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Original research article

Comparison of left side or right side vagotomy in the rat subjected to acute pancreatitis

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ABSTRACT

Purpose: We aimed to evaluate the effects of unilateral vagotomy (right-VR or left-VL) on the severity of caerulein-induced acute pancreatitis (AP).
Material and methods: VR or VL was done in Wistar rats 4 days before AP, except in control, sham operated group. Following 5 h administration of subcutaneous injections of caerulein, the pancreatic blood flow (PBF), serum lipase and IL-10 in caval blood samples were measured. The pancreatic specimens were taken from sacrificed rats for the assessment of MDA-4-HNE and morphology.
Results: PBF decreased from 310 ± 20 ml/min/100 g of tissue in control rats to 130 ± 12 units in AP ($p < 0.01$). VR and VL alleviated this effect to 234 ± 22 and 229 ± 26 units, respectively, ($p < 0.01$). There was an immense increase of serum lipase in AP, from 100 ± 7 U/L up to 5220 ± 210 U/L ($p < 0.01$). Only VL limited this increase to 3469 ± 300 U/L ($p < 0.01$). Serum IL-10 increased uniformly in AP, without any effect of preceding VR or VL. VL performed in rats subjected subsequently to AP resulted in stronger reduction of histological changes, such as pancreatic edema and leukocyte infiltration, than the above parameters in AP rats with VR. MDA + 4-HNE increased from 7.5 ± 0.1 pmol/g of tissue in control group to 30.6 ± 3 units in AP group ($p < 0.01$). Concentration of MDA + 4-HNE in pancreatic tissue achieved 16.48 ± 3 pmol/g after VR and 13.84 ± 4 pmol/g following VL.
Conclusion: Our observation might suggest that protective effect of VL could be stronger than VR in the protection on AP. However changes of PBF seem to be similar in both groups of rats.

1. Introduction

Vagal nerves provide parasympathetic innervation for the main part of the gastrointestinal system, including the pancreas. Most of the vagal fibers (90%) send the afferent signals to the central nervous system, and the remaining 10% of them provide the delivery of descending information from the brain to the gut, being the part of vago-vagal reflex [1–4]. Vagal innervation of the pancreas originates from neurons located in the dorsal nucleus of the brainstem, known as Dorsal Vagal Complex (DVC), which is responsible for central nervous control of pancreatic function [4–8].

Stimulation of vagal nerves increases exocrine and endocrine functions of pancreas, enhances pancreatic blood flow (PBF) and activates gastrointestinal motility [1,3–6,9,10]. Total vagotomy abolished nervous phase of pancreatic and gastric secretion and reduces the intestinal phases of these secretions [9–11].

Acute pancreatitis (AP) is a sterile inflammatory process of the pancreatic gland, which also affects other organs [12]. Pathomechanism of this inflammatory process has not been fully elucidated. One of the commonly accepted hypotheses explains that AP is related to premature activation of digestive enzymes (mainly trypsinogen) in the pancreatic tissue. It is accompanied by the significant reduction of PBF and activation of coagulation and complement systems [12,13]. The inflammatory process leads to the impairment of pancreatic microcirculation and pancreatic edema. Reduction of PBF results in the accumulation of inflammatory mediators in the pancreatic tissue. Toxic substances and metabolic products such as oxygen and nitrogen species (ROS and RNS), platelets activating factor (PAF), nitric oxide (NO) and

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cytokines produce pancreatic cell damage and aggravate inflammatory process in the pancreas [12–15].

Previous reports show that vagal nerves could be implicated in the development of AP, however, controversial observations were published concerning the effects of vagal nerves and vagotomy on the severity of pancreatic inflammation [15,17]. In our previous study, we demonstrated, that bilateral vagotomy alleviated the severity of AP [17]. However, pancreatic innervation originates in the main part, from the left vagal nerve and perhaps the transection of one of the vagal branches could produce different effect from that observed after total vagotomy.

The aim of the present study was to evaluate the effects of transection of a single vagal nerve (left or right) to assess the involvement of each of these vagal branches in the pathogenesis of AP.

In this study we investigated the severity of caerulein-induced pancreatitis in the rats subjected to:

1) vagotomy of right vagal nerve (VR)
2) vagotomy of left vagal nerve (VL)

Serum lipase activity, serum IL-10 concentration, lipid peroxidation products in the pancreatic tissue, PBF and pancreatic morphology were evaluated as indicators of the intensity of inflammatory process in the pancreas.

2. Material and methods

2.1. Materials

The following items were purchased: caerulein from Sigma-Aldrich; St. Louis, USA, lipase from Kodak Ektachem (Eastman Kodak Company; Rochester NY, USA), Vetbutal from Biowet (Puławy, Poland), ELISA IL-6 kit was from R&D systems (Minneapolis MN, USA), ELISA IL-10 kit was from R&D systems (Minneapolis MN, USA), malonylodialdehyde and 4-hydroxynonenal (MDA + 4-HNE) from Bioxytech LPO-586 kit (Oxis International, Inc., Portland, USA).

2.2. Animals and experimental protocol

All procedures were approved by the Jagiellonian University Ethic Committee for Animal Studies (approval number: 138/2014) and performed in accordance with the policies regarding the human care and use of laboratory animals.

