Physiological Role of Targeting of the Receptor for Advanced Glycation End Products and Its Involvement in Severe Acute Pancreatitis

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ABSTRACT
Leukocyte infiltration and damage to pancreatic acinar cells serve as key indicators of severe acute pancreatitis (AP) [1]. However, the signaling pathways involved in pancreatic inflammation and tissue damage remain unclear. This study explores the impact of inhibiting the receptor for advanced glycation end products (RAGE) signaling in AP. We examined the role of RAGE signaling by administering a RAGE inhibitor (anti-RAGE) (500 µg/kg) to C57BL/6 mice prior to inducing pancreatitis with taurocholate injection into the pancreatic duct. Anti-RAGE treatment led to a reduction in blood amylase levels, neutrophil infiltration in the pancreas, hemorrhage, and edema caused by taurocholate-induced pancreatitis. Additionally, anti-RAGE administration lowered MPO activity in both the pancreas and lungs. Intraperitoneal (IP) injection of anti-RAGE significantly reduced CXCL2 and IL-6 concentrations in the pancreas and plasma, respectively, in response to taurocholate-induced pancreatitis. However, RAGE inhibition did not directly affect secretagogue-induced trypsinogen activation in pancreatic acinar cells in vitro. These findings reveal novel signaling pathways in AP and suggest that targeting RAGE may serve as a promising therapeutic approach for severe AP.
Key words: Amylase, Chemokines, Inflammation, Leukocytes, and Pancreas

INTRODUCTION

Severe acute pancreatitis (AP) is associated with high morbidity and mortality rates [1]. Managing patients with severe AP remains a significant challenge for clinicians, as treatment options are largely limited to supportive therapies due to an incomplete understanding of its pathophysiology. While trypsinogen activation is widely recognized as an initial event in AP, leukocyte recruitment and impaired microvascular

perfusion are key contributors to disease progression [2-4]. Since trypsinogen activation occurs early and transiently, prolonged pancreatic inflammation may serve as a more effective therapeutic target [5].

Neutrophil infiltration is a hallmark of the inflammatory response, and several studies have highlighted its critical role in severe AP [6,7]. The recruitment of neutrophils involves multiple sequential steps mediated by specific adhesion molecules, such as P-selectin and Lymphocyte Antigen-1 (LFA-1) [8,9]. Additionally, chemokines play a crucial role in guiding leukocytes to extravascular sites [10,11]. Among them, CXC chemokines like CXCL1 and CXCL2 are key drivers of neutrophil accumulation [12]. CXCR2, a receptor expressed on neutrophils, has been identified as a mediator of pancreatic neutrophil extravasation in response to CXCL1 and CXCL2 signaling [13,14].

The receptor for advanced glycation end-products (RAGE), a member of the immunoglobulin superfamily, plays a pivotal role in regulating nucleosomal proinflammatory activity in macrophages [15]. Studies have shown that RAGE knockout in macrophages suppresses nucleosome-induced activation of absent in melanoma 2 (AIM2), thereby reducing the release of proinflammatory mediators [16]. Moreover, targeted deletion of RAGE or AIM2 expression in mice provides protection against L-arginine- or cerulein-induced AP in experimental models.

Considering these findings, we hypothesize that RAGE signaling may play a role in the progression of severe AP. To investigate this, we utilized a taurocholate-induced mouse model of severe AP and administered anti-RAGE to inhibit RAGE activity.

MATERIALS AND METHODS

Animals

Male C57BL/6 mice (20–25 g) were maintained under a 12-hour light/dark cycle with free access to food and water in the laboratory. All experimental procedures were approved by the Ethical Committee of Hawler Medical University, College of Pharmacy. Mice were anesthetized via intraperitoneal (i.p.) injection using 75 mg/kg ketamine hydrochloride (Hoffman-La Roche, Basel, Switzerland) and 25 mg/kg xylazine (Janssen Pharmaceutica, Beerse, Belgium).

Taurocholate perfusion

Anesthetized mice underwent a midline laparotomy, during which the second part of the duodenum and the Vater's papilla were identified. Traction sutures were placed 1 cm from the papilla, and a small incision was made parallel to the Vater's papilla through the duodenal wall using a 23G needle. A polyethylene catheter, connected to a microinfusion pump (CMA/100, Carnegie Medicin, Stockholm, Sweden), was inserted 1 mm into the common bile duct through the perforated duodenal wall. The hepatic duct was then secured, and the liver hilum was clamped.

