ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN — POLONIA
VOL. LVII, N 1, 33 SECTIO D 2002

Department of Gastroenterology, Medical University of Lublin

MARIUSZ SZCZERBIŃSKI, KRZYSZTOF CELIŃSKI,
MARIA SŁOMKA, BEATA KASZTELAN-SZCZERBIŃSKA,
HALINA CICHOŻ-LACH

Influence of adenosine receptors on the development of caerulein-induced acute pancreatitis

Adenosine is a potent, endogenous proinflammatory factor released by cells under metabolically unfavourable conditions, e.g. hypoxia, ischaemia (13). Reperfusion of ischaemic and hypoxaemic tissues results in locally increased permeability of vessels and organ oedema associated with neutrophil accumulation in microcirculation. The interaction of neutrophils and endothelial cells, on the other hand, leads to microcirculation impairment. Adenosine is involved in the inflammatory reactions by its action on neutrophils and A_2 receptors of the endothelium inhibiting chematoxia, phagocytosis and adhesion of activated leucocytes to the endothelium, decreasing the oxygen free radical release and thrombocyte aggregation and activity (1).

Acute pancreatitis leads to hypoxia – the secondary phenomenon to decreased blood supply of this organ. This, in turn, results in dysfunction of intracellular organelles which may activate lysosomal and digestive enzymes and initiate autodigestion and tissue damage within the pancreas. Leucocytes get activated and expression of adhesive molecules is higher, which enables margination and adhesion of activated leucocytes to the endothelium and, as a result of this, their diapedesis into the inflammatory focus. Activated leucocytes are the source of proinflammatory cytokins and oxygen free radicals intensifying the inflammatory response. Li et al. (11) reported that adenosine and its analogues were likely to prevent partially the activation of the above-mentioned processes during ischaemia in acute pancreatitis.

Adenosine receptors were found in blood vessels (the smooth muscles and endothelium) and in cell membranes involved in the cascade of inflammatory processes, i.e. in the neutrophils, basophils, lymphocytes, mastocytes, macrophages and thrombocytes (13). They mediate the influence of adenosine and its analogues on vasodilatation and modulation of the inflammatory process in acute pancreatitis.

OBJECTIVE

The aim of the study was to determine the influence of the substances acting with adenosine receptors on the development of experimental caerulein-induced acute pancreatitis. The severity of inflammatory processes was assessed on the basis of the plasma amylase activity, pancreatic weight and intensity of histopathological changes in the pancreatic tissue samples.

MATERIAL AND METHODS

The examinations were performed in Wistar, male rats weighing 250-300g in two stages. The first stage was to evaluate the effects of the substances stimulating and blocking adenosine receptors on normal pancreas; the second one assessed the action of these substances in the course of caerulein-induced acute pancreatitis.

In the first stage, the animals were randomly divided into 5 groups: group I – controls receiving only the 12h intravenous infusion of 0.15 M NaCl and groups 2-5 – in which animals were injected intraperitoneally with the substances examined in the following doses: group II – DPCPZ, 1mg/kg, A_1 receptor antagonist: group III – CGS 21680, 1mg/kg, A_2 receptor agonist; group IV – ZM 241385, 3mg/kg, A_2 receptor antagonist; and group V – IB MECA, 0.5mg/kg, A_3 receptor agonist.

In the second stage, the animals were also divided into 5 groups: group I in which acute pancreatitis was induced according to the method of Lampel and Kern (9) by the 12h intravenous infusion of caerulein in the dose of 5μg/kg/h, and groups 2-5 in which identical caerulein infusion was preceded by intraperitoneal injections of the substances studied in the following doses: group II – DPCPX, 1mg/kg, group III – CGS21680, 1mg/kg, group IV – ZM241385, 3mg/kg and group V – IB MECA, 0.5 mg/kg. The samples were collected directly after caerulein or saline infusion.

After the 12h infusion with saline or caerulein, the rats were anaesthetized with ether and weighted. Then, the peritoneal cavity was opened and blood samples collected to determine plasma amylase activities. The pancreas was excised, weighted and tissue samples collected. The pancreatic weight was determined in comparison with the body weight. The amylase activity was expressed in IU.

The statistical analysis was performed using the Student's t and Cochran-Cox tests. The results were presented as average values ± standard variation (SD). The values were statistically significant when $p<0.05$. The histopathological parameters were evaluated in the descriptive manner. The extension of oedema and degrees of leucocyte infiltration and pancreatic cell vacuolization were assessed.