The experiments were carried out on 50 male Wistar rats weighting 240–260 g. Animals were kept in a temperature-controlled environment in a 12/12 light/dark cycle, with free access to food and water. Four days before induction of AP vagotomy of a single vagal nerve was performed. The surgery was done under pentobarbital anesthesia (Vetbutal given intraperitoneally at a dose 0.06 g/kg body weight). Animals underwent transection of right or left branch of vagal nerve (two separate groups). During the surgery, abdominal wall was open, stomach was exposed and selective vagotomy was performed by cutting each of vagal nerve branches below the diaphragm (intersection of the anterior and posterior Latarjet's nerve). Sham-operation - the abdominal cavity was open to keep similar condition to vagotomized rats. The surgery procedures were performed under sterile conditions. Disposable gloves and sterilized surgical equipment were used for this procedure.

Four days after vagotomy the study on the rats was performed. Rats were fasted for 24 h prior to the experiments, but access to water was not limited. Animals were divided into 6 separate groups. Half of groups received caerulein to induce AP. The remaining rats received physiological saline, instead of caerulein. Each experimental group consisted of 8 rats, except for the AP group which included 10 rats.

AP was induced by subcutaneous injection of caerulein at total dose of 25 μg/kg (10 injections x 2.5 μg/kg). Caerulein was administrated every 30 min during 5 h. The total volume of injected caerulein solution was 2 ml. Caerulein-induced model of AP used in the study was presented in previously published studies [14,16].

Experimental groups:

1 Control group – rats injected subcutaneously with 0.2 ml of vehicle saline every 30 min (n = 8)
2 Acute pancreatitis group (AP) (n = 10)
3 Vagotomy of right vagal nerve (VR-control) – group of rats subjected to right vagotomy, followed by injection of vehicle saline (n = 8)
4 Vagotomy of right vagal nerve with AP (VR-AP) – group of rats subjected to right vagotomy followed by caerulein injection to produce AP (n = 8)
5 Vagotomy of left vagal nerve (VL-control) – group of rats subjected to vagotomy of left vagal nerve followed by injection with 0.2 ml vehicle saline (n = 8)
6 Vagotomy of left vagal nerve with AP (VL-AP) – group of rats subjected to vagotomy of left vagal nerve followed by caerulein injection to produce AP (n = 8)

Following 5 h administration of caerulein, rats were anesthetized with pentobarbital anesthesia (Vetbutal given at dose 0.06 g/kg body weight). Animals remained under anesthesia during the procedures of measuring PBF, taking blood for evaluation of serum lipase and IL-10, and pancreatitis tissue samples to assess pancreatic morphology and generation of lipid peroxidation products. At the end of experiment rats were sacrificed by cervical dislocation.

2.3. Examination of pancreatic blood flow (PBF)

Measurement of PBF in the rats was performed by laser Doppler flowmeter using Laserflo, model BPM 403 A. To determine the neutral zero, the first measurement was performed on the surface of white tissue paper. Laser emission area was 1 mm^2 and the depth of penetration into the tissue was 3–6 mm. PBF was measured in 5 different regions of the pancreas. Each measurement takes 1 min. The blood flow rate was expressed as ml/min/100 g tissue as a mean value from 5 different areas of the pancreas [18].

2.4. Biochemical parameters

Blood samples were collected from the caval vein to estimate the serum lipase activity and serum concentration of IL-10. The blood samples, were left for 2 h at room temperature for clotting and then centrifuged (at 3500 rpm for 10 min). Serum samples were immediately frozen and kept at −80 °C until analysis. To assess lipase activity we used Lipa DT slides (DT analyzer system) as reported in previous study [18]. Serum concentration of IL-10 was measured by ELISA commercial kit (R&D systems, Minneapolis MN, USA). Determinations were made on the ELx808™ Absorbance Microplate Reader by the Biotek.

2.5. Pancreatic weight and histological examination

Rats were sacrificed by cervical dislocation. The pancreata were carefully dissected, rinsed and weighted. Samples of pancreatic tissue were collected and processed for histopathological assessment. Collected pancreatic samples were cooled on ice and protected from the light. The temperature of rinsing solution was about 10 °C. Pancreatic tissue samples were collected from the main body of the pancreas, located close to the spleen. Histological studies were carried out on pancreatic samples fixed in 10% formalin and stained with hematoxylin and eosin. The slices were examined under light microscopy (magnification 100x) by an expert who was not familiar with the experimental code. The histological changes were scored according to the previous study in 250 fields (5 fields x 50 slices) [18]. The histological grading of edema, neutrophil infiltration and vacuolization changes were assessed using a range from 0 to 3 as previously described (for edema: 0 = no

edema, 1 = interlobular edema, 2 = interlobular edema and moderate intralobular edema, 3 = interlobular edema and severe intralobular edema; for neutrophil infiltration: 0 = no infiltration, 1 = mild perivascular neutrophil infiltration, 2 = moderate perivascular and interlobular neutrophil infiltration, 3 = abundant perivascular inter - and intralobular neutrophil infiltration; for vacuolization: 0 = absent, 1 = less than 25%, 2 = 25–50% and 3 = more than 50% of acinar cells) [18,19].

2.6. Determination of MDA + 4-HNE concentration

Pancreatic tissue samples were taken in order to determine lipid peroxidation products - malonylodialdehyde and 4-hydroxynonenal (MDA + 4-HNE) - as indicators of radical oxygen species (ROS) formation in pancreatic tissue. Samples were homogenized using Homogenizer T 25 Digital Ultra-Turrax according to the procedure and measured using Bioxytech LPO-586 kit (Oxis International, Inc., Portland, USA) as reported previously. MDA + 4-HNE concentration was calculated per gram of pancreatic tissue [18].

2.7. Statistical analysis

Results were expressed as means (n = 8; for AP group: n = 10) ± SEM. Comparison of the differences between the mean values of various groups of experiments was made by analysis of variance or the Student's *t* test for unpaired data and Wilcoxon test for paired data. Differences with a p value of < 0.05 were considered statistically significant.