To induce pancreatitis, 10 µl of 5% sodium taurocholate (Sigma, St. Louis, MO, USA) was infused into the pancreatic duct over 10 minutes. Following the infusion, the catheter and hepatic duct clamp were removed. The duodenal puncture site was closed using a purse-string suture, traction sutures were removed, and the abdominal wall was closed in two layers. Mice were allowed to recover with free access to food and water.

To inhibit RAGE signaling, anti-RAGE antibodies (500 µg/kg, Abcam, Cambridge, MA) or vehicle (PBS) were administered intraperitoneally (i.p.) prior to bile duct cannulation. The dosage and administration protocol were based on a previous study [17]. Sham-operated mice underwent laparotomy and pancreatic duct infusion with phosphate-buffered saline (PBS) and received an i.p. injection of the vehicle (PBS, n = 6). All mice were euthanized 24 hours after pancreatitis induction, and study parameters were evaluated.

Amylase activity

Amylase activity levels were measured in blood samples collected from the tail vein of mice using a commercially available assay (Reflotron®, Roche Diagnostics GmbH, Mannheim, Germany).

Leukocyte counts

Systemic differential blood counts were conducted using blood samples collected from the tail vein. The blood was diluted at a 1:20 ratio with Türk's solution (Merck, Darmstadt, Germany). Leukocytes were classified as mononuclear or polymorphonuclear cells using a Bürker chamber.

Myeloperoxidase (MPO) activity

A small portion of pancreatic tissue (pancreatic head) and lung tissue was collected for myeloperoxidase (MPO) analysis. Before freezing, the tissues were weighed and homogenized in 1 ml of a PBS and aprotinin mixture (4:1 ratio) containing 10,000 KIE/ml aprotinin (Trasylol®, Bayer HealthCare AG, Leverkusen, Germany) for 1 minute. The homogenized samples were then centrifuged at 15,339×g for 10 minutes,

and the supernatant was stored at −20°C. The MPO assay was performed using the remaining pellet.

For MPO measurement, the pellets were resuspended in 1 ml of 0.5% hexadecyltrimethylammonium bromide (HTAB) and frozen for 24 hours. After thawing, the samples were sonicated for 90 seconds, incubated in a water bath at 60°C for 2 hours, and then the MPO activity in the supernatant was measured. Enzyme activity was determined using a spectrophotometric method, where MPO catalyzes the redox reaction of hydrogen peroxide (H_2O_2), leading to absorbance changes at 450 nm (reference filter at 540 nm) at 25°C. MPO activity was expressed as MPO units per gram of tissue.

Morphologic evaluation of pancreas

Pancreatic tissue was fixed in 4% formaldehyde phosphate buffer, followed by dehydration and paraffin embedding. The embedded samples were then sectioned into 6 µm slices and stained with hematoxylin and eosin (H&E). Prepared slides were examined using light microscopy. The severity of pancreatitis was assessed in a blinded manner based on a previously established scoring system, evaluating parameters such as edema, acinar cell necrosis, hemorrhage, and neutrophil infiltration on a scale from 0 (absent) to 4 (extensive), as previously described [18].

Enzyme-linked immunosorbent assay (ELISA)

CXCL2 levels in pancreatic tissue and IL-6 concentrations in plasma were measured using double-antibody quantifying enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems Europe, Abingdon, UK). Recombinant murine CXCL2 and IL-6 were

used as standards. The minimum detectable protein concentration for the assay was less than 0.5 pg/ml.

Acinar cell isolation

Pancreatic acinar cells were isolated using collagenase digestion and gentle shearing, following previously established protocols [26]. The cells were suspended in oxygen-saturated HEPES-Ringer buffer (pH 7.4) and passed through a 150 µm cell strainer (Partec, Cörlitz, Germany). Isolated acinar cells (1×10^7 cells per well) were pre-incubated with either phosphate-buffered saline (PBS) or GGTI-2133 (100 µM) for 30 minutes and then stimulated with 100 nM cerulein at 37°C for 30 minutes in duplicate experiments.

Following incubation, the buffer was discarded, and the cells were washed twice with a buffer (pH 6.5) containing 250 mM sucrose, 5 mM 3-(morpholino)propanesulfonic acid (MOPS), and 1 mM $MgSO_4$. The cells were then homogenized in cold (4°C) MOPS buffer using a Potter-Elvehjem glass homogenizer. The homogenate was centrifuged at 56×g for 5 minutes, and the supernatant was collected for enzymatic analysis.