RESULTS

The animals which received the substances examined before the intravenous infusion of 0.15 M NaCl showed no statistically significant changes in the pancreatic weight and plasma amylase activity compared to controls (Table 1). Moreover, the histopathological specimens collected from the above groups and controls were normal with no significant differences.

Table 1. Influence of adenosine receptors agonists and antagonists administration on serum amylase activity and pancreatic weight

Group	**Plasma amylase activity (kU/l)**	**Pancreatic weight [%]**
Control	4.15 ± 0.70	0.45 ± 0.07
Caerulein	30.12 ± 2.64^{A}	1.25 ± 0.14^{A}
DPCPX + caerulein	30.83 ± 2.55	1.28 ± 0.20
CGS 21680 + caerulein	19.10 ± 2.80^{AB}	0.85 ± 0.16^{AB}
ZM 241385 + caerulein	40.12 ± 2.25^{AB}	1.46 ± 0.15^{AB}
IB-MECA + caerulein	30.22 ± 2.91	1.25 ± 0.21
DPCPX	1.95 ± 0.50	0.46 ± 0.06
CGS 21680	2.02 ± 0.58	0.45 ± 0.08
ZM 241385	1.89 ± 0.65	0.43 ± 0.07
IB-MECA	2.05 ± 0.65	0.43 ± 0.07

* Pancreatic weight is expressed as percentage of rat's weight.

A $p<0.05$ compared with control;

B $p<0.05$ compared with the value of caerulein given alone.

The 12h intravenous caerulein infusion induced acute pancreatitis. The pancreas was enlarged, oedematous and a twofold increase in its weight was observed. There was almost an 8-fold increase in plasma amylase activity (Table 1). On histopathology, all the animals had interlobular and marked intralobular oedema. Perivascular leucocyte infiltration was observed and in some animals the features of diffuse infiltration. The majority of follicular cells showed marked vacuolization.

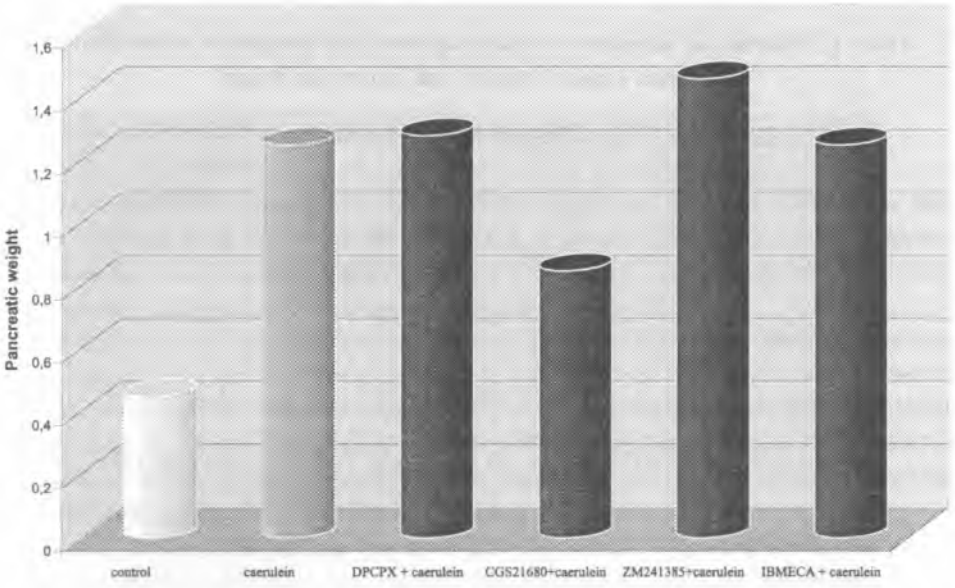

Fig. 1. Influence of adenosine receptors agonists and antagonists administration on serum pancreatic weight expressed as percentage of rat's weight

The intraperitoneal administration of the A_2 receptor agonist (CGS 21680, group 3) before induced acute pancreatitis reduced the organ injury. The A_2 receptor agonist statistically significantly decreased the pancreatic weight gain compared to the control groups (Fig. 1). Similar observations concerned the plasma amylase activity; which was statistically significantly lower after the CGS 21680 administration (Fig. 2). The histopathological picture revealed markedly decreased oedema limited to the interlobular oedema. The leucocyte infiltration of the pancreatic tissue was almost completely reduced. Vacuolization involved significantly a lower number of follicular cells; compared to the histopathological picture in caerulein-infused animals, its intensity was substantially reduced.

