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Effects of capsaicin on expression of adipokines in gastrointestinal system of rats

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Capsaicin is a major bioactive compound of hot peppers, with effects such as preventing gastric ulcers and inhibiting gastric acid secretion, and suggested to have mostly beneficial effects in the gastrointestinal system. Adipokines are bioactive proteins that regulate biological processes such as energy homeostasis, glucose and lipid metabolism, appetite and immunity. We aimed to detect the possible effects of orally taken capsaicin on the expression of some adipokines in the digestive tract sections of rats by immunohistochemistry. The control group (n=10) was fed with standard rat chow, while the experimental group (n=10) was fed with chow containing 0.04% capsaicin. For immunohistochemical stain, samples were obtained from the gastric, duodenal and pancreatic tissues of rats. The tissue sections of all groups were stained for adiponectin, leptin, ghrelin, resistin and visfatin. For adiponectin and ghrelin there was no difference between two groups in the duodenum, stomach, and pancreatic tissue. For leptin, staining was more intense in the experimental group in pancreatic tissue, but no difference was observed between the groups in the duodenum or stomach. For resistin, no immune reaction was observed in the duodenum, whereas in the stomach the staining was higher in the experimental group. For visfatin, in duodenum, the immun reaction was more intense in the experimental group. Our findings showed that capsaicin caused some changes in the expression of adiponectin, leptin, ghrelin, resistin and visfatin in the digestive tract. Therefore, it was suggested that capsaicin may affect some functions of adipokines such as appetite, glucose and lipid metabolism regulation.

Keywords: Adipokine, Capsaicin, Duodenum, Immunohistochemistry, Pancreas, Stomach

Capsaicin (C18H27N03), an important active compound derived from the hot red pepper known as *Capsicum annuum* belonging to the *Solanaceae* family, provides a spicy sensation and has been identified for numerous beneficial roles in the human organism, including the treatment of pain[1], inflammation and cancer[2].

The main function of adipose tissue is to store triglycerides under conditions of caloric excess and release them during starvation, to provide mechanical protection of organs and thermoregulation. Adipose tissue is also considered an endocrine organ. Adipose tissue produces various bioactive substances known as peptides, immune molecules and inflammatory molecules, such as adipokines (if produced only by adipose tissue) or adipocytokines (produced mainly by adipocytes but also by other tissues)[3]. Adipokines are proteins that carry cell-to-cell signaling through autocrine, endocrine and paracrine pathways[4]. Adipocytokines play a crucial role in regulating satiety and appetite, fat distribution, insulin secretion and sensitivity, energy expenditure, inflammation, endothelial function, blood pressure, and hemostasis[5,6].

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Leptin, known as the satiety hormone, adiponectin, which increases insulin sensitivity and provides energy homeostasis[7], ghrelin, an endogenous ligand of the growth hormone secretagogue receptor (GHS-R)[8,9], resistin, which is rich in cysteine and plays a regulatory role in adipogenesis[10], pre-B-cell colony-enhancing factor (PBEF, visfatin), a cytokine-like molecule involved in the early phase of B-cell differentiation, are some of these adipocytokines. At the systemic level, adipokines regulate or modulate various biological processes in target organs such as the brain, liver, muscles, vasculature, heart, pancreas and immune system[6,11]. Almost all digestive diseases are associated with altered adipokine profiles[12]. The function, molecular targets and clinical relevance of many adipokines are still unknown.

In our study, we aimed to determine the possible effects of CAP (Capsaicin) on the expression of some adipocytokines (adiponectin, leptin, ghrelin, resistin, visfatin) in the gastric, duodenal, and pancreatic tissues of the digestive system of rats fed with CAP added feed for 2 months by immunohistochemical staining method. By examining these effects, we hope to gain insights into the role of CAP in modulating adipocytokine profiles and its implications for metabolic health.

Material and Methods

Animals

The study was carried out at Bursa Uludag University Experimental Animal Breeding and Research Center and Faculty of Veterinary Medicine, Department of Histology-Embryology. The study material consisted of 20 male Sprague Dawley rats (30-day-old).

