ENVIGO

Research Models and Services

Mutant Rats

Zucker rat

To ensure optimal research outcomes, continue to maintain this model on Teklad Global Diet 2018S (18% Protein Rodent Diet)

Reaching your goals in diabetes and obesity studies can be a challenge or a success depending on the reliability of your research models. The *Lepr*^{fa} mutation was discovered in 1961 in the 13M outbred rat stock by Lois and Theodore Zucker. This model has since been well characterized as a model of obesity, showing commonly published metabolic symptoms including insulin resistance and hyperlipidemia.

HsdHlr:ZUCKER-*Lepr*^{fa}

Molecular characteristics

- *Lepr*^{fa}/*Lepr*$^{+}$ heterozygotes do not show partial expression of the Leprfa phenotype (51,61)
- *Lepr*^{fa} is an autosomal recessive mutation on chromosome 5 (51,61)
- Missense mutation of Gln to Pro residue at position 269 of the leptin receptor (8,55)
- Leptin resistance due to decreased functional leptin receptor (3,13,47,48,54)

Metabolic characteristics

- Variable hyperglycemia (4,5,6,8,9,15,29,49,51,64,65)
- Glucose intolerance (6,8,9,51,54,60) at 11–13 weeks (49)
- Obesity (5,6,7,11,15,19,23,29,40,41,44,47,48,51,53) at four-five weeks of age (39,49)
- Hyperinsulinemia (5,6,7,9,14,15,19,22,23,24,29,37,45, 49,53,54,64,65) as early as 21 days of age (51)
- Insulin-resistance (5,6,8,15,19,21,23,26,29,62,64,65) including liver (8,53), skeletal muscle (8), adipose tissue (8) and heart (60)
- Hyperphagia (5,11,12,13,15,17,19,22,23,29,49,51,53,54)
- Hyperlipidemia (4,5,6,15,19,29,30,32,38,39,43,49,51, 59,60) including adipose tissue and liver (62,65)
- Decreased metabolic rate (15,17,22,29,55,63) at 8 weeks of age (58)
- Adipocyte hyperplasia (25) and hypertrophy (29)
- Enhanced energy efficiency (42,52,53,63)
- Reduced body temperature (40,51,55)
- Hypercorticosteronemia (23,25,46,47,48,50,51)
- Increased oxidative stress (30,31,34) in heart (2,4,6) and liver (20,59)

Cardiovascular characteristics

- Borderline hypertension (1,4,5,6,7,14,18,19,24,30,31, 32,34,35,40,41,55,57,65) at six weeks of age (49)
- Abnormal vascular reactivity (2,10,19,26,27,28,30,31, 32,35,49,55)
- Cardiac hypertrophy (57)
- Increased mean arterial pressure (1,19,55)
- Attenuated baroreflex (1,19,32,55)

Hepatic and renal characteristics

- Elevated hepatic glycolysis (56,59)
- Impaired hepatic glycogen synthesis (3,52,53)
- Steatosis (9,16,29,58,59,65)
- Proteinuria (14,38,45)
- Reduced dopamine receptor function in the kidneys (4,5,6,41)
- Focal segment glomerulosclerosis (38,44,45)
- Elevated tubular sodium reabsorption (1,5,6,7)
- Increased urine albumin excretion (28,34,45)
- Adrenal hypertrophy (46,47,48) and hyperplasia (50)

Neurological characteristics

- Altered sympathetic and parasympathetic activity (7,19,22,23,29,30,31,32,39,43,46,51,55,63)
- Peripheral neuropathy (22,39,51,63)
- Altered neuropeptide Y regulation (22,23,29,43,46,51)
- Increased hypothalmic-pituitary-adrenal axis activity (40,48,50)

Muscular characteristics

- Diminished GLUT-4 protein translocation of glucose (21,36,49,50,60)
- Reduced microvessel density in the musculature (31,32,33)
- Remodeling of skeletal muscle microvasculature (31,32)
- Premature skeletal muscle fatigue (33)

Additional characteristics

- Infertility in homozygotes (37,43,54)
- Islet hyperplasia (14,29) and hypertrophy (29)
- Impaired thyroid hormone metabolism (19,54,64)
- Organomegaly (57)

