

LETTER

Ritonavir and Disulfiram May Be Synergistic in Lowering Active Interleukin-18 Levels in Acute Pancreatitis, and thereby Hasten Recovery

Richard Eric Kast

Department of Psychiatry, University of Vermont. Burlington, VT, USA

Summary

Interleukin-18 (IL-18) is one of the mediators of both pancreas damage and systemic complications like hypotension and multi-organ dysfunction during acute pancreatitis. IL-18 is generated intracellularly from pro-IL-18 by caspase-1 mediated proteolysis. Active caspase-1 itself is generated intracellularly by the action of the inflammasome, autocatalysis and other stimuli. The anti-retroviral drug ritonavir inhibits conversion of inactive pro-caspase-1 to active caspase-1. Since ritonavir is well tolerated in short-term use it may therefore prove useful in treating acute pancreatitis by lowering caspase-1 mediated IL-18 formation and the many inflammatory mediators downstream from that. The alcoholism treatment drug disulfiram has been in continuous use since the 1950s. It likewise has a low risk profile. Disulfiram inhibits several human proteases, among them caspase-1. Given the current morbidity and mortality of pancreatitis, research should be directed to ritonavir and disulfiram as treatment options for illnesses like pancreatitis where excessive IL-18 contributes to pathology. The first clinically used angiotensin converting enzyme inhibitor, captopril, has shown potent caspase-1 inhibiting activity as well and should be investigated in rodent models of human pancreatitis.

Introduction

This short note reviews the role of interleukin-18 (IL-18) in acute pancreatitis. IL-18 is a narrow yet important aspect of acute pancreatitis. Narrow because many other inflammatory mediators are active in acute pancreatitis, but important because: a) many of the other inflammatory mediators arise secondary to IL-18; and B) we happen to have several medicines, in use for other purposes for decades, that pre-clinical and murine studies have indicated happily have ability to lower active IL-18 formation. Also giving IL-18 particular importance is: c) the cause of early mortality in acute pancreatitis is mostly due to systemic inflammation, for which IL-18 is an important driving force [1, 2, 3].

Alcohol abuse and cholelithiasis account for 90% of acute pancreatitis, with autoimmune, genetic, hyperlipidemia, obesity and other factors as less common predisposing factors [1, 2, 3]. Diverse secondary morbidity is seen, with chronic pain as a common sequela. Mortality rate is not trivial by multiorgan dysfunction that in extreme forms leads to multiorgan failure[1, 2, 3]. The clinical picture is dominated by fierce pain, hypotension, and susceptibility to secondary infection. Hepatitis and pneumonia are common. Endoscopic or surgical decompression procedures, necrotic tissue removal can help. Medical interventions seem limited to

supportive measures, antibiotics for secondary infection, etc. and have not changed much in the last 50 years [1, 2, 3]. This short note presents data indicating that three old drugs, ritonavir, disulfiram, and captopril, have potential to lower IL-18 and may therefore be of benefit in treating pancreatitis.

Pancreatitis and IL-18

The chain of events surrounding IL-18 activation in general is depicted in Figure 1. That IL-18 is an important and active link in the generation of human pancreatitis [4, 5, 6, 7, 8, 9]. There are many others. The core event in acute pancreatitis is pancreatic tissue destruction by trypsin generation within the pancreas. To what extent that ectopic trypsin activation is driven by IL-18 or excessive IL-18 is driven by events secondary to trypsin activation is unknown. Whichever is primary in pancreatic tissue destruction, the systemic inflammation and multiorgan failure of pancreatitis that is responsible for a considerable proportion of early deaths in acute pancreatitis, is largely mediated by

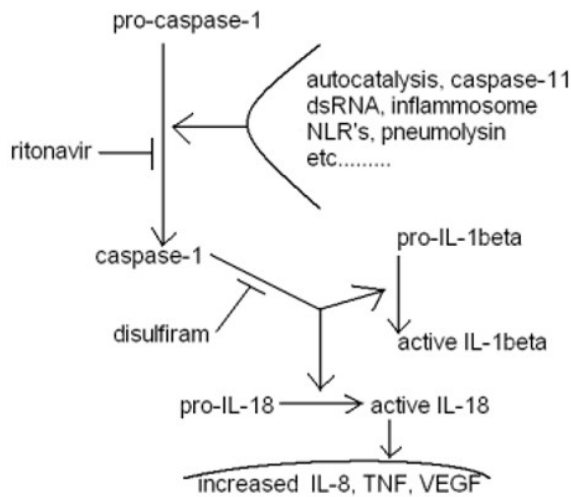


Figure 1. Schematic diagram of how disulfiram and ritonavir have been shown to act at two separate steps in path to generation of active interleukin-1beta and interleukin-18 with consequent inflammation in pancreatitis.

