Academia Open
Vol. 11 No. 1 (2026): June
DOI: 10.21070/acopen.11.2026.13310

Academia Open

By Universitas Muhammadiyah Sidoarjo

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol. 11 No. 1 (2026): June
DOI: 10.21070/acopen.11.2026.13310

Table Of Contents

Academia Open
Vol. 11 No. 1 (2026): June
DOI: 10.21070/acopen.11.2026.13310

Originality Statement

The author[s] declare that this article is their own work and to the best of their knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the published of any other published materials, except where due acknowledgement is made in the article. Any contribution made to the research by others, with whom author[s] have work, is explicitly acknowledged in the article.

Conflict of Interest Statement

The author[s] declare that this article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright Statement

Academia Open
Vol. 11 No. 1 (2026): June
DOI: 10.21070/acopen.11.2026.13310

EDITORIAL TEAM

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol. 11 No. 1 (2026): June
DOI: 10.21070/acopen.11.2026.13310

Article information

Check this article update (crossmark)

Check this article impact (*)

Save this article to Mendeley

(*) Time for indexing process is various, depends on indexing database platform

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol. 11 No. 1 (2026): June
DOI: 10.21070/acopen.11.2026.13310

Alterations in the Adaptation of Pancreatic Enzymes to Food Quality under the Influence of Hexachlorocyclohexane and Tetramethylthiuram Disulfide

Babadjanova F.A., babadjanovaf68@gmail.com,(1)
Department of Pharmacology, Normal and Pathological Physiology, Tashkent State Medical University, Uzbekistan
Askaryants V.P., vera_petrovna_56@mail.ru,(2)
Department of Pharmacology, Normal and Pathological Physiology, Tashkent State Medical University, Uzbekistan
Yunusov A.A., babadjanovaf68@gmail.com,(3)
Department of Pharmacology, Normal and Pathological Physiology, Tashkent State Medical University, Uzbekistan

(1) Corresponding author

Abstract

General Background: The pancreas demonstrates adaptive capacity to modify enzymatic secretion in response to dietary composition, a mechanism essential for efficient nutrient hydrolysis and metabolic homeostasis. **Specific Background:** Organochlorine pesticides, particularly hexachlorocyclohexane (HCH) and tetramethylthiuram disulfide (TMTD), have been associated with digestive system disorders, yet their effects on pancreatic enzymatic adaptation and intestinal enzyme-forming function remain inadequately characterized. **Knowledge Gap:** The extent to which chronic pesticide exposure disrupts the pancreas's ability to adapt enzyme secretion to qualitative changes in food composition, and how these compounds affect small intestinal hydrolytic capacity, has not been systematically investigated. **Aims:** This study examined the effects of chronic HCH (1/20 LD_{50} for 30 days) and TMTD (1/20 LD_{50} for 60 days) exposure on pancreatic enzymatic adaptation to protein-rich and fat-rich dietary stimuli in rats, alongside assessment of small intestinal enzyme-forming function. **Results:** Control animals exhibited adaptive increases in protease activity following protein intake and lipase activity following fat intake within intestinal chyme; HCH exposure delayed these adaptive responses, whereas TMTD completely abolished pancreatic enzymatic adaptation to food quality, with both pesticides significantly suppressing intestinal enzyme activities. **Novelty:** This investigation provides the first systematic evidence that organochlorine pesticides disrupt both pancreatic adaptive mechanisms and intestinal hydrolytic enzyme function in a dose-dependent and time-dependent manner. **Implications:** These findings indicate that pesticide exposure compromises digestive efficiency through dual mechanisms affecting pancreatic regulation and intestinal enzymatic capacity, potentially contributing to metabolic dysfunction in exposed populations.

Keywords : Pancreatic Enzyme Adaptation, Hexachlorocyclohexane Toxicity, Tetramethylthiuram Disulfide, Intestinal Enzyme Function, Organochlorine Pesticide Effects

Highlight :

- Chronic HCH exposure delays pancreatic adaptive response to dietary protein and fat stimuli.
- TMTD completely abolishes enzymatic adaptation mechanisms in exocrine pancreatic secretion regulation.
- Organochlorine pesticides suppress intestinal enzyme activity while paradoxically increasing mucosal amylase levels.

