Transgenic and Recombinant Resistin Impair Skeletal Muscle Glucose Metabolism in the Spontaneously Hypertensive Rat

Received for publication, May 9, 2003, and in revised form, August 26, 2003
Published, JBC Papers in Press, August 27, 2003, DOI 10.1074/jbc.M304869200

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Increased serum levels of resistin, a molecule secreted by fat cells, have been proposed as a possible mechanistic link between obesity and insulin resistance. To further investigate the effects of resistin on glucose metabolism, we derived a novel transgenic strain of spontaneously hypertensive rats expressing the mouse resistin gene under the control of the fat-specific aP2 promoter and also performed in vitro studies of the effects of recombinant resistin on glucose metabolism in isolated skeletal muscle. Expression of the resistin transgene was detected by Northern blot analysis in adipose tissue and by real-time PCR in skeletal muscle and was associated with increased serum fatty acids and muscle triglycerides, impaired skeletal muscle glucose metabolism, and glucose intolerance in the absence of any changes in serum resistin concentrations. In skeletal muscle isolated from non-transgenic spontaneously hypertensive rats, in vitro incubation with recombinant resistin significantly inhibited insulin-stimulated glycogen production and reduced glucose oxidation. These findings raise the possibility that autocrine effects of resistin in adipocytes, leading to release of other prodiabetic effectors from fat and/or paracrine action of resistin secreted by adipocytes embedded within skeletal muscle, may contribute to the pathogenesis of disordered skeletal muscle glucose metabolism and impaired glucose tolerance.

In industrialized societies, type 2 diabetes is a common cause of morbidity and mortality that is characterized by insulin resistance often in association with central obesity. However, the mechanisms that underlie the widely recognized relationship between obesity and insulin resistance remain to be defined. Although skeletal muscles are quantitatively the most important site of insulin-stimulated glucose disposal (1), adipose tissue clearly exerts a major influence on carbohydrate metabolism because changes in body fat mass can have substantial effects on insulin action and glucose tolerance. Moreover, recent studies demonstrating that adipose tissue can secrete a number of molecules that modulate carbohydrate and lipid metabolism strongly suggest that body fat is more than just a passive reservoir for fuel in the form of triglycerides.

Recently, a new hormone produced by fat cells and termed resistin was discovered that could represent an important link between obesity and insulin-resistant diabetes (2–4). Resistin is a cysteine-rich polypeptide expressed primarily in white adipose tissue that is induced during 3T3-L1 adipogenesis and may also serve as a feedback regulator to inhibit adipocyte generation (2–4). Message and protein levels of resistin are decreased by fasting and increased by refeeding, possibly in response to changes in insulin levels (2, 4). Moreover, Steppan et al. (2) have found that treatment of mice with recombinant resistin can impair glucose tolerance and that administration of anti-resistin antibody improves blood glucose and insulin action in mice with diet-induced obesity (2). Incubation of 3T3-L1 adipocytes with recombinant resistin has also been reported to inhibit insulin-stimulated glucose uptake (2). In addition, resistin mRNA levels can be suppressed by exposure to either fatty acids or ligands for the peroxisome proliferator-activated receptor γ (2). However, in various rodent models of obesity, conflicting results have been reported regarding the effects of systemically administered peroxisome proliferator-activated receptor γ ligands on resistin expression, perhaps because of the fact that these ligands can influence a host of factors that may differentially regulate resistin (5–8).

