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Some aspects of trypsin's involvement in the regulation of physiological functions

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Introduction

Currently, the relevance of studying serine proteases secreted by exocrine glands into the bloodstream is increasing due to the increased interest in research related to protease-activated receptors (PARs). PARs are a family of G protein-coupled receptors consisting of four members and characterized by an irreversible proteolytic activation mechanism (Chandrabalan and Ramachandran, 2021). PARs are localized on the cell membranes of various organs and tissues, and their functional activity is regulated by interaction with various proteases such as trypsin, thrombin, etc (Zhao et al., 2014). Currently, serine proteases are considered not only as classical enzymes, but also as signaling molecules actively involved in the regulation of physiological and pathological processes not only in the gastrointestinal tract, but also in other body systems (Aleynik et al., 2018).

Previously, such a serine protease as trypsin was considered as one of the main digestive enzymes that specifically cleave the peptide bonds of proteins.

It is generally recognized that trypsin is an agonist of PAR2 receptors. It has been shown that trypsin, by activating PAR-2, which are present in large quantities on the surface of acinar cells and pancreatic duct cells, enhances cytokine secretion and regulates the exocrine function of the pancreas due to the negative feedback mechanism (Hirota et al., 2006).

Opinion

The involvement of trypsin in the regulation of physiological functions in animals of various species

There is evidence of the specific involvement of trypsin in the regulation of physiological functions in animals of various species.

For example, in experiments on rats, it was found that restricting access to water led to a significant increase in trypsin activity in the blood, and restricting feed caused a decrease in this indicator compared with animals with free access to food and water (Kuzmina et al., 2023). Studies on Leghorn roosters have shown that after feeding, there was an increase in trypsin activity in the blood and a multiple increase in the content of nitric oxide donors, which was confirmed by an increase in the concentration of Fe(NO)n in plasma (Vertiprakhov et al., 2023a).

There is evidence that PAR2 is expressed on both vascular endothelium and smooth muscle cells, suggesting its role in the regulation of vascular reactivity. The effects of the activating peptide PAR2 (PAR2-AP) were inhibited by L-NAME, which indicates the

involvement of nitric oxide (NO) in these processes. It was shown that the direct effect of trypsin on vascular smooth muscle cells PAR2 caused venoconstriction. It should be noted that arterial vasodilation initiated by the action of vascular PAR2 agonists promoted the release of vasodilating mediators such as NO (Alberelli and De Candia, 2014). It is known that NO is involved in a number of physiological processes, including vasodilation, platelet function regulation, neurotransmission, immunomodulation, and control of metabolic processes (Jon, 2022). The relationship between the NO level and trypsin activity was also discovered during experiments on chickens (Vertiprakhov and Ovchinnikova, 2022).

It was found that an imbalance between the content of NO and endothelins may presumably indicate the development of necrotizing pancreatitis. However, the role of trypsin in the development of this imbalance remains unclear. It is known that the regulation of NO formation in the body is largely related to the renin-angiotensin system (RAS). It was revealed that there is a tissue race in the pancreas and all its main components present in the pancreas are activated when it is damaged. Moreover, in this pathology, trypsin can cause the formation of angiotensin II (AngII) from angiotensinogen at a slightly acidic pH, regardless of the action of the angiotensin-converting enzyme (Furukawa et al., 2013). It has also been established that local RAS is involved in the production of NO in the intestinal mucosa. Stimulation of AT2 receptors (AT2R) AngII of the pig jejunum mucosa led to an increase in the release of NO by epithelial cells into the intestinal lumen (Zamolodchikova et al., 2016).

In the regulation of hemodynamics and vascular tone, the mechanism of NO release is important, which can be induced by AngII processing products that have pronounced vasodilating properties. These metabolites play a key role in the modulation of vascular reactivity and can significantly influence the processes of blood pressure regulation (Dielis et al., 2005). It has been demonstrated that trypsin, when administered intramuscularly, causes a decrease in blood pressure and an increase in heart rate in rabbits (Galiga et al., 2025). This is consistent with data on the hypotensive effect of PAR2 activation (Chia et al., 2011; Wang et al., 2022).

It was noted that in cows, goats and poultry, trypsin activity in blood serum varies in various ways. When analyzing the enzyme activity in the blood of laying hens, a positive relationship was found between egg production and trypsin activity, which makes it possible to use this indicator to assess metabolic processes in the bird's body (Vertiprakhov et al., 2023b). In this regard, it is interesting to consider trypsin as a PAR2 agonist in the gastrointestinal tract.