The animals were fed *ad libitum* with pelleted rat food, had free access to drinking water, and were kept in an environment with a 12-hour light/ dark cycle, a temperature of 21-23 °C, and a humidity of 50-60%. Pellet feed containing 0.04% CAP was prepared for the experimental group. The rats were divided into two groups as experiment (n=10) fed with capsaicin-containing chow and control (n=10) fed standard rat chow, and fed in separate cages for 60 days. When the rats reached 90 days of age, they were anesthetized with ketamine-xylazine and euthanized by cervical dislocation. All experimental applications in the study were approved by Bursa Uludag University Animal Care and Use Committee (Decision No: 2021-10/02).

Tissue samples collection

Samples were taken from the duodenum, stomach and pancreas tissues of both control and experimental group of rats and fixed in paraformaldehyde solution for 48 hours. Then, they were washed in running tap water. Dehydration was applied in graded alcohols according to the immunohistochemical procedure, and they were made transparent in xylene and embedded in paraffin blocks.

Immunohistochemistry

From the paraffin blocks prepared from duodenum, stomach and pancreas tissues, 4-5µM sections were taken on slides coated with Poly-L-lysine solution. After deparaffinization in xylene, the sections were passed through graded alcohols. Indirect Streptavidin-Biotin Peroxidase immunohistochemical method was applied with specific antibodies to determine the effect on adiponectin, leptin, ghrelin, resistin and visfatin expressions in stomach, duodenum and pancreas tissue sections. Rabbit polyclonal primary antibodies were used in the study. To reveal antigens, preparations were kept in a microwave oven at 700 watts for 3 intervals of 5 minutes each in citrate buffer solution. Sections were then treated with 3% hydrogen peroxide for 10 minutes to eliminate endogenous peroxidase activity. A blocking solution was applied to the tissue and kept at room temperature for 1 hour to prevent nonspecific staining. Preparations were incubated with the primary antibody in a humidity chamber at +4°C overnight. Negative controls were incubated with only the antibody dilution solution overnight. Preparations were then treated with biotinylated secondary antibody and HRP-streptavidin for 20 minutes each. Afterward, they were incubated with 3'3-diamino-benzidine hydrochloride (DAB) chromogen (Cell Signaling, 8059S) under a light microscope and counterstained with Harris hematoxylin. Washing was done with PBS solution 3 times for 5 minutes after each step, and no washing was applied after the blocking step. After nuclear staining, the preparations were washed in tap water, quickly passed through graded alcohols, polished in xylol, and covered with entellan. The antibodies used and their dilutions are as follows: Adiponectin (Bioss, 0471R) 1/400 dilution, Resistin (Bioss, 0795R) 1/250 dilution, Visfatin (PBEF1) (Bioss, 0272R) 1/1000 dilution, Leptin (Bioss, 4604R) 1/500 dilution, Ghrelin (Phoenix, H-031-31) 1/1000 dilution. A biotinylated secondary antibody of Histostatin-Plus Rabbit Primary Kit (Invitrogen, 856743) was used.

Gradation

Two independent observers performed the staining assessment on the tissues. Each observer evaluated and graded the staining intensity in five randomly selected areas of each tissue section. The gradation of positive reaction was assessed as follows, weak (+), normal (++), strong (+++). The slides were viewed with a Nikon ecilipse 80i Microscope-Ds Camera Control Unit DS-L1, and then images were taken.

Results

The expression of 5 different adipokines was examined in the samples taken from 3 different organs of the digestive system (stomach, duodenum, pancreas) of rats in the control and experimental groups using the immunohistochemistry method.

Duodenum

For leptin, adiponectin and ghrelin, moderate staining was observed in crypts and villus epithelial cells in both control and experimental groups. For adiponectin, staining was also detected in some cells in the lamina propria (Fig. 1). For resistin, no staining was observed in either control or experimental groups. For visfatin, staining was again observed in crypts and villus epithelial cells in both groups, with

more intense staining in the experimental group compared to the control group (Table 1 & Fig. 2).

