hsz-2017-0136.
29. Wice B.M., Wang S., Crimmins D.L., Diggs-Andrews K.A., Althage M.C., Ford E.L., Tran H., Ohlendorf M., Griest T.A., Wang Q., Fisher S.J., Ladenson J.H., Polonsky K.S. Xenin-25 potentiates glucose-dependent insulinotropic polypeptide action via a novel cholinergic relay mechanism. *J Biol Chem*. 2010;285(26):19842–53. https://doi.org/10.1074/jbc.M110.129304.
30. Perry R.A., Craig S.L., Gault V.A., Flatt P.R., Irwin N. A novel neurotensin/xenin fusion peptide enhances β-cell function and exhibits antidiabetic efficacy in high-fat fed mice. *Biosci Rep*. 2021;41(8):BSR20211275. https://doi.org/10.1042/BSR20211275.
31. Silvestre R.A., Rodríguez-Gallardo J., Egido E.M., Hernández R., Marco J. Stimulatory effect of xenin-8 on insulin and glucagon secretion in the perfused rat pancreas. *Regul Pept*. 2003;115(1):25–29. https://doi.org/10.1016/s0167-0115(03)00147-2.
32. Wice B.M., Reeds D.N., Tran H.D., Crimmins D.L., Patterson B.W., Dunai J., Wallendorf M.J., Ladenson J.H., Villareal D.T., Polonsky K.S. Xenin-25 amplifies GIP-mediated insulin secretion in humans with normal and impaired glucose tolerance but not type 2 diabetes. *Diabetes*. 2012;61(7):1793–800. https://doi.org/10.2337/db11-1451.
33. Feurle G.E., Heger M., Niebergall-Roth E., Teyssen S., Fried M., Eberle C., Singer M.V., Hamscher G. Gastroenteropancreatic effects of xenin in the dog. *J Pept Res*. 1997;49(4):324–330. https://doi.org/10.1111/j.1399-3011.1997.tb01132.x.
34. Craig S.L., Gault V.A., Flatt P.R., Irwin N. The methionine aminopeptidase 2 inhibitor, TNP-470, enhances the antidiabetic properties of sitagliptin in mice by upregulating xenin. *Biochem Pharmacol*. 2021;183:114355. https://doi.org/10.1016/j.bcp.2020.114355.
35. Hasib A., Khan D., Craig S.L., Gault V.A., Flatt P.R., Irwin N. Antidiabetic effects and sustained metabolic benefits of sub-chronic co-administration of exendin-4/gastrin and xenin-8-Gln in high fat fed mice. *Eur J Pharmacol*. 2019;865:172733. https://doi.org/10.1016/j.ejphar.2019.172733.
36. Arslan N., Sayin O., Tokgoz Y. Evaluation of serum xenin and ghrelin levels and their relationship with nonalcoholic fatty liver disease and insulin resistance in obese adolescents. *J Endocrinol Invest*. 2014;37(11):1091–1097. https://doi.org/10.1007/s40618-014-0160-z.
37. Bhavya S., Lew P.S., Mizuno T.M. Stimulation of white adipose tissue lipolysis by xenin, a neurotensin-related peptide. *Biochem Biophys Res Commun*. 2018;498(4):842–848. https://doi.org/10.1016/j.bbrc.2018.03.067.
38. Bhavya S., Lew P.S., Mizuno T.M. Central action of xenin affects the expression of lipid metabolism-related genes and proteins in mouse white adipose tissue. *Neuropeptides*. 2017;63:67–73. https://doi.org/10.1016/j.npep.2017.01.007.
39. Anlauf M., Weihe E., Hartschuh W., Hamscher G., Feurle G.E. Localization of xenin-immunoreactive cells in the duodenal mucosa of humans and various mammals. *J Histochem Cytochem*. 2000;48(12):1617–1626. https://doi.org/10.1177/002215540004801205.

40. Kim E.R., Mizuno T.M. Xenin delays gastric emptying rate and activates the brainstem in mice. *Neurosci Lett*. 2010;481(1):59–63. https://doi.org/10.1016/j.neulet.2010.06.055.
41. Stoschus B., Hamscher G., Ikonomou S., Partoulas G., Eberle C., Sauerbruch T., Feurle G.E. Effect of omeprazole treatment on plasma concentrations of the gastric peptides, xenin, gastrin and somatostatin, and of pepsinogen. *J Pept Res*. 1998;52(1):27–33. https://doi.org/10.1111/j.1399-3011.1998.tb00649.x.
