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Therapeutic administration of orlistat, rosiglitazone or the chemokine receptor antagonist RS102895 fails to improve the severity of acute pancreatitis in obese mice

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Abstract

Objectives—Currently there is no therapy for severe acute pancreatitis except for supportive care. The lipase inhibitor orlistat, the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone, and chemokine receptor-2 antagonists attenuate the severity of acute pancreatitis in rodents if administered prior to or at the time of induction of pancreatitis. However, it is unknown whether these treatments are effective if administered therapeutically after induction of pancreatitis.

Methods—Male C57BL6 mice with diet-induced obesity received two injections of mrIL-12 (150 ng/mouse) and mrIL-18 (750 ng/mouse) intraperitoneally at 24 h intervals. Mice were injected 2, 24, and 48 hours after the second injection of IL-12+IL-18 with orlistat (2 mg/mouse), rosiglitazone (0.4 mg/mouse), RS102895 (0.3 mg/mouse), or vehicle (20µL DMSO and 80 µL canola oil) and euthanized after 72 hours.

Results—Orlistat decreased intraabdominal fat necrosis compared to vehicle ($p<0.05$). However, none of the drug treatments produced significant decreases in pancreatic edema, acinar necrosis, or intrapancreatic fat necrosis.

Conclusions—Drugs previously shown to improve the severity of acute pancreatitis when given prior to or at the time of induction of pancreatitis, failed to do so when administered therapeutically in the IL-12+IL-18 model.

Keywords

diet-induced obesity; inflammation; adipokines; lipotoxicity

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INTRODUCTION

Acute pancreatitis (AP) is the diagnosis accounting for the most gastroenterologic hospital admissions, and kills approximately 1 in 100,000 Americans annually.¹ Currently there is no therapy for AP except for supportive care, including aggressive intravenous fluid resuscitation.² Several agents have shown promise attenuating the severity of AP in rodents if administered prior to or at the time of induction of pancreatitis. However, it is not known whether these agents are effective when administered therapeutically following induction of AP, particularly in the setting of the severe AP associated with obesity.

Orlistat is a lipase inhibitor approved for oral use in humans for weight loss. Orlistat administration beginning at the time of induction of AP reduces plasma lipase and pancreatic neutrophil infiltration in rats administered sodium taurocholate by retrograde injection.³ Similarly, orlistat administered between injections of IL-12+IL-18 decreases the severity of AP in genetically obese mice.^{4,5} Mice lacking lipoprotein lipase have more circulating chylomicrons compared to wild-type mice, though their pancreatic lipase activity remains unchanged, and have more severe caerulein-induced AP.⁶ These observations together implicate pancreatic lipase and lipid substrate as key in the development of necrosis in AP, particularly in the context of obesity.

Rosiglitazone is a peroxisome proliferator-activator receptor (PPAR)- γ agonist with anti-inflammatory as well as insulin-sensitizing properties.⁷ Rosiglitazone attenuates the increase in chemokine production by visceral adipocytes in response to arachidonic acid⁸ and promotes M2 polarization of visceral adipose tissue macrophages in obese mice.⁹ Rosiglitazone decreases the severity of AP when administered both before and after sodium taurocholate retrograde infusion in rats,^{10,11} although a decrease in AP severity is not seen by all investigators using the caerulein model.¹²⁻¹⁴ Preventative administration of rosiglitazone also improves recovery in rats with AP induced by L-arginine¹⁵ as well as survival and recovery in obese mice with AP induced by IL-12+IL-18,¹⁶ but does not consistently improve histopathologic scores of pancreatic injury in the L-arginine model.¹⁵

Mice deficient in chemokine receptor-2 (CCR2) or its ligand CCL2 have decreased pancreatic edema in the caerulein model of AP.¹⁷ Moreover, mice deficient in CCL2 have less pancreatic infiltration of CD11b⁺ cells, and are protected from macrophage infiltration and pancreatic acinar necrosis in several models of AP.¹⁸ A CCR2 antagonist, bindarit (2-methyl-2-[[1-(phenylmethyl)-1H-indazol-3-yl]methoxy]propanoic acid) decreases the severity of AP in rats when administered concurrently with sodium taurocholate retrograde infusion.¹⁹ The CCR2 antagonist RS102895 that we used in our study has not yet been evaluated for efficacy in ameliorating the severity of AP in preclinical models.

Injection of IL-12+IL-18 produces mild AP in lean mice and severe AP in both genetic and diet-induced obese mice.^{4,20,21} This model is characterized by sterile inflammation, which is the common thread in AP clinically despite multiple triggering mechanisms (pancreatic duct distension from gallstone obstruction, anatomic variants or acinarization during endoscopic

retrograde cholangiopancreatography; drug-related, including alcohol; and rarely mutations in pancreatic enzymes or their activators).

