Beneficial effects of bacterially-derived tryptophan metabolite indole-3-propionic acid *in vitro* and *in vivo* and its association with obese/T2D patients undergoing bariatric surgery

C. Cavanaugh, M. Jennis, G. Leo, J. Mabus, J. Lenhard, P. Hornby. Janssen, Spring House.

Introduction: The intestine and microbiome contribute to metabolic diseases (Type 2 diabetes, T2D, and obesity). This is in part due to increased inflammation[1] and intestinal permeability[2] resulting in metabolic endotoxemia that is associated with insulin resistance. Roux en Y Gastric Bypass surgery (RYGB) is efficacious by multiple mechanisms, including the composition of gut microbiome. Recent data from global metabolomics in obese and T2D patients showed reduced levels of bacterially-derived tryptophan metabolites, including indole-3-propionic acid (IPA), compared to lean non-diabetics[3]. IPA modulates intestinal inflammation[4], but its role in metabolic disease is unknown. Therefore, IPA was evaluated for effects on intestinal permeability *in vitro* and in Diet-Induced Obese (DIO) mice, as well as the plasma levels in patients before and after RYGB surgery.

Methods: Human intestinal epithelial T84 cell monolayers were cultured in transwells in the presence of pro-inflammatory cytokines (IFN-γ; 5ng/ml) or vehicle (24 h) as well as IPA (4 h). Apical addition of FITC-dextran (4kDa,1mg/ml) assessed paracellular permeability. DIO C57BL6 mice (19 wk high fat diet) were orally gavaged dailywith vehicle (PBS) or IPA (20mg/kg for 4 days) and intestinal permeability was assessed after oral FITC-dextran.

Results: IPA had little effect on monolayer permeability (vehicle), but ameliorated the enhanced permeability induced by IFNγ (left; *p<0.05) and in DIO mice (right). In obese diabetic patients (n = 9) plasma IPA is reduced relative to lean (n = 7) and the reduced levels are reversed by 3 months post-surgery.

Conclusion: A bacterially-derived tryptophan metabolite, IPA, is reduced in patients and increased after RYGB surgery. IPA reduces intestinal permeability *in vitro*, and in DIO mice therefore it mayin part benefit patients through improved intestinal barrier function in the context of metabolic endotoxemia.

1. Osborn O et al. (2012). Nat Med **18**:363-374. 2. Cani P et al. (2008). Diabetes **57**:1470-1481. 3. Sarosiek K et al. (2016) J Diabetes Res; http://dx.doi.org/10.1155/2016/3467403. 4. Venkatesh M et al. (2014) Immunity **41**:296-310