42. Van de Sande-Lee S., Cardoso A.R., Garlipp C.R., Chaim E.A., Pareja J.C., Geloneze B., Velloso L.A. Cerebrospinal fluid xenin levels during body mass reduction: no evidence for obesity-associated defective transport across the blood-brain barrier. *Int J Obes (Lond)*. 2013;37(3):416–419. https://doi.org/10.1038/ijo.2012.70.
43. Cooke J.H., Patterson M., Patel S.R., Smith K.L., Ghatei M.A., Bloom S.R., Murphy K.G. Peripheral and central administration of xenin and neurotensin suppress food intake in rodents. *Obesity (Silver Spring)*. 2009;17(6):1135–1143. https://doi.org/10.1038/oby.2008.652.
44. Leckstrom A., Kim E.R., Wong D., Mizuno T.M. Xenin, a gastrointestinal peptide, regulates feeding independent of the melanocortin signaling pathway. *Diabetes*. 2009;58(1):87–94. https://doi.org/10.2337/db08-0260.
45. Kim E.R., Xu Y., Mizuno T.M. Impaired suppression of feeding by the gut hormone xenin in type I interleukin-1 receptor-deficient mice. *Behav Brain Res*. 2014;261:60–64. https://doi.org/10.1016/j.bbr.2013.12.005.
46. Saito S., Hashimoto H., Wakashin H., Ishibane M., Pae S., Saito S., Reien Y., Hirayama Y., Seo Y., Mizushima T., Anzai N. Central administered xenin induced Fos expression in nesfatin-1 neurons in rats. *Brain Res Bull*. 2023;204:110788. https://doi.org/10.1016/j.brainresbull.2023.110788.
47. Schusdziarra V., Zimmermann J.P., Schick R.R. Importance of orexigenic counter-regulation for multiple targeted feeding inhibition. *Obes Res*. 2004;12(4):627–632. https://doi.org/10.1038/oby.2004.72.
48. Nandar W., Milligan J.M., Cline M.A. Mechanisms of xenin-induced anorectic response in chicks (Gallus gallus). *Gen Comp Endocrinol*. 2008;157(1):58–62. https://doi.org/10.1016/j.ygcen.2008.03.012.
49. Kaji I., Akiba Y., Kato I., Maruta K., Kuwahara A., Kaunitz J.D. Xenin augments duodenal anion secretion via activation of afferent neural pathways. *J Pharmacol Exp Ther*. 2017;361(1):151–161. https://doi.org/10.1124/jpet.116.238485.
50. Kamiyama Y., Aihara R., Nakabayashi T., Mochiki E., Asao T., Kuwano H. The peptide hormone xenin induces gallbladder contractions in conscious dogs. *Neurogastroenterol Motil*. 2007;19(3):233–240. https://doi.org/10.1111/j.1365-2982.2006.00881.x.
51. Onaga T., Yasui Y., Hayashi H. Neurotensin and xenin stimulates pancreatic exocrine secretion through the peripheral cholinergic nerves in conscious sheep. *Gen Comp Endocrinol*. 2022;326:114073. https://doi.org/10.1016/j.ygcen.2022.114073.
52. Vita N., Oury-Donat F., Chalon P., Guillemot M., Kaghad M., Bachy A., Thurneyssen O., Garcia S., Poinot-Chazel C., Caselas P., Keane P., Le Fur G., Maffrand J.P., Soubrie P., Caput D., Ferrara P. Neurotensin is an antagonist of the human neurotensin NT2 receptor expressed in Chinese hamster ovary cells. *Eur J Pharmacol*. 1998;360(2-3):265–272. https://doi.org/10.1016/s0014-2999(98)00678-5.
53. Onaga T., Hayashi H., Yasui Y. Effects of xenin-25 on insulin and glucagon secretions in healthy conscious sheep. *Domest Anim Endocrinol*. 2021;77:106635. https://doi.org/10.1016/j.domaniend.2021.106635.
54. White J.F., Noinaj N., Shibata Y., Love J., Kloss B., Xu F., Gvozdenovic-Jeremic J., Shah P, Shiloach J., Tate C.G., Grisshammer R. Structure of the agonist-bound neurotensin receptor. *Nature*. 2012;490(7421):508–513. https://doi.org/10.1038/nature11558.
