

I will respond to each reviewer's comments individually.

Response to reviewer 03081313

The reviewer suggested that we include a table or figure and adjust the reference format. We have added 2 figures and changed the references.

Response to reviewer 00947129:

The reviewer states that this is very similar to a review that we published last year. While it is true that many of the topics covered are similar, we have included a variety of new information within these topics or changed the focus of the topics themselves. It is our intention in this article to emphasize potential novel target for treatment of acute pancreatitis. I apologize that one section was inadvertently included that was the same as the previous article; this inappropriate oversight has been rectified. Below I will address major points.

Major points:

- 1) The abstract should be more specific and at least list the covered topics. At the suggestion of the reviewer, we have changed the abstract.
- 2) The title of some of the sections are odd, in particular, we have included a heading entitled Introduction, and have change the title of the section describing the effects of ethanol on calcium mobilization from Effects of Ethanol on the Inappropriate Activation of Pancreatic Enzymes to Effects of Ethanol on the Cellular Mobilization of Calcium and the Inappropriate Activation of Pancreatic Enzymes.
- 3) A number of paragraphs do not contain any references. Initially, we had assumed that these two introductory paragraphs contained information that was common knowledge. To help the uninitiated reader, we have included references in these paragraphs.
- 4) The mortality rate of sever acute pancreatitis can be greater than 10%. We have changed this figure to from 10% to 10- 30%.
- 5) The possible role of ductal cells in alcohol acute pancreatitis was not discussed. We have rectified thi omission and now include a section discussing the possible involvement of ductal cells in alcoholic acute pancreatitis.
- 6) There are a lot of redundancies in this paper. We have removed a number of redundancies including the statement regarding NF-kB on page 5.
- 7) SERCA is very important regulator of intracellular calcium yet it is not mentioned on page 5-6 in the discussion of the Cellular Mobilization of Calcium and the Inappropriate Activation of Pancreatic Enzymes. To avoid redundancies and supply continuity we discuss SERCA in the mitochondrial dysfunction section.
- 8) The fact that pancreatic stellate cells express ADH may have an important role in the development of alcoholic pancreatitis does not make sense. We have expanded this thought so as not to confuse the reader. On page 15 what is meant by acute pancreatitis in general? Pancreatitis in general is

- meant to refer to acute pancreatitis caused by any factor and not specific to alcoholic acute pancreatitis.
- 9) There is no need to abbreviate things only mention once. We have removed such abbreviations.
  - 10) The conclusion that inhibiting FAEE synthase is in the conclusions but not discussed in the text. Thank you for catching this oversight. The discussion regarding the effectiveness of FAEE synthase inhibition was inadvertently deleted. We have now included that discussion.
  - 11) References are missing the PMID. They now include the PMID and the DOI.
  - 12) The paper would benefit from some figures. We have included two figures
  - 13) We have once again proof read the manuscript in an attempt to catch any typos.

#### Response to reviewer 02526196

The reviewer suggested that we include an introduction and reformat the manuscript. We have taken these comments very seriously and added an abstract and introduction. Additionally, at the suggestion of the reviewer we have added two figures. We have chosen to keep the current targets for treatment at the end of the article and have included the experimental evidence and rationale for the use of these treatments in the discussion of the pathogenesis of alcoholic pancreatitis. We have also added a running title and reformatted the references.

#### Response to reviewer 03002252

The reviewer's only comment was that we should include some schematic figures. We have included two figures.

#### Response to reviewer 02462595

This reviewer felt the manuscript was just fine as written. The reviewer made one comment regarding punctuation, which we have changed.

#### Response to reviewer 00053888

This reviewer felt this was an excellent review. The reviewer's only comment was that the manuscript would benefit from the inclusion of figures. In response to this comment we have added two figures.