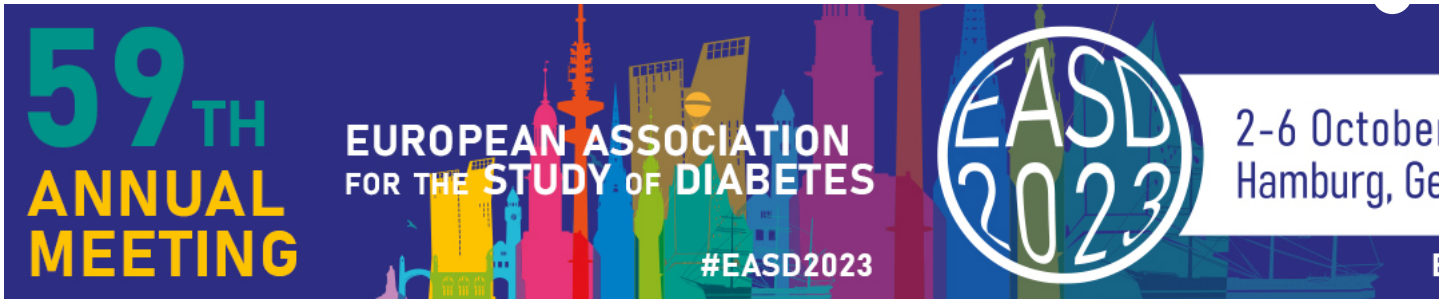

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Restoration of impaired portal glucose sensing by targeted manipulation of GLP-1r density in a translational model of insulin resistance

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Abstract:
Background and aims: 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. 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. Insulin sensitivity was determined in all animals with a euglycaemic-hyperinsulinaemic clamp. 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 radioligand and a catheter, exiting in the portal connective tissue, was then fixed at this location during laparoscopy. 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 coded images, the quantitative metric of receptor density, 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 were also computed as references of large 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, but not MET or EX, 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 the pathogenesis and optimal management of insulin resistance /type 2 diabetes in humans now require evaluation, especially as DHT can be delivered for extended periods using a controlled drug release pellet.

GLP-1r density (expressed in Vt - mL/cm3)

		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
	Dihydrotestosterone	3.34 ± 0.047	0.45 ± 0.043	0.27 ± 0.012
	Metformin	0.34 ± 0.012 *	0.42 ± 0.100	0.34 ± 0.056
	Exenatide	0.31 ± 0.071 *	0.41 ± 0.180	0.35 ± 0.098

Mean ± SEM, * indicates a significant difference from lean group at p<0.05

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