55. Feurle G.E., Metzger J.W., Grudinski A., Hamscher G. Interaction of xenin with the neurotensin receptor of guinea pig enteral smooth muscles. *Peptides*. 2002;23(3):523-529. https://doi.org/10.1016/s0196-9781(01)00637-4. Corrected and republished in: *Peptides*. 2002;23(8):1519–1525. https://doi.org/10.1016/s0196-9781(02)00064-5.
56. Martin C.M., Parthsarathy V., Pathak V., Gault V.A., Flatt P.R., Irwin N. Characterisation of the biological activity of xenin-25 degradation fragment peptides. *J Endocrinol*. 2014;221(2):193–200. https://doi.org/10.1530/JOE-13-0617.
57. Craig S.L., Gault V.A., McClean S., Hamscher G., Irwin N. Effects of an enzymatically stable C-terminal hexapseudopeptide fragment peptide of xenin-25, ψ-xenin-6, on pancreatic islet function and metabolism. *Mol Cell Endocrinol*. 2019;496:110523. https://doi.org/10.1016/j.mce.2019.110523.
58. Martin C.M., Gault V.A., McClean S., Flatt P.R., Irwin N. Degradation, insulin secretion, glucose-lowering and GIP additive actions of a palmitate-derivatised analogue of xenin-25. *Biochem Pharmacol*. 2012;84(3):312–319. https://doi.org/10.1016/j.bcp.2012.04.015.
59. Denver P., Gault V.A., McClean P.L. Sustained high-fat diet modulates inflammation, insulin signalling and cognition in mice and a modified xenin peptide ameliorates neuropathology in a chronic high-fat model. *Diabetes Obes Metab*. 2018;20(5):1166–1175. https://doi.org/10.1111/dom.13210.
60. Parthsarathy V., Irwin N., Hasib A., Martin C.M., McClean S., Bhat V.K., Ng M.T., Flatt P.R., Gault V.A. A novel chemically modified analogue of xenin-25 exhibits improved glucose-lowering and insulin-releasing properties. *Biochim Biophys Acta*. 2016;1860(4):757–764. https://doi.org/10.1016/j.bbagen.2016.01.015.
61. Craig S.L., Perry R.A., Vyavahare S.S., Ng M.T., Gault V.A., Flatt P.R., Irwin N. A GIP/xenin hybrid in combination with exendin-4 improves metabolic status in db/db diabetic mice and promotes enduring antidiabetic benefits in high fat fed mice. *Biochem Pharmacol*. 2020;171:113723. https://doi.org/10.1016/j.bcp.2019.113723.
62. Cho Y.M., Kieffer T.J. K-cells and glucose-dependent insulinotropic polypeptide in health and disease. *Vitam Horm*. 2010;84:111–150. https://doi.org/10.1016/B978-0-12-381517-0.00004-7.

63. Hasib A., Ng M.T., Tanday N., Craig S.L., Gault V.A., Flatt P.R., Irwin N. Exendin-4(Lys27 PAL)/gastrin/xenin-8-Gln: A novel acylated GLP-1/gastrin/xenin hybrid peptide that improves metabolic status in obese-diabetic (ob/ob) mice. *Diabetes Metab Res Rev*. 2019;35(3):e3106. https://doi.org/10.1002/dmrr.3106.
64. Hasib A., Ng M.T., Gault V.A., Khan D., Parthsarathy V., Flatt P.R., Irwin N. An enzymatically stable GIP/xenin hybrid peptide restores GIP sensitivity, enhances beta cell function and improves glucose homeostasis in high-fat-fed mice. *Diabetologia*. 2017;60(3):541–552. https://doi.org/10.1007/s00125-016-4186-y.
65. Martin C.M., Parthsarathy V., Hasib A., Ng M.T., McClean S., Flatt P.R., Gault V.A., Irwin N. Biological activity and antidiabetic potential of C-terminal octapeptide fragments of the gut-derived hormone xenin. *PLoS One*. 2016;11(3):e0152818. https://doi.org/10.1371/journal.pone.0152818.
66. Hasib A., Ng M.T., Khan D., Gault V.A., Flatt P.R., Irwin N. A novel GLP-1/xenin hybrid peptide improves glucose homeostasis, circulating lipids and restores GIP sensitivity in high fat fed mice. *Peptides*. 2018;100:202–211. https://doi.org/10.1016/j.peptides.2017.10.015.

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