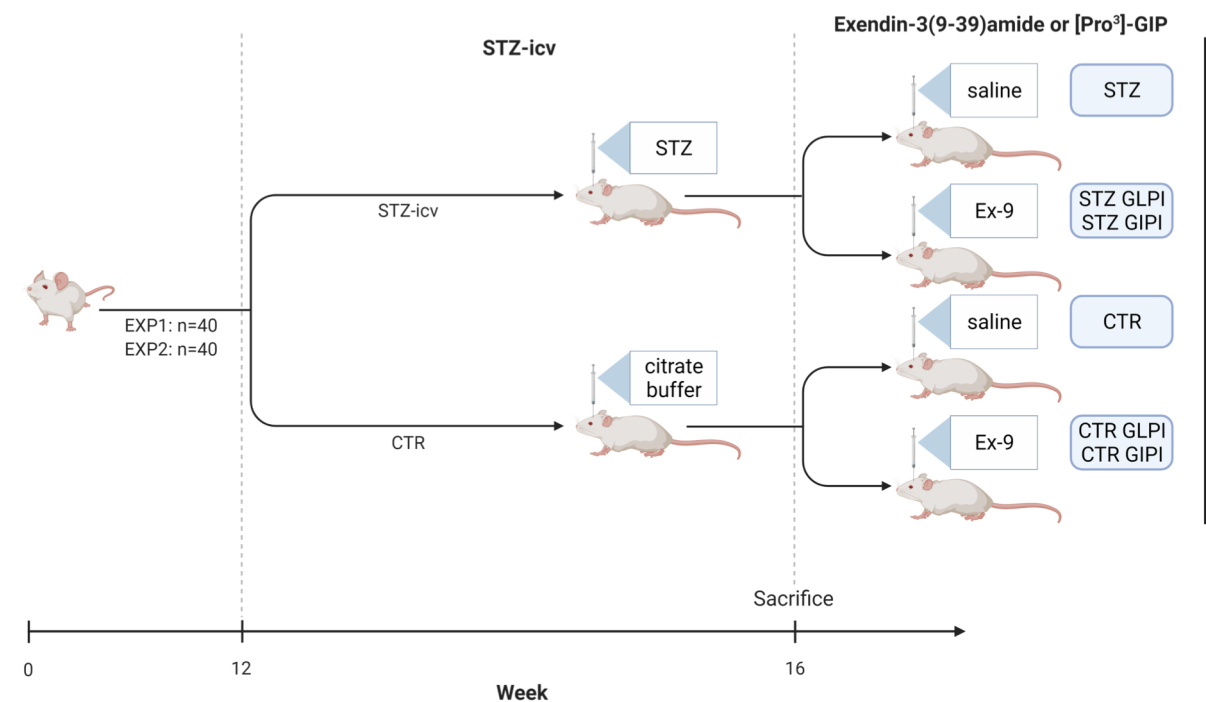


Aim:

The gastrointestinal tract and the brain-gut axis are involved in the etiopathogenesis and progression of Alzheimer's disease (AD) by promoting metabolic dysfunction and inflammation. Failure of the gastrointestinal barrier accompanied by the breach of intestinal microorganisms, amyloid β , and proinflammatory mediators have been reported in animal models of familial AD, however, the role of the gastrointestinal tract has so far never been examined in non-transgenic models attempting to recapitulate pathogenetic processes driving neurodegeneration in ~95% of AD patients. The aim was to explore pathophysiological changes of the gastrointestinal tract and the brain-gut incretin axis in the intracerebroventricular streptozotocin-induced (STZ-icv) rat model of sporadic AD.