References

1. Alonso-Galicia, M., Brands, M. W., Zappe, D. H., & Hall, J. E. (1996). Hypertension in obese Zucker rats: Role of angiotensin II and adrenergic activity. Hypertension, 28, 1047-1054.
2. Andrews, T. J., Laight, D. W., Änggård, E. E., & Carrier, M. J. (2000). Investigation of Endothelial Hyperactivity in the obese Zucker rat In-situ: Reversal by vitamin E. J Pharm Pharmacol, 52, 83-86.
3. Arden, C., Green, A. R., Hampson, H. J., Aiston, S., Härndahl, L., Greenberg, C. C., et al. (2006). Increased sensitivity of glycogen synthesis to phosphorylase-a and impaired expression of the glycogen-targeting protein R6 in hepatocytes from insulin-resistant Zucker *fa/fa* rats. FEBS, 273, 1989-1999.
4. Banday, A. A., Fazili, F. R., Marwaha, A., & Lokhandwala, M. F. (2007). Mitogen-activated protein kinase upregulation reduces renal D1 receptor affinity and G-protein coupling in obese rats. Kidney International, 71, 397-406.
5. Banday, A. A., Hussain, T., & Lokhandwala, M. F. (2004). Renal dopamine D1 receptor dysfunction is acquired and not inherited in obese Zucker rats. Am J Physiol Renal Physiol, 287, F109-F116.
6. Banday, A. A., Marwaha, A., Tallam, L. S., & Lakhandwala, M. F. (2005). Tempol reduces oxidative stress, improves insulin sensitivity, decreases renal dopamine D1 receptor hyperphosphorylation, and restores D1 receptor-G-Protein coupling and function in obese Zucker rats. Diabetes, 54, 2219-2226.
7. Becker, M., Umrani, D., Lokhandwala, M. F., & Hussain, T. (2003). Increased renal angiotensin II AT1 receptor function in obese Zucker rat. Clinical and Experimental Hypertension, 25, 35-47.
8. Berthiaume, N., & Zinker, B. A. (2002). Metabolic responses in a model of insulin resistance: Comparison between oral glucose and meal tolerance tests. Metabolism, 51, 595-598.
9. Blomqvist, M., Carrier, M., Andrews, T., Pettersson, K., Månsson, J.-E., Rynmark, B.-M., et al. (2005). In vivo administration of the C16:o fatty acid isoform of sulfatide increases pancreatic sulfatide and enhances glucosestimulated insulin secretion in Zucker fatty (fa/fa) rats. Diabetes/Metabolism Research and Reviews, 21, 158-166.
10. Bohlen, H. G. (2004). Protein kinase ßII in Zucker obese rats compromises oxygen and flow-mediated regulation of nitric oxide formation. Am J Physiol Heart Circ Physiol, 286, 492-497.
11. Boules, M., Cusack, B., Zhao, L., Fauq, A., McCormick, D. J., & Richelson, E. (2000). A novel neurotensin peptide analog given extracranially decreases food intake and weight in rodents. Brain Research, 865, 35-44.
12. Brown, L. M., Benoit, S. C., Woods, S. C., & Clegg, D. J. (2007). Intraventicular (i3vt) ghrelin increases good intake in fatty Zucker rats. Peptides, 28, 612-616.
13. Brunner, L., Nick, H.-P., Cumin, F., Chiesi, M., Baum, H.-P., Whitebread, S., et al. (1997). Leptin is a physiologically important regulator of food intake. International Journal of Obesity, 21, 1152-1160.
14. Buckingham, R. E., Al-Barazanji, K. A., Toseland, C. D. N., Slaughter, M., Connor, S. C., West, A., et al. (1998). Peroxisome proliferator-activated receptor-γ agonist, rosiglitazone, protects against nephropathy and pancreatic islet abnormalities in Zucker fatty rats. Diabetes, 47, 1326-1334.
15. Cai, X. J., Lister, C. A., Buckingham, R. E., Pickavance, L., Wilding, J., Arch, J. R. S., et al. (2000). Down-regulation of orexin gene expression by severe obesity in the rats: studies in Zucker fatty and Zucker diabetic fatty rats and effects of rosiglitzaone. Molecular Brain Research, 77, 131-137.
16. Charu, T., Prescott, L., & Koneru, B. (1998). Critical preservation injury in rat fatty liver is to hepatocytes, not sinusoidal lining cells. Transplantation, 65, 167-172.
17. Choi, S., Noh, J., Hirose, R., Ferell, L, Bedolli, M., Roberts, J. P., et al. (2005). Mild hypothermia provides significant protection against ischemia/reperfusion injury in livers of obese and lean rats. Ann Surg, 241, 470-476.