Stomach

For leptin and adiponectin, moderate staining was observed in the cytoplasm of the principal cells in the lower half of the lamina propria in both control and experimental groups (Fig. 3). For visfatin, intense staining was again observed in the cytoplasm of primitive cells in the lower half of the lamina propria in both control and experimental groups. For ghrelin, strong staining was detected in X/A cells with endocrine functions located in the oxyntic glands in the experimental and control groups. For resistin, moderate staining was detected in the cytoplasm of some cells in the lower half of the lamina propria where the gastric glands are located in the experimental group (Fig. 4). In contrast, mild staining was observed in some cells in the lower part of the lamina propria in the control group. The experimental group exhibited a higher level of staining compared to the control group. (Table 1).

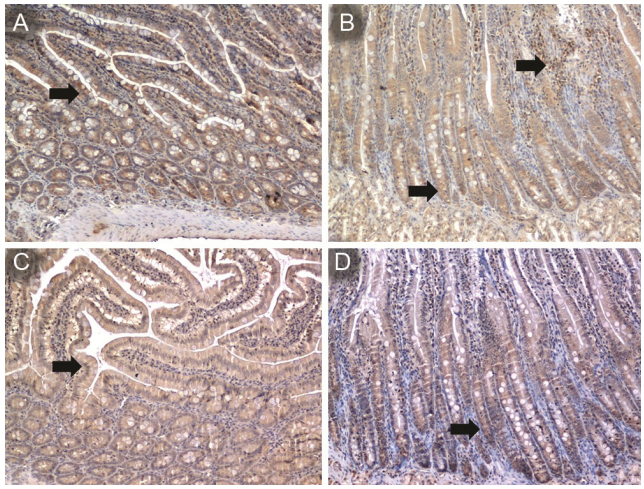

Fig. 1 — Adiponectin and Leptin staining in duodenum (A) Control Group Adiponectin, (B) Experimental Group Adiponectin. Adiponectin-positive cells (arrows). (C) Control Group Leptin, (D) Experimental Group Leptin. Leptin-positive cells (arrows). ×100.

Pancreas

For adiponectin and ghrelin, staining was detected in endocrine cells in islets of Langerhans in the experimental and control groups (Fig. 5 & Fig. 6). The staining intensity was similar in the experimental and control groups and was moderate for adiponectin and weak for ghrelin. For visfatin, strong staining was observed in endocrine pancreatic cells in both experimental and control groups (Fig. 6). For leptin, staining was observed in endocrine islets in both groups, but the degree of staining was more intense in the experimental group than in the control group (Fig. 5). For resistin, mild staining was observed in

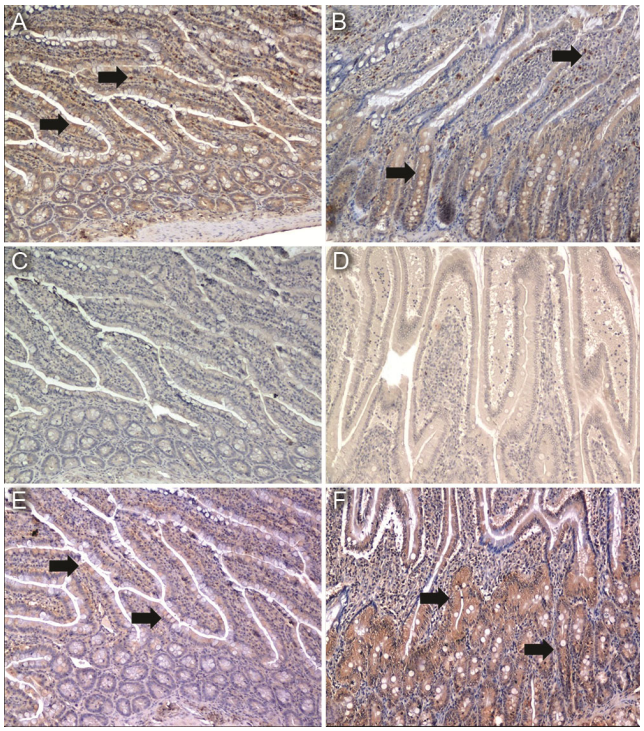

Fig. 2 — Ghrelin, Resistin and visfatin staining in duodenum (A) Control Group Ghrelin, (B) Experimental Group Ghrelin. Ghrelin-positive cells (arrows). (C) Control Group Resistin, (D) Experimental Group Resistin. (E) Control Group Visfatin, (F) Experimental Group Visfatin. Visfatin-positive cells (arrows). ×100.