The intraperitoneal administration of the A_2 receptor antagonist (ZM 241385, group 4) before induced acute pancreatitis enhanced the pancreas damage. The pancreatic oedema was massive, pancreatic weight gain higher (Fig. 1). An increase in the plasma amylase

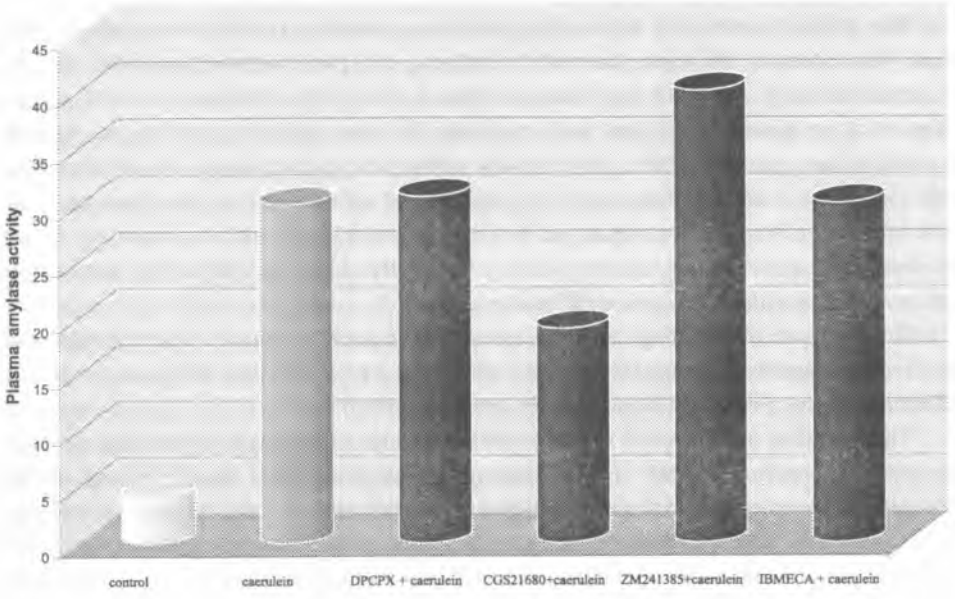

Fig. 2. Influence of adenosine receptors agonists and antagonists administration on serum amylase activity

activity was statistically significant (Fig. 2). The histopathological picture showed marked enhancement of inter- and intralobular oedema, intensive perivascular leucocyte infiltration with the features of diffuse infiltration in the majority of animals in this group. Vacuolization involved all the follicular cells and showed high intensity in comparison with the histopathological findings in the caerulein-infused animals.

The A_1 receptor blockade (DPCPX, group 2) as well as A_3 receptor stimulation (IB MECA, group 5) in the animals with induced acute pancreatitis did not affect the pancreatic weight (Fig. 1), plasma amylase activity (Fig. 2) or histopathological picture of the pancreas.

DISCUSSION

The aim of the study was to determine the effects of adenosine receptor agonists and antagonists on the development of caerulein-induced acute pancreatitis.

The majority of the studies presently carried out concern the relation between the cascade of events in acute pancreatitis and factors which may modulate it. One of such factors is adenosine, an important physiological modulator of the inflammatory process in its various stages which affects adenosine receptors located on many biological targets (13).

The study performed by us revealed that the adenosine A_2 receptor stimulation before the induction of acute pancreatitis reduced the pancreas damage while the A_2 receptor blockade enhanced the caerulein-induced injury. The protective action of adenosine in acute pancreatitis is not fully explained. It seems that this mechanism induces vasodilatation, prevents pancreatic activation of the transcription factor, NF-kB responsible for synthesis of proinflammatory interleukins and adhesive molecules, stimulates synthesis of antiinflammatory cytokins, inhibits chemotaxis and adhesion of leucocytes to the endothelium, decreases aggregation of activation of thrombocytes and inhibits production of oxygen free radicals by activated leucocytes.