Trypsin activity was measured fluorometrically using Boc-Glu-Ala-Arg-AMC as a substrate, as described previously [19]. A 200 µl aliquot of the acinar cell homogenate was added to a cuvette containing assay buffer (50 mM Tris, 150 mM NaCl, 1 mM $CaCl_2$, and 0.1% BSA, pH 8.0). The reaction was initiated by adding the substrate, and trypsin activity was monitored based on fluorescence emission at 440 nm in response to excitation at 380 nm. Trypsin levels (pg/ml) were quantified using a standard curve generated with purified trypsin. The viability of pancreatic acinar cells was greater than 95%, as determined by the trypan blue dye exclusion test.

Statistical analysis

Due to the non-parametric nature of the data, the Mann–Whitney test was employed for statistical analysis, with a significance level set at $P \leq 0.05$. The number of animals used in the experiments is denoted by “n.” Additionally, the data are presented as mean values ± standard error of the mean (SEM).

RESULTS

RAGE controls pancreatic tissue damage

To evaluate the role of RAGE in severe acute pancreatitis (AP), amylase activity was measured as an indicator of tissue damage in the pancreas. We observed that infusion of taurocholate into the pancreatic duct resulted in a dramatic 8-fold increase in blood amylase concentration (Table 1). Treatment with the RAGE inhibitor reduced the levels of blood amylase activity induced by retrograde infusion of taurocholate, decreasing from (660.4 ± 64 µKat/L to 304 ± 6 µKat/L, P<0.05). (Table 1).

Table 1. Blood amylase levels (µKat/L) in sham mice and taurocholate-exposed mice pretreated with either vehicle or the RAGE inhibitor (500 µg/kg).

Parameters	Mean	SE
Sham	64.13	±3
Taurocholate	660.4*	±2
Anti-RAGE	304#	±6

Blood samples were collected 24 hours after the induction of pancreatitis. The data are presented as means ± SEM, with a sample size of n = 6. Statistical significance is indicated as follows: *P < 0.05 compared to the PBS group and #P < 0.05 compared to the Vehicle + Taurocholate group.

Tissue morphology analysis revealed normal pancreatic microarchitecture in the negative control mice. In contrast, taurocholate induction resulted in significant structural degradation of the pancreatic tissue, characterized by acinar cell necrosis, edema formation, and neutrophil accumulation (Table 2). These results suggest that RAGE inhibition provides protection against tissue destruction induced by

taurocholate. The administration of anti-RAGE reduced taurocholate-induced hemorrhage significantly (P<0.05) in the pancreas (Table 2). Furthermore, acinar necrosis decreased by 59%, and the number of extravascular leukocytes in pancreatitis mice was reduced by significantly with anti-RAGE treatment (Table 2).

Table 2. RAGE regulates tissue damage in AP.

Parameters	Hemorrhage (Scores)	Acinar cell necrosis (Scores)	Edema formation (Scores)	Neutrophil infiltration (Scores)
Sham	1.0	0.4	1.0	0.8
Taurocholate	5.0*	4.5*	4.5*	4.0*
Anti-RAGE+Taurocholate	2.0#	2.0#	2.0#	1.0#

The analysis of hemorrhage, acinar necrosis, edema formation, and neutrophil infiltration was conducted in sham (PBS) animals and taurocholate-exposed mice pretreated with either vehicle or the RAGE inhibitor (500 µg/kg). Samples were collected 24 hours after the induction of pancreatitis. The data are presented as means ± SEM, with a sample size of n = 6. Statistical significance is indicated as follows: *P < 0.05 compared to the PBS group and #P < 0.05 compared to the Vehicle + Taurocholate group.

The taurocholate challenge led to a decline in the number of circulating polymorphonuclear leukocytes (PMNLs) and mononuclear leukocytes (MNLs), indicating that systemic activation persisted (Table 3). However, RAGE inhibition significantly prevented the reduction in systemic leukocytes caused by taurocholate (Table 3).

Table 3. Systemic leukocyte differential counts

	PMNL	MNL
PBS	1 ± 0.8	13.0 ± 0.6
Taurocholate	0.5 ± 0.4*****	4.0 ± 0.2*****
Anti-RAGE + Taurocholate	1.0 ± 0.4#	7.4 ± 0.2#

Blood samples were collected from sham mice and taurocholate-treated animals pretreated with either vehicle or the RAGE inhibitor (500 µg/kg). The cells were classified as mononuclear leukocytes (MNLs) and polymorphonuclear leukocytes (PMNLs). The data are presented as mean ± SEM, with a concentration of 10^6 cells/ml and a sample size of n = 6. Statistical significance is indicated as follows: #P < 0.05 compared to the PBS group and *P < 0.05 compared to the Vehicle + Taurocholate group.