Table 1 — Intensity of adipokine expression detected by immunohistochemistry in the duodenum, stomach and pancreas tissue of control and experimental groups

Adipokine	Duodenum		Stomach		Pancreas	
	Control group	Experimental group	Control group	Experimental group	Control group	Experimental group
Leptin	++	++	++	++	+	++
Adiponectin	++	++	++	++	++	++
Ghrelin	++	++	+++	+++	+	+
Resistin	-	-	+	++	-	+
Visfatin	+	++	+++	+++	+++	+++

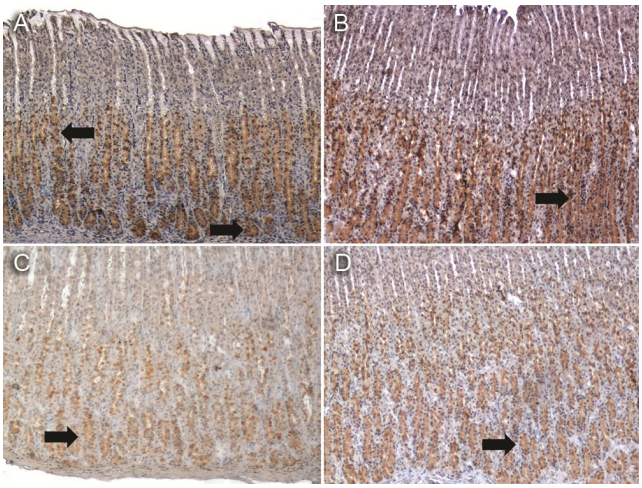

Fig. 3 — Adiponectin and Leptin staining in stomach (A) Control Group Adiponectin, (B) Experimental Group Adiponectin. Adiponectin-positive cells (arrows). (C) Control Group Leptin, (D) Experimental Group Leptin. Leptin-positive cells (arrows). ×100.

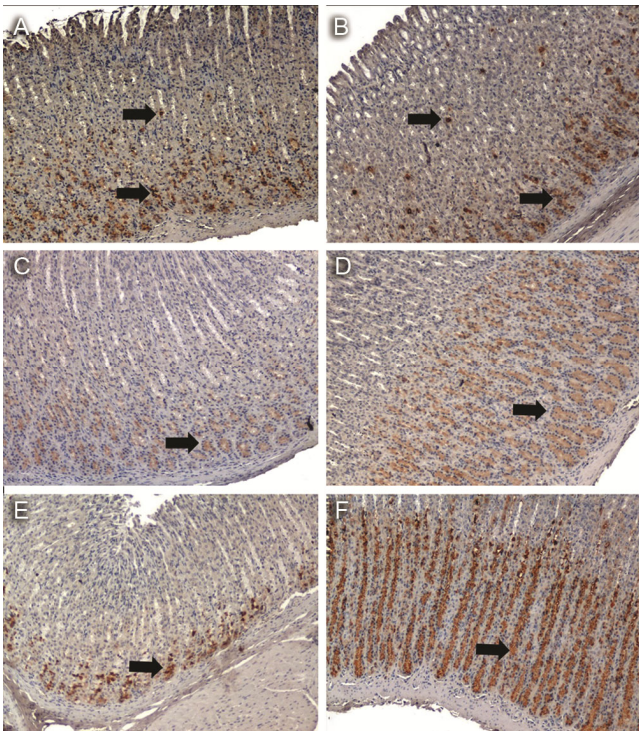

Fig. 4 — Ghrelin, Resistin and visfatin staining in stomach (A) Control Group Ghrelin, (B) Experimental Group Ghrelin. Ghrelin-positive cells (arrows). (C) Control Group Resistin, (D) Experimental Group Resistin. Resistin-positive cells (arrows). (E) Control Group Visfatin, (F) Experimental Group Visfatin. Visfatin-positive cells (arrows). ×100.

the endocrine cells of the islets of Langerhans in the experimental group, while no staining was observed in the control group (Table 1 & Fig. 6).

