Renalase agonist, BP1002, alleviates visceral hypersensitivity and reduces excitability of pancreas-innervating neurons in a mouse model of acute pancreatitis.

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Abstract

Acute pancreatitis (AP) is a life-threatening gastrointestinal condition with many possible causes, the most common being chronic alcohol consumption. Severe epigastric pain is the most common presenting symptom of AP. Management of this pain relies on opioids and NSAIDs, and there is a need for alternatives for pain management in AP. We are studying the efficacy of novel therapeutic peptide and renalase agonist, BP1002, for treating pain in a mouse model of acute pancreatitis. BP1002 potentiates the activity of renalase, an enzyme with pro-survival and anti-inflammatory activities that has been found to be positively associated with better outcomes in both mice and humans. Our lab has demonstrated that administration of BP1002 *in vivo* reduces visceral pain response in a mouse model of AP. In this study we use whole-cell patch clamp electrophysiology to assess if administering BP1002 will reduce excitability of pancreas-innervating dorsal root ganglia neurons in mice with AP. Male BALB/c mice received injection of CTB555 into the long head of the pancreas to label afferent nerve terminals in the pancreas. After 2 weeks mice received BP1002 or vehicle injection at the beginning of a course of hourly injections of cerulein over two days (14 injections total). Bilateral thoracic dorsal root ganglia (T9-12) were then removed, enzymatically and mechanically dissociated and plated for overnight incubation. Whole-cell current clamp recordings were obtained from DRG neurons that contained the fluorescent CTB555 label. The firing frequency of recorded neurons was decreased in the mice that received BP1002, indicating a decrease in neuronal excitability. Future work will examine the molecular and cellular nature of pancreas-innervating neuronal subtypes implicated in the mechanism of action of BP1002. This study has far reaching clinical implications for the treatment of acute pancreatitis.

Non-expert summary

Acute pancreatitis is associated with severe abdominal pain and managing this pain presents a clinical challenge. We are studying a drug (BP1002) that may be useful for treating pancreatitis. in mice that have acute pancreatitis, we have found previously that BP1002 reduces their pain behaviors. In this study we are using the same mouse model of acute pancreatitis and testing the excitability of the nerves that detect pain in the pancreas.