Because the incidence and severity of AP is greater in obese individuals^{4,22,23} and no therapies for this disease are currently available, we sought to determine whether the lipase inhibitor orlistat, the PPAR- γ agonist rosiglitazone, and the CCR2 antagonist RS102895 are effective when administered therapeutically following induction of AP in obese mice using the IL-12+IL-18 model.

MATERIALS AND METHODS

Animals, induction of AP, and drug treatments

Animal protocols were approved by the Animal Care and Use Committee of the University of Illinois at Chicago. For dietary induction of obesity, male C57BL6 mice from The Jackson Laboratory (Bar Harbor, ME) were fed a high-fat diet (60 Kcal% fat; Research Diets, New Brunswick, NJ) ad libitum for 13 weeks, beginning at 4 weeks of age. Treatment groups were randomized by randomly selecting mice from the same shipment with the same birth date.

Murine rIL-12 and rIL-18 (R&D Systems, Minneapolis, MN, and Medical & Biological Laboratories Co., Nagoya, Japan) were administered intraperitoneally at 150 ng/mouse and 750 ng/mouse, respectively, at 24 h intervals, for a total of two injections, as described previously.^{20,21} Mice were injected intraperitoneally at 2, 24, and 48 hours after the second injection of IL-12+IL-18 with rosiglitazone (0.4 mg/mouse; ~10mg/kg¹⁵), orlistat (2 mg/mouse; ~50 mg/kg⁴), or RS102895 [1-[2-[4-(trifluoromethyl)phenyl]ethyl]-spiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one] (0.3 mg/mouse; ~7.5 mg/kg²⁴). Control mice received vehicle, consisting of 20 μ L DMSO and 80 μ L canola oil vehicle at the same time points. Mice were euthanized at 3 days after the second injection of IL-12+IL-18; at this time pancreatic pathology is at its most severe.²⁵ Severity of intraabdominal adipose necrosis was quantified macroscopically as described previously.²⁵ Blood was collected at the time of euthanasia in EDTA-treated tubes. A portion of pancreas was fixed in 10% buffered formalin for histological evaluation.

Miscellaneous measurements

Blood glucose levels were measured using the TRUEtrack glucose monitoring system (Nipro Diagnostics, Fort Lauderdale, FL). Complete cell counts with automated differential were measured with a Hemavet 950FS (Drew Scientific, Dallas, TX). Levels of adiponectin, galectin-3, osteopontin, and TIMP-1 in plasma were measured by ELISA with kits from R&D Systems (Minneapolis, MN). Levels of IL-6 and CCL2 in plasma were measured by ELISA with kits from eBioscience (San Diego, CA). Plasma levels of fatty acid and blood urea nitrogen were measured using kits from Cayman Chemicals (Ann Arbor, MI) and Sigma (St. Louis, MO), respectively.

Histologic analysis

For histological assessment, the pancreata were fixed in 10% buffered formalin, dehydrated, and embedded in paraffin. Sections were stained with hematoxylin and eosin for scoring by two investigators (R.J.C. and G.F.) blinded to the experimental groups, using a scoring system described previously.²¹

Statistical analysis

Data are expressed as means $\pm$ SEM. Differences were determined by one-way ANOVAs of individual drug treatments versus DMSO vehicle controls. Differences among drug treatments were not analyzed. Pearson's correlation coefficients were obtained for histologic outcomes versus body weight across all treatments. Statistical analyses were performed using SAS 9.1 for Windows (Cary, NC).

RESULTS

Severity of AP in drug treatments and controls

All mice had microscopic evidence of AP, with patchy severe edema, inflammatory infiltrate, acinar necrosis, and intrapancreatic fat necrosis (Figures 1 and 2). None of the treatments significantly altered the severity of pancreatic edema, acinar necrosis, or intrapancreatic fat necrosis (Figure 1A). However, rosiglitazone significantly increased the inflammatory infiltrate score (Figure 1A). On the other hand, the lipase inhibitor orlistat significantly decreased intraabdominal fat necrosis, as scored grossly on opening of the peritoneum and retroperitoneum at sacrifice (Figure 1B).

The pancreatic infiltrate was further characterized by scoring of the prevalence of leukocyte populations histologically. Compared to DMSO vehicle, rosiglitazone increased infiltration by each leukocyte population, including lymphocytes (Figure 3A), macrophages (Figure 3B), and neutrophils (Figure 3C), whereas RS102895 selectively increased pancreatic infiltration by neutrophils (Figure 3C). None of the pharmacologic treatments had any significant effects on absolute number or proportion of circulating leukocyte subsets, hemoglobin or platelet counts compared to DMSO vehicle controls (Table 1).