Trypsin, an agonist of PAR2, in the regulation of the gastrointestinal tract

Digestive proteases such as trypsin and chymotrypsin are usually synthesized as inactive precursors. Pancreatic acinar cells express several isoforms of trypsinogen: trypsinogen I, II, IV and mesotrypsinogen. After secretion from the pancreatic ducts, trypsinogen is converted into trypsin on the brush border of enterocytes under the action of enteropeptidase. Active trypsin, in turn, promotes its own activation, acts on chymotrypsinogen, activates PAR-2, thereby increasing paracellular permeability (Agawa et al., 2022). It should be noted that the gastrointestinal epithelium is a promising area of PAR research due to the fact that the gastrointestinal tract is constantly exposed to the greatest number of proteases, both luminal and secreted by the mucous membrane.

A number of studies have revealed that PAR is expressed throughout the gastrointestinal tract, from the salivary glands to the stomach, along the entire length of the intestine, in the pancreas and liver (Hyun et al., 2010; Oliveira et al., 2021).

It has been established that PAR2 modulates acute and chronic inflammatory processes in the gastrointestinal tract in both humans and animals (Lambertini et al., 2020; Zhao et al., 2012).

The intestine is an effective barrier that protects the body from the penetration of pathogenic microorganisms and potentially harmful macromolecules, and also performs its main function—digestion and absorption of nutrients (Weström et al., 2020). The intestine is also one of the main components of the immune system, designed to protect the body from harmful microbes and toxins that enter it with animal feed (Kulkarni et al., 2021).

It has been found that increased intestinal proteolysis and signaling via PAR2 are associated with inflammatory bowel diseases and irritable bowel syndrome, conditions that are often associated with changes in the intestinal microbiome (Lakemeyer et al., 2025).

Special consideration should be given to such a group of pathogenic factors as mycotoxins, which are often present in the feed of farm animals and birds.

Mycotoxins are harmful secondary metabolites produced by mold fungi and have a detrimental effect on human and animal health (Eskola et al., 2020). There are more than 200 known species of molds that produce mycotoxins. The most common harmful mycotoxins polluting feed and feed materials include aflatoxin B1 (AFB1), HT-2, T-2, ochratoxin A, fumonisin B1, zearalenone, citrinin, etc. (Binder, 2007). T-2 and HT-2 toxins are often found in poultry feed, which are among the most dangerous trichothecene mycotoxins and cause gastroenteritis, necrosis of the skin and oral mucosa, as well as disorders of the central nervous system (Gómez-Osorio et al., 2024).

The results of studies on broiler chickens with a 12-finger cannula have shown that experimental mycotoxicosis caused by T-2 toxin results in a decrease in trypsin activity in blood plasma. In freeze-dried droppings with mycotoxicosis, on the contrary, there was a 2.0-fold increase in trypsin activity compared with the control (Vertipra et al., 2022).

Considering the role of trypsin as a PAR2 agonist in the intestine, as well as the variety of functions performed by PARs in this organ, and their wide presence in various cell types, it can be concluded that this enzyme is important in the development of gastrointestinal pathology caused by mycotoxins (Soreide et al., 2006).

The functional role of the intestinal microbiota and its contribution to the transmission of PAR signals through various microbial proteases or by stimulating the activity of proteases in the intestinal mucosa, as well as the differential regulation of PAR expression profiles in the intestine, requires further study (Gummadi and Gonska, 2025).

Conclusion

These data are consistent with the idea that trypsin is not only a digestive enzyme, but also an important multifunctional signaling molecule that, as a PAR2 agonist, plays an important role in regulating a number of metabolic processes.

The results of numerous experimental studies reviewed in this article suggest that the assessment of trypsin activity in blood serum can serve as a diagnostic method for detecting inflammatory processes and exocrine insufficiency of the pancreas, as well as inflammatory processes in the intestine. Therefore, trypsin can be considered as an informative biomarker of the state of the animal body.

Author contributions

IK: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. ST: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. VV: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.