Based on measurements of resistin expression in fat tissue in humans and in animals with type 2 diabetes and obesity, a number of investigators have recently raised questions regarding the potential relevance of resistin to the pathogenesis of insulin resistance. For example, whereas some investigators have found evidence of resistin expression in samples of human subcutaneous and abdominal fat (9, 10), others have found it difficult to detect mRNA for resistin in either adipocytes or subcutaneous adipose tissue isolated from insulin-resistant subjects (11). Expression of resistin in white adipose tissue has also been reported to be significantly decreased in several animal models of obesity-associated insulin resistance (6, 12, 13). However, the lack of correlation between resistin mRNA levels in isolated adipocytes and insulin resistance does not exclude the possibility that resistin may be contributing to the pathogenesis of disordered carbohydrate metabolism in either liver or skeletal muscle. In Sprague-Dawley rats, intra-arterial infusion of recombinant resistin over a period of 5 h has recently
been reported to promote glucose intolerance by impairing insulin action on hepatic glucose metabolism (14). This observation raises the possibility that local secretion of resistin-like molecules into the portal venous circulation might play a role in the pathogenesis of type 2 diabetes. It is also conceivable that paracrine effects of resistin produced by adipocytes embedded deep within skeletal muscle might contribute to the pathogenesis of impaired glucose tolerance in the absence of changes in either circulating levels of resistin or resistin expression in visceral or superficial subcutaneous fat. However, few studies have been performed to directly investigate the effects of resistin on skeletal muscle glucose metabolism or the relationship between circulating levels of resistin and glucose tolerance.

In this study, we investigated the chronic effects of resistin on glucose metabolism in the spontaneously hypertensive rat (SHR), a widely studied animal model of the hypertension metabolic syndrome that is predisposed to insulin resistance due at least in part to a genetic defect in the CD36 fatty acid transporter (15–17). We have found that transgenic expression of the mouse resistin gene under the control of the aP2 promoter in the SHR induces dyslipidemia and increased muscle triglycerides, impairs oxidative and non-oxidative glucose disposal in skeletal muscle, and promotes glucose intolerance in the absence of detectable changes in circulating levels of resistin or insulin. In addition, we observed that recombinant resistin can inhibit glucose oxidation and insulin-stimulated glycolysis in freshly isolated soleus muscle from non-transgenic SHR. These findings raise the possibility that paracrine actions of resistin secreted by adipocytes embedded within skeletal muscle or autocrine effects of resistin in adipocytes leading to the release of other prodiabetic effector molecules from fat or both may contribute to the pathogenesis of disordered skeletal muscle glucose metabolism and impaired glucose tolerance.

MATERIALS AND METHODS

Generation of Transgenic Rats

Animals—The resistin transgene was expressed on the genetic background of the SHR/Ola strain (15–17). The rats were housed in an air-conditioned animal facility and allowed free access to food and water. Metabolic phenotypes were assessed in male control SHR (n = 10) and male resistin-transgenic SHR (n = 10) after the rats were fed a diet with 60% fructose (K4102.0 diet, Hope Farms, Woerden, The Netherlands) from the age of 5 weeks for 15 days. All of the experiments were performed in agreement with the Animal Protection Law of the Czech Republic (311/1997) and were approved by the Ethics Committee of the Institute of Physiology, Czech Academy of Sciences (Prague, Czech Republic).

Transgenic Strain Derivation—Transgenic SHR were derived by microinjection of zygotes with a mouse resistin cDNA construct that was prepared by reverse transcriptase PCR of RNA from fat tissue of a BALB/c mouse. Resistin primers were designed according to the published resistin sequence (2). The construct contained, in addition to cDNA of the mouse resistin gene, rabbit β-globin intron 2, a growth hormone poly(A) signal and the fat-specific aP2 promoter vector (kindly provided by Dr. Farid Chehab, University of California, San Francisco, CA). Microinjections of recombinant DNA into one or both pronuclei of zygotes of the SHR/Ola strain (15–17) performed in agreement with the Animal Protection Law of the Czech Republic (311/1997) and were approved by the Ethics Committee of the Institute of Physiology, Czech Academy of Sciences (Prague, Czech Republic).

