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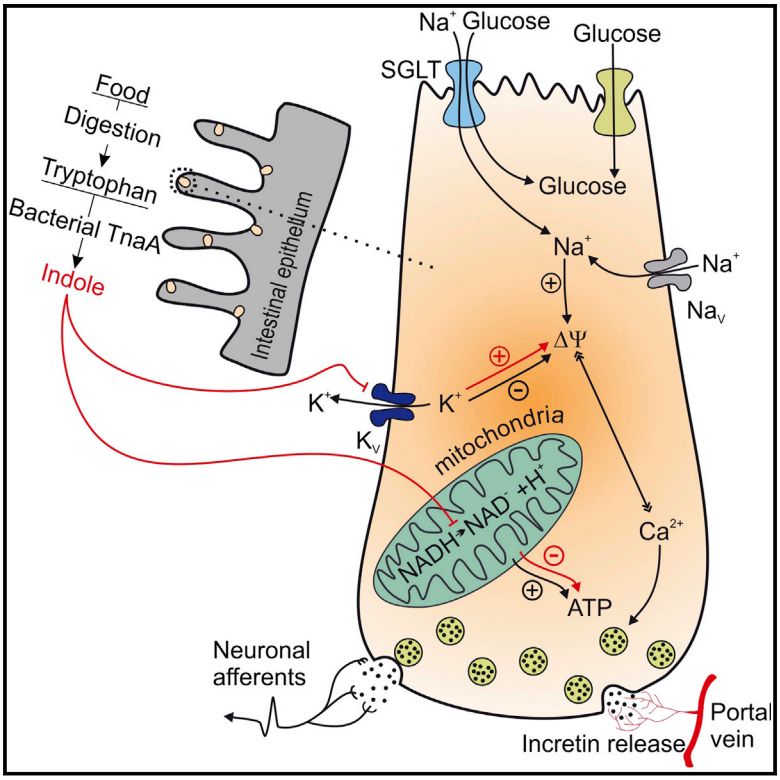
Bacterial Metabolite Indole Modulates Incretin Secretion from Intestinal Enteroendocrine L Cells

Graphical Abstract



Highlights

Bacterial metabolite indole modulates secretion of incretin peptide GLP-1

Indole widens the width of action potentials fired by L cells and elevates GLP-1

Prolonged exposure to indole inhibits ATP production and thus GLP-1 secretion

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In Brief

Indole is the main metabolite produced by gut bacteria from tryptophan. Chimerel et al. demonstrate that indole modulates the hormone secretion of enteroendocrine L cells and reveal the molecular mechanism behind this modulation. These findings suggest that the production of indole by bacteria could have a major impact on host metabolism.

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Bacterial Metabolite Indole Modulates Incretin Secretion from Intestinal Enteroendocrine L Cells

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SUMMARY

It has long been speculated that metabolites, produced by gut microbiota, influence host metabolism in health and diseases. Here, we reveal that indole, a metabolite produced from the dissimilation of tryptophan, is able to modulate the secretion of glucagon-like peptide-1 (GLP-1) from immortalized and primary mouse colonic L cells. Indole increased GLP-1 release during short exposures, but it reduced secretion over longer periods. These effects were attributed to the ability of indole to affect two key molecular mechanisms in L cells. On the one hand, indole inhibited voltage-gated K^+ channels, increased the temporal width of action potentials fired by L cells, and led to enhanced Ca^{2+} entry, thereby acutely stimulating GLP-1 secretion. On the other hand, indole slowed ATP production by blocking NADH dehydrogenase, thus leading to a prolonged reduction of GLP-1 secretion. Our results identify indole as a signaling molecule by which gut microbiota communicate with L cells and influence host metabolism.

INTRODUCTION

Obesity is one of the biggest health and socioeconomic issues of the 21st century, with the number of obese individuals worldwide almost doubling within the last 30 years. People suffering from obesity are at high risk of developing other metabolic diseases such as type 2 diabetes mellitus (T2DM), cardiovascular disease, and nonalcoholic fatty liver disease (Nicholson et al., 2012). Increasing physical activity and reducing food intake are recommended when treating obesity and associated metabolic diseases, but outcomes are only moderately successful as such lifestyle changes are not sustained long-term by most patients. Alternative strategies therefore need to be developed in order to control body weight more effectively. Anorectic gut hormones such as glucagon-like peptide 1 (GLP-1) and peptide YY are secreted into the circulatory system by enteroendocrine L cells in response to changes in the content of the gut lumen and are at the frontline of the search for new therapies. Gut hormones play essential roles in a wide range of metabolic functions such as the regulation of food absorption, appetite, and glucose homeostasis. As a consequence, drugs that enhance GLP-1 action are now widely used in the treatment of T2DM (Garber et al., 2009; Nauck et al., 2009; Zinman et al., 2009) and are under investigation for the treatment of obesity (Marre et al., 2009). Attention is also turning toward the enteroendocrine L cells themselves and whether they could be targeted for the treatment of obesity and diabetes.

Enteroendocrine L cells are distributed along the length of the intestinal epithelium and thus make direct contact with the gut microbiota. The colon not only harbors the highest density of enteroendocrine L cells within the intestine, but it is also host to the largest number of bacteria. Although it is widely believed that gut microbiota can modulate the function of colonic L cells, our understanding of the molecular mechanisms underlying this potential crosstalk is limited (Cani et al., 2013; Devaraj et al., 2013). Among the metabolites produced by bacteria in the gut, recent attention has focused on short-chain fatty acids, produced by the fermentation of unabsorbed starch and nonstarch polysaccharides. Short chain fatty acids activate G protein coupled receptors (GPCRs) expressed on the plasma membrane of L cells, enhancing L cell number and secretion (Cani et al., 2013; Petersen et al., 2014; Plaisancié et al., 1995; Psichas et al., 2014; Tarini and Wolever, 2010; Tolhurst et al., 2012). Many other bacterial metabolites are also abundantly present within the luminal contents of the colon (Nyangale et al., 2012). Here we focused on a metabolite of tryptophan, indole, as it has recently been shown that plasma tryptophan concentrations are decreased in mice following Roux-en-Y gastric bypass surgery (Mutch et al., 2009) and elevated in people with a high risk of developing T2DM (Wang et al., 2011). Moreover, indole production has been shown previously to vary with the dietary tryptophan content in human subjects (Bryan, 1966).

Indole, the most prevalent metabolite of tryptophan, is produced by a wide range of bacterial species, including those belonging to the genera Escherichia, Bacteroides, and Clostridium (DeMoss and Moser, 1969; Lee and Lee, 2010; Smith and Macfarlane, 1996). These bacterial species use tryptophanase to degrade tryptophan into indole, pyruvate, and ammonia,