

Bile Acid Synthesis and 12-Hydroxylation are Increased, and Bile Acid Transport is Impaired in Human Obesity

Rebecca Haeusler, Columbia Univ, New York, NY; **Stefania Camastra**, **Monica Nannipieri**, Brenno Astiarraga, Univ of Pisa Sch of Med, Pisa, Italy; **Jose Castro-Perez**, **Dan Xie**, **Liangu Wang**, **Manu Chakravarthy**, Merck Res Labs, Kenilworth, NJ; **Ele Ferrannini**, CNR Inst of Clinical Physiology, Pisa, Italy

Bile acids (BAs) are now recognized as important signaling molecules. They have the ability to regulate a variety of physiologic processes, including those governing metabolism of glucose, triglycerides, and cholesterol. We hypothesize that obesity is associated with alterations in BA synthesis or turnover that may contribute to metabolic dysregulation. To test this, we measured serum BAs and markers of BA synthesis after overnight fasting, during a hyperinsulinemic-euglycemic clamp, or a mixed meal tolerance test in 11 nonobese and 32 obese subjects. We also analyzed BA transporter expression in specimens of human liver, duodenum, jejunum, ileum, colon, and pancreas. We found that BA synthesis markers were twofold higher ($P < 0.01$) and preferentially 12-hydroxylated ($P < 0.05$) in obese subjects, and both measures were correlated with clamp-derived insulin sensitivity ($r = -0.62$, $P < 0.0001$ and $r = -0.39$, $P = 0.01$, respectively). Insulin infusion acutely reduced serum BAs in nonobese subjects, but this effect was blunted in obese subjects (-44.2% versus -4.2% , $P < 0.05$). The rise in serum BAs postprandially was also relatively blunted in obese subjects ($+402\%$ versus $+133\%$, $P < 0.01$). Liver expression of the Na^+ -taurocholate cotransporting polypeptide (NTCP) and the bile salt export pump (BSEP) were negatively correlated with BMI ($r = -0.37$, $P = 0.02$ and $r = -0.48$, $P = 0.001$, respectively). We conclude that obesity is associated with increased BA synthesis, preferential 12-hydroxylation, and decreased hepatic BA transport. These findings reveal new pathophysiological aspects of BA action in obesity that may lend themselves to therapeutic targeting in metabolic disease.

Disclosure Block:

R. Haeusler: None. **S. Camastra:** None. **M. Nannipieri:** None. **B. Astiarraga:** None. **J. Castro-Perez:** Employment; Significant; employee of Merck Research Laboratories. **D. Xie:** Employment; Significant; employee of Merck Research Laboratories. **L. Wang:** Employment; Significant; employee of Merck Research Laboratories. **M. Chakravarthy:** Employment; Significant; employee of Merck Research Laboratories. **E. Ferrannini:** None.