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References

Agawa, S., Futagami, S., Yamawaki, H., Tsushima, R., Higuchi, K., Habiro, M., et al. (2022). Trypsin may be associated with duodenal eosinophils through the expression of PAR2 in early chronic pancreatitis and functional dyspepsia with pancreatic enzyme abnormalities. *PLoS One* 17 (10), e0275341. doi:10.1371/journal.pone.0275341

Alberelli, M. A., and De Candia, E. (2014). Functional role of protease activated receptors in vascular biology. *Vasc. Pharmacol.* 62 (2), 72–81. doi:10.1016/j.vph.2014.06.001

Aleynik, V. A., Babich, S. M., Zhuraeva, M. A., and Zulunova, I. B. (2018). Trypsin as a modifying factor in liver utilization of pentagastrin. *Inter. J. Appl. Fund. Res.* 9, 30–34. Available online at: https://applied-research.ru/ru/article/view?id=12382Russ. (Accessed November 2025)

Binder, E. M. (2007). Managing the risk of mycotoxins in modern feed production. *Anim. Feed Sci. Technol.* 133, 149–166. doi:10.1016/j.anifeedsci.2006.08.008

Chandrabalan, A., and Ramachandran, R. (2021). Molecular mechanisms regulating Proteinase-Activated Receptors (PARs). *FEBS J.* 288 (8), 2697–2726. doi:10.1111/febs.15829

Chia, E., Kagota, S., Wijekoon, E. P., and McGuire, J. J. (2011). Protection of protease-activated receptor 2 mediated vasodilatation against angiotensin II-induced vascular dysfunction in mice. *BMC Pharmacol.* 11, 10. doi:10.1186/1471-2210-11-10

Dielis, A. W., Smid, M., Spronk, H. M., Hamulyak, K., Kroon, A. A., ten Cate, H., et al. (2005). The prothrombotic paradox of hypertension: role of the renin-angiotensin and kallikrein-kinin systems. *Hypertension* 46 (6), 1236–1242. doi:10.1161/01.HYP.0000193538.20705.23

Eskola, M., Kos, G., Elliott, C. T., Hajšlová, J., Mayar, S., and Krska, R. (2020). Worldwide contamination of food-crops with mycotoxins: validity of the widely cited 'FAO estimate' of 25. *Crit. Rev. Food Sci. Nutr.* 60 (16), 2773–2789. doi:10.1080/10408398.2019.1658570

Furukawa, H., Shinmura, A., Tajima, H., Tsukada, T., Nakanuma, S., Okamoto, K., et al. (2013). Concentration of tissue angiotensin II increases with severity of experimental pancreatitis. *Mol. Med. Rep.* 8 (2), 335–338. doi:10.3892/mmr.2013.1509

Galiga, S. D., Karamushkina, S. V., and Kralinina, A. V. (2025). Features of hemodynamic regulation in rabbits during parenteral administration of trypsin. *Timiryazev Biol. J.* (2), 202532401. doi:10.26897/2949-4710-2025-3-2-4-01

Gómez-Osorio, L. M., Vasiljevic, M., Raj, J., Chaparro-Gutierréz, J. J., and López-Osorio, S. (2024). Mycotoxins and coccidiosis in poultry - co-occurrence, interaction, and effects. *Front. Vet. Sci.* 11, 1387856. doi:10.3389/fvets.2024.1387856

Gummadi, V. V., and Gonska, T. (2025). Serum trypsin is a reliable biomarker of pancreas function. *Pancreas* 54 (4), e360–e368. doi:10.1097/MPA.0000000000002445

Hirota, M., Ohmuraya, M., and Baba, H. (2006). The role of trypsin, trypsin inhibitor, and trypsin receptor in the onset and aggravation of pancreatitis. *J. Gastroenterol.* 41, 832–836. doi:10.1007/s00535-006-1874-2

Hyun, E., Andrade-Gordon, P., Steinhoff, M., Beck, P. L., and Vergnolle, N. (2010). Contribution of bone marrow-derived cells to the pro-inflammatory effects of protease-activated receptor-2 in colitis. *Inflamm. Res.* 59 (9), 699–709. doi:10.1007/s00011-010-0181-9

Jon, O. (2022). Lundberg and eddie weitzberg nitric oxide signaling in health and disease. *Cell* 185, 2853–2879. doi:10.1016/j.cell.2022.06.010

Kulkarni, S., Kurapati, S., and Bogunovic, M. (2021). Neuro-innate immune interactions in gut mucosal immunity. *Curr. Opin. Immunol.* 68, 64–71. doi:10.1016/j.coi.2020.09.007