Degree of obesity and pancreatitis severity

At day 0, the day of the second injection of IL-12+IL-18, body weights were not significantly different among mice in the different groups (Table 2). As expected, mice lost weight following induction of AP (Figure 4).^{20,21} None of the drug treatments significantly affected the degree of weight loss. Moreover, none of the drug treatments significantly affected plasma free fatty acid concentrations or levels of blood urea nitrogen (Table 2). Across the drug treatments, all of the histologic endpoints were significantly positively correlated with the starting body weights of the mice (Table 3).

Effects of orlistat, rosiglitazone, and RS-102895 on adipokines and cytokines

We measured several adipokines and cytokines to further characterize the effects of the drugs on the inflammatory response in AP. As expected, rosiglitazone increased plasma adiponectin levels over DMSO controls (Figure 5A), whereas the other treatments did not

significantly affect circulating adiponectin levels. There was a trend toward decreased circulating tissue inhibitor of metalloproteinase (TIMP)-1 in mice administered orlistat versus DMSO controls ($p=0.08$; Figure 5B), but no significant differences with any treatment group. There were no significant differences between any of the drug treatments and DMSO vehicle controls in plasma levels of IL-6, CCL-2, osteopontin, or galectin-3 (Table 2).

DISCUSSION

There is an unmet need for pharmacologic agents that will decrease the severity of AP. However, as we show in this report, therapeutic treatment with orlistat, rosiglitazone or RS102895 fails to significantly improve the severity of AP on histologic evaluation. This is disappointing because these agents or agents in their pharmacologic classes have previously been shown to improve the severity of AP when given prior to or at the time of induction of AP in rodent models.

We do show that orlistat decreases intra-abdominal fat necrosis when given following the induction of AP, similarly to when orlistat is administered between doses of IL-12+IL-18 in obese mice.^{4,5} The lack of protection from pancreatic edema, acinar necrosis, and intrapancreatic fat necrosis in mice treated with orlistat in this study may be related not only to the timing of doses, but also the vehicle used (DMSO/canola oil in our study vs. 30% ethanol in other experiments)⁴. The trend toward a decrease in TIMP-1 in mice treated with orlistat may translate into less fibrosis during recovery from acute pancreatitis,²⁶ though we did not measure time points after 3 days and therefore could not evaluate the presence of possible foci of fibrosis.

Our finding of increased lymphocytes, macrophages, and neutrophils in pancreas of obese mice with AP treated therapeutically with rosiglitazone is surprising, though it may represent a difference relating to the timing of rosiglitazone dosing. Pancreatic infiltrate is decreased at day 7 of AP compared to controls when rosiglitazone is given orally and chronically in a preventative manner to obese mice.¹⁶ Obese humans treated with a thiazolidinedione for 21 days had decreases in neutrophil and macrophage markers in skeletal adipose tissue.²⁷ Rosiglitazone given chronically increases fat infiltration of the pancreas in obese mice,²⁸ an effect that is expected to exacerbate AP severity.⁴ We did not quantitate the fat infiltration of pancreata in this study, but it seems unlikely that three doses of rosiglitazone would increase fat infiltration. The adipokine osteopontin is unchanged in rosiglitazone-treated obese mice in the current study, though it is increased when rosiglitazone is given chronically in a preventative manner.¹⁶ The increase in circulating adiponectin in rosiglitazone-treated mice is in agreement with previous findings¹⁶ and adipocyte culture data.⁸ Adiponectin is thought to be protective in AP: 1) adiponectin levels are inversely correlated with the severity of AP clinically, though this is confounded by its inverse correlation with adipose mass,²⁹ and 2) adiponectin-deficient mice experience more severe AP induced by caerulein than wild-type controls.³⁰ The lack of an effect of adiponectin elevation on histopathologic measures of AP severity in our study may be related to the timing of rosiglitazone dosing. However, it should be noted that administration

of exogenous adiponectin from does not protect against caerulein-induced AP in obese mice.³¹

We expected, but did not observe, a decrease in pancreatic inflammatory infiltrate in AP with therapeutic administration of the CCR2 antagonist RS102895. Although we may have missed an earlier effect by examining pancreata only at day 3, these results may also represent an effect of timing of administration of this agent. We did not observe a compensatory increase in circulating CCL-2 levels with RS102895, though this was seen with the CCR2 antagonist Bindarit in rats.¹⁹

Limitations of our study include evaluation of a single dose for each drug and a single time point for disease severity. Therefore, we cannot exclude the possibility that the same drugs may be efficacious if administered at different doses or that they may affect disease severity at earlier or later time points, particularly in the recovery phase. We also did not assess the effect of therapeutic administration of these compounds in lean animals and we limited our study to a single model of AP. Finally, because pancreatic edema was only evaluated histologically, fixation artifacts may have influenced the results.