Phenotypic Analysis

Gene Expression Analysis of Transgenic SHR Rats—Northern blot analysis was used to confirm expression of the mouse resistin transgene and endogenous rat resistin gene in adipose tissue. The probe for Northern analysis was prepared by random primer labeling of the first 580 bp of the mouse resistin transgene cut and purified from the transgene construct. Real-time PCR analysis was used to test for possible expression of the mouse resistin transgene in skeletal muscle. The cyclophilin (peptidylprolyl isomerase A) gene was used as an internal control with expression of the mouse resistin transgene relative to cyclophilin being determined in triplicate using the preferred method of Muller et al. (19, 20). The DNA was prepared by reverse transcription of soleus muscle mRNA using random primers followed by real-time PCR amplification using QuantiTect SYBR Green reagents (Qiagen, Inc., Valencia, CA) on an Opticon continuous fluorescence detector (MJ Research, Waltham, MA). The upstream primers were 5′-caac atgc gaca caa ca-3′ (cyclophilin A) and 5′-aga gag cac acg aag cct-3′ (mouse resistin). The downstream primers were 5′-tcc gca act acg tcc-3′ (cyclophilin A) and 5′-tgct cca gtt tac ctg a-3′ (mouse resistin).

Western Blot Analysis—Proteins were extracted from 2 g of epididymal fat. Fat tissue was homogenized with 4 ml of ice-cold extracting buffer (0.3 M Tris-Cl, 0.14 M NaCl, 0.03 M KCl, 1% (w/v) SDS, 1% (v/v) Tween 20, pH 7.4) and 80 μl of protease inhibitors (protease inhibitor mixture for mammalian tissues, Sigma) for 1 min on ice. The samples were then agitated for 1 min by vortex and incubated for 10 min at 37 °C. Afterward, the samples were centrifuged for 10 min, 5300 g, at 4 °C. The water phase was used as a protein extract. For SDS electrophoresis, the protein extracts were agitated with 2 volumes of sample buffer containing β-mercaptoethanol (Laemmli buffer system according to Molecular Probenet manual from Bio-Rad) and heated to 95 °C for 5 min. Samples were loaded on polyacrylamide gel (4% stacking gel and 13% resolving gel), and the electrophoresis was run at 70 V. The load of samples was 30 μl. For Western blotting, a wet protein transfer was done using Mini Trans-Blot electrophoretic transfer cell (Bio-Rad) with transfer buffer (25 mM Tris, 192 mM glycine, 20% v/v methanol, 0.5% w/v SDS, pH 8.3) and nitrocellulose membrane (pore size 0.2 μm, Bio-Rad). Conditions were 20 V for 16 h at 4 °C. The membrane was blocked in 0.01 M phosphate-buffered saline, pH 7.4 (Sigma), containing 3% nonfat dry milk (Sigma) for 30 min at room temperature. Resistin protein was detected with a rabbit anti-mouse resistin antibody (Alpha Diagnostic International, Inc., San Antonio, TX). The antibody does not distinguish between mouse and human. Horseradish peroxidaselabeled donkey anti-rabbit IgG antibody was used as a secondary antibody. Primary and secondary antibodies were diluted in 0.01 M phosphate-buffered saline containing 1.5% nonfat dry milk. The incubation with the primary antibody was overnight at 4 °C and with the conjugate for 1 h at room temperature. The membrane then was treated with the ECL (Amersham Biosciences), and the signal was detected using the Luminiscent Image analysis system (LAS-1000+, Fuji) and quantified by AIDA image analyzer program (Raytest).

Oral Glucose Tolerance Testing—Oral glucose tolerance tests (OGTT) were performed using a glucose load of 0.05 mg/100 g body weight after water deprivation from the experimental animals for 7 h of fasting. Blood was drawn from the tail with heparinized capillary tubes and CO2 as described previously (21, 22). The soleus muscles were attached to a stainless steel frame in situ at in vivo length by special clips and separated from other muscles and tendons and immediately incubated for 2 h in Krebs-Ringer bicarbonate buffer, pH 7.4, that contained 5.5 mM unlabeled glucose, 0.5 μCi/ml [14C]-U-glucose, and 3 mg/ml bovine serum albumin (Armour, Fraction V) with or without 250 μCi/ml 3H-glucose from the tail with insulin (0.2 μU/ml) and the glucose load (0-min time point) and at 30, 60, and 120 min thereafter.

