The copper-deficient model of injury is one for studying pancreatic regeneration. Here we can see the destruction of pancreatic parenchyma, concomitant liver injury and regeneration of both organs during the recovery phase of the experiment. 

Aims & Methods: The aim of our work was to study the expression of insulin and glucagon in pancreas and liver tissue in rat copper-deficient model of injury, 24 white Wistar male rats (80-100 g weight) were maintained on copper-deficient diet (MP Biomedicals, USA) containing a relatively non-toxic copper-chelating agent, triethylenetetramine tetrahydrochloride in final concentration of 0.6% w/w for 8 weeks, and then returned to normal rat chow for another 8 weeks (recovery phase). Groups of 3 animals each were killed after 2, 4, 6, and 8 weeks of copper-deficient diet and 2, 4, 6, and 8 weeks of recovery phase. Paraffin sections of liver and pancreas were stained immunohistochemically using antibodies to insulin and glucagon. The level of these hormones was measured in the blood of rats.

Results: After 4 weeks of copper-deficient diet we observed glucagon-positive cells in peripheral part of the islets as well as single glucagon-positive cells and their clusters resembling newly formed islets. Expression of glucagon was maximally evident 8 weeks after copper-deficient diet and continued to be at the same level 2 and 4 weeks after rats were returned to normal rat chow. Groups of glucagon-positive hepatocyte-like cells were found in the pericentral areas of liver, solitary glucagon-positive hepatocyte-like cells in liver parenchyma during all weeks of our experiment. The maximum of glucagon expression in liver was detected 2 weeks after return to normal rat chow. Glucagon-positive cells were observed only in peripheral part of the pancreatic islets after 8 weeks of copper deficiency. Expression of glucagon in liver decreased alongside; glucagon-positive cells were located predominantly in pericentral areas. Insulin-positive cells were found in central part of the pancreatic islets during the experiment. Insulin-positive hepatocyte-like cells were detected in the pericentral areas and in liver parenchyma from 4th to 6th weeks of diet, the number of these cells was the highest after 6 weeks of copper-deficient diet. After 8 weeks of diet we observed insulin-positive small round cells – at least 1 positive cell was around every tenth central vein (these cells were single after 4 and 6 weeks of diet). Appearance of the insulin-positive hepatocyte-like cells was accompanied with increase of insulin level in venous blood. The maximum of insulin expression in liver coincided with the highest concentration of insulin in venous blood after 6 weeks of diet. After rats were transferred to normal rat chow, we observed solitary insulin-positive small round cells in liver tissue until 2nd week. Later positive cells were not detected in liver.

Conclusion: We suppose that glucagon-positive pancreatic islet cells are probably the source of pancreas regeneration in rat copper-deficient model; the appearance of glucagon- and insulin-positive cells in liver tissue confirms common origin of these organs and can be the response reaction for the pancreatic tissue injury. 

Disclosure of Interest: All authors have declared no conflicts of interest.

References

P0086 CYCLIC ADENOSINE MONOPHOSPHATE PRODUCTION STIMULATED BY ORAII AND EXTENDED SYNAPTOTHIN 1 J. Fanczal, T. Madacyz, P. Hegyi, A. Mulini, S. Muellerm, J. Malith1,2
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Introduction: Cyclic adenosine monophosphate (cAMP) and Ca2+ signaling play crucial secretory regulatory functions of epithelial cells. The two signaling system have multiple synergistic interactions helping to optimize the cellular response to stimulation. One of the interfaces between the store operated (SOC) and cAMP signaling is Ca2+ cycle8 (ACC) that increase CAM production, however its exact molecular mechanism is not known.

Aims & Methods: In this project we wanted to characterize the interactions of cAMP and Ca2+ signaling further focusing on the molecular components of SOC. Human embryonic kidney (HEK) cells were transfected with plasmids encoding the proteins of interest. Cellular CAM production was measured by fluorescence resonance energy transfer (FRET) using the cAMP reporter Epac. Results: The stimulation of the cells with 5μM forskolin and 100μM 3-isobutyl-1-methylxanthine (IBMX) resulted in reversible elevation in CAM production. The expression of AC8 significantly elevated the cAMP response, whereas, Orail induced spontaneous CAM production and a massive increase in the stimulated CAM production. The production of Orail was completely Ca2+ independent. Extended synaptothin 1 (E-Set1), a recently described endoplasmic reticum-plasma membrane tethering protein increased the cAMP response, similarly to Orail.

Conclusion: Our results showed that Orail and E-Set1 play an important role in the regulation of cAMP production. However further studies are required to clarify the mechanisms of the interaction. 

Disclosure of Interest: All authors have declared no conflicts of interest.

P0087 VX-809 RESTORES THE EXPRESSION DEFECT OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR CAUSED BY ALCOHOL IN CAPAN-1 CELLS J. Malith1, T. Madacyz, P. Pallagi2, P. Hegyi1
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Introduction: Excessive ethanol consumption is one of the most common causes of acute and chronic pancreatitis. Earlier we showed that ethanol and ethanol metabolites cause severe damage in the function and expression of the cystic fibrosis transmembrane conductance regulator (CFTR), which increases the severity of acute ethanol-induced pancreatitis. There are new compounds available, such as lumacaftor (VX-809), to correct the impaired CFTR expression in cystic fibrosis patients, however additional potential utility of this compound in pancreatitis treatment has never been investigated.

Aims & Methods: Our aim was to test the effect of VX-809 treatment on the CFTR expression during ethanol exposure. CFTR expression was evaluated by immunofluorescent staining in Capan-1 cells. The cells were incubated with 100 μM ethanol, 10 μM VX-809, or their combination for 24h. Images were captured by confocal microscopy.

Results: As reported earlier exposure of Capan-1 cells to 100 μM ethanol for 24 hours significantly decreased the plasma membrane expression of CFTR. In parallel the cytoplasmic CFTR expression was increased. 10 μM VX-809 alone increased the cytoplasmic CFTR expression of the CFTR expression. Notably, application of 10 μM VX-809 in pretreatment (treatment started 6h prior to ethanol exposure), or post-treatment (treatment started 6h after to ethanol exposure) significantly improved the plasma membrane expression of CFTR.

Conclusion: These preliminary findings suggest that VX-809 might be able to restore the CFTR expression defect caused by alcohol. Further extended in vitro and in vivo studies need to clarify the effect of VX-809 on alcohol-induced pancreatitis.

Disclosure of Interest: All authors have declared no conflicts of interest.