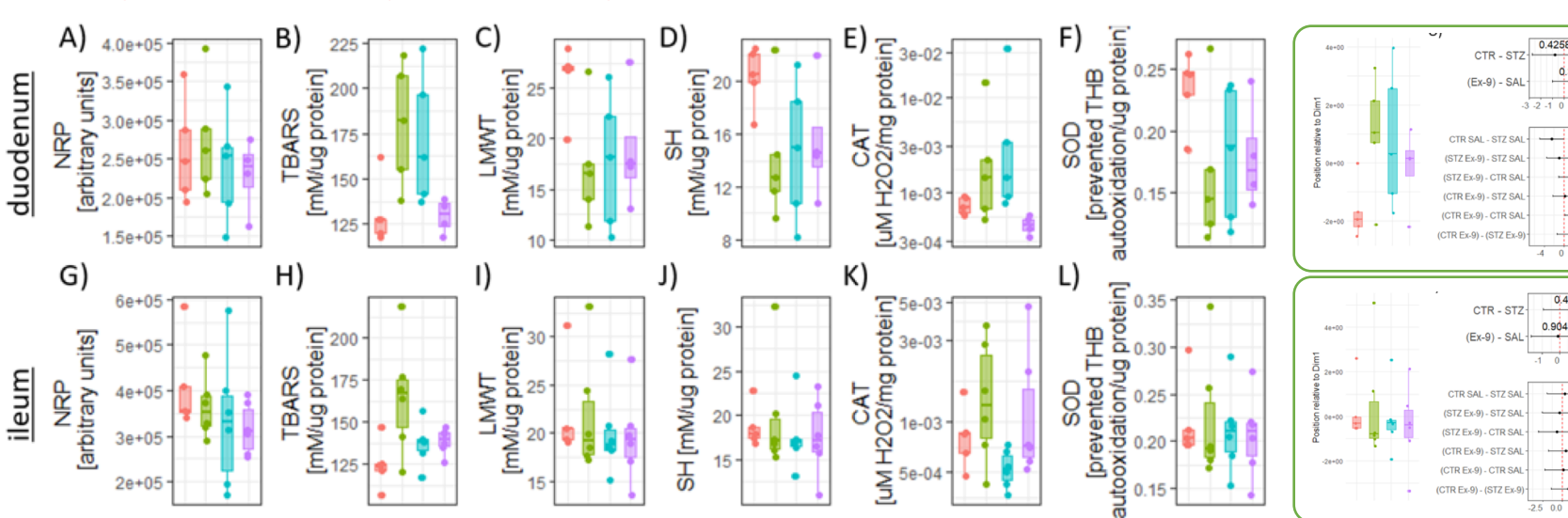
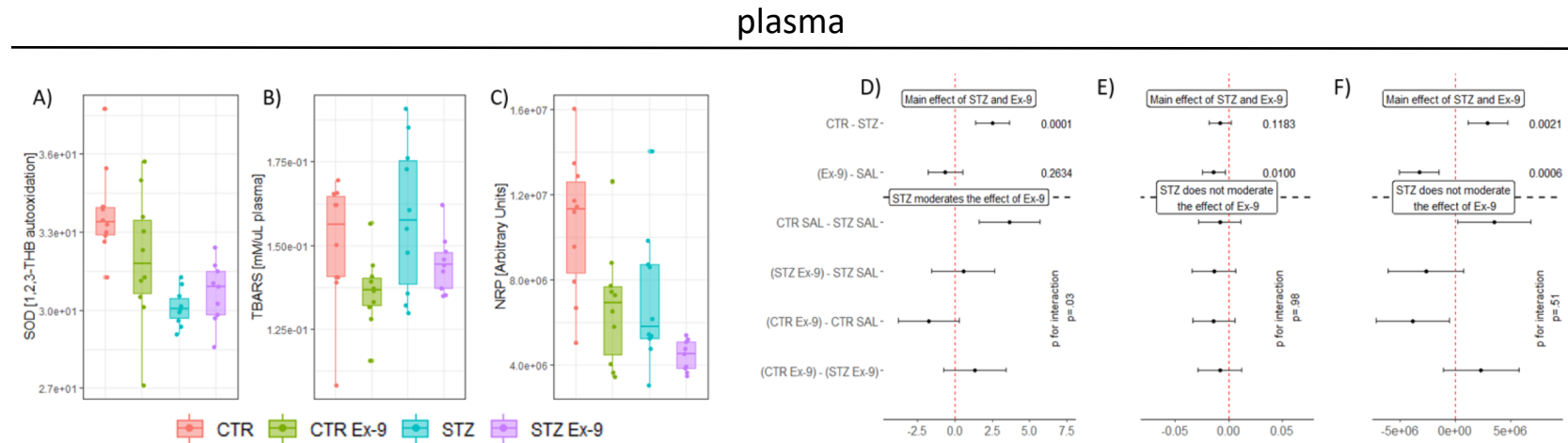
Methods:

Two separate cohorts of control and STZ-icv-treated rats (3mg/kg) were subjected to acute intracerebroventricular administration of either glucagon-like peptide-1 (GLP-1) or glucose-dependent insulinotropic polypeptide (GIP) inhibitor 1 month after the STZ-icv treatment. Chronic effects of STZ-icv, acute effects of incretin antagonists, and their interaction were explored by analyzing plasma lipid peroxidation (TBARS), superoxide dismutase (SOD) and nitrocellulose redox permanganometry (NRP), and duodenal and ileal TBARS, NRP, SOD, catalase activity and low molecular and protein sulfhydryls. The effects of STZ-icv on the gastrointestinal epithelial cell turnover were analyzed by morphometry and multiplex fluorescent signal amplification of caspase-3.