Reduced pancreas damage and decreased plasma amylase activity observed after the A_2 receptor agonist administration may result from its vasodilating effects preventing a decrease in the pancreatic blood flow in acute pancreatitis.

The disorders of pancreatic microcirculation are one of the main causes of acute pancreatitis progression. Hypoxia due to vasoconstriction develops in the early stage of the disease. In caerulein-induced acute pancreatitis, a decrease in local blood flow was observed, even by 50% of the baseline value (6). Beside the disorders of perfusion, acute pancreatitis was also characterized by reduced flow in microcirculation of the liver, kidney, stomach, large intestine and skeletal muscles. However, perfusion in other organs was not so markedly decreased as that in the pancreas. This implies that the pancreas has specific mechanisms which impair its local blood flow. Kusterer (8) suggested the following sequence of events in pancreatic microcirculation in acute pancreatitis: increased vascular permeability, shrinkage of interlobular arterioles, ischaemia, capillary perfusion stasis, reperfusion and adhesion of leucocytes to the endothelium of interlobular vessels. This sequence implies the role of an ischaemia/reperfusion phenomenon in microcirculation disorders of the pancreas in acute pancreatitis. Adenosine and its analogues may be important mediators of vasodilatation, especially under the conditions of impaired oxygen supply. The A_2 receptor located in the smooth muscle cells of blood vessel walls participates in this action. Its participation in the vascular tone regulation was also confirmed by the studies concerning the A_2 receptor antagonist. It was showed that ZM 241385 eliminated vasodilatation responses induced by adenosine and caused increased activation of stimulated neutrophils (14). Many authors observed improved organ microcirculation after the administration of adenosine or its analogues. Granger (4) reported that adenosine was an endogenous substance with protective effects in myocardial ischaemia. The adenosine administration resulted in smaller range of ischaemic lesions in myocardial infarction and improved coronary flow. Vasodilatation and improved blood flow in the pancreas caused by adenosine or its analogues partly prevents the development of pancreatic inflammatory changes. Fenton et al. (12) found out that adenosine acted as a potent vasodilator not only by its effects on smooth muscles. Their findings indicate that it also stimulated the NO production in the arterial endothelium. The protective effects of NO in acute pancreatitis result from its properties. NO is thought to be an important factor maintaining the baseline tone of small arteries and arterioles and thus

maintaining the blood supply to important organs, i.e. the heart, lungs and peripheral organs. Moreover, NO inhibits aggregation and adhesion of thrombocytes and neutrophils to the vessel walls. It is generally accepted that NO is a cellular transmitter. It may diffuse through membranes and affect adjacent cells. This mechanism is thought to be the main mechanism of NO actions in the tissues. NO is a biological signalling molecule which may also affect the main proteins or signal pathways in apoptosis (3). Its deficiency favours the neutrophil accumulation accompanied by an increase in the number of dead follicular cells in the pancreas. On the other hand, Tsukahara et al. (2) showed the cytotoxic effects of NO generated in pulmonary macrophages in acute pancreatitis. There are some findings which do not confirm direct toxic effects of NO (*per se*) but suggest that NO plays a permissive role for toxicity induced by glutamic acid. It is increasingly accepted that in ischaemia NO is likely to be both protective and cytotoxic in action in a dose-dependent manner.

After overmaximal caerulein stimulation, the pancreas shows increased activation of the transcription factor, NF-kB. This factor regulates transcription of proinflammatory cytokins: IL-1, IL-6, IL-8, TNFα, adhesive molecules, ICAM-1, VCAM, E-selectine and P-selectine. These observations indicate that the factor may play an important role in initiating and spreading the inflammatory response. The studies performed by Li et al. (11) show that adenosine and its analogues prevent the activation of NF-kB transcription in ischaemia.

In acute pancreatitis, numerous proinflammatory cytokins are released (TNFα, IL-1, IL-6, IL-8) whose concentration is related to the disease severity and multi-organ complications. The antiinflammatory effects of adenosine also involve its influence on the cytokin release. Le Moine et al. (10) showed that adenosine increased secretion of interleukin-10 (IL-10) by monocytes and thus participated in inhibiting the TNFα release, and determined that adenosine inhibited TNFα and IL-6 expression in macrophages. Schmid et al. (15) showed that the IL-1-therapy decreased caerulein-induced pancreatitis. The administration of IL-10 after inducing acute pancreatitis led to significantly decreased level of mRNA for TFNα and TFNα protein in the pancreas. The mechanism of action of adenosine described above is particularly relevant in the severe phase of acute pancreatitis when the balance between cytokins and their antagonists is disturbed and the disease becomes destructive for remote organs. Some authors suggest that anticytokin treatment is effective in the experimental model of acute pancreatitis. However, it should be stressed that the protective effects can be observed only when cytokins are blocked before the failure of remote organs and peak cytokin concentrations have occurred.

