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Restoration of impaired portal glucose sensing by targeted manipulation of GLP-1r density in a translational model of insulin resistance

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Abstract:
Aim/Introduction: The portal glucose sensor informs the brain of changes in glucose inflow via vagal afferents that are dependent on the glucagon-like peptide-1 (GLP-1) receptor (GLP-1r). We have shown that GLP-1r expression within the portal vein is markedly reduced in a translational model of insulin resistance (IR), associated with altered glucose signaling to the brain (1). We now investigated the potential for restoring reduced portal GLP-1r expression in IR animals using a targeted infusion of bioactive molecules, which have been demonstrated to increase GLP-1r expression in vitro. **Materials and Methods:** Five groups, each of five miniature Yucatan minipigs, aged three years, were used. One group was maintained lean and insulin sensitive, while the remaining four were made IR by a high fat-high sucrose diet for 4 months. The precise portal location of the low-density GLP-1r area (compared to lean animals) was initially defined using PET/CT imaging after the administration of 68Ga-DO3A- exendin-4 and a catheter, exiting in the portal connective tissue, was then fixed at this location during 3D guided laparoscopy based on PET/CT results. This catheter was used to infuse continuously either saline, dihydrotestosterone (DHT, 10 µg/kg/24H), metformin (MET, 2 mg/kg/24H), or exenatide (EX, 0.01 µg/kg/24H), i.e., molecules known to increase GLP-1r density in vitro. After 2 months continuous infusion, PET/CT imaging was repeated in all animals using the same GLP-1r radioligand. Vt/Vs coded images, were obtained from PET/CT concurrently with monitoring of the arterial input function extracted from an arteriovenous shunt and radioHPLC of the authentic ligand in the plasma. Duodenal and pancreatic Vt/Vs were also computed as references of GLP-1r expression organs. **Results:** In IR animals, there was a marked reduction in GLP-1r density at the portal vein ($p<0.05$), but not in the pancreas or duodenum (see table). Treatment with DHT increased GLP-1r density at the portal vein substantially to be comparable to that in lean animals. The other treatments had no effect on portal GLP-1r density. Furthermore, no treatment affected the GLP-1r density in the pancreas or duodenum. **Conclusion:** Localized administration of DHT normalises portal GLP-1r density in IR animals, without affecting GLP-1r density in other organs. Accordingly, it is possible to restore impaired glucose sensing in IR animals. The implications for optimal management of insulin resistance /type 2 diabetes now require evaluation in humans. **References:** (1) Malbert et al, Diabetes, 021 Jan;70(1):99-110. doi: 10.2337/db20-0361

GLP-1r density (expressed in Vt - mL/cm3), Mean ± SEM, * different from insulin sensitive

	Portal vein	Pancreas	Duodenum
Insulin sensitive Saline	4.80 ± 0.139	0.47 ± 0.028	0.38 ± 0.004
Insulin resistant Saline	0.22 ± 0.074 *	0.36 ± 0.008	0.22 ± 0.001
Insulin resistant DHT	3.34 ± 0.047	0.45 ± 0.043	0.27 ± 0.012
Insulin resistant MET	0.34 ± 0.012 *	0.42 ± 0.100	0.34 ± 0.056
Insulin resistant Ex	0.31 ± 0.071 *	0.41 ± 0.180	0.35 ± 0.098

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