dsRNA: double stranded RNA
 NLR: nod-like receptor, intracellular receptors of similar function to the outer cell membrane toll-like receptors
 TLR toll-like receptor
 TNF: tumor necrosis factor-alpha
 VEGF: vascular endothelial growth factor

inflammatory mediators secondary to excessive IL-18 that is in turn generated via upregulated and disinhibited caspase-1 action within the inflamed, necrotic pancreas [4].

IL-18 is an 18 kDa active cytokine generated by proteolytic cleavage of an inactive 24 kDa form, pro-IL-18, by the action of caspase-1 [3, 4, 10, 11] (Figure 1). IL-18 plays a central role in both adaptive, antigen driven immunity and innate, pathogen associated molecular pattern, pathogen associated molecular pattern, driven inflammation [10, 11].

Notable synthesis of IL-18 occurs in articular chondrocytes, keratinocytes, Kupfer cells, macrophages, osteoblasts, and synovial cells [12]. Exceptional levels, up to 1,000 times the upper reference limit, are seen in rheumatoid arthritis, and particularly adult-onset Still's disease [12].

In experimental pancreatitis induced by retrograde instillation of sodium taurocholate into the common duct in rats, lung injury ensues consequent to the provoked pancreatitis, as it often does in human pancreatitis. If these rats are given an experimental intraperitoneal caspase-1 inhibitor, lowered indexes of lung injury were seen commensurate with the lowered circulating IL-18 [13].

In patients with chronic pancreatitis, circulating IL-18 levels are considerably elevated [4, 5, 6, 7]. Acute pancreatitis is associated with a 5-fold increase in circulating IL-18 [7] and levels are roughly proportional to acute pancreatitis severity [8, 9] and immunohistochemistry of pancreas tissue shows elevated IL-18 content [5].

Tumor necrosis factor-alpha (TNF) levels are likewise elevated in pancreatitis. TNF and IL-18 levels tend to parallel each other [8, 9] supporting the suggestion that following daily TNF levels in acute pancreatitis patients might provide fast feedback on patient trajectory allowing faster response and preemptive interventions to impending deterioration. It is suspected but has not been established that elevated IL-18 or TNF presage clinical deterioration. This matter needs further study.

Multiorgan dysfunction becomes more common as IL-18 level rises [14]. Ascitic fluid associated with acute pancreatitis has massive IL-18 content [14].

Ritonavir

A schema of how ritonavir and disulfiram inhibit the IL-18 activation process is depicted in Figure 1. Ritonavir is a 721 Da, short half-life (several hours), hepatically eliminated, orally active HIV protease inhibitor used to treat HIV infection since 1996. In addition to inhibiting the HIV protease, ritonavir is a potent inhibitor of human liver P450-3A4 activity and has been shown to block the conversion of inactive, 45 kDa pro-caspase-1 to active, 20 kDa subunits that dimerize to form catalytically active caspase-1 [15, 16, 17].

Disulfiram

Disulfiram is a 296 Da, long half-life (days), hepatically eliminated, orally active acetaldehyde dehydrogenase inhibitor used since 1950s to help recovering alcoholics abstain from drinking alcohol by generating high and extremely unpleasant levels of acetaldehyde should alcohol be consumed during treatment. Disulfiram also inhibits several caspases important for inflammation, among them caspase-1 [18], as depicted in Figure 1.

Captopril

In vitro, the oldest angiotensin converting enzyme (ACE) inhibitor in clinical use, captopril, also showed caspase-1 inhibiting effects in nM range [19] and could be considered as well for clinical use in lowering IL-18 destructive activity in pancreatitis if rodent studies confirmed benefit in experimental pancreatitis.

Conclusion

If pre-clinical and murine studies support the projected pancreatitis protection and IL-18 lowering effect of captopril, disulfiram, or ritonavir, clinical study of these in acute pancreatitis patients who are showing multiorgan signs, elevated IL-18, and

deteriorating course under standard treatment, should be considered.

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Correspondance

Richard Eric Kast
University of Vermont
2 Church Street
Burlington, VT 05401
USA
Phone: +1-802.863.2462
Fax: +1-802.863.2462
E-mail: rekast@email.com

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