Skeletal Muscle Glycogen Synthesis and Glucose Oxidation—Glycogen synthesis and glucose oxidation were determined in isolated soleus muscle by measuring the incorporation of [1-14C]-U-glucose into glycogen and CO2 as described previously (21, 22). The soleus muscles were attached to a stainless steel frame in situ at in vivo length by special clips and separated from other muscles and tendons and immediately incubated for 2 h in Krebs-Ringer bicarbonate buffer, pH 7.4, that contained 5.5 mM unlabeled glucose, 0.5 μCi/ml [14C]-U-glucose, and 3 mg/ml bovine serum albumin (Armour, Fraction V) with or without 250 μCi/ml 3H-glucose from the tail with insulin (0.2 μU/ml) and the glucose load (0-min time point) and at 30, 60, and 120 min thereafter.

Tissue Triglyceride Measurements—For determination of triglycerides in liver and soleus muscle, tissues were powdered under liquid N2 and extracted for 16 h in chloroform and methanol (2:1). The solution was centrifuged. The organic phase was removed and evaporated under N2. The resulting pellet was dissolved in isopropl alcohol, and triglyceride content was determined by enzymatic assay (Pliva-Lachema, Brno, Czech Republic).

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above in soleus muscles isolated from 7-week-old male SHR/Ola (SHR). Glycogenesis and glucose oxidation were measured as described previously for rat resistin. Two transcripts for the endogenous rat resistin gene were detected in epididymal fat tissue of transgene-positive rats and transgene-negative controls with molecular weights corresponding to those previously reported for rat resistin. Real-time PCR analysis showed that the transgene-negative controls with molecular weights corresponding to those previously reported for rat resistin. Western blot analysis of resistin protein in adipose tissue isolated from transgene-negative controls and transgene-positive rats using a monoclonal antibody that does not distinguish rat and mouse resistin proteins. Transgenic rats exhibited a modest increase of resistin protein (170%) compared with control SHR rats (100%), which express only endogenous rat resistin.

**TABLE I**

| Strain | Body weight (g) | Epididymal fat weight (g/100 g body weight) | Serum resistin (ng/ml) |
|--------|-----------------|---------------------------------------------|-----------------------|
| SHR control | 280 ± 3 | 1.05 ± 0.05 | 21.8 ± 2.6 |
| SHR-TG | 278 ± 6 | 1.05 ± 0.06 | 21.5 ± 2.4 |

**RESULTS**

**Transgenic Expression of Resistin**—Transgene-positive SHR and transgene-negative controls were identified by genotyping offspring derived from crosses of a founder male with transgene-negative SHR females. In the epididymal fat from the SHR transgene-positive line, Northern blot analysis confirmed the expression of both the mouse resistin transgene and the endogenous rat resistin gene (Fig. 1a). The transgene-negative controls showed expression of only the endogenous rat resistin gene. Fig. 1a shows the presence of the 0.8- and 1.4-kb pair transcripts that are characteristic of endogenous rat resistin in both the transgene-positive SHR and in a transgene-negative control. These two transcripts are similar in size to those previously reported for the rat, which is known to express two resistin transcripts, whereas the mouse expresses only one resistin transcript (4). In the SHR-transgenic line, a single transcript for the mouse resistin transgene could be detected in moderate amounts that is distinct in size from the endogenous rat resistin transcripts and that is slightly larger than the wild type mouse resistin transcript because of its longer 3′-untranslated tail. In addition to detecting mRNA for the mouse resistin transgene by Northern blot analysis in epididymal fat from the transgenic strain, we were able to detect low level skeletal muscle expression of the mouse resistin transgene relative to that of cyclophilin by real-time PCR (Fig. 1b). Transgene-negative controls showed no expression of the mouse resistin gene in fat or muscle when tested by either Northern blot analysis or real-time PCR. Western blot analysis of adipose tissue demonstrated greater expression of resistin protein in the transgene-positive rats than in transgene-negative controls (Fig. 1c).

