Correlation between the intestinal region-specific thickening of ganglionic basement membrane and regionally decreased matrix metalloproteinase 9 expression in myenteric ganglia in type 1 diabetes

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The importance of the neuronal microenvironment has been recently highlighted in gut region-specific diabetic enteric neuropathy. Regionally distinct thickening of endothelial basement membrane (BM) of intestinal capillaries supplying the myenteric ganglia coincide with neuronal damage in different intestinal segments. Reduced degradation of matrix components may contribute to the imbalance of extracellular matrix dynamics resulting in BM thickening.
Therefore, we aimed to evaluate the effects of type 1 diabetes and immediate insulin replacement on BM thickness surrounding myenteric ganglia as well as the expression of matrix metalloproteinase 9 (MMP9) and its tissue inhibitor (TIMP1) in myenteric ganglia and their environment along the small intestine using fluorescent immunohistochemistry, post-embedding immunogold electron microscopy and qPCR.
Ten weeks after the onset of hyperglycaemia, the ganglionic BM was significantly thickened in the diabetic ileum, while it remained intact in the duodenum. The immediate insulin treatment prevented the diabetes-related thickening of the BM surrounding the ileal myenteric ganglia. Quantification of particle density showed an increasing tendency for MMP9 and a decreasing tendency for TIMP1 from the proximal to the distal small intestine under control conditions. In the diabetic ileum, the number of MMP9-indicating gold particles decreased in all cell types, however, it remained unchanged in all duodenal compartments. The MMP9/TIMP1 ratio was also decreased in ileal ganglia only. However, a marked segment-specific induction was revealed in MMP9 and TIMP1 at the mRNA levels.
These findings support that the regional decrease in MMP9 expression in myenteric ganglia and their microenvironment may contribute to extracellular matrix accumulation, resulting in a region-specific thickening of ganglionic BM and diabetic damage of enteric neurons.