3. Results

3.1. Pancreatic blood flow

In the control group of rats, PBF amounted to 310 ± 20 ml/min/100 g of pancreatic tissue. Vagotomy of one of the vagal nerves (right or left) did not change the PBF (275 ± 25 ml/min/100 g and 270 ± 12 ml/min/100 g of tissue, respectively).

In the AP animals, PBF was markedly decreased, compared to the normal value, to 130 ± 12 ml/min/100 g. Both types of vagotomy (right or left) performed prior to AP resulted in the increase of this parameter (234 ± 22 ml/min/100 g of tissue and 229 ± 26 ml/min/100 g respectively) as compared to AP rats without vagotomy (Fig. 1).

3.2. Serum lipase activity

In the control animals, mean serum lipase activity was 100 ± 7 U/L. In rats with VL alone (without AP) the lipase activity was slightly decreased, as compared to the control group of rats, and amounted to 86 ± 16 U/L. VR did not change the serum lipase activity (95 ± 6 U/L). In the rats subjected to caerulein overstimulation, serum lipase activity increased up to 5220 ± 210 U/L. In AP rats subjected to VL serum lipase activity was attenuated (3469 ± 300 U/L), while VR did not affect the activity of this enzyme, compared to the group of rats with AP alone (5000 ± 330 U/L) (Fig. 2).

3.3. Serum concentration of IL-10

In the control group, serum concentration of IL-10 was 6 ± 1.8 pg/mL. No visible changes of serum IL-10 concentration after single vagal nerve transection (left or right) were observed. Administration of caerulein to produce AP resulted in the increase of IL-10 serum concentration (14 ± 1.6 pg/mL). Unilateral vagotomy (right or left) performed in rats subjected to AP did not affect serum concentration of this interleukin (right was 14 ± 1.8 pg/mL and left 15 ± 2 pg/mL) as compared to the value measured in rats with AP alone (Fig. 3).

3.4. Pancreatic weight

Mean pancreatic weight in the control group of rats was 850 ± 80 mg. In rats subjected to vagotomy alone (without AP) pancreatic weight was not significantly different from control value. Pancreatic weight of rats subjected to caerulein administration (AP group) increased almost twice as compared to control value (1650 ± 80 mg *vs* 850 ± 80 mg). VL performed in the rats subjected subsequently to AP, resulted in the reduction of pancreatic weight, that was decreased approximately by 40% in this group (1100 ± 100 mg), as compared to the AP group without vagotomy. VR performed prior to the caerulein-induced AP also reduced pancreatic weight (1475 ± 100 mg), compared to the rats with AP alone, but this reduction was less pronounced as compared to the decrease observed after VL (Fig. 4).

3.5. Histological assessment

In control animals, histological evaluation did not reveal any

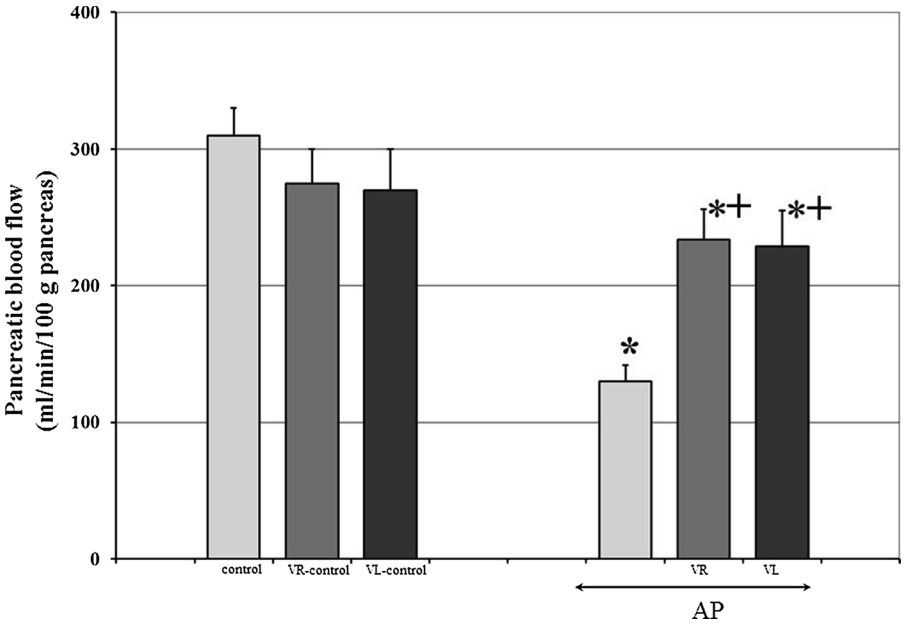

Fig. 1. Pancreatic blood flow in the rats with caerulein-induced acute pancreatitis (AP) with or without unilateral vagotomy. Asterisk (*) indicates decrease ($p < 0.01$) below the values obtained from the control animals. Cross (+) indicates increase ($p < 0.01$) as compared to the values obtained from the rats with caerulein induced AP without vagotomy. Control value was obtained from the rats treated with vehicle saline alone.