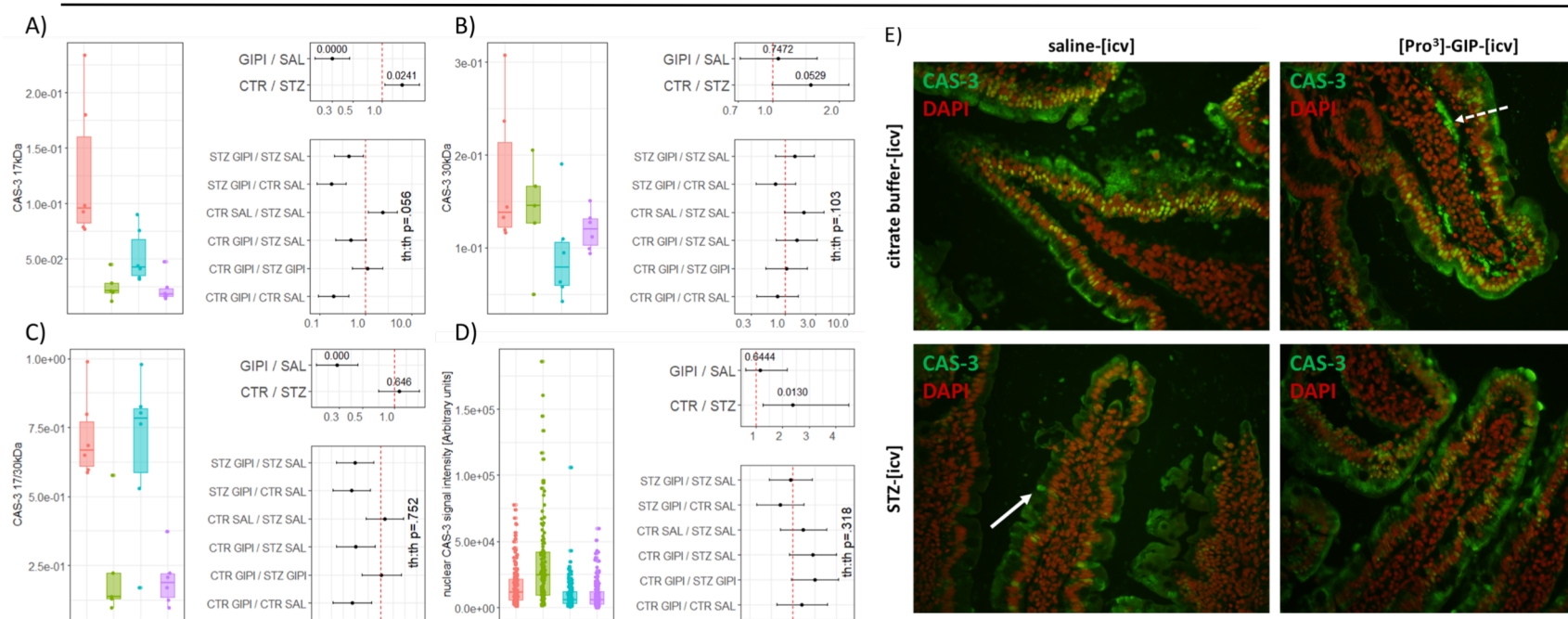


Results:

