ELLEGAARD
GÖTTINGEN MINIPIGS

Cardiometabolic Disease Models

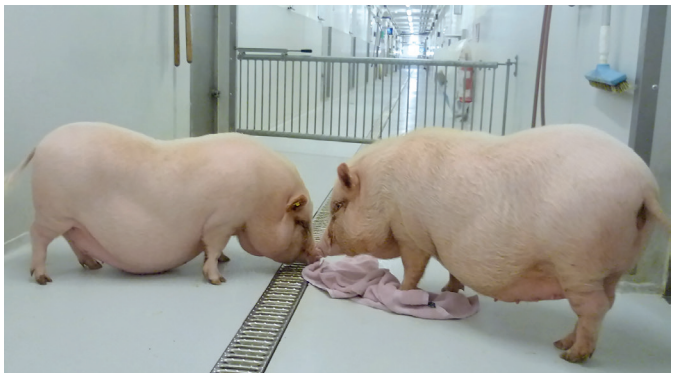
Göttingen Minipigs are very prone to obesity, and even chow feeding results in gross obesity if the minipigs are not kept on a restricted diet.[1] In a recent Newsletter, the experiences running studies with very obese animals are described in two articles.[2] Male animals are much less prone to develop obesity compared to the females but will do so if they are castrated.[3] The fat is stored mostly as subcutaneous fat, but substantial amounts are also stored as visceral fat.[4,5] Brown adipose tissue is not found, as the UCP-1 gene is a pseudogene in pigs.[6] In studies with different anti-obesity compounds, DEXA- and MR-scanning have been used to monitor the effects on the body composition.[7-9]

It is not possible to induce overt diabetes in large animal models (except from non-human primates) by means of diet feeding. Chemical destruction of the beta cells by streptozotocin (STZ) or a similar compound can be used to produce a type 1-like diabetes, and a simple and reliable protocol for this was described recently.[10] As described in the same article, type 2 diabetes is more difficult to model, but several groups find it useful to combine diet-induced obesity, that causes insulin resistance, with low dose STZ treatment.

It is possible to obtain marked obesity, insulin resistance, low grade inflammation and dyslipidemia in small Göttingen Minipigs by feeding them with a high fat diet for a few months.[5] Therapeutic effects on food-intake and body composition, and on the metabolism of glucose and lipids, can thus be studied in a much quicker and easier way. However, the absolute weight loss that can be obtained in adult, very obese animals will more likely be a reduced weight gain in the smaller, moderately obese ones. The degree of insulin resistance can be assessed by performing an IVGTT, using an index based on measurements of insulin and glucose.[11] It is important to notice that Hb1Ac cannot be used in pigs, as porcine erythrocytes are practically impermeable to glucose.[12] Fructosamine can be used instead.[13]

Moderate to severe human-like atherosclerosis develops in approximately 6-9 months in castrated male Göttingen Minipigs fed atherogenic diet high in fat and cholesterol.[13] The plaque lesions show high resemblance to those found in humans and are located the same places, i.e. in both the coronary arteries and the abdominal aorta.[13] The potential to study the lesions by imaging such as PET-MR scanning further provides a basis for performing studies with high translatability to clinical studies.[14] To that end, animals with the most severe lesions can be preselected based on a simple 2D ultrasound scan of the abdominal aorta. In addition, Göttingen Minipigs are often used to model infarcts and infarct-based heart failure.[15]

Recent, unpublished studies have shown us that severe non-alcoholic steatohepatitis (NASH) can be induced in Göttingen Minipigs by using a choline-deficient high fat diet. Severe steatosis drives the inflammation and fibrosis in the model. On a more "regular" high fat diet, it is practically impossible to induce marked steatosis in a porcine liver, possibly because the liver in the pig is not the primary site for de novo lipogenesis, and pigs have a high potential for storing fat in peripheral adipose depots.[16] The disease progression can be followed in the same way as in the clinic - including by imaging and ultrasound-guided biopsies.