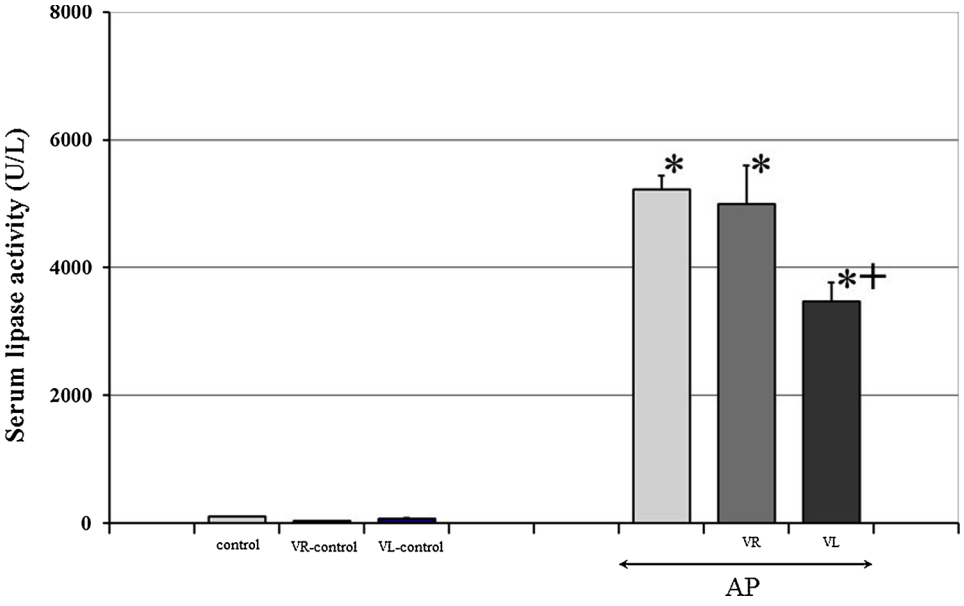

Fig. 2. Serum lipase activity in rats with caerulein-induced acute pancreatitis (AP) with or without unilateral vagotomy. Asterisk (*) indicates rise ($p < 0.01$) as compared to the values obtained from the control animals. Cross (+) indicates decrease ($p < 0.01$) as compared to the values obtained from the rats with caerulein induced AP without vagotomy. Control value was obtained from the rats treated with vehicle saline alone.

indication of inflammation in the pancreatic tissue (edema 0.1 ± 0.1; neutrophil infiltration 0.0 ± 0.0; vacuolization 0.0 ± 0.0). Vagotomy alone (left or right) did not affect pancreatic morphology. In the AP group, pancreatic edema, neutrophil infiltration and vacuolization were observed (edema 2.5 ± 0.5; neutrophil infiltration 2.3 ± 0.4; vacuolization 2.5 ± 0.0). Vagotomy performed in rats subjected then to AP resulted in the marked reduction of all the above mentioned parameters of AP and this alleviation of inflammatory changes in the pancreas was more pronounced in the rats with AP subjected to VL. Vagotomy of vagal nerves (right or left) to AP attenuated pancreatic edema (2.0 ± 0.5 and 1.4 ± 0.5, respectively), neutrophil infiltration (2.1 ± 0.4 and 1.8 ± 0.5, respectively) and vacuolization (2.3 ± 0.4 and 1.7 ± 0.5, respectively) (Table 1; Fig. 5).

3.6. Pancreatic content of MDA + 4-HNE

In the control group of rats, mean concentration of MDA + 4-HNE in the pancreas was 7.5 ± 0.1 pmol/g of pancreatic tissue. No changes in the amount of MDA + 4-HNE after vagotomy (right or left) were observed. In the AP rats, pancreatic MDA + 4-HNE achieved 30.6 ± 3 pmol/g of pancreatic tissue. In the pancreas of vagotomized rats with AP the concentrations of MDA + 4-HNE in pancreatic tissue were decreased compared to the values obtained in rats with AP alone. Concentration of MDA + 4-HNE in pancreatic tissue achieved 16.48 ± 3 pmol/g after VR and 13.84 ± 4 pmol/g following VL (Fig. 6).

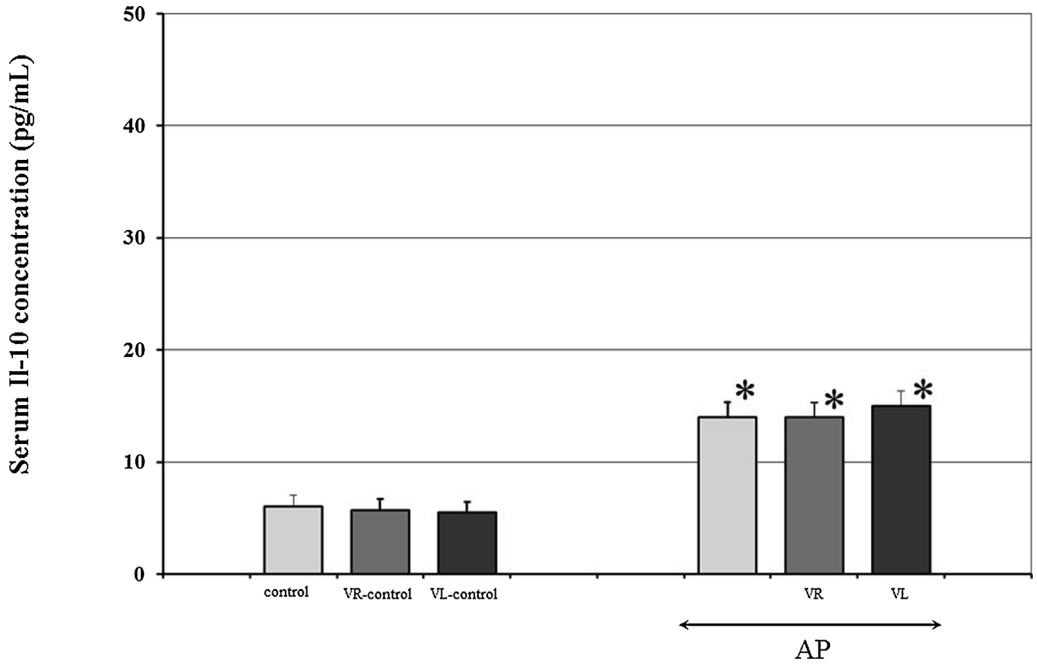

Fig. 3. Serum IL-10 concentration in rats with caerulein-induced acute pancreatitis (AP) with or without unilateral vagotomy. Asterisk (*) indicates increase ($p < 0.01$) comparing to the value obtained from the control animals. Control value was obtained from the rats treated with vehicle saline alone.

