Alcohol predisposes obese mice to acute pancreatitis via adipose triglyceride lipase-dependent visceral adipocyte lipolysis

We read with great interest articles by Wang et al and Hegyi et al, in which the authors reported that alcohol increased the risk of hereditary susceptibility to chronic pancreatitis. These results indicated an interaction effect between environmental and genetic risk factors on the development of pancreatitis. Epidemiological data suggested that alcohol abuse increased the risk of acute pancreatitis (AP) in people with type 2 diabetes mellitus (adjusted HR 86.3 (65.3–111.0)). However, no study investigated the synergistic effect between obesity and alcohol excess on AP development. Here we report the combination of acute alcohol intake and obesity causes AP with multiorgan injury (MOI) in mice, mediated by visceral adipocyte tissue (VAT) lipolysis.

The schedule of high-fat feeding and ethanol administration is shown in figure 1A. Body weight was significantly higher in the high-fat (obese) than the chow (lean) group after 12 weeks (figure 1B). Acute ethanol administration in obese mice induced significant increases in pancreatic histopathology scores (oedema, inflammation and necrosis; figure 1C), elevated circulating pancreatic enzymes (figure 1D), pancreatic and lung myeloperoxidase, and serum interleukin-6 levels (figure 1E). Time-course changes in this obese alcoholic acute pancreatitis (OA-AP) model showed pancreatic injury parameters were significantly elevated from 3 to 6 hours after the first ethanol injection, with rises in MOI indices (online supplemental figure 1A–F); almost all parameters peaked at 12 hours. In contrast, acute ethanol administration in lean mice caused only mild pancreatic oedema without discernable pancreatic necrosis or elevations of MOI indices.

We speculated that lipolysis from excess abdominal fat is critical to OA-AP, releasing free fatty acids (FFAs) from ethanol-induced VAT lipolysis. Indeed, fat saponification was seen in the peritoneal cavity and around the pancreas of ethanol-treated obese mice (online supplemental figure 2A,B). Circulating baseline FFA levels were higher in obese mice than in lean mice, which were further increased after acute ethanol administration (figure 1F). FFA and glycerol release over 3 hours from freshly isolated epididymal VAT of ethanol-treated obese mice was higher than that of lean mice (figure 1G). While pancreatic amylase or pancreatic triglyceride lipase (PNLIP) were comparable (figure 1H), adipose triglyceride lipase (ATGL) of ethanol-treated epididymal VAT was, however, significantly higher than from lean mice (figure 1I).

To confirm our hypothesis, we injected ethanol and adipocytes simultaneously...
into the abdominal cavity of lean mice, which recapitulated all features of OA-AP (figure 2A–F). Inhibition of lipolysis using specific ATGL inhibitor atglistatin significantly reduced pancreas histopathology scores, serum pancreatic enzymes, serum MOI indices and serum FFA levels, while PNLIP inhibitor orlistat had a minimal effect (figure 2G–L). These findings indicate ethanol-induced VAT lipolysis via ATGL activation is central to the pathogenesis of OA-AP. This mechanism parallels the protective systemic effects of ATGL inhibition in burn injury, distinct from systemic lipotoxicity consequent on leakage of PNLIP from the injured pancreas. Interestingly, we found both atglistatin and orlistat were protective against caerulein-induced AP in obese mice (online supplemental figure 2C–G), mirroring patients with COVID-19 where PNLIP-mediated and ATGL-mediated lipotoxicity may both take place after disease onset.

In summary, our study reports that obesity and alcohol act synergistically in the pathogenesis of onset and development of MOI in OA-AP through induction of ATGL-mediated VAT lipolysis. High amounts of ethanol alone may be insufficient to induce clinical AP and is not sufficient to induce murine experimental AP. A genetic predisposition or a susceptible precondition may be required, if not the presence of a cofactor, as in murine fatty acid ethyl ester AP induced by ethanol with palmitoleic or palmitic acid. Obesity is an alternative, which our model suggests may be targeted by ATGL inhibition.

Xinmin Yang,1,2 Linbo Yao,1,3 Lei Dai,4 Mei Yuan,1 Wenhua He,5 Tingting Liu,1 Xianghui Fu,6 Jing Xue,5 Robert Sutton,6 Qing Xia,1 Wei Huang1,2,3

1Department of Integrated Traditional Chinese and Western Medicine, Sichuan Provincial Pancreatitis Centre and West China-Liverpool Biomedical Research Centre, West China Hospital, Sichuan University, Chengdu, People’s Republic of China 2Institutes for Systems Genetics & Immunology and Inflammation, Frontiers Science Centre for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu, People’s Republic of China 3West China Biobanks, Department of Clinical Research Management, West China Hospital, Sichuan University, Chengdu, People’s Republic of China 4State Key Laboratory of Biotherapy and Cancer Centre, West China Hospital, Sichuan University and Collaborative Innovation Centre for Biotherapy, Chengdu, People’s Republic of China 5Department of Gastroenterology, First Affiliated Hospital of Nanchang University, Nanchang, People’s Republic of China 6Division of Endocrinology and Metabolism, State Key Laboratory of Biotherapy and Cancer Centre, West China Hospital, Sichuan University and Collaborative Innovation Centre for Biotherapy, Chengdu, People’s Republic of China 7State Key Laboratory of Oncogenes and Related Genes, Stem Cell Research Centre, Ren Ji Hospital, School of Medicine, Shanghai Cancer Institute, Shanghai Jiao Tong University, Shanghai, People’s Republic of China 8Liverpancreatitis Research Group, Liverpool University Hospitals NHS Foundation Trust and Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, UK

Correspondence to Dr Wei Huang, Department of Integrated Traditional Chinese and Western Medicine, Sichuan Provincial Pancreatitis Centre and West China-Liverpool Biomedical Research Centre, West China Hospital, Sichuan University, 5B Floor 2nd Building, Tianfu Life Science Park of Hi-Tech Industrial Development Zone, No. 88 Keyuan South Road,
OPEN ACCESS

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/. © Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2022-326958).

To cite Yang X, Yao L, Dai L, et al. Gut Epub ahead of print: [please include Day Month Year]. doi:10.1136/gutjnl-2022-326958

Received 12 January 2022
Accepted 12 March 2022

Gut 2022;0:1–3. doi:10.1136/gutjnl-2022-326958

ORCID iDs
Wenhua He http://orcid.org/0000-0001-5499-1346

REFERENCES