Inhibition Of The Zonulin-Dependent Increased Intestinal Permeability Can Prevent The Onset Of Type 1 Diabetes In BB/Wor Rats

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Background: Several studies suggest that an increased intestinal permeability (IP) due to alteration of intestinal tight junctions (tj) can be involved in the pathogenesis of many autoimmune diseases, including Type 1 diabetes (T1D). We have recently described a novel protein, zonulin, that dictates tj competency. Structure-function analysis of the protein allowed us to engineer a synthetic peptide (FZI/0) that prevents zonulin binding to its target receptor. Using BB/Wor diabetic-prone (DP) rats as an animal model of T1D, we have demonstrated an increase in intraluminal zonulin concentration compared to diabetic-resistant (DR) rats that paralleled the increase in IP and preceded the onset of T1D.

Aim: To establish whether FZI/0 can prevent the onset of T1D by affecting the IP.

Methods: BB/Wor DP rats were randomized at age 20 days into a treatment group that received drinking water plus 10 ug/ml FZI/0 in bicarbonate, and a placebo group that received only bicarbonate. In vivo IP using Lactulose/Mannitol assay and serum zonulin and glucose levels were monitored every 10 days. Rats with blood glucose ≥200mg/dl were considered diabetic and were sacrificed within 24 hours of reaching the diabetic status. The small intestines were mounted in Ussing chambers to measure transepithelial intestinal resistance (TEER). Measurement of intraluminal zonulin was determined by sandwich ELISA. BB/Wor DR rats were used as controls.

Results: Untreated DP rats showed increased zonulin levels starting at age 40 days that paralleled an increase in in vivo IP. FZI/0-treated rats also showed elevated zonulin serum levels, however no changes in IP where detected. Eighty percent of the untreated DP rats (12/15) and 27% of the DP FZI/0-treated rats (4/15) progressed to the diabetic state. The average age of onset of diabetes was significantly delayed in treated rats (77.5 3.5 days) compared to untreated animals (69.2 2.9, p=0.048). DP rats that developed T1D showed a significant decrement in TEER in the ileum as compared to DR rats, while DP rats treated with FZI/0 showed a TEER that was similar to that detected in DR rats. Intraluminal zonulin was significantly elevated in DP rats as compared to DR rats, irrespective of the FZI/0 treatment.

Conclusions: Our findings suggest that there is a correlation between intraluminal zonulin and IP. Daily administration of the zonulin binding inhibitor FZI/0 blocks the zonulin permeating effect in the gut, so preventing the onset of T1D in genetically susceptible BB/Wor rat.