In the pathogenesis of acute pancreatitis, the role of platelet activating factor (PAF) has also been confirmed. PAF, similarly to IL-1 and TNFα, was shown to be responsible for multi-organ damage. The use of PAF receptor antagonist-Lexipafant significantly reduces the acute pancreatitis severity. The PAF receptors were found in the endothelial cells of the pancreatic vessels, pancreatic follicular cells, macrophages, monocytes and neutrophils (7). Exogenous adenosine or its analogues decreased the arachidonic acid

release and synthesis of leucotrien B_4 (LTB4) occurring after neutrophil stimulation by PAF. This effect was achieved through A_2 receptors. Adenosine and its analogues reduced the production of oxygen reactive forms in PAF activated neutrophils and adhesion of those cells to the endothelium.

In the recent years, many authors were concerned with oxidative stress and its role in the development of acute pancreatitis. Oxygen metabolism, although indispensable, is risky for cells due to the formation of partially reduced oxygen compounds. The results of numerous studies associate oxygen free radicals with pathogenesis of many diseases, including acute pancreatitis as some of these radicals escape the antioxidative network control and react with human biological targets (5). The studies concerning the relation between oxidative stress and inflammatory responses in caerulein-induced acute pancreatitis showed that the expression of genes responsible for antioxidative protein production (c-FOS, oxygenases of hem-1 and metallothionein I) is accompanied by mRNA expression for IL-1b, IL-6 and TNFα (2). The phagocyte stimulation of granulocytes observed in acute pancreatitis results in increased production of oxygen reactive forms. With the help of granulocyte oxidase and myeloperoxidase, hydrogen peroxide, hydroxylic and peroxide radicals and "singlet oxygen" are formed resulting in "oxygen storm". Impairment of blood flow leads to a decrease in endogenous oxygen free radical utilization and this reduces tissue antioxidative capacity, which, in turn, results in oxidative stress. Oxygen free radicals through peroxidation of structural lipids in the cell membranes damage the walls of capillaries and follicular cells increasing their permeability. This intensifies the enzyme release and the inflammatory process advances. Bullough (1) showed that through A_2 receptors adenosine inhibited the oxygen-free radical formation by stimulated leucocytes, decreased their phagocytosis and adhesion to the endothelial cells. These findings indicate that adenosine may have an important function in protecting the organism against oxidative stress.

CONCLUSIONS

The administration of adenosine A_2 receptor agonists reduces the severity of organ damage in caerulein-induced acute pancreatitis in rats. This action is likely to result from modulating effects of the above-described substances on various stages of the cascade of inflammatory responses. The study, however, did not show any effects of the A_1 receptor agonist A_3 receptor antagonist on the inflammatory process in the experimental model presented.