Kuzmina, I. V., Ovchinnikova, N. V., and Tolpygo, S. M. (2023). Activity of the proteolytic enzyme trypsin in rat serum under conditions of water and food deprivation. *Bull. Exp. Biol. Med.* 175 (5), 540–544. doi:10.47056/0365-9615-2023-175-5-540-544

Lakemeyer, M., Latorre, R., Blazkova, K., Wood, H. M., Jensen, D. D., Shakil, N., et al. (2025). A Bacteroides fragilis protease activates host PAR2 to induce intestinal pain and inflammation. *Cell Host Microbe* 33 (10), 1686–1702.e11. doi:10.1016/j.chom.2025.09.010

Lambertini, C., Zannoni, A., Romagnoli, N., Bombardi, C., Morini, M., Dondi, F., et al. (2020). Expression of proteinase-activated receptor 2 during Colon volvulus in the horse. *Front. Vet. Sci.* 7, 589367. doi:10.3389/fvets.2020.589367

Oliveira, K. A., Torquato, R. J. S., Lustosa, DCGG, Ribeiro, T., Nascimento, B. W. L., de Oliveira, L. C. G., et al. (2021). Proteolytic activity of *Triatoma infestans* saliva associated with PAR-2 activation and vasodilation. *J. Venom. Anim. Toxins Incl. Trop. Dis.* 27, e20200098. doi:10.1590/1678-9199-JVATITD-2020-0098

Soreide, K., Janssen, E. A., Korner, H., and Baak, J. P. (2006). Trypsin in colorectal cancer: molecular biological mechanisms of proliferation, invasion, and metastasis. *J. Pathol.* 209, 147–156. doi:10.1002/path.1999

Vertiprakhov, V., Grozina, A., Kislova, I., Ovchinnikova, N., and Koshcheeva, M. (2022). "The duodenal activity of the enzymes and biochemical blood indices in broilers with experimental T2-Toxicosis fed absorbent with or without proteolytic enzyme preparation," in *Fundamental and applied scientific research in the development of agriculture in the Far East (AFE-2021). AFE 2021. Lecture notes in networks and systems*. Editors A. Muratov, and S. Ignateva (Cham: Springer), 354, 983–991. doi:10.1007/978-3-030-91405-9_111

Vertiprakhov, V. G., and Ovchinnikova, N. V. (2022). The activity of trypsin in the pancreatic juice and blood of poultry increases simultaneously in the postprandial period. *Front. Physiol.* 13, 874664. doi:10.3389/fphys.2022.874664

Vertiprakhov, V. G., Trukhachev, V. I., and Ovchinnikova, N. V. (2023a). Trypsin cycling in poultry is associated with metabolic regulation. *Front. Physiol.* 14, 1226546. doi:10.3389/fphys.2023.1226546

Vertiprakhov, V. G., Selionova, M. I., and Malorodov, V. V. (2023b). Trypsin as a new marker of metabolism in animals. *Timiryazevsky Biol. J.* 1, 53–58. doi:10.26897/2949-4710-2023-1-53-58

Wang, A. N., Carlos, J., Singh, K. K., Fraser, G. M., and McGuire, J. J. (2022). Endothelium dysfunction in hind limb arteries of male Zucker Diabetic-Sprague Dawley rats. *Biochem. Pharmacol.* 206, 115319. doi:10.1016/j.bcp.2022.115319

Weström, B., Arévalo Sureda, E., Pierzynowska, K., Pierzynowski, S. G., and Pérez-Cano, F. J. (2020). The immature gut barrier and its importance in establishing immunity in newborn mammals. *Front. Immunol.* 11, 1153. doi:10.3389/fimmu.2020.01153

Zamolodchikova, T. S., Shoibonov, B. B., and Tolpygo, S. M. (2016). Local renin-angiotensin system of small intestine. *Eksp. Klin. Gastroenterol.* 12, 97–104.

Zhao, J. H., Dong, L., Shi, H. T., Wang, Z. Y., Shi, H. Y., and Ding, H. (2012). The expression of protease-activated receptor 2 and 4 in the colon of irritable bowel syndrome patients. *Dig. Dis. Sci.* 57 (1), 58–64. doi:10.1007/s10620-011-1827-3

Zhao, P., Metcalf, M., and Bunnett, N. W. (2014). Biased signaling of protease-activated receptors. *Front. Endocrinol. (Lausanne)* 5, 67. doi:10.3389/fendo.2014.00067