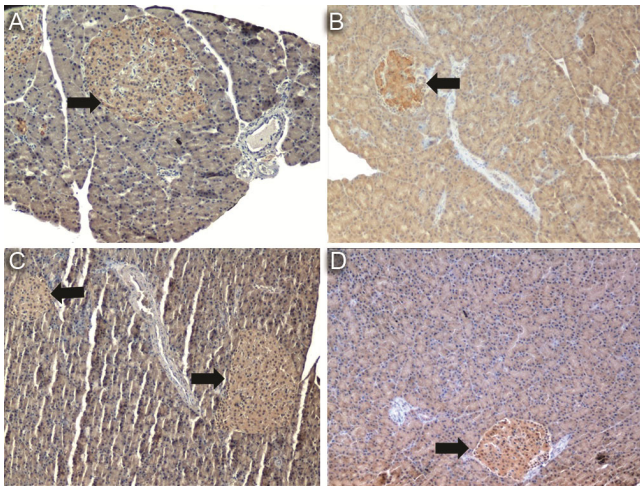

Fig. 5 — Adiponectin and Leptin staining in pancreas (A) Control Group Adiponectin, (B) Experimental Group Adiponectin. Adiponectin-positive islet cells (arrows). (C) Control Group Leptin, (D) Experimental Group Leptin. Leptin-positive islet cells (arrows). ×100.

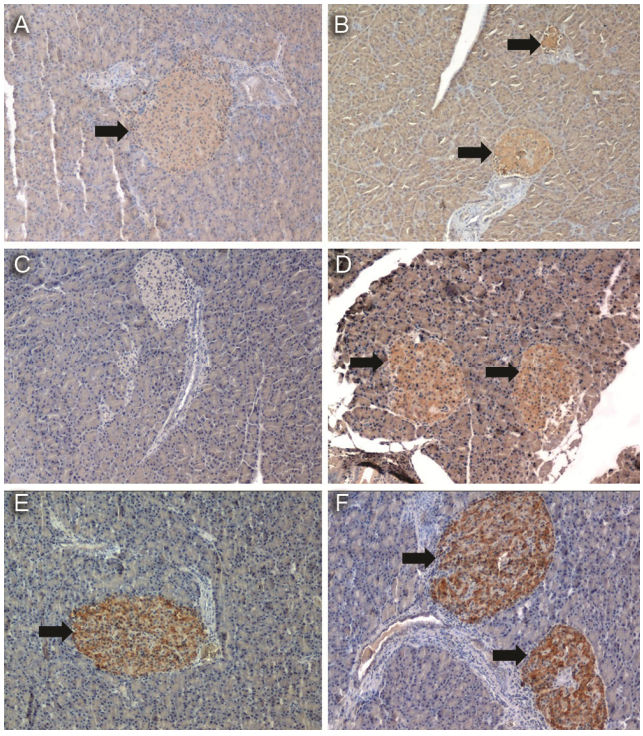

Fig. 6 — Ghrelin, Resistin and visfatin staining in pancreas (A) Control Group Ghrelin, (B) Experimental Group Ghrelin. Ghrelin-positive islet cells (arrows). (C) Control Group Resistin, (D) Experimental Group Resistin. Resistin-positive islet cells (arrows). (E) Control Group Visfatin, (F) Experimental Group Visfatin. Visfatin-positve islet cells (arrows). ×100.

Discussion

CAP, an important active compound derived from red hot peppers and shown to have many beneficial effects in the existing literature, has complex effects

on the gastrointestinal tract. As a selective agonist of TRPV1, capsaicin plays an important role in the regulation of intestinal function in humans. CAP also protects against mucosal damage in the stomach and intestine[13]. A recent study of more than 512,000 adults found that consumption of spicy foods was associated with a lower risk of gastrointestinal cancers, including esophageal, stomach and colon cancer[14]. In a study in rats, CAP has been shown to increase the length and diameter of microvilli in the small intestine, thereby expanding the absorption surface[15].