REFERENCES

1. Bullough D. A. et al.: Adenosine activates A_2 receptors to inhibit neutrophil adhesion and injury to isolated cardiac myocytes. J. Immunol., 155, 2579, 1995.
2. Długosz J. W.: Patogeneza ostrego zapalenia trzustki na progu nowego stulecia. Postępy Nauk Medycznych, t. XII, nr 1-2, 5, 1999.
3. Dumont A. et al.: Hydrogen peroxide-induced apoptosis is CD95-independent, requires the release of mitochondria-derived reactive oxygen species and the activation of NF-kappa B. Oncogene, 18(3), 747, 1999.
4. Granger C. B.: Adenosine for myocardial protection in acute myocardial infarction. Am. J. Cardiol., 19, 79, 44, 1997.
5. Halliwell B.: Oxygen radicals, nitric oxide and human inflammatory joint disease. Ann. Rheum. Dis., 54(6), 505, 1995.
6. Klar E. et al.: Pancreatic ischaemia in experimental acute pancreatitis: mechanism, significance and therapy. Br. J. Surg., 77, 1205, 1990.
7. Konturek S. J. et al.: Role of platelet activating factor in pathogenesis of acute pancreatitis in rats. Gut, 33, 1268, 1992.
8. Kusterer K. et al.: Arterial constriction, ischaemia-reperfusion, and leukocyte adherence in acute pancreatitis. Am. J. Physiol., 265, G165, 1993.
9. Lampel M., Kern H. F.: Acute interstitial pancreatitis in the rat induced by excessive doses of pancreatic secretagogue. Virchows Arch. A. Pathol. Anat., 373, 97, 1977.
10. Le Moine O. et al.: Adenosine enhances IL-10 secretion by human monocytes. J. Immunol., 156(11), 4408, 1996.
11. Li C. et al.: Adenosine prevents activation of transcription factor NF-kappa B and enhances activator protein-1 binding activity in ischemic rat heart. Surgery, 127(2), 161, 2000.
12. Li J. M. et al.: Adenosine enhances nitric oxide production by vascular endothelial cells. Am. J. Physiol., 269, C519, 1995.
13. Mirabet M. et al.: Expression of A_2 adenosine receptors in human lymphocytes: their role in T cell activation. J. Cell Sci.,112, 491, 1999.
14. Poucher S. M. et al.: Pharmacodynamics of ZM 241385, a potent A_2 adenosine receptor antagonist, after enteric administration in rat, cat and dog. J. Pharm. Pharmacol., 48(6), 601, 1996.
15. Schmid R. M., Adler G.: Cytokiny w ostrym zapaleniu trzustki – nowe koncepcje patofizjologiczne. Eur. J. Gastroenterology & Hepatology, 11, 125, 1999.

2001.10.10

SUMMARY

Acute pancreatitis leads to hypoxia caused by vasoconstriction and to activation of lysosomal and digestive enzymes resulting in pancreas autodigestion and damage. This causes activation of leucocytes and increased expression of adhesive molecules enabling margination and adhesion of activated leucocytes to the endothelium. Activated leucocytes are the source of proinflammatory cytokins and oxygen-free radicals which intensify the inflammatory response. The reports indicating that adenosine may prevent activation of the above-mentioned processes in ischaemia prompted us to undertake this study.

The study was performed in two stages. The first stage was to evaluate the effects of agonists and antagonists of adenosine receptors on normal pancreas while the second one was to determine the influence of these substances on the development of caerulein-induced acute pancreatitis.

During the first stage, the animals were injected intraperitoneally with the substances examined: the A_1 receptor antagonist – DPCPX, the A_2 receptor agonist – CGS 21680, the A_2 receptor antagonist – ZM 241385 and the A_3 receptor agonist – IB-MECA and then received intravenous saline. The control animals were subjected only to the 12 h intravenous infusion of 0.15 M NaCl. During the second stage, after the intraperitoneal administration of adenosine receptor agonists and antagonists (as in the first stage), acute pancreatitis was induced with the 12h intravenous infusion of 5μg/kg/h caerulein. Identical acute pancreatitis was induced in the control animals, however no other substances were administered. The pancreatic tissue samples were collected directly after intravenous infusion. The severity of inflammatory processes in the pancreas was evaluated on the basis of the plasma amylase activity, pancreatic weight and enhancement of histopathological changes observed in this organ.

In the animals infused with saline alone, no effects of the substances examined on the pancreatic weight, plasma amylase activity and histopathological features were observed. The intravenous caerulein infusion induced acute pancreatitis expressed as bigger pancreatic weight, increased plasma amylase activity and tissue damage (oedema, cell vacuolization, leucocyte infiltration). The A_2 receptor agonist administration preceding the induction of acute pancreatitis decreased the pancreas damage caused by caerulein. Lower weight of the pancreas and decreased plasma amylase activities were observed; on histopathological examination – oedema, leucocyte infiltration and intensity of alveolar cell vacuolization were lower. On the other hand, intraperitoneal pretreatment with the A_2 receptor antagonist intensified the pancreas injury. The A_1 receptor blockade and A_3 receptor stimulation in the animals injected with caerulein did not affect the pancreatic weight, plasma amylase activity or histopathological picture of the organ.

The administration of A_2 receptor agonists decreases the organ injury in caerulein-induced acute pancreatitis in rats. This action may result from modulating effects of these substances on different stages of the cascade of inflammatory reactions. However,

the present study did not reveal any effect of the A_1 receptor agonist or A_3 receptor antagonist on inflammatory processes in the experimental model described.