**Effects of Resistin Transgene on Body Weight, Serum Phenotypes, and Tissue Lipid Levels**—At the time of sacrifice, there were no significant differences between transgene-positive rats and transgene-negative controls with respect to either body weight or epididymal fat weight (Table I). Serum resistin levels were similar between SHR transgene-positive rats and transgene-negative controls as measured by an immunoassay that cross-reacts with mouse and rat resistin (Table I). Serum concentrations of insulin and glucose in transgene-positive rats, 1.2 ± 0.10 nmol/liter and 6.7 ± 0.2 mmol/liter, were similar to those in transgene-negative controls, 1.2 ± 0.13 nmol/liter and 6.8 ± 0.2 mmol/liter, respectively. In transgene-positive rats, serum levels of leptin, 3.8 ± 0.8 ng/ml, were also not different compared with those in transgene negative controls, 3.9 ± 0.7.
Effects of Resistin Transgene on Skeletal Muscle Glucose Metabolism—In soleus muscle isolated from transgenic SHR expressing the mouse resistin gene, glycogen synthesis and glucose oxidation were significantly reduced in both the presence and absence of insulin (Fig. 4, a and b). Thus, both non-oxidative and oxidative glucose metabolism were impaired in skeletal muscle of transgenic rats compared with controls. These findings are in accord with the recent studies of Moon et al. (23) in which recombinant resistin was found to inhibit glucose uptake in cultured L6 skeletal muscle cells in both the presence and absence of insulin. However, in the studies of Moon et al. (23), the effects of recombinant resistin on metabolic pathways of glucose disposal were not investigated and the extent to which the effects of recombinant resistin on glucose metabolism in L6 cells resemble those in skeletal muscle tissue is unknown. The current findings indicate that transgenic expression of resistin can impair both of the main pathways that mediate skeletal muscle glucose disposal even in isolated tissue that has not been previously exposed to increased circulating levels of resistin in vivo or to additional recombinant resistin in vitro.

Effects of Recombinant Resistin on Skeletal Muscle Glucose Metabolism—Incubation of isolated soleus muscle from non-transgenic SHR with recombinant resistin significantly impaired insulin-stimulated glycogen synthesis (Fig. 5a). Skeletal muscle glycogen synthesis was significantly lower in the presence of recombinant resistin plus insulin than in the presence of insulin alone. Although recombinant resistin also showed a tendency to reduce basal glycogen synthesis in the absence of insulin, the effect did not achieve statistical significance (Fig. 5a). Incubation of soleus muscle from non-transgenic SHR with recombinant resistin significantly reduced basal glucose oxidation (no insulin) and caused a borderline decrease (p = 0.07) in glucose oxidation in the presence of insulin (Fig. 5b). These findings in SHR soleus muscle incubated with recombinant resistin show remarkable similarity to the results in soleus muscle isolated from transgenic SHR that express the mouse aP2 resistin transgene.

**DISCUSSION**

The discovery of resistin initially provoked great interest in the potential role of resistin-related molecules in the pathogenesis of insulin resistance and type 2 diabetes. More recently, a number of reports have been published that might seem to raise doubts regarding the possibility of an important relationship between resistin and various metabolic disturbances that are characteristic of obesity and type 2 diabetes. For example,
some investigators have noted that in humans, little or no correlation exists between resistin mRNA levels in adipose tissue or adipocytes and diabetes, insulin resistance, or body mass index (10, 11, 24). In a variety of animal models of obesity that are associated with insulin resistance, expression of resistin in white adipose tissue has also been reported to be significantly decreased (6, 12, 13), prompting some investigators to conclude that “resistin seems to be at work to improve rather than cause insulin resistance in obesity” and even to suggest that “the use of the term resistin is not appropriate in this regard” (13). However, given the complex nature of multifactorial disorders similar to insulin resistance and type 2 diabetes, the often unpredictable relationship between mRNA levels and protein levels as well as the lack of knowledge regarding potential feedback relationships between insulin resistance and resistin expression, it is premature to discount a potential role for resistin in the pathogenesis of insulin resistance in either humans or in animals (25).