Published date: 2026-01-21

Academia Open
Vol. 11 No. 1 (2026): June
DOI: 10.21070/acopen.11.2026.13310

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol. 11 No. 1 (2026): June
DOI: 10.21070/acopen.11.2026.13310

Introduction

At present, the majority of researchers believe that the pancreas possesses a pronounced ability to adapt the enzymatic composition of its secretion to the qualitative characteristics of food intake. This adaptive capacity of the pancreas represents an important mechanism ensuring efficient hydrolysis of dietary substrates and manifests itself in a selective increase in the secretion of enzymes corresponding to the predominant nutrient component of the diet. Alterations in this adaptive response may be regarded as a highly sensitive indicator of disturbances in the exocrine function of the pancreas [1].

The available data on the effects of hexachlorocyclohexane (HCH) and tetramethylthiuram disulfide (TMTD) on basal pancreatic secretion do not provide sufficient insight into changes in the adaptability of pancreatic enzymes to food quality under exposure to these compounds. To clarify this issue, it was necessary to investigate the activity of pancreatic enzymes in the small intestinal chyme and pancreatic tissue homogenates at defined time intervals following the administration of various dietary stimuli to experimental animals [2].

In the present study, pesticides were administered at a single dose equivalent to 1/20 of the LD_{50}. Rats received HCH for 30 days and TMTD for 60 days. The selection of these exposure periods was based on the results of previous studies demonstrating significant alterations in pancreatic exocrine secretion within the specified time frames [3]. In animals from these experimental groups, the adaptive response of the pancreas to high-protein and high-fat dietary stimuli was evaluated by determining the activity of lipase, proteases, and amylase in pancreatic homogenates and intestinal chyme under fasting conditions and at 1, 2, and 3 hours after feeding the rats 3 g of raw meat or butter [4].

In control animals, changes in enzyme activity within the pancreatic homogenates following the administration of dietary stimuli did not exhibit an adaptive pattern. In contrast, shifts in enzyme activity observed in the intestinal chyme could be interpreted as adaptive responses. Specifically, after administration of a protein-rich stimulus, control animals demonstrated a predominant increase in protease activity in the chyme. Under fasting conditions, proteolytic activity was 680 ± 10 units, while 1, 2, and 3 hours after feeding it increased to 2270 ± 10, 2720 ± 330, and 2270 ± 10 units, respectively [5].

A preferential increase in lipase activity in the chyme was observed following fat administration. Fasting lipase activity was recorded at 140 ± 10 units, whereas 1, 2, and 3 hours after feeding it reached 340 ± 20, 470 ± 30, and 240 ± 30 units, respectively. The activity of other enzymes increased to a lesser extent and returned to baseline levels during the course of the experiment [6].

In rats treated with HCH, a delayed adaptive increase in protease and lipase activity in the intestinal chyme was observed following the administration of the corresponding dietary stimuli [7]. Proteolytic activity increased only by the end of the second hour of the experiment, whereas lipolytic activity rose during the third hour.

Administration of TMTD resulted in complete suppression of the adaptive pancreatic response to the qualitative composition of food stimuli. Throughout the entire experimental period, no increase in the activity of the corresponding enzymes in the intestinal chyme was observed either after protein or fat feeding. Thus, HCH and TMTD, in addition to causing significant alterations in spontaneous pancreatic secretion, disrupt the enzymatic adaptation of the pancreas to food intake. This impairment was more pronounced during the initial, complex reflex phase of secretion, suggesting that these compounds exert their effects on the pancreas primarily through neural regulatory mechanisms [8].

Methadology

The experiments were carried out on adult laboratory rats (both sexes), kept under standard vivarium conditions with free access to water and a standard laboratory diet. Animals were housed at controlled temperature (20–22 °C) and a 12:12 h light–dark cycle. All experimental procedures were conducted in accordance with generally accepted principles of laboratory animal care and use.

Hexachlorocyclohexane (HCH) was used in a purified form containing 96% of the γ-isomer. Tetramethylthiuram disulfide (TMTD) was obtained in analytical-grade purity. The compounds were administered in doses calculated as fractions of the median lethal dose (LD_{50}), based on toxicological data from previous studies.