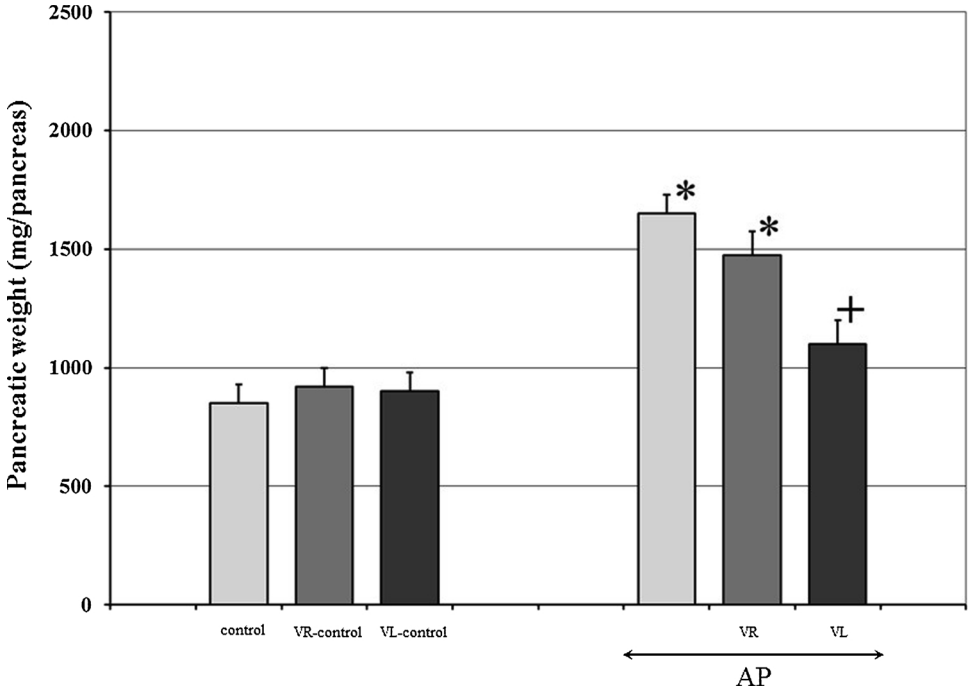

Fig. 4. Pancreatic weight in rats with caerulein-induced acute pancreatitis (AP) with or without unilateral vagotomy. Asterisk (*) indicates increase ($p < 0.01$) as compared to the values obtained from the control animals. Cross (+) indicates decrease ($p < 0.01$) as compared to the values obtained from the rats with caerulein induced AP without vagotomy. Control value was obtained from the rats treated with vehicle saline alone.

Table 1
Morphology of pancreatic tissue taken from rats with caerulein-induced acute pancreatitis (AP) alone, from AP rats with unilateral vagotomy and from control animals (VL – vagotomy of left vagal nerve, VR – vagotomy of right vagal nerve). Asterisk (*) indicates changes ($p < 0.01$) as compared to the values obtained from the control rats. Cross (+) indicates decreases ($p < 0.01$) as compared to the values obtained from the rats with caerulein induced AP without vagotomy. Control value was obtained from the rats treated with vehicle saline alone.

	edema	neutrophil infiltration	vacuolization
control	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
VR-control	0.2 ± 0.0	0.2 ± 0.0	0.0 ± 0.0
VL-control	0.2 ± 0.0	0.1 ± 0.0	0.0 ± 0.0
AP	2.5 ± 0.5*	2.3 ± 0.4*	2.5 ± 0.0*
VR-AP	2.0 ± 0.5*	2.1 ± 0.4*	2.3 ± 0.4*
VL-AP	1.4 ± 0.5*	1.8 ± 0.5*	1.7 ± 0.5*

4. Discussion

Our previous study has shown that bilateral vagotomy significantly reduced the severity of AP induced by caerulein overstimulation. The limitation of pancreatic inflammation was manifested as reductions of pancreatic weight and serum lipase activity, as decrease of MDA + 4-HNE in the pancreatic tissue, whereas PBF and serum IL-10 concentration were increased [17].

As we demonstrate in the present study, the unilateral vagotomy could also contribute to the pancreatic protection. Probable explanation involves reduced secretion of pancreatic enzymes in vagotomized animals, since the secretion of digestive enzymes is dependent on the activation of the cholinergic nervous system. Eliminating one (left or right) vagal nerve reduced the stimulatory, cholinergic drive to the pancreas [17]. The strong reduction of inflammatory changes was observed in the rats with VL. Removing left vagal nerve markedly reduced the intensity of inflammation perhaps due to the prevalence of left vagal nerve in pancreatic innervation and predominance of this vagal branch in the stimulation of pancreas exocrine function.