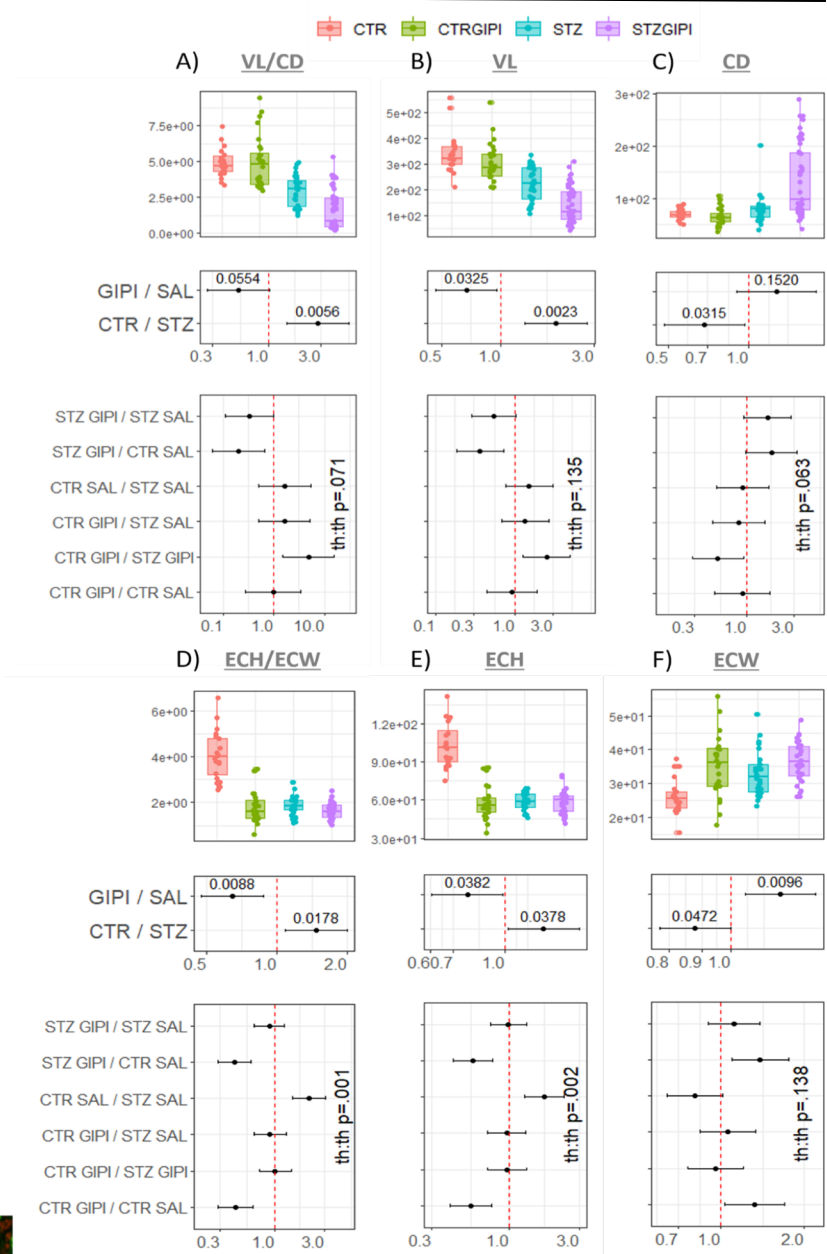
Redox homeostasis is shifted toward a pro-oxidative state in the STZ-icv duodenum, but not in the ileum in comparison with the controls. Oxidative stress in the STZ-icv duodenum is accompanied by the decreased villus length/crypt depth ratio, epithelial cell flattening, and decreased expression and activation of epithelial caspase-3. Treatment-treatment interaction analysis indicates STZ-icv might affect the functioning of the brain-gut incretin axis.



GI barrier epithelial apoptosis



morphometric analysis of the GI barrier



Conclusions:

Pathophysiological changes of the gastrointestinal tract in the STZ-icv rat model of AD speak in favor of redox dyshomeostasis with a pro-oxidative shift and impaired epithelial cell turnover and apoptosis contributing to the dysfunctional gastrointestinal barrier that might promote systemic and central inflammation. Dysregulation of the brain-gut axis in the STZ-icv rats is characterized by resistance of gut to a central inhibition of GLP-1 and GIP receptors.

The presented results have been preprinted on bioRxiv: Homolak et al. 2021 Disbalance of the intestinal epithelial cell turnover and apoptosis in a rat model of sporadic Alzheimer's disease.

Homolak et al. 2021 Failure of the brain glucagon-like peptide-1-mediated control of intestinal redox homeostasis in a rat model of sporadic Alzheimer's disease.



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GLPI – Exendin-3(9-39)amide
GIP – [Pro³]-GIP