Wpływ receptorów adenozynowych na rozwój eksperymentalnego ostrego zapalenia trzustki wywołanego ceruleiną

W przebiegu OZT (ostrego zapalenia trzustki) dochodzi do hipoksji w wyniku wazokonstrykcji oraz do aktywacji enzymów lizosomalnych i trawiennych powodujących samotrawienie i uszkodzenie trzustki. W konsekwencji dochodzi do pobudzenia leukocytów oraz zwiększenia ekspresji cząstek adhezyjnych, umożliwiających marginację i adhezję pobudzonych leukocytów do śródbłonka naczyń. Pobudzone leukocyty są źródłem prozapalnych cytokin i wolnych rodników tlenowych, które nasilają odczyn zapalny. Doniesienia o tym, że adenozyna może zapobiegać aktywacji wymienionych procesów w przebiegu niedokrwienia, skłoniły nas do przeprowadzenia badania.

Doświadczenie wykonano w dwóch etapach. Pierwszy miał na celu ocenę wpływu agonistów i antagonistów receptorów adenozynowych na nieuszkodzoną, prawidłową trzustkę, a drugi miał określić wpływ tych substancji na rozwój OZT indukowanego ceruleiną.

Podczas pierwszego etapu doświadczenia, po dootrzewnowych iniekcjach badanych substancji, odpowiednio: DPCPX – antagonisty receptora A_1, CGS 21680 – agonisty receptora A_2, ZM241385 – antagonisty receptora A_2, IB-MECA – agonisty receptora A_3, zwierzęta otrzymywały dożylną infuzję soli fizjologicznej. Zwierzętom z grupy kontrolnej podawano wyłącznie dwunastogodzinną dożylną infuzję 0,15 M NaCl. W drugim etapie doświadczenia, po dootrzewnowym podaniu, podobnie jak w pierwszym etapie, agonisty lub antagonisty receptorów adenozynowych, u badanych zwierząt wywoływano OZT, podając dwunastogodzinną dożylną infuzję ceruleiny w dawce 5 mg/kg/h. Grupę odniesienia stanowiły zwierzęta, którym przed identyczną indukcją OZT nie podawano żadnych innych substancji. Próbki tkanki trzustkowej pobierano bezpośrednio po zakończeniu dożylnych infuzji. Intensywność procesu zapalnego w trzustce oceniano na podstawie aktywności amylazy w osoczu, wielkości masy trzustki oraz nasilenia zmian histopatologicznych w tym narządzie.

U zwierząt, którym podawano wyłącznie infuzję soli fizjologicznej, nie obserwowano wpływu badanych substancji na wielkość masy trzustki, aktywność osoczowej amylazy i obraz histopatologiczny trzustki. Dożylny wlew ceruleiny indukował u badanych zwierząt OZT, wyrażające się wzrostem masy trzustki, osoczowej aktywności amylazy oraz uszkodzeniem tkanki narządu (obrzęk, wakuolizacja komórek, naciek leukocytarny). Podanie agonisty receptora A_2, poprzedzające indukcję OZT, zmniejszało uszkodzenie trzustki wywoływane ceruleiną. Obserwowano mniejszy przyrost masy tego narządu, niższą aktywność amylazy w osoczu, a w badaniu histopatologicznym - mniejszy obrzęk, infiltrację leukocytarną tkanki trzustkowej oraz intensywność wakuolizacji komórek pęcherzykowych. Natomiast wcześniejsze dootrzewnowe podanie antagonisty receptora A_2 nasilało uszko-

dzenie narządu. Blokada receptora A_1 oraz pobudzenie receptora A_3 u zwierząt, którym podawano ceruleinę, nie miały wpływu zarówno na masę trzustki, aktywność osoczowej amylazy, jak i obraz histopatologiczny narządu.

Podanie agonisty receptora adenozynowego A_2 zmniejsza intensywność uszkodzenia narządu w przebiegu indukowanego ceruleiną OZT u szczurów. Oddziaływanie to może wynikać z modulującego wpływu wymienionej substancji na różne etapy kaskady reakcji zapalnych. Przeprowadzone badanie nie wykazało natomiast wpływu agonisty receptora A_1 oraz antagonisty receptora A_3 na przebieg procesu zapalnego w opisywanym modelu doświadczalnym.