In our study, resist in expression was not observed in the duodenum of rats fed with normal chow and rats fed with CAP. When we looked at the results of immunohistochemistry for adiponectin, leptin and ghrelin, neither localization nor staining intensity differences were detected between the groups. Accordingly, we can say that CAP at the ratio we used had no significant effect on the expression of these adipokines (adiponectin, leptin, ghrelin) in the duodenum of rats. CAP has been observed to increase glucose absorption from the small intestine in healthy human subjects[16]. However, it has also been reported that glucose absorption within intestine is auto-regulated through reverse and forward mechanisms. Neural reflexes involving capsaicin-sensitive afferent fibers mediate this regulation. These neural reflexes may help defend against hyperglycemia during a meal[17]. Glucose has been reported to increase visfatin levels in adipocytes[18]. Fukuhara *et al*.[19] reported that visfatin plays a physiological role in lowering plasma glucose concentration in mice. In our study, more intense duodenal staining in the experimental group compared to the control group suggests that the effect of visfatin on glucose homeostasis may have increased as a physiological response to capsaicin's increased glucose absorption from the intestines. Since there are no studies on the effects of capsaicin on visfatin in the duodenum, a more comprehensive study in which glucose levels are also examined can be performed to obtain more enlightening information. Considering that the guts are often referred to as the body's second brain and play a significant role in glucose absorption and homeostasis, it is important to note that the effects of visfatin and CAP should be supported by various studies.

In our study, adiponectin, leptin and visfatin expression in the stomach showed staining in pepsinogen-secreting principal (chief) cells in the lower half of the gastric mucosa. This suggests that these adipokines may play a role in the physiology of epithelial cells, including the regulation of pepsinogen and gastric acid secretion. In parallel with previous studies, we found intense staining in X/A cells with endocrine functions for ghrelin. We did not observe any difference in the localization and staining intensity of the other four adipokines (adiponectin, leptin, ghrelin and visfatin) except resistin in the rat stomach between the experimental group and the control group, suggesting that CAP has no effect on these four adipokines in the stomach. In a study conducted in rats, Nogueirasa *et al*.[20] observed intense resistin immunoreactivity in the stomach, mainly in oxyntic and neuroendocrine cells. The fact that resistin expression in the gastrointestinal tract and resistin mRNA levels in adipose tissue vary depending on nutritional status (decreases in fasting and increases in refeeding) suggests that resistin has an important role in maintaining metabolic homeostasis[10,21]. The localization of resistin in neuroendocrine cells of the stomach indicates that resistin may play a role in the regulation of the amine precursor uptake and decarboxylation (APUD) system. Central administration of resistin has been reported to provide short-term satiety in mice[22]. Idrizaj *et al*. [23] reported a significant increase in nNOS expression in myenteric plexus neurons following resistin administration in a study conducted on the fundus of mice. nNOS isoform produces nitric oxide, which has a function in the control of gastrointestinal motility. NO is considered the main inhibitory neurotransmitter responsible for gastric smooth muscle relaxation in both humans and rodents. Adiponectin and resistin have been reported to affect gastric activity and facilitate smooth muscle relaxation by showing inhibitory effects through NO-dependent mechanism in rodents[23-25].

In another study, it was reported that CAP increased the release of CGRP (Calcitonin gene related peptide) and NO neurotransmitters and showed gastric mucosal protection effect as a result of stimulating TRPV1 channels[26]. A human study demonstrated that TRPV1 expression was similar in the gastrointestinal tract of both morbidly obese patients and normal weight subjects. This finding suggests that drugs targeting TRPV1 could be effective for patients with obesity[27]. In rat and dog, CAP has been reported to induce CGRP release and inhibit gastric secretion[28]. In rats administered intragastric CAP, CAP has been proven to induce the

release of nitric oxide, which may be beneficial for gastric mucosal blood perfusion[26]. In our study, the more intense staining of resistin in the CAP-fed experimental group compared to the control group indicates that CAP has a positive effect on resistin expression. Therefore, it was suggested that CAP may act through resistin to increase NO release, relax the fundus muscles and inhibit gastric secretion. When comparing our findings with data from previous studies, it appears that CAP's increase in CGRP release and stimulation of TRPV1 channels may have led to an increase in resistin release. This suggests that CAP's effect on nitric oxide release could be mediated by resistin. The short-term feeling of satiety induced by resistin application might be due to smooth muscle relaxation caused by nitric oxide release, which results in decreased gastric motility. This reduction in gastric motility may lead to appetite suppression and a feeling of fullness. The combined effect of CAP and resistin could potentially offer new approaches to preventing obesity.