Regulation of neutrophils by RAGE

The levels of myeloperoxidase (MPO) in pancreatic and lung tissues were used as indicators of neutrophil extravasation. Our results showed that taurocholate infusion led to an 8-fold increase in pancreatic MPO levels (Table 4). RAGE inhibition significantly decrease in MPO levels in the pancreas induced by taurocholate (Table 4).

Table 4. MPO levels in the Pancreas (U/g/Tissue)

Parameters	**Mean**	**SE**
Sham	1.0	0.2

Taurocholate	6.6*	0.4
Anti-RAGE+ Taurocholate	2.0 #	2.0

RAGE regulates the accumulation of neutrophils induced by taurocholate. MPO levels were measured in the pancreas of sham (PBS) animals and taurocholate-treated mice that were pretreated with either vehicle or the RAGE inhibitor (500 µg/kg). Samples were collected 24 hours after the induction of pancreatitis. The data are expressed as means ± SEM, with a sample size of n = 6. Statistical significance is indicated as follows: *P < 0.05 compared to the PBS group and #P < 0.05 compared to the Vehicle + Taurocholate group.

Neutrophil activation in the pulmonary microvasculature occurs as part of a systemic inflammatory response in severe acute pancreatitis (AP). Additionally, we found that taurocholate infusion significantly increased MPO activity in the lung (Table 5). RAGE inhibition led to a reduction of MPO activity in the lung by more than 66% in mice treated with taurocholate (Table 5).

Table 5. MPO levels in the Lung (U/g/Tissue).

Parameters	**Mean**	**SE**
Sham	1.4	±2
Taurocholate	5.23*	±6
Anti-RAGE+ Taurocholate	1.9#	±4

RAGE regulates the accumulation of neutrophils induced by taurocholate, as indicated by MPO levels in the lungs of sham (PBS) animals and taurocholate-exposed mice pretreated with either vehicle or the RAGE inhibitor (500 µg/kg). Samples were

collected 24 hours after the induction of pancreatitis. The data are presented as means ± SEM, with a sample size of n = 5. Statistical significance is indicated as follows: *P < 0.05 compared to the PBS group and #P < 0.05 compared to the Vehicle + Taurocholate group.

We also showed that taurocholate challenge significantly increased the concentration of CXCL2 in the pancreas (Table 6). Administration of anti-RAGE markedly reduced CXCL2 levels in the inflamed pancreatic tissue of taurocholate-treated mice (Table 6).

Table 6. CXCL2 levels in the pancreas (pg/mg)

Parameters	**Mean**	**SE**
Sham	42.2	±6
Taurocholate	188.6*	±4
Anti-RAGE+ taurocholate	90.6#	±6

CXCL2 levels in the pancreas were measured in sham (PBS) animals and taurocholate-exposed mice pretreated with either vehicle or the RAGE inhibitor (500 µg/kg). Samples were collected 24 hours after the induction of pancreatitis. The data are expressed as means ± SEM, with a sample size of n = 6. Statistical significance is indicated as follows: *P < 0.05 compared to the PBS group and #P < 0.05 compared to the Vehicle + Taurocholate group.

Furthermore, taurocholate challenges significantly elevated IL-6 plasma concentrations, while administration of anti-RAGE normalized IL-6 plasma levels in mice with pancreatitis (Table 7).

Table 7. IL6 levels in plasma (ng/ml).

Parameters	Mean	SE
Sham	4.8	±3
Taurocholate	146*	±4
Anti-RAGE	88 #	±4

Levels were measured in sham (PBS) animals and taurocholate-exposed mice pretreated with either vehicle or the RAGE inhibitor (500 µg/kg). Samples were collected 24 hours after the induction of pancreatitis. The data are presented as means ± SEM, with a sample size of n = 5. Statistical significance is indicated as follows: *P < 0.05 compared to the PBS group and #P < 0.05 compared to the Vehicle + Taurocholate group.

Trypsinogen activation in vitro

Next, we investigated whether RAGE would regulate trypsinogen activation in pancreatic acinar cells in vitro. To do this, acinar cells were isolated from mouse pancreas and incubated with cerulein. We observed that trypsinogen activation in the acinar cells increased by more than 8-fold when stimulated by cerulein compared to unstimulated acinar cells (Table 8). Furthermore, preincubation of the mouse acinar cells with the RAGE inhibitor did not impact secretagogue-induced trypsinogen activation (Table 8).

Table 8. Trypsinogen levels in pancreas invitro.

