T2:P2a-057
BETA-ADRENOCEPTORS AND HUMAN ENERGY METABOLISM
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Aims: To study the functional role of beta-adrenoceptors (AR) in human energy metabolism, which so far has not been fully elucidated.

Methods: A total of 16 normal weight males received four treatments in random order. After an overnight fast, the subjects were given a placebo or beta-AR antagonist (betaxolol 0.5 mg) or betaxolol 0.5 mg or placebo, 2 hours later they received the beta-AR agonist (TAK-677 0.5 mg) or placebo. The following combinations were tested: placebo+placebo, placebo+TAK-677, bupropion+TAK-677 and mephedrine+TAK-677. Energy expenditure (EE), heart rate (HR), blood pressure (BP) and finger tremor (FT) were measured in supine position and venous blood was collected at regular time intervals pre- and 4 hr post-agonist administration.

Results: TAK-677 significantly increased EE, FT, HR, systolic BP and plasma concentrations of FFA, glycerol, insulin, glucose, and lactate, and increased AMPK phosphorylation compared with placebo (P < 0.05). Plasma catecholamines were not affected. The TAK-677-induced changes in lactate and potassium were fully blocked by bupropion administration. Most of the other TAK-677-induced effects were no longer statistically significant after administration of the beta,-AR blocker mephedrine, except for part of the increases in lactate and insulin (P<0.05) and EE (P=0.06), which may therefore be beta,-AR mediated.

Conclusions: Beta-adrenoceptor stimulation by means of a pharmacological agent increases energy metabolism in humans. This justifies further research on the therapeutic role of beta-adrenoceptor agonists in the treatment of human obesity.

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REDUCED INSULIN SENSITIVITY AND GLUCOSE TOLERANCE IN DGAT-1 KNOCKOUT MICE
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Aims: To investigate energy and glucose homeostasis in C57Bl/6J mice that lack acyl-CoA:diacylglycerol acyltransferase-1, the final enzyme of triglyceride synthesis.

Methods: DGAT-1−/− (C57Bl/6 background; Jackson Labs) and C57Bl/6 +/+ mice were maintained on standard chow diet from 8 to 22 weeks of age. Blood glucose following injection of insulin, oral glucose tolerance and energy expenditure were measured at 12, 13 and 19-20 weeks of age, respectively.

Results: Male +/+ mice displayed increased energy expenditure and food intake per g body weight compared to age-matched +/+ mice. They were -3g heavier than +/+ mice, but there was no difference in the body weight gain. In contrast, female +/+ mice had higher energy expenditure, but similar food intake and a reduced weight gain compared to +/+ mice. Increases in energy expenditure in −/− mice were magnified during a daytime fast. Terminal fat pad weights were reduced in both sexes of −/− mice, and DEXA scans indicated a reduction in whole-body fat composition, with an increase in whole-body lean mass. Both sexes of −/− mice showed poor glucose tolerance and insulin sensitivity. Fasting plasma insulin was nil at 21 weeks in male −/− mice, and NEFA and triglycerides were raised in both sexes. Both plasma adiponectin and leptin were reduced, possibly suggesting reduced adipocyte numbers.

Conclusions: Consistent with previous reports for mice on a mixed background, knockout of DGAT-1 increased energy expenditure and reduced whole-body fat mass. By contrast with previous reports, the ability of the body to dispose of a glucose load was impaired and insulin sensitivity was reduced.

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INSULIN-SENSITIZING EFFECT OF ROSIGLITAZONE IN A RAT MODEL OF DIET-INDUCED OBESITY
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Aims: To examine the effects of rosiglitazone (RSG) on insulin sensitivity in diet-induced obese (DIO) rats, and the involvement of leptin and hypothalamic neuropeptides in weight gain during treatment.

Methods: Wistar rats were fed with chow (n=8) or chow plus insulin (DIO) for 13 weeks. DIO rats received orally either vehicle (n=8) or RSG (n=8, 10mg/kg daily) for 28 days. White fat (WAT) leptin mRNA was quantified using Northern blotting and hypothalamic gene expression (NPY, AGRP and POMC) by real-time PCR (Taqman™).

Results: Diet-induced obesity in rats is accompanied by increased circulating triglyceride (TG), glucose, insulin and leptin. Energy intake and body weight were higher in RSG-treated rats than DIO rats. RSG normalized plasma TG and insulin sensitivity in DIO rats (HOMA: RSG, 18.2 ±1 vs DIO, 50 ±12; P<0.01). The elevated WAT leptin mRNA and plasma leptin levels in DIO rats compared with chow-fed rats were normalized by RSG. In DIO rats, hypothalamic AGRP gene expression was reduced by 39% (P<0.05), whereas NPY and POMC expression remained unchanged compared with chow-fed rats. RSG treatment increased AGRP mRNA levels by 47% compared with DIO rats (P<0.05), but did not alter other hypothalamic genes examined.

Conclusions: RSG ameliorates metabolic abnormalities and improves insulin sensitivity in rats with diet-induced obesity. Normalized leptin production and upregulation of hypothalamic AGRP expression by RSG might contribute to hyperphagia and weight gain during treatment.

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GREEN TEA CATECHIN, EGCG (TEAVIGO), REGULATES ADIPOGENESIS AND PREVENTS TZD-INDUCED WEIGHT GAIN IN DB/DB MICE
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Epigallocatechin-3-gallate (EGCG) is a major component of green tea polyphenols and known to have antioxidant, anti-inflammatory and chemopreventive properties. Tea catechins have been reported to reduce body weight and visceral fat mass in diet-induced obese (DIO) mice. The aim of this work was to investigate the potential antiobesity effect of EGCG both in vitro and in vivo. Mouse preadipocyte stem cells, 3T3-L1, were differentiated into adipocytes with a mixture of insulin, dexamethasone and BMP. Cotreatment with EGCG showed a dose-dependent inhibition of adipogenesis. In addition, EGCG prevented adipogenesis induced by another class of compounds, PPARy-specific activator TZDs, such as ciglitazone, rosiglitazone, and pioglitazone. Consistent with these observations, the expression of adipogenesis-related genes, such as key transcriptional regulators of adipogenesis (C/EBPα and PPARγ), and adipocyte-differentiation-related genes (adipin-2 and Acrp30), was reduced by EGCG treatment in 3T3-L1-2 cells during adipogenesis. For in vivo investigation, male db/db mice (n=10/group) were administered EGCG (1% w/v of diet), rosiglitazone (5 mg/kg/day), the combination of EGCG and rosiglitazone, or placebo for 4 weeks. Compared to the control group, rosiglitazone increased adipose mass (+24.3%). Cotreatment with EGCG totally inhibited this adverse effect (-8.9%). Therefore, administration of EGCG together with the well-established antidiabetic drugs, TZDs, may be beneficial to the treatment of Type 2 diabetes.