Metformin directly triggers GLP-1 and PYY secretion in human colon and ileum

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Background: Metformin is the first-line therapy for type 2 diabetes (T2D) for more than half a century. The exact mechanisms that mediate its blood glucose-lowering effect remain uncertain. Recent reports of superior efficacy of delayed-release oral formulations of metformin over the parenteral route suggest at least part of its anti-diabetic action is gut-mediated. There is evidence suggesting chronic metformin treatment increases plasma levels of GLP-1 and PYY, secretory products of the enteroendocrine L cells which are pivotal in glucose and energy homeostasis. We hypothesized metformin directly triggers release of these peptides from human ileal and colonic mucosae, where the highest density of L cells are found.

Method: An *ex vivo* preparation of human mucosa for secretion assay was developed from surgically resected human colon and ileum sections; mucosal tissue was obtained from 46 human colons (11 with T2D) and 10 ileums (3 with T2D) soon after surgical resection. 15-minute static incubations of the preparations with metformin were performed and the secretion supernatants were assayed for GLP-1 and PYY content.

Results: Acute exposure of human gut mucosal tissue to 10 μM metformin significantly induced GLP-1 and PYY release. This stimulatory effect was preserved across BMI and T2D subjects. GLP-1 and PYY co-release was tightly correlated. Metformin-induced GLP-1 and PYY release was blocked by AMPK inhibition and by inhibiting transporters associated with metformin internalization.

Conclusion: We demonstrated acute exposure of the human gut mucosa to metformin significantly triggers GLP-1 and PYY release, independent of any neural inputs. We also showed that AMPK activation and internalization of metformin were required for metformin-induced GLP-1 and PYY release from the mucosa. This mechanism may subserve weight loss and glycaemia benefits of metformin and are in-line with the growing acceptance that the gastrointestinal tract is the primary site of metformin's action.