Transection of vagal nerves in animals subjected subsequently to AP produced attenuation of serum lipase activity increase. Similar results were received by Lugea et al. [20]. But so far, there are no publications showing the effect of unilateral vagotomy on the AP. We also observed a decrease of serum lipase, however, our current study presents the different effects of selective VR or VL. As we have noted, VL produced more pronounced fall of serum lipase activity in the AP rats than did VR. Reduced vacuolization of acinar cells was observed in histopathological examination of pancreas in rats subjected to the left vagal nerve transection followed by AP, comparing to the AP animals with intact vagal nerves. This indicated that eliminating the influence of left vagal nerve on the pancreas alleviated the severity of pancreatic inflammation. Another evidence of reduced process of inflammation was in the decrease of MDA + 4-HNE concentration in the pancreatic tissue of vagotomized rats subjected to AP. This reduction of oxidative stress could probably be due to the increase of PBF in these rats and possibly to the reduced secretory drive to the pancreas. Improvement of PBF that was observed after unilateral transection of vagal nerve (right or left), probably resulted in the washing out of the inflammatory cells and local inflammatory mediators as well as in the partial removal of lipid peroxidation products - MDA + 4-HNE - from the pancreatic tissue of the AP rats.

The anti-inflammatory IL-10 was reported to be increased as the result of pancreatic protection. IL-10 could also be elevated in the AP, as was shown in a previous clinical study [21]. This interleukin peaks within 24 h after the induction of AP and after this time, a decrease in this particle was observed [19,21]. Lin et al. [22] demonstrated that IL-10 induced anti-apoptotic effects affecting the signal transducer and activator of transcription 3 (STAT3). They found that IL-10 attenuated brain microvascular endothelial cells apoptosis. In AP, IL-10 improves the blood brain barrier permeability through strengthening of claudin-5 expression and by the STAT3 pathway-mediated anti-apoptotic effects on brain microvascular endothelial cells.

The opposite effect of vagotomy on the severity of AP was observed by Sun et al. [15] in their study performed on dogs. The authors reported that elimination of the vagal drive to the pancreas aggravated AP, whereas we observed a protective effect of vagotomy. The difference between their results and our present and previous [17] study might be due to the use of different experimental models, since Sun et al. [15] used necrotizing pancreatitis induced by sodium taurocholate in the dogs, whereas our model was edematous caerulein-induced pancreatitis in the rats [15]. In addition they performed

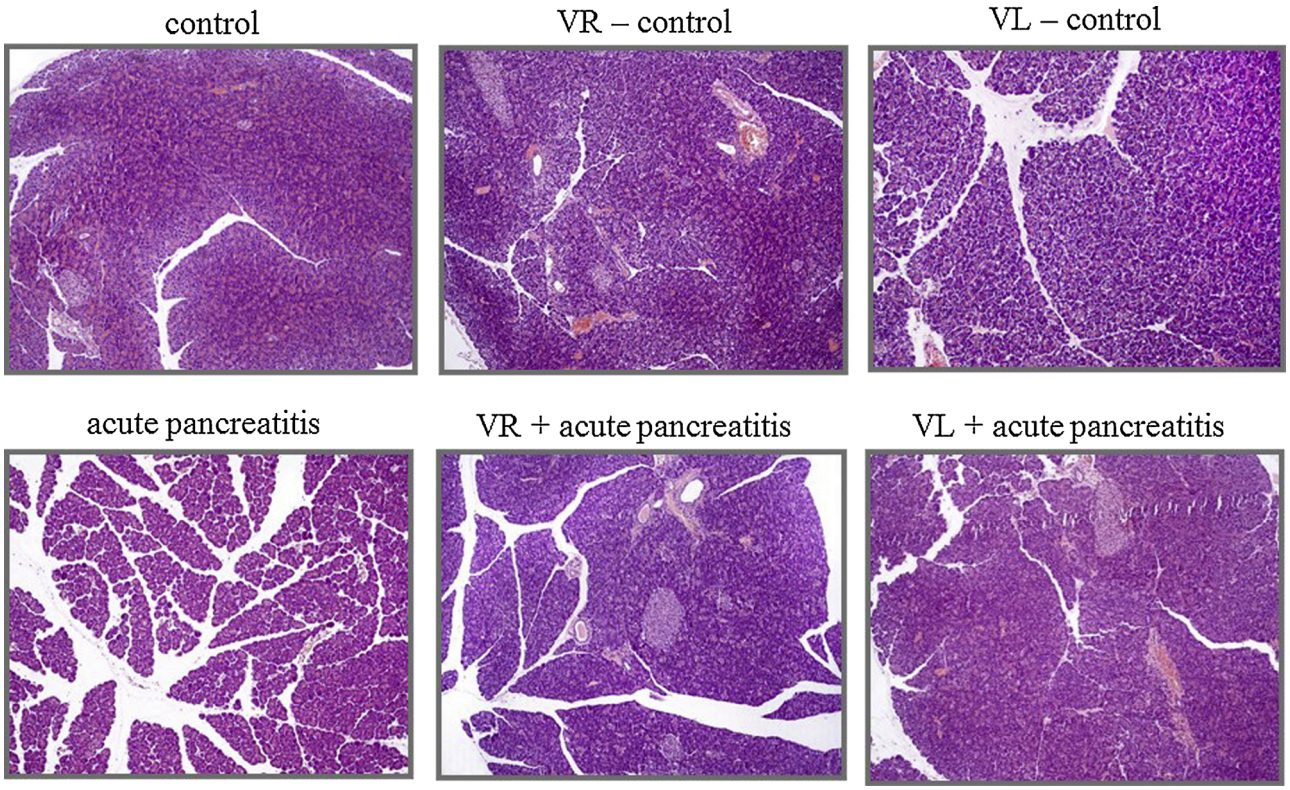

Fig. 5. Histological feature of the pancreatic tissue taken from control group, from group of rats without vagal nerves, from animals with caerulein-induced acute pancreatitis (AP), and from AP rats with unilateral vagotomy (VL – vagotomy of left vagal nerve, VR – vagotomy of right vagal nerve). Hematoxylin and eosin (H&E) stain, magnification 100 × .