In conclusion, drugs previously shown to improve the severity of AP, when administered in a preventative fashion, failed to do so when given therapeutically following induction of AP in obese mice. These potential agents have yet to be evaluated for their therapeutic effectiveness in other models of AP.

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Figure 1.

A) Histologic scores of pancreatic edema, acinar necrosis, and intrapancreatic fat necrosis, and B) gross intraabdominal fat necrosis at day 3 of acute pancreatitis in obese mice administered DMSO (vehicle), orlistat, rosiglitazone or RS102895. Data are expressed as mean $\pm$ SEM of 7 mice per group, except for intrapancreatic fat necrosis (DMSO n=5, orlistat n=6, rosiglitazone n=7, RS102895 n=5). * $p < 0.05$ compared to DMSO vehicle group.

Figure 2. Hematoxylin and eosin-stained pancreas sections at day 3 of acute pancreatitis in obese mice administered DMSO (vehicle), orlistat, rosiglitazone or RS102895.

Figure 3. Histologic scores of pancreatic infiltrate with A) lymphocytes, B) macrophages, and C) neutrophils at day 3 of acute pancreatitis in obese mice administered DMSO (vehicle), orlistat, rosiglitazone or RS102895. Data are expressed means $\pm$ SEM of 7 mice per group. * $p < 0.05$ compared to DMSO vehicle group.

Figure 4.
Body weights of mice following induction of acute pancreatitis. Values are means $\pm$ SEM.

Figure 5.

Concentrations of A) adiponectin and B) TIMP-1 at day 3 of acute pancreatitis in obese mice administered DMSO (vehicle), orlistat, rosiglitazone, or RS102895. Data are expressed means $\pm$ SEM of 7 mice per group. * $p < 0.05$ compared to DMSO vehicle group.

Table 1

Hematologic parameters

	DMSO	ORLISTAT	ROSIGLITAZONE	RS102895
WBC ($10^3/\text{ml}$)	8.0 $\pm$ 1.1	8.1 $\pm$ 1.0	9.7 $\pm$ 1.2	5.8 $\pm$ 0.9
%NE	34 $\pm$ 5	25 $\pm$ 4	27 $\pm$ 2	39 $\pm$ 6
%LY	62 $\pm$ 5	70 $\pm$ 3	69 $\pm$ 2	56 $\pm$ 5
%MO	3.1 $\pm$ 0.4	3.3 $\pm$ 0.2	3.2 $\pm$ 0.4	3.9 $\pm$ 0.8
%EO	1.0 $\pm$ 0.2	1.0 $\pm$ 0.5	0.9 $\pm$ 0.4	1.4 $\pm$ 0.6
%BA	0.21 $\pm$ 0.07	0.23 $\pm$ 0.14	0.21 $\pm$ 0.13	0.33 $\pm$ 0.17
Hgb (g/dl)	11.6 $\pm$ 0.4	11.4 $\pm$ 0.4	11.4 $\pm$ 0.2	11.5 $\pm$ 0.4
Platelets ($10^3/\text{ml}$)	693 $\pm$ 38	695 $\pm$ 81	671 $\pm$ 66	606 $\pm$ 76

White blood cell (WBC) counts, neutrophil (NE), lymphocyte (LY), monocyte (MO), eosinophil (EO) and basophil (BA) percentages, hemoglobin (Hgb) levels, and platelet number in EDTA-treated blood. Data are expressed as means $\pm$ SEM of 7 mice per group.

Table 2

Baseline body weight and plasma concentrations of blood urea nitrogen, free fatty acids, cytokines and adipokines at day 3 in mice with AP.

	DMSO	ORLISTAT	ROSIGLITAZONE	RS102895
Baseline body weight (g)	39.2±1.7	39.5±1.8	39.1±1.7	38.8±2.0
BUN (mg/dL)	16.5±3.5	20.1±3.6	15.9±2.3	17.9±3.1
Free fatty acids (μM)	579±27	526±28	554±20	570±29
IL-6 (pg/mL)	62±10	44±17	39±16	55±10
CCL-2 (pg/mL)	574±116	457±82	448±64	726±124
Osteopontin (pg/mL)	339±68	361±116	366±46	407±67
Galectin-3 (pg/mL)	616±105	677±171	668±47	658±86

Data are expressed as means ± SEM. N=7 mice per treatment except for CCL-2, for which n=6 in the DMSO group due to contamination of one sample.

Table 3

Correlation of body weight at day 0 with microscopic scores of pancreatitis severity at day 3 in mice with AP.

	Pearson's correlation coefficient (r)	P value
Edema	0.49	<0.05
Infiltrate	0.43	<0.05
Acinar necrosis	0.47	<0.05
Fat necrosis	0.59	<0.005
Total score	0.55	<0.01

N=23 mice. Pancreatic sections of five of the 28 mice in the study had no visible intrapancreatic fat and were therefore not included in the correlation analysis.