18. Cumin, F., Baum, H.-P., de Gasparo, M., & Levens, N. (1997). Removal of endogenous leptin from the circulation by the kidney. International Journal of Obesity, 21, 495- 504.
19. D'Angelo, G., Mintz, J. D., Tidwell, J. E., Schreihofer, A. M., Pollock, D. M., & Stepp, D. W. (2006). Exaggerated cardiovascular stress responses and impaired ß-adrenergicmediated pressor recovery in obese Zucker rats. Hypertension, 48, 1109-1115.
20. Dikdan, G. S., Saba, S. C., dela Torre, A. N., Roth, J., Wang, S., & Koneru, B. (2004). Role of oxidative stress in the increased activation of signal transducers and activators of transcription-3 in the fatty livers of obese Zucker rats. Surgery, 136, 677-685.
21. Dokken, B. B., & Henriksen, E. J. (2006). Chronic selective glucogen synthase kinase-3 inhibition enhances glucose disposal and muscle insulin action in prediabetic obese Zucker rats. Am J Physiol Endocrinol Metab, 291, 207-213.
22. Dryden, S. Frankish, H. M., Wang, Q., Pickavance, L., & Williams, G. (1996). The serotonergic agent fluoxetine reduces neuropeptide Y levels and neuropeptide Y secretion in the hypothalamus of lean and obese rats. Neuroscience, 72, 557-566.
23. Dryden, S., Pickavance, L., Frankish, H. M., & Williams, G. (1995). Increased neuropeptide Y secretion in the hypothalamic paraventricular nucleus of obese (fa/fa) Zucker rats. Brain Research, 690, 185-188.
24. Duarte, J., Martinez, A., Bermejo, A., Vera, B., Gámez, M. J., Cabo, P., et al. (1999). Cardiovascular effects of captopril and enalapril in obese Zucker rats. European Journal of Pharmacology, 365, 225-232.
25. Edwards, E., King, J. A., & Fray, J. (2000). Hypertension and insulin resistant models have divergent propensities in learned helpless behavior in rodents. AJH, 13, 659-665.
26. Erdös, B., Snipes, J. A., Kis, B., Miller, A. W., & Busija, D. W. (2004). Vasoconstrictor mechanisms in the cerebral circulation are unaffected by insulin resistance. Am J Physiol Regul Integr Comp Physiol, 287, 1456-1461.
27. Erdös, B., Snipes, J. A., Miller, A. W., & Busija, D. W. (2004). Cerebrovascular dysfunction in Zucker obese rats is mediated by oxidative stress and protein kinase C. Diabetes, 53, 1352-1359.
28. Erdös, B., Snipes, J. A., Tulbert, C. D., Katakam, P., Miller, A. W., & Busija, D. W. (2006). Rosuvastatin improves cerebrovascular function in Zucker obese rats by inhibiting NAD(P)H oxidase-dependent superoxide production. Am J Physiol Heart Circ Physiol, 290, H1264-H1270.
29. Ferrari, B., Arnold, M., Carr, R. D., Langhans, W., Pacini, G., Bodvarsdóttir, T. B., et al. (2005). Subdiaphragmatic vagal differentiation affects body weight gain and glucose metabolism in obese male Zucker (*fa/fa*) rats. Am J Physiol Regul Integr Comp Physiol, 289, 1027-1034.
30. Frisbee, J. C. (2004). Enhanced arteriolar α-adrenergic constriction impairs dilator responses and skeletal muscle perfusion in obese Zucker rats. J Appl Physiol, 97, 764-772.
31. Frisbee, J. C. (2003). Impaired skeletal muscle perfusion in obese Zucker rats. Am J Physiol Regul Integr Comp Physiol, 285, 1124-1134.
32. Frisbee, J. C. (2003). Remodeling of the skeletal muscle microcirculation increases resistance of perfusion in obese Zucker rats. Am J Physiol Heart Circ Physiol, 285, 104-111.
33. Frisbee, J. C., Samora, J. B., Peterson, J., & Bryner, R. (2006). Exercise training blunts microvascular rarefaction in the metabolic syndrome. Am J Physiol Heart Circ Physiol, 291, 2483-2492.
34. Frisbee, J. C., & Stepp, D. W. (2001). Impaired NOdependent dilation of skeletal muscle arterioles in hypertensive diabetic obese Zucker rats. Am J Physiol Heart Circ Physiol, 281, 1304-1311.
35. Fulton, D. M., Harris, M. B., Kemp, B. E., Venema, M. B., Marrero, M. B. & Stepp, D.W. (2004). Insulin resistance does not diminish eNOS expression, phosphorylation, or binding to HSP-90. Am J Physiol. Heart Circ. Physiol, 287, H2384-93.