When we look at the results of immunohistochemistry in pancreatic tissue of rats, we can say that adiponectin, ghrelin and visfatin were localized in the endocrine pancreas in both control and experimental groups and CAP had no effect on the expression of these adipokines. However, in our study, we found that there were intergroup differences in leptin and resistin. Leptin plays an important role in food intake, lipolysis and body weight control[29]. Leptin regulates the secretion of hormones from the pancreatic islets[30]. Numerous animal studies using different approaches have shown that leptin inhibits insulin gene expression and insulin secretion. Regarding the data on the presence and localization of leptin and its receptor in the endocrine pancreas[31,32], it has been reported that leptin may regulate the function of the endocrine pancreas via possible autocrine action, particularly by changing the membrane potential and secretory activity of alpha (α) and beta (β) endocrine cells[33,32]. The effect of leptin on β cells is an important factor in the regulation of glucose metabolism[33]. For the role of leptin in regulating insulin levels, *in vivo* studies in mice and rats confirm the suppressive function of leptin on insulin secretion[34,35]. In a study on the immunolocalization of leptin and leptin receptors in the equine pancreas, leptin diffuses throughout the pancreatic islets, suggesting that all endocrine cells can secrete this peptide[36]. The role of capsaicin-sensitive nerve fibers in glucose homeostasis was demonstrated in a study in which a delayed recovery of plasma glucose levels was observed following insulin-induced hypoglycemia in capsaicin-treated newborn rats[37]. In our study, we found that leptin was distributed throughout the endocrine cells in the islets of Langerhans in both the control and experimental groups. Leptin staining was more intense in the experimental group than in the control group. This suggests that CAP may enhance the stabilizing effect of leptin on glucose homeostasis by suppressing insulin in the pancreas.

A study in the pancreas of rodents shows that resistin expression occurs specifically in β cells as in all endocrine islets[38]. Another study in humans reported that resistin was found in endocrine cells in the pancreas[39]. Most studies in mice and humans suggest that resistin has a role in insulin resistance and glucose homeostasis. According to the results of immunostaining in pancreatic tissue, resistin expression was not observed in the control group. However, in the experimental group, staining was observed in most cells extending from the center to the periphery of the pancreatic islets, with the exception of a few cells. This widespread distribution of resistin in islet cells indicates its presence in both α and β cells, which are responsible for secreting insulin and glucagon and are the most prevalent in the islets. The localization of resistin in pancreatic tissue suggests it may play a role in glucose homeostasis, as indicated by previous studies. The observed difference in staining between the control and experimental groups in our study suggests that CAP may have increased resistin expression as a result of its effect on insulin.

Our results showed that the localization and possible functions of leptin and resistin in the pancreas are similar. In order to better understand the effects of leptin and resistin on glucose homeostasis in the pancreas, more comprehensive studies at different CAP concentrations are required.

Conclusion

This study shows that the localization and expression of 5 adipocytokines (adiponectin, ghrelin, leptin, resistin, visfatin), which have important roles in many processes in the body and still hold some mysteries. We studied these adipocytokines in three distinct organs (duodenum, stomach, pancreas) that have essential functions. Additionally, we explored the effect of orally administered CAP on these expressions. We showed that CAP increased the expression of visfatin in the duodenum, resistin in the

stomach, and leptin and resistin in the pancreas of rats. Further studies are needed to fully elucidate the unclear roles of these adipokines in duodenal, gastric, and pancreatic tissues and their potential therapeutic benefits

Conflict of interest

The authors have no conflict of interest to declare.

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