"I find it fascinating to work with metabolic diseases in Göttingen Minipigs and have done so for many years. It is important to acknowledge that it is not an area where one model fits all - typically it needs to be adapted to the specific aim of the study."

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References

1. Raun K, von Voss P, Knudsen LB. Liraglutide, a once-daily human glucagon-like peptide-1 analog, minimizes food intake in severely obese minipigs. Obesity (Silver Spring) 2007;15:1710-6
2. Ellegaard Göttingen Minipigs Newsletter no. 49. www.minipigs.dk
3. Christoffersen BO, Gade LP, Golozoubova V, Svendsen O, Raun K. Influence of castration-induced testosterone and estradiol deficiency on obesity and glucose metabolism in male Göttingen minipigs. Steroids 2010;75:676-84
4. Val-Laillet D, Blat S, Louveau I, Malbert CH. A computed tomography scan application to evaluate adiposity in a minipig model of human obesity. Br J Nutr 2010;104:1719-28
5. Christoffersen B, Golozoubova V, Pacini G, Svendsen O, Raun K. The young Göttingen minipig as a model of childhood and adolescent obesity: influence of diet and gender. Obesity (Silver Spring) 2013;21:149-58
6. Berg F, Gustafson U, Andersson L. The uncoupling protein 1 gene (UCP1) is disrupted in the pig lineage: a genetic explanation for poor thermoregulation in piglets. PLoS Genet 2006 Aug 18;2(8):e129
7. Renner S, Blutke A, Dobenecker B, et al. Metabolic syndrome and extensive adipose tissue inflammation in morbidly obese Göttingen minipigs. Mol Metab. 2018;16:180-190
8. Christoffersen B, Straarup EM, Lykkegaard K, et al. FGF21 decreases food intake and body weight in obese Göttingen minipigs. Diabetes Obes Metab 2019;21:592-600
9. Christoffersen BØ, Skyggebjerg RB, Bugge A, et al. Long-acting CCK analogue NN9056 lowers food intake and body weight in obese Göttingen Minipigs. Int J Obes (Lond) 2019 Jun 7. doi: 10.1038/s41366-019-0386-0. [Epub ahead of print]
10. Ellegaard Göttingen Minipigs Newsletter no. 47. www.minipigs.dk
11. Christoffersen B, Ribel U, Raun K, Golozoubova V, Pacini G. Evaluation of different methods for assessment of insulin sensitivity in Gottingen minipigs: introduction of a new, simpler method. Am J Physiol Regul Integr Comp Physiol 2009;297:R1195-201
12. Higgins PJ, Garlick RL, Bunn HF. Glycosylated hemoglobin in human and animal red cells. Role of glucose permeability. Diabetes 1982;31:743-8
13. Ludvigsen TP, Kirk RK, Christoffersen BØ, et al. Göttingen minipig model of diet-induced atherosclerosis: influence of mild streptozotocin-induced diabetes on lesion severity and markers of inflammation evaluated in obese, obese and diabetic, and lean control animals. J Transl Med 2015 Sep 22;13:312. doi: 10.1186/s12967-015-0670-2
14. Ludvigsen TP, Pedersen SF, Vegge A, et al. 18F-FDG PET/MR-imaging in a Göttingen Minipig model of atherosclerosis: Correlations with histology and quantitative gene expression. Atherosclerosis 2019;285:55-63
15. Schuleri KH, Boyle AJ, Centola M, et al. The adult Göttingen minipig as a model for chronic heart failure after myocardial infarction: focus on cardiovascular imaging and regenerative therapies. Comp Med 2008;58:568-79
16. Schumacher-Petersen C, Christoffersen BØ, Kirk RK, et al. Experimental non-alcoholic steatohepatitis in Göttingen Minipigs: consequences of high fat-fructose-cholesterol diet and diabetes. J Transl Med 2019 Apr 3;17(1):110. doi: 10.1186/s12967-019-1854-y

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