Animal Model of Obesity Zucker Fatty Rats

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Laboratory Zucker Fatty (ZF) rats are used in human disease studies as a model of obesity with accompanying hyperlipidemia and hypertension. While this model is most widely used in studies on genetic obesity, ZF rats are also used in studies on MetS and non-insulin-dependent obesity-related diabetes. ZF rats are characterized by a recessive mutation in the leptin receptor gene (called “fa”), which leads to polyphagia, with the consequent development of obesity at around four weeks of age. The causes of obesity in ZF rats also include hypertrophy and adipocyte hyperplasia, which are linked to their genetic predisposition. Other conditions observed in ZF rats include hyperinsulinemia and impaired glucose tolerance, which do not lead to overt diabetes.

laboratory animal models metabolic syndrome polyphenols

1. Animal Model of Obesity Zucker Fatty Rats (fa/fa)

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Studies conducted using this animal model have shown that many polyphenolic substances have potentially beneficial metabolic effects in extracts or individual compounds.

2. Red Wine

Grapes and red wine are rich sources of phenolic acids, flavonols, quercetin, (+)-catechin, dihydroflavonols, anthocyanins, catechins, and stilbenes [3][4]. Red wine polyphenols were first noticed as very useful with the identification of the theory called the “French Paradox”. This theory pointed out that the high amount of red wine polyphenols consumed by the French every year is responsible for the comparatively low level of coronary heart disease (CHD) among the French population [5][6]. The French concept later became the reason for investigating the role of red wine constituents as cardioprotective factors. Following these findings, scientific studies proved their protective action in the vascular system. Moreover, compounds from red wine protect against cerebrovascular incidents [7]. Additionally, in vitro studies evidenced that the supplementation of red wine polyphenols reduced

inflammation and NADPH oxidase activity and increased endothelial nitric oxide production [8][9]. In vivo, animal studies seem to confirm these findings. An animal model study investigated dietary supplementation with red wine polyphenol extract on metabolic, circulatory, and vascular changes. The analysis found that the polyphenol extracts improved glucose metabolism by reducing serum glucose levels and improved lipid profiles by lowering triglyceride and LDL cholesterol levels. In turn, echocardiographic measurements showed an increase in fractional shortening and cardiac output. The analysis also showed an increase in nitric oxide (NO) bioavailability associated with increased endothelial NO-synthase (eNOS) activity and, consequently, a reduction in peripheral arterial resistance. In turn, the decreased expression of NADPH oxidase inhibited the release of superoxide anions [10]. The decline in vascular tone is probably linked to the modulation of the expression of cyclooxygenase (COX) and COX-derived vasoconstrictive agents via a mechanism that involves the NF-κB pathway. The vasoprotective effect of the dietary supplementation of red vine polyphenols is also associated with a reduction in the release of vasoconstrictive factors such as thromboxane-A2 and 8-isporostone [11][12].

3. Green Tea

Green tea is a rich source of catechins, including epigallocatechin gallate (EGCG), an organic chemical compound belonging to the polyphenol family. Green tea extract, as well as EGCG alone, were analyzed in studies on ZF rats to verify their impact on weight, lipid profile, and glucose metabolism. One study investigated the protective effects and molecular mechanisms of action of green tea polyphenols in non-alcoholic fatty liver disease (NAFLD). In that study, pathological metabolic changes in hepatocytes identical to those seen in humans with NAFLD were induced in ZF rats by a high-fat diet. A decrease in body weight and a statistically significant reduction in visceral fat (31.0%, $p < 0.01$) were observed in rats treated with green tea polyphenols compared with controls. Moreover, significant decreases in fasting insulin, glucose, and lipid levels were observed. The observed reduction in hepatic lipogenesis was linked to the upregulation of the AMPK pathway [13]. In another study, an intraperitoneal injection of green tea catechin extract, mainly containing EGCG, was found to reduce food intake and body weight and lead to a number of changes in the endocrine system, including a reduction in the blood levels of testosterone, estradiol, leptin, insulin, IGF-1, LH, glucose, cholesterol, and triglycerides. This experiment was performed on Sprague Dawley and Zucker Fatty rats. Similar effects were observed in both groups, suggesting that the effect of EGCG on appetite control is independent of leptin. The effective dose of EGCG was approximately 30–50 mg/kg BW. The loss in body weight was reversible. When the administration of EGCG was stopped, the rats regained their weight [14]. The beneficial effect of green tea polyphenols on weight gain attenuation, the reduction in visceral fat accumulation, and the decline in insulin level and fasting serum glucose may be associated with molecular changes in the expression of insulin signaling protein in skeletal muscle. The polyphenols from green tea administered to Zucker Fatty (ZF) rats fed a high-fat diet at a dose of 200 mg/kg of body weight for 8 weeks resulted in lower insulin resistance. Immunoblotting revealed that the expression and translocation of glucose transporter-4 were enhanced in skeletal muscle. The insulin-stimulated glucose uptake by isolated muscle in ZF rats treated with green tea polyphenols increased as well. Moreover, a decrease in the activation of the inhibitory protein kinase isoform, PKC-θ, which is muscle-specific, was also observed. This outcome shows that the effects of polyphenols from green tea may be associated with the impact on skeletal muscle insulin sensitivity [15]. The

ingestion of green tea polyphenols can ameliorate the metabolic abnormalities linked with MetS and promote favorable molecular effects.

4. Quercetin

Quercetin is a bioflavonol found in numerous plant foods, such as beans, red onion, lettuce, broccoli, citrus, tea, wine, and herbs. It is believed that quercetin has significant antioxidant potential and thus shows protective effects concerning osteoporosis, cardiovascular disease, neuropathy, and even some types of cancer, for example, breast cancer, lung cancer, and colon cancer [16][17][18][19][20]. Moreover, it is characterized by anti-inflammatory, antiobesity, antihyperlipidemic, antihypercholesterolemic, neuroprotective, antihypertensive (via vasodilator effects), and antiatherosclerotic properties [17][21][22]. The role of quercetin in organism metabolism is assumed to be mediated via the activation of transcription factors such as PPAR-γ, AMPk, NF-κB, or SIRT1 [19][23]. A daily quercetin dose of 2 mg/kg BW or 10 mg/kg BW administered to obese ZF rats for ten weeks resulted in reduced dyslipidemia, hypertension, and insulin resistance. However, only the use of the higher dose reduced body weight and produced anti-inflammatory effects by lowering TNF-alpha production in visceral adipose tissue. The decline in body weight was associated with an increase in the plasma concentration of adiponectin, reduced levels of which are observed in obesity, type 2 diabetes, and hypertension. The vasoprotective effects of quercetin were shown to be mediated by an increase in eNOS expression [24].

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