Animals were divided into control and experimental groups.

In the chronic exposure experiments, rats received HCH at a dose of 1/20 LD_{50} for 30 days or TMTD at a dose of 1/20 LD_{50} for 60 days.

In additional series, HCH was administered at doses of 1/3 LD_{50} (single administration) and 1/50 LD_{50} (long-term exposure up to six months) to assess dose-dependent and time-dependent effects.

To evaluate the adaptive capacity of pancreatic enzyme secretion to food quality, enzyme activity was determined under fasting conditions and after administration of specific dietary stimuli. After an overnight fast, rats were fed 3 g of either raw meat (protein-rich stimulus) or butter (fat-rich stimulus). Animals were sacrificed at 1, 2, and 3 hours after feeding.

Pancreatic tissue homogenates and small-intestinal chyme samples were collected for biochemical analysis. The activity of lipase, proteases, and amylase was measured using standard enzymological methods. Enzyme activity was expressed in conventional units and analyzed as indicators of adaptive pancreatic response to qualitative changes in diet.

The functional state of the small intestine was assessed by determining the mass of the mucosal scraping from the entire small intestine and measuring enzyme activity in mucosal homogenates. The following enzymes were analyzed:

Enzyme activity was calculated both per 1 g of raw mucosal mass (specific activity) and for the total mass of the mucosa (total activity). This approach allowed assessment of both enzymatic capacity and structural-functional changes in the intestinal mucosa.

For chronic exposure experiments, measurements were performed at multiple time points (15, 30, 60, 120, and 180 days) to track the dynamics of enzymatic and morphological changes. In recovery experiments, enzymatic activity was evaluated 30 days after cessation of pesticide administration. All data were expressed as mean ± standard error of the mean (M ± m). Statistical significance of differences between control and experimental groups was assessed using standard parametric methods. Differences were considered statistically significant at $p \leq 0.05$.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol. 11 No. 1 (2026): June
DOI: 10.21070/acopen.11.2026.13310

Results and Discussion

The Effect of Pesticides on the Enzyme-Forming Function of the Small Intestine

Dietary substances undergo only limited chemical processing in the stomach. Their hydrolysis is carried out mainly in the small intestine, where the absorption of the resulting products takes place. The breakdown of high-molecular-weight compounds into smaller fragments in the lumen of the small intestine is ensured by pancreatic enzymes. The final stages of hydrolysis are performed by intestinal enzymes located on the surface of enterocyte membranes and, in part, intracellularly. At present, more than two dozen enteral enzymes have been identified [9]. However, to characterize the physiological state of the small intestine under various conditions, the most commonly studied enzymes are enterokinase, peptidases, monoglyceride lipase, alkaline phosphatase, disaccharidases, and amylase enzymes involved in the digestion of the main dietary components: proteins, fats, and carbohydrates [10].

The intestinal mucosa is a highly metabolically active structure. Its complete renewal in different animal species occurs within 36-144 hours. Therefore, toxic chemicals whose primary mechanism of action in warm-blooded organisms involves interference with metabolic processes should exert a noticeable effect on the functions of the small intestine [11].

Changes in the activity of small-intestinal enzymes under the influence of organochlorine pesticides. Researchers studying the health status of individuals working with organochlorine pesticides have reported frequent disorders of the digestive system. However, these studies provide no information on pesticide-induced changes in the small intestine [12]. Animal experiments have shown that acute poisoning leads to catarrhal inflammation, most pronounced in the upper sections of the small intestine. Extensive areas of mucosal necrosis may also develop. Chronic exposure of animals to hexachlorocyclohexane (HCH) has been associated with thickening of the small-intestinal wall and epithelial desquamation.

Our experiments demonstrated that HCH causes significant alterations in the enzyme-forming function of the small intestine both after a single administration of relatively high doses and during chronic exposure to low doses [13].