Parameters	Mean	SE

Negative control	2100	±14
cerulein	6200*	±8
Anti-RAGE	5400	±6

Trypsinogen activation in acinar cells was assessed in negative control cells and in cells exposed to cerulein with either PBS or Anti-RAGE (100 µM). The activation was quantified by measuring trypsin enzymatic activity fluorometrically using Boc-Gln-Ala-Arg-MCA as the substrate, as detailed in the Materials and Methods section. Trypsin levels were calculated using a standard curve created from assays of purified trypsin. The data are presented as means ± SEM, with a sample size of n = 6. Statistical significance is indicated as *P < 0.05 compared to the negative control.

DISCUSSION

The mechanisms underlying pathological inflammation in pancreatitis remain inadequately understood. Our study is the first to reveal that RAGE serves as a significant pathophysiological regulator in severe acute pancreatitis (SAP). Our findings suggest that RAGE plays a critical role in regulating neutrophils and the production of CXC chemokines within the pancreas. Additionally, RAGE inhibition not only decreases neutrophil recruitment in the pancreatic tissue of mice but also reduces acinar cell necrosis and blood amylase levels in SAP. Furthermore, RAGE inhibition prevents the formation of IL-6 and the extravasation of neutrophils in the lungs, indicating that RAGE influences inflammation on both local and systemic levels in SAP. Previous research has indicated that the depletion of RAGE or AIM2 can diminish tissue injury, lower systemic inflammation, and offer protection against severe inflammatory responses in mice. In our current study, the use of a specific RAGE inhibitor resulted in a significant reduction of tissue damage in SAP. Notably, administering anti-RAGE intraperitoneally decreased the taurocholate-induced rise in blood amylase levels and acinar cell necrosis significantly, suggesting that RAGE is a key player in tissue damage in SAP. These findings provide the first evidence linking RAGE signaling mechanisms to the pathophysiology of acute pancreatitis, thereby enhancing our understanding of RAGE's anti-inflammatory effects in this condition.

Considerable evidence supports the notion that neutrophil recruitment is a central feature of acute pancreatitis. Studies have shown that reducing neutrophil levels or inhibiting their recruitment can protect against tissue injury in pancreatitis. In our investigation, taurocholate challenge led to elevated MPO levels and an increased number of recruited neutrophils in the inflamed pancreas. Treatment with anti-RAGE significantly decreased MPO activity significantly, and reduced the presence of extravascular neutrophils in pancreatic tissues, underscoring RAGE signaling as a critical regulator of neutrophil recruitment in the pancreas. Given the essential role of neutrophils in the pathophysiology of pancreatitis, the impact of RAGE inhibition on neutrophil activation and infiltration may clarify RAGE's protective effect on inflamed tissue. Moreover, systemic complications of SAP include the extravasation of

inflammatory cells into the lungs. We found that taurocholate treatment increased MPO activity in the lungs, and importantly, anti-RAGE treatment reduced MPO levels in the lungs of taurocholate-exposed mice, indicating that RAGE also regulates systemic neutrophil extravasation in SAP. Our results further reinforce the concept that RAGE modulates systemic inflammation, as anti-RAGE treatment significantly lowered IL-6 plasma levels induced by taurocholate, a key marker of systemic inflammation linked to increased mortality in septic patients.

CXC chemokines CXCL1 and CXCL2 are known to facilitate the movement of leukocytes to sites of inflammation, and their specific roles in pancreatitis have been suggested. We observed that taurocholate significantly elevated pancreatic CXCL2 levels, while anti-RAGE treatment dramatically decreased these levels in inflamed pancreatic tissue, indicating that RAGE is involved in regulating CXCL2 production. This finding helps elucidate RAGE's inhibitory effect on neutrophil infiltration in SAP, suggesting that RAGE may regulate this process through CXCL2 production in the pancreas.

It is generally accepted that trypsinogen activation is crucial to the pathophysiology of acute pancreatitis. We examined whether RAGE is involved in trypsin activation in acinar cells. However, our results indicate that RAGE does not influence trypsin activation triggered by secretagogues in isolated acinar cells, suggesting that RAGE is not directly implicated in trypsin activation.

In our conclusion data demonstration, RAGE signaling is a key regulator of tissue injury in severe acute pancreatitis. We show that RAGE inhibition reduces CXCL2 production and neutrophil recruitment in the pancreas, leading to decreased tissue damage. Additionally, blocking RAGE activity in models of pancreatitis mitigates systemic inflammation and pulmonary neutrophil infiltration. This research delineates a novel signaling pathway in acute pancreatitis and underscores the potential of targeting RAGE to modulate local and systemic inflammation in severe acute pancreatitis.

AUTHORSHIP

All authors are contributed equally

Conflict of interest:

The authors state no conflict of interest.

Reference:

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