vagotomy after induction of AP, whereas in our rat model vagotomy preceded AP and was done 4 days before induction of pancreatic inflammation. Our animals became adapted to vagotomy (looking at PBF) before induction of AP. In the study of Sun et al. [15] AP started just after vagotomy, however they observed that 3 days after vagotomy the inflammation of the pancreas became attenuated. This attenuation of pancreatitis could be possibly due to the adaptation of pancreas to new conditions (vagotomy) and perhaps also due to beginning of pancreatitis resolution. A certain mechanism of adaptation to vagotomy could be observed in our model of AP, regarding PBF, that was not different in vagotomized animals, from that observed in the control, non-vagotomized rats.

In our present study, we observed the significant increase of IL-10 blood level in AP rats, but this increase was relatively small, probably due to the slow dynamic of IL-10 activation and synthesis. Since the blood samples have been taken from the rats 6 h after the induction of caerulein-induced pancreatitis, the rise of this interleukin was not as prominent as could be after 24 h. However, VL produced the small

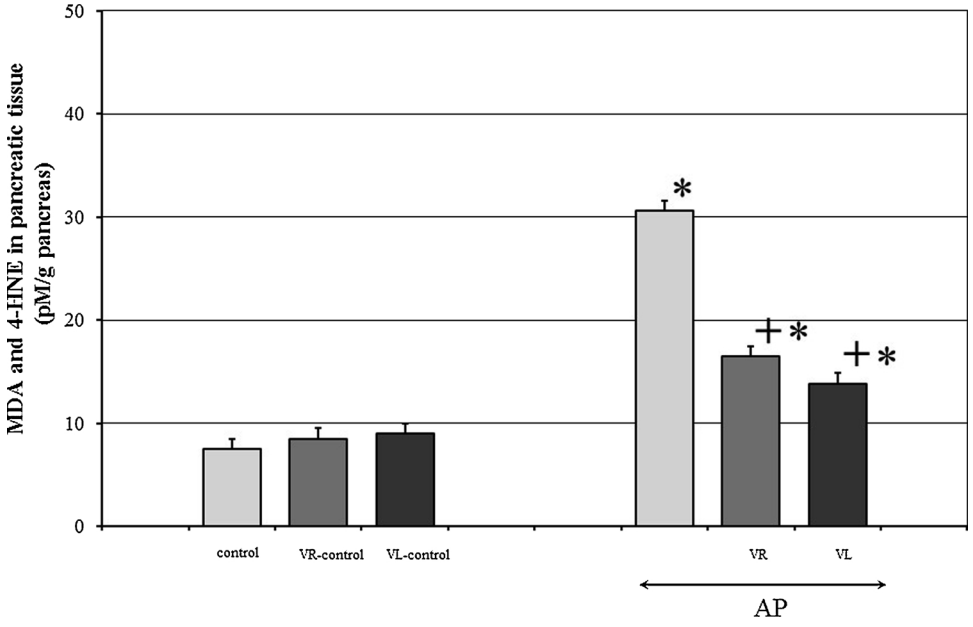

Fig. 6. MDA and 4-HNE concentration in pancreatic tissue taken from the rats with caerulein- induced acute pancreatitis (AP) with or without unilateral vagotomy. Asterisk (*) indicates increase ($p < 0.01$) above the values obtained from the control animals. Cross (+) indicates reduction ($p < 0.01$) below the values obtained from the rats with caerulein induced AP without vagotomy. Control value presents results obtained from the rats treated with vehicle saline alone.

insignificant rise of IL-10, indicating that elimination of the influence of the left vagal nerve on the pancreas resulted in the strengthening of pancreatic defense.

The results of histopathological assessment of pancreatic gland taken from the AP rats subjected to transection of one of the vagal nerves confirmed the weakness of pancreatic inflammation in this gland, that was manifested by attenuated inter- and intra- lobular edema limited neutrophil infiltration and reduced cell vacuolization as compared to the AP rats without vagotomy [17]. In the present study we observed reduced neutrophil infiltration following VL but not VR.

As we suggested in our previous study [17], the limitation of pancreatic enzymes secretion after vagotomy might have a protective effect on the pancreas. The damaging effects of inflammatory mediators on the pancreatic gland were decreased by the improvement of PBF and amelioration of toxic products from the pancreas.

Our present study confirmed and reinforced the observation, that vagotomy has protective effect on AP.

5. Conclusions

We can conclude that the marked attenuation of some inflammatory parameters such as: serum lipase activity, MDA + 4-HNE in pancreatic tissue, pancreatic edema and leukocyte infiltration in the AP rats with VL might suggest that protective effect of VL could be stronger than VR in the protection on AP. However, changes of PBF and IL-10 seem to be similar in the AP rats with VL and VR.

Our previous and present observations could have the impact on the treatment of patients with AP. Inhibition of exocrine pancreatic secretion by pharmacological blockade of cholinergic receptors in these patients could hopefully alleviate the severity of AP.

Conflict of interests

The authors declare no conflict of interests.

Financial disclosure

The authors have no funding to disclose.