In experiments conducted on rats, the functional state of the small intestine was assessed by measuring the mass of the scraping of the entire small-intestinal mucosa and the activity of the main enzymes in its homogenate: monoglyceride lipase (according to the method of A.M. Ugolev and M.Yu. Chernyakhovskaya), glycyl-valine dipeptidase (according to A.M. Ugolev and N.M. Timofeeva), alkaline phosphatase (Bodansky method), amylase (A.M. Ugolev method), and invertase (A.M. Ugolev and N.N. Iezuitova method). A purified preparation of HCH containing 96% of the gamma isomer was used in the experiments. The activity of the enzymes (monoglyceride lipase, glycyl-valine dipeptidase, alkaline phosphatase, amylase, and invertase) was calculated per 1 g of raw mucosal scraping mass (“specific activity”) and for the total mass of the mucosa (“total activity”).

Twenty-four hours after a single administration of a relatively high dose of HCH (1/3 LD_{50}), a slight decrease in the mass of the small-intestinal mucosal scraping was observed. In experimental rats, it amounted to 2.63 ± 0.07 g compared with 3.00 ± 0.05 g in control animals. The mass of the small-intestinal mucosa depends mainly on two processes: the rate of formation of new enterocytes from crypt cells and the intensity of their shedding from the villi. Taking into account the possible enhancement of epithelial desquamation under the influence of HCH, it can be assumed that the reduction in mucosal scraping mass observed in our experiments is associated with intensification of this process [14].

At the same time, a decrease in the activity of intestinal enzymes was noted: monoglyceride lipase by 27%, glycyl-valine dipeptidase by 37%, invertase by 30%, and alkaline phosphatase by 31% (Table). As a result of the reduction in mucosal mass, the total enzyme activity decreased to an even greater extent by 36%, 44%, and 40%, respectively. In contrast, amylolytic activity increased sharply: specific activity increased 5.7-fold, while total activity increased fivefold.

Table 1. Specific and Total Enzyme Activities in the Small-Intestinal Mucosa of Rats 24 Hours after a Single Administration of Hexachlorocyclohexane (HCH) at a Dose of 1/3 LD_{50} (M ± m)

Enzyme	Specific activity (Experimental)	Specific activity (Control)		Total activity (Experimental)	Total activity (Control)	P
Monoglyceride lipase	5.82 ± 0.19	7.99 ± 0.36	0.001	15.99 ± 1.16	2 4.96 ± 1.84	0.002
Glycyl-valine dipeptidase	7.13 ± 0.82	1 1.26 ± 0.76	0.01	18.26 ± 2.35	3 3.83 ± 2.42	0.001
Invertase	22.23 ± 0.86	3 1.53 ± 2.60	0.01	58.43 ± 2.67	9 4.09 ± 6.73	0.001
Alkaline phosphatase	5.70 ± 0.26	8.27 ± 0.52	0.001	14.96 ± 0.78	2 4.74 ± 1.65	0.001

Academia Open
Vol. 11 No. 1 (2026): June
DOI: 10.21070/acopen.11.2026.13310

Enzyme	Specific activity (Experimental)	Specific activity (Control)		Total activity (Experimental)	Total activity (Control)	P
Amylase	199.75 ± 19.77	3 4.88 ± 7.86	0.001	529.5 0 ± 54.72	1 05.09 ± 24.16	0.001

Amylolytic activity of the small-intestinal mucosa is determined by pancreatic α-amylase adsorbed onto the surface of enterocytes from the intestinal chyme, as well as by γ-amylase synthesized directly by the enterocytes themselves. Administration of hexachlorocyclohexane (HCH) at a dose of 1/3 LD_{50} suppresses pancreatic amylase secretion. Therefore, the increase in amylolytic activity of the small-intestinal mucosal homogenate observed after HCH administration may be explained either by enhanced synthesis of intestinal γ-amylase or by increased stability of α-amylase binding to the enterocyte membrane. The reduction in the activity of intrinsic intestinal enzymes is evidently associated with inhibition of their synthesis within intestinal cells [15].