36. Fürnsinn, C., Noe, C., Herdlicka, R., Roden, M., Nowotny, P., Leighton, B., et al. (1997). More marked stimulation by lithium than insulin of the glucogenic pathway in rat skeletal muscle. Am J Physiol Emdocrinol Metab, 273, 514- 520.
37. Fürnsinn, C., Nowotny, P., Brunmair, B., Gras, F., Roden, M., Waldhäusl, W., et al. (2002). Thiazolidinediones influence plasma steroids of male obese Zucker rats. Endocrinology, 143, 327-330.
38. Gassler, N., Elger, M., Kränzlin, B., Kriz, W., & Gretz, N. (2001). Podocyte injury underlies the progression of focal segmental glomerulosclerosis in the *fa/fa* Zucker rat. Kidney International, 60, 106-116.
39. Hakkak, R., Holley, A. W., MacLeod, S. L., Simpson, P. M., Fuchs, G. J., Jo, C. H., et al. (2005). Obesity promotes 7,12-dimethylbenz(a)anthracene-induced mammary tumor development in female Zucker rats. Breast Cancer Research, 7, 627-633.
40. Heinrichs, S. C., Joppa, M., Lapsansky, J., Jeske, K., Nelson, R., & de Souza, E. (2001). Selective stimulatory actions of corticotrophin-releasing factor ligands on correlates of energy balance. Physiology and Behavior, 74, 5-13.
41. Hussain, T., Beheray, S. A., & Lokhandwala, M. F. (1999). Defective dopamine receptor function in proximal tubules of obese Zucker rats. Hypertension, 34, 1091-1096.
42. Jarosz, P. A. (2007). The effect of Kappa opioid receptor antagonism on energy expenditure in the obese Zucker rat. Biological Research for Nursing, 8, 294-299.
43. Keen-Rhinehart, E., Kalra, S. P., & Kalra, P. S. (2004). Leptin-receptor gene transfer into the arcuate nucleus of female fatty Zucker rats using recombinant adenoassociated viral vectors stimulates the hypothalamopituitary- gonadal axis. Biology of Reproduction, 71, 266-272.
44. Kim, C. H., Vaziri, N. D., & Rodriguez-Iturbe, B. (2007). Integrin expression and H_2O_2 production in circulating and splenic leukocytes of obese rats. Obesity, 15, 2209-2216.
45. Li, Z., Rodríguez-Iturbe, B., Ni, Z., Shahkarami, A., Sepassi, L., & Vaziri, N. D. (2005). Effect of hereditary obesity on renal expressions of NO synthase, caveolin-1, AKt, guanylate cyclase, and calmodulin. Kidney International, 68, 2766-2772.
46. Livingstone, D. E. W., Jones, G. C., Smith, K., Jamieson, P. M., Andrew, R., Kenyon, C. J., et al. (2000). Understanding the role of glucocorticoids in obesity: Tissuespecific alterations of corticosterone metabolism in obese Zucker rats. Endocrinology, 141, 560-563.
47. Livingstone, D. E. W., Kenyon, C. J., & Walker, B. R. (2000). Mechanisms of dysregulation of 11ß-hydroxysteriod dehydrogenase type 1 in obese Zucker rats. Endocrinology, 167, 533-539.
48. Livingstone, D. E. W., & Walker, B. R. (2003). Is 11ß-Hydroxysteriod Dehydrogenase type 1 a therapeutic target? Effects of Carbenoxolone in lean and obese Zucker rats. JPET, 203, 167-172.
49. Maher, M. A., Banz, W. J., & Zemel, M. B. (1995). Variations of blood pressures in lean Zucker rats fed low or high fat diets. J Nutr, 125, 2618-2622.
50. Mattsson, C., Lai, M., Noble, J., McKinney, E., Yau, J. L., Seckl, J. R., et al. (2003). Obese Zucker rats have reduced mineralocorticoid receptor and 11ß-Hydroxysteriod Dehydrogenase type 1 expression in hippocampus-Implication for dysregulation of the hypothalamic-pituitaryadrenal axis in obesity. Endocrinology, 144, 2997-3003.
51. McNeill, J. H. (Ed.). (1999). Experimental Models of Diabetes. CRC Press: Boca Raton.
52. Obeid, O. A., Jamal, Z. M., Hwalla, N., & Emery, P. W. (2006). The effect of glutamine and dihydroxyacetone supplementation on food intake, weight gain, and postprandial glycogen synthesis in female Zucker rats. Nutrition, 22, 794-801.
53. Obeid, O. A., Powell-Tuck, J., & Emery, P. W. (2000). The postprandial rates of glycogen and lipid synthesis of lean and obese female Zucker rats. International Journal of Obesity, 24, 508-513.

