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Editorial Open Access

Utilizing a Dietary Supplement to Modify Small Intestinal Secretory Function

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Editorial

During the last decade the hypothesis that consuming genistein may modify intestinal secretory function has been investigated. This is of importance in clinically relevant illnesses whereby intestinal abnormalities result in modifications of secretory function, for example in Cystic Fibrosis (CF) and diabetes. Fortunately, both of these diseases have murine models to better test the effects of dietary manipulations.

Genistein, a naturally occurring isoflavononic phytoestrogen found in soy [1], is readily absorbed across the intestines and reaches micro molar concentrations in the serum of individuals consuming a soy milk diet [2]. Within the small intestine, chloride secretion occurs at the crypts, a process that requires several transporters working in concert (Figure 1). The $Na^+/K^+/2Cl^-$ (NKCC1) co-transporter provides the entry point for Cl^- into the epithelial crypt cells, a driving force for Cl^- exit across the apical membrane is maintained by recycling of K^+ across the basolateral membrane, the Na^+/K^+-ATPase maintains Na^+ and K^+ concentration gradients across the membrane, and the major route for Cl^- exit (secretion) across the apical membrane into the lumen is via the CF trans membrane conductance regulatory protein, CFTR, Cl^- channel [3,4]. Loss of any individual transporter (or the regulation of) will result in intestinal secretory dysfunction.

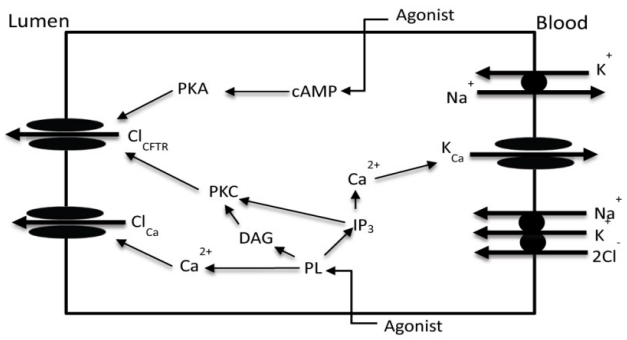

Figure 1: Simplified cartoon of a crypt cell within the small intestine: the site of chloride secretion. PKC: Protein Kinase C; DAG: Diacylglycerol; IP: Inositol Triphosphate; PL: Phospholipase; PKA: Protein Kinase A.

Genistein is a known modifier of several of those key proteins/transporters involved in successful intestinal secretory transport; NKCC1 [5], K^+ channels [6] and CFTR [7]. Indeed, initial studies revealed several beneficial effects of acute application of genistein to freshly isolated intestinal tissue. Acute application of genistein (75 µm) to jejunal tissue from male Swiss Webster mice has been shown to elicit increased trans epithelial ion secretion (a measure of chloride secretion), via inhibition of a PDE3-mediated pathway [8,9], whereas acute application of genistein (50 µm) to duodenal tissue from C57BL6J mice has been shown to stimulate HCO_3^- secretion via an estrogen receptor/PI3K pathway [10]. Those studies, and others, led the way to the development of dietary studies. Consumption of a genistein-containing diet (600 mg genistein/kg diet) for 4-weeks has been shown to increase trans epithelial chloride secretion across jejunum in lean (C57BL6J) female mice [11], while concomitantly increasing serum genistein levels to low micro molar range (comparable to humans consuming soy milk). In broiler chickens, improvements in intestinal morphometry have been measured (villus length, villus width, crypt depth, villus length/crypt depth ratio) following dietary genistein (5 mg genistein/kg feed) [12], indicating such food additives can promote gut health and function.

Murine models exhibiting intestinal secretory dysfunction such as those with CF and diabetic obesity provide useful settings with which to test genistein's effects. Mice homozygous for the DF508 mutation (the most common clinical mutation) are characterized with severe intestinal disease requiring continual treatment with laxative for survival [13]. This murine model mimics the intestinal obstruction (meconium ileus) seen in some CF patients [14]. Examination of the effects of dietary supplementation with genistein (600 mg genistein/kg diet) in the absence of laxative, in DF508 CF mice between 21-65 days of age, resulted in a significant increase in survival rate from 68% to 84% [15], suggesting potential therapeutic benefits. Favorable effects of genistein consumption on jejunal function in the diabetic obese ob/ob mouse have recently been evaluated. This diabetic obese mouse model exhibits a slowed gastrointestinal transit, thus mimicking one of the clinical symptoms noted in diabetics [16,17]. After consuming genistein (600 mg genistein/kg diet) for a period of 4-weeks, ob/ob mice had rescued basal Trans epithelial chloride secretion (i.e., levels returned to those measured in lean controls). Interestingly, genistein's beneficial effect on jejunum secretory function was mediated by sex-dependent mechanisms: Increasing KCa sensitive transepithelial secretion in females, and increasing both Na^+/K^+-ATPase activity along with NKCC1 expression in males [18], suggesting potential novel pharmacotherapeutic objectives in the treatment of intestinal dysfunction in diabetes.

The aforementioned studies aimed at improving intestinal secretory transport are relevant given that loss of secretory function can lead to increased bacterial translocation. There is no doubt that the mechanism(s) of action of dietary genistein are complex and its targets are countless and complicated, with sex-differences making matters more interesting. Thus, it is incumbent upon the scientific community to be especially rigorous and thorough in the assessment of the usefulness of such dietary manipulations. That said, understanding the

benefits of dietary supplementation with genistein in experimentally clinically relevant models of intestinal secretory dysfunction will certainly pave the way towards potential future applicability in clinical settings.

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