Prolonged administration of HCH at a dose of 1/20 LD_{50} made it possible to trace long-term changes in the enzyme-forming function of the small intestine. This dose also led to a decrease in the mass of the small-intestinal mucosal scraping. On the 15th and 30th days of the experiment, mucosal mass decreased by 27%, and by the 60th day by 30%. At later stages of observation (120–180 days), differences in mucosal mass between experimental and control rats were minimal. Due to the reduction in mucosal mass, total enzyme activity decreased to a greater extent than specific activity. Thus, on the 15th, 30th, and 60th days, monoglyceride lipase activity calculated per 1 g of mucosal scraping decreased by 31%, 21%, and 23%, respectively, whereas activity calculated for the entire mucosal mass decreased by 49%, 42%, and 47%. By the fourth and sixth months of the experiment, indices of lipolytic activity had recovered.

Glycyl-valine dipeptidase activity in experimental animals declined from the 15th day until the end of the fourth month of HCH administration. On day 15, specific dipeptidase activity decreased by 17% and total activity by 39%. One month after the start of exposure, these reductions reached 28% and 47%, respectively; after two months, 29% and 51%; and after four months, 13% and 17%. By the sixth month, dipeptidase activity in experimental animals did not differ from that of controls.

Invertase activity was reduced at all time points examined. After 15 days of exposure, activity of this enzyme was suppressed by approximately one third, while its total reserve decreased by nearly half. These reductions progressed, reaching a maximum by the end of the second month, when activity decreased by about 69%. From the fourth to the sixth month, a partial tendency toward recovery of invertase activity was observed; however, it remained lower than control values—by nearly 50% at the end of the fourth month and by about 20% at the sixth month.

Indices of alkaline phosphatase activity, similar to those of invertase, were decreased throughout the entire experiment, with reductions in total activity being more pronounced than those in specific activity.

Changes in amylolytic activity exhibited a wave-like pattern. By the 15th day of exposure, specific and total amylase activities decreased by 40% and 55%, respectively. One month after the beginning of the experiment, amylolytic activity in experimental rats did not differ from control values, whereas by the second month maximal suppression of amylase activity was observed. From the fourth month onward, both specific and total amylase activities increased compared with the two-month values but remained on average 47% below control levels. By the sixth month, amylase activity increased sharply and significantly exceeded control values.

Assessment of the enzyme-forming function of the small intestine 30 days after cessation of HCH administration revealed no marked differences between experimental and control animals.

Long-term administration of HCH at a dose of 1/50 LD_{50} for one month resulted in a 22% increase in the mass of the small-intestinal mucosa in experimental animals. From the end of the second month, mucosal mass began to decline and by the end of the fourth month had decreased by 18%. By the end of the six-month experiment, mucosal mass in experimental and control animals was similar.

At a dose of 1/50 LD_{50}, HCH did not produce significant changes in lipolytic activity, while the total mucosal reserve of this enzyme varied over time in accordance with changes in mucosal mass. One month after the start of administration, total monoglyceride lipase activity exceeded control values by 27%, whereas after two and four months it was 15% and 23% lower than control, respectively. By the sixth month, the total monoglyceride lipase content in the intestinal mucosa of experimental and control rats was nearly identical.

Glycyl-valine dipeptidase activity, both per unit mass and in the entire mucosa, began to increase from the 15th day of exposure. After one month, specific dipeptidase activity exceeded control levels by 39%, and total activity due to both increased specific activity and increased enterocyte mass rose by 73%. After two months, dipeptidase activity in experimental animals did not differ from controls. By the end of the experiment (fourth and sixth months), dipeptidase activity decreased by approximately 18%. The total mucosal reserve of this enzyme was markedly reduced by the fourth month (by 31%) as a result of simultaneous decreases in specific activity and mucosal mass. By the sixth month, a tendency toward recovery was observed, although control levels were not reached.

Invertase activity increased one month after the beginning of exposure: specific activity by 35% and total activity due to increased specific activity and mucosal mass by 64%. After two months, these indices declined, and by the fourth month reductions reached 46% for specific activity and 56% for total activity. At six months, invertase activity increased relative to the four-month level but remained on average 30% below control values.

Alkaline phosphatase activity decreased only at later stages of the experiment by 35% at four months and by 17% at six months. The

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

total mucosal reserve of this enzyme changed in a pattern similar to that of total invertase activity: one month after HCH administration, total alkaline phosphatase activity increased by 35%, then began to decline after two months; by the fourth month it increased again but did not reach control values.