54. Östman, E. M., Elmståhl, H. G. M., Molin, G., Lundquist, I., & Björck, I. M. E. (2005). A diet based on wheat bread baked with lactic acid improves glucose tolerance in hyperinsulinemic Zucker (*fa/fa*) rats. Journal of Cereal Science, 42, 300-308.

55. Overton, J. M., Williams, T. D., Chambers, J. B., & Rashotte, M. E. (2001). Cardiovascular and metabolic responses to fasting and thermoneutrality are conserved in obese Zucker rats. Am J Physiol Regulatory Integrative Comp Physiol, 280, 1007-1015.

56. Payne, V. A., Arden, C., Lange, A. J., & Agius, L. (2007). Contributions of glucokinase and phosphofructokinase-2/ fructose biphosphatase-2 to the elevated glycolysis in hepatocytes from Zucker *fa/fa* rats. Am J Physiol Regul Integr Comp Physiol, 293, 618-625.

57. Ren, J., Walsh, M. F., Jefferson, L., Natavio, M., Ilg, K. J., Sowers, J. R., et al. (2000). Basal and ethanol-induced cardiac contractile response in lean and obese Zucker rat hearts. J Biomed Sci, 7, 390-400

58. Selzner, M., & Clavier, P.-A. (2000). Failure of regeneration of the steatotic liver: disruption at two different levels in the regeneration pathway. Hepatology, 31, 35-42.

59. Serkova, N. J., Jackman, M., Brown, J. L., Liu, T., Hirose, R., Roberts, J. P., et al. (2006). Metabolic profiling of livers and blood from obese Zucker rats. Journal of Hepatology, 44, 956-062.

60. Sidell, R. J., Cole, M. A., Draper, M. J., Desrois, M., Buckingham, R. E., & Clarke, K. (2002). Thiazolidinedione treatment normalizes insulin resistance and ischemic injury in the Zucker fatty rat heart. Diabetes, 51, 1110-1117.

61. Strobl, W., Knerer, B., Gratzi, R., Arbeiter, K., Lin-Lee, Y.-C., & Patsch, W. (1993). Altered regulation of apolipoprotein A-IV gene expression in the liver of the genetically obese Zucker rat. J Clin Invest, 92, 1766-1773.

62. Thyfault, J. P., Cree, M. G., Zheng, D., Zwetsloot, J. J., Tapscott, E. B., Koves, T. R., et al. (2007). Contraction of insulin-resistant muscle normalizes insulin action in association with increased mitochondrial activity and fatty acid catabolism. Am J Physiol Cell Physiol, 292, C729-C739.

63. Tonello, C., Giordano, A., Cozzi, V., Cinti, S., Stock, M. J., Carruba, M. O., et al. (1999). Role of sympathetic activity in controlling the expression of vascular endothelial growth factor in brown fat cells of lean and genetically obese rats. FEBS Letters, 442, 167-172.

64. Torrance, C. J., Devente, J. E., Jones, J. P., & Dohm, C. L. (1997). Effects of thyroid hormone on GLUT4 glucose transporter gene expression and NIDDM in rats. Endocrinology, 138, 1204-1214.

65. Tovar, A. R., Torre-Villalvazo, I., Ochoa, M., Elías, A. L., Ortíz, V., Aguilar-Salinas, C. A., et al. (2005). Soy protein reduces hepatic lipotoxicity in hyperinsulinemic obese Zucker *fa/fa* rats. J Lipid Res, 46, 1823-1832.

Contact us

North America 800.793.7287 EU and Asia envigo.com/contactus info@envigo.com

Envigo RMS Division, 8520 Allison Pointe Blvd., Suite 400, Indianapolis, IN 46250, United States

RMS-1116-EU-01-PS-226