The author contribution

Study Design: Joanna Szklarczyk, Jolanta Jaworek
Data Collection: Romana Tomaszewska, Joanna Szklarczyk, Michalina Kot
Statistical Analysis: Zbigniew Śliwowski, Joanna Bonior
Data Interpretation: Joanna Szklarczyk, Jolanta Jaworek
Manuscript Preparation: Jolanta Jaworek, Joanna Szklarczyk
Literature Search: Joanna Szklarczyk
Funds collection: n/a.

References

[1] Singer MV, Niebergall-Roth E. Secretion from acinar cells of the exocrine pancreas: role of enteropancreatic reflexes and cholecystokinin. Cell Biol Int 2009;33(1):1–9.
[2] Tracey KJ. The neurology of the immune system: neural reflexes regulate immunity. Neuron 2009;15;64(1):28–32.
[3] Noble MD, Liddle RA. Neurohormonal control of exocrine pancreatic secretion. Curr Opin Gastroenterol 2005;21(5):531–7.
[4] Pavlov VA, Tracey KJ. Controlling inflammation: the cholinergic anti-inflammatory pathway. Biochem Soc Trans 2006;34(6):1037–40.
[5] Jaworek J, Nawrot-Porąbka K, Leja-Szpak A, Konturek SJ. Brain-gut axis in the modulation of pancreatic enzyme secretion. J Physiol Pharmacol 2010;61(5):523–31.
[6] Nawrot-Porąbka K, Jaworek J, Leja-Szpak A, Szklarczyk J, Konturek SJ, Reiter RJ. Luminal melatonin stimulates pancreatic enzyme secretion via activation of serotonin-dependent nerves. Pharmacol Rep 2013;65(2):494–504.
[7] Viard E, Rogers RC, Hermann GE. Systemic cholecystokinin amplifies vago-vagal reflex responses recorded in vagal motor neurones. J Physiol 2012;590(3):631–46.
[8] Love JA, Yi E, Smith TG. Autonomic pathways regulating pancreatic exocrine secretion. Auton Neurosci 2007;133:19–34.
[9] Sobocki J, Krolczyk G, Herman RM, Matyja A, Thor PJ. Influence of vagal nerve stimulation on food intake and body weight—results of experimental studies. J Physiol Pharmacol 2005;56(6):27–33.
[10] Niebergall-Roth E, Singer MV. Enteropancreatic reflexes mediating the pancreatic enzyme response to nutrients. Auton Neurosci 2006;125(1-2):62–9.
[11] Chandra R, Liddle RA. Recent advances in the regulation of pancreatic secretion. Curr Opin Gastroenterol 2014;30(5):490–4.
[12] Takuma K, Kamisawa T, Hara S, Tabata T, Kuruma S, Chiba K, et al. Etiology of recurrent acute pancreatitis, with special emphasis on pancreaticobiliary malformation. Adv Med Sci 2012;57(2):244–50.
[13] Manohar M, Verma AK, Venkateshaiah SU, Sanders NL, Mishra A. Pathogenic mechanisms of pancreatitis. Word J Gastrointest Pharmacol Ther 2017;8(1):10–25.
[14] Robert A, Lum JT, Lancaster C, Olafsson AS, Kolbasa KP, Nezamis JE. Prevention by prostaglandins of caerulein-induced pancreatitis in rats. Lab Invest 1989;60(5):677–91.
[15] Sun JJ, Chu ZJ, Zhang YM, Qi SF, Chang YC, Xin SY, et al. Beneficial effect of splanchnic nerve transection and harmful effect of vagotomy on acute necrotizing pancreatitis in the dog. Dig Dis Sci 2015;60(1):118–26.
[16] Jaworek J, Szklarczyk J, Jaworek AK, Nawrot-Porąbka K, Leja-Szpak A, Bonior J, et al. Protective effect of melatonin on acute pancreatitis. Int J Inflam 2012(23):173675–82.
[17] Szklarczyk J, Jaworek J, Czech U, Bonior J, Kot M, Tomaszewska R. Bilateral vagotomy attenuates the severity of secretagogue-induced acute pancreatitis in the rat. Adv Med Sci 2014;59(2). 172-17.
[18] Jaworek J, Jachimczak B, Tomaszewska R, Konturek PC, Pawlik WW, Sendur R, et al. Protective action of lipopolysacharides in rat caerulein-induced pancreatitis: role of nitric oxide. Digestion 2000;61(1):1–13.
[19] Andrzejewska A, Długosz JW, Augustynowicz A. Effect of endothelin-1 receptor antagonists on histological and ultrastructural changes in the pancreas and trypsinogen activation in the early course of caerulein-induced acute pancreatitis in rats. World J Gastroenterol 2005;28;11(8):1115–1121.
[20] Lugea A, Gong J, Nguyen J, Nieto J, French SW, Pando SJ. Cholinergic mediation of alcohol-induced experimental Pancreatitis. Alcohol Clin Exp Res 2010;34(10):1768–81.
[21] Wereszczyńska-Siemiatkowska U, Dabrowski A, Siemiątkowski A, Mroczko B, Laszewicz B, Gabryelewicz A. Serum profiles of E-selectin, interleukin-10, and interleukin-6 and oxidative stress parameters in patients with acute pancreatitis and nonpancreatic acute abdominal pain. Pancreas 2003;26(2):144–52.
[22] Lin R, Chen F, Wen S, Teng T, Pan Y, Huang H. Interleukin-10 attenuates impairment of the blood-brain barrier in a severe acute pancreatitis rat model. J Inflamm 2018;27(15):4.