At early stages of exposure (15 days, 1 and 2 months), amylolytic activity did not change. By the fourth month, a marked decrease in amylase activity (by 47%) and in its total mucosal reserve (by 57%) was observed. By the sixth month, both specific and total amylase activities increased sharply, by approximately 170% each.

One month after cessation of HCH administration at a dose of 1/50 LD_{50}, enzymatic activity and intestinal mucosal mass in experimental and control rats were practically identical.

Conclusion

Summarizing the experimental findings on the effects of hexachlorocyclohexane (HCH) on the hydrolytic function of the small intestine, it can be concluded that a characteristic feature of its action is the suppression of enteral enzyme activity. An exception is amylase, whose activity increases when the compound is administered in relatively low doses by the end of the observation period, as well as after a single administration of a comparatively high dose.

References

1. G. F. Korotko, Pancreatic Secretion. Krasnodar, Russia: Kuban State Medical University Press, 2005, p. 312.
2. T. L. Mastracci and L. Sussel, “The endocrine pancreas: Insights into development, differentiation, and diabetes,” Wiley Interdisciplinary Reviews: Membrane Transport and Signaling, vol. 1, no. 5, pp. 609–628, 2012, doi: 10.1002/wdev.44.
3. A. M. Gorbacheva and N. V. Zaitseva, “Diabetes mellitus, chronic pancreatitis, and primary hyperparathyroidism: Is there a link?” Diabetes Mellitus, vol. 22, no. 4, pp. 392–398, 2019, doi: 10.14341/DM9952.
4. S. A. Sayed and S. Mukherjee, “Physiology, pancreas,” in StatPearls. Treasure Island, FL, USA: StatPearls Publishing, 2021.
5. S. V. Koleshko and R. E. Lis, “Modeling pathological processes in the pancreas that closely resemble clinical practice,” Journal of GrSMU, no. 2 (26), pp. 159–162, 2009.
6. World Health Organization, Global Report on Diabetes. Geneva, Switzerland: World Health Organization, 2018, p. 88.
7. S. Yu. Kontsevaya, “Pathophysiological aspects of the development of alloxan-induced diabetes mellitus in rats in experimental conditions,” Modern Problems of Science and Education, no. 5, pp. 12–15, 2015.
8. A. M. Ugolev and N. N. Timofeeva, “Determination of amylolytic activity,” in Investigation of the Digestive System in Humans. Leningrad, USSR: Nauka, 1969, pp. 187–192.
9. E. Yu. Lomakina, O. V. Taratina, and E. A. Belousova, “Chronic pancreatitis and diabetes mellitus: A review of the literature,” Diabetes Mellitus, vol. 22, no. 4, pp. 525–534, 2019.
10. S. Tani, H. Itoh, Y. Okabayashi, et al., “New model of acute necrotizing pancreatitis induced by excessive doses of arginine in rats,” Digestive Diseases and Sciences, vol. 35, no. 3, pp. 367–374, 2006.
11. N. P. Dmitrenko, T. O. Kishko, and S. Shandrenko, “Arginine: Biological effects and influence on nitric oxide synthesis,” Ukrainian Journal of Chemotherapy, no. 1–2 (22), 2008.
12. R. Dawra, R. Sharif, P. Phillips, et al., “Development of a new mouse model of acute pancreatitis induced by administration of L-arginine,” American Journal of Physiology – Gastrointestinal and Liver Physiology, vol. 292, pp. G1009–G1018, 2006.
13. T. A. Shaymardonov, “Sayidahmadxo‘ja Siddiqiy-Ajziyning qofiya qo‘llash mahorati,” Yosh Olimlar Axborotnomasi – Vestnik Molodykh Uchenykh, vol. 1, no. 1, pp. 147–152, 2024.
14. P. A. Kholkhojayevich, “Regional Factors, Principles and Directions of Small Business Development”, AJEBM, vol. 8, no. 12, pp. 6178–6186, Dec. 2025.
15. A. M. Ugolev, “Membrane Digestion and Its Role in the Adaptation of Digestive Enzymes,” Physiological Reviews, vol. 55, no. 4, pp. 766–803, 1975, doi: 10.1152/physrev.1975.55.4.766.