

# Zucker rat

## HsdHlr:ZUCKER-*Lep<sup>fa</sup>*

Reaching your goals in diabetes and obesity studies can be a challenge or a success depending on the reliability of your research models. The *Lep<sup>fa</sup>* 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.

### CHARACTERISTICS

#### Molecular characteristics

- *Lep<sup>fa</sup>/Lep<sup>+</sup>* heterozygotes do not show partial expression of the *Lep<sup>fa</sup>* phenotype (51,61)
- *Lep<sup>fa</sup>* 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 hypothalamic-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)



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