In the current studies, we have found that transgenic expression of mouse resistin under control of the aP2 promoter on the genetic background of the SHR induces increases in serum and skeletal muscle lipid levels, impairs oxidative and non-oxidative glucose disposal in skeletal muscle, and promotes glucose intolerance in the absence of detectable changes in circulating levels of resistin, insulin, or leptin. Similar results were obtained with transgenic expression of mouse resistin under the control of a universal elongation factor–1α promoter.2 Thus, the current findings are probably related to the effects of transgenic expression of resistin rather than the effects of transgenic expression the aP2 promoter. In addition, we observed that recombinant resistin can attenuate glucose oxidation and greatly inhibit insulin-stimulated glycogenesis in freshly isolated soleus muscle from non-transgenic SHR. These findings are consistent with the studies of Steppan et al. (2) in which intraperitoneal injection of recombinant resistin was found to acutely impair glucose tolerance in C57BL/6J mice and suggest that, at least under the environmental and genetic circumstances of the current study, resistin may contribute to impaired glucose tolerance by way of effects on skeletal muscle glucose metabolism.

Although the current studies have focused on the effects of resistin on skeletal muscle glucose metabolism, they should not be taken to imply that the glucose intolerance observed in the SHR resistin-transgenic strain is only, or even largely, a consequence of skeletal muscle insulin resistance. In a comprehensive series of experiments using the pancreatic insulin clamp technique in conscious Sprague-Dawley rats, Rajala et al. (14) recently found that intra-arterial infusion of recombinant resistin over a period of 5 h can impair insulin action on hepatic glucose production. Other investigators have reported that recombinant resistin can inhibit insulin-stimulated glucose uptake in cultured 3T3-L1 adipocytes and in L6 skeletal muscle cells (2, 23). These studies, together with the current findings in isolated skeletal muscle preparations from transgenic and non-transgenic rats, suggest that resistin may contribute to the pathogenesis of insulin resistance through effects on multiple target tissues. The relative importance of these effects of resistin in different target tissues might also depend on the environmental and genetic circumstances under which they are studied.

In the experiments of Rajala et al. (14) in Sprague-Dawley rats, the short term intra-arterial infusion of recombinant resistin acutely impaired hepatic glucoseogenesis without significantly affecting peripheral glucose uptake. However, short term infusions of recombinant resistin may not necessarily reflect the chronic metabolic effects of resistin in vivo and do not have the potential to reveal autocrine or paracrine meta-

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2 M. Pravenec, L. Kazdová, V. Landa, V. Zídek, J. Wang, N. Qi, and T. W. Kurtz, unpublished results.
The metabolic effects of resistin in skeletal muscle can impair muscle glucose metabolism under a variety of other environmental and genetic circumstances.

**REFERENCES**

1. DeFronzo, D. J., Bonadonna, R. C., and Ferrannini, E. (1992) Diabetes Care 15, 318–368.
2. Steppan, C. M., Bailey, S. T., Bhat, S., Brown, E. J., Banerjee, R. R., Wright, C. M., Patel, H. R., Ahima, R. S., and Lazar, M. A. (2001) Nature 409, 367–372.
3. Holcomb, I. N., Kabakoff, R. C., Chan, B., Baker, T. W., Gurney, A., Henzel, W., Nelson, C., Lowman, H. B., Wright, B. D., Shelton, N. J., Frantz, G. D., Tumas, D. R., Peale, F. V., Jr., Shelton, D. L., and Hebert, C. C. (2000) EMBO J. 19, 4046–4055.
4. Kim, K. H., Lee, K., Moon, Y. S., and Sul, H. S. (2001) J. Biol. Chem. 276, 11253–11256.
5. Banerjee, R. R., and Lazar, M. A. (2003) J. Mol. Med. 81, 218–226.
6. Juan, C. C., Au, L. C., Fang, V. S., Kang, S. F., Ko, Y. H., Kuo, S. F., Hsu, Y. P., Kowch, C. F., and Ho, L. T. (2001) Biochem. Biophys. Res. Commun. 289, 1328–1333.
7. Moore, G. B. T., Chapman, H., Holder, J. C., Laster, C. A., Piercy, V., Smith, S. A., and Clapham, J. C. (2001) Biochem. Biophys. Res. Commun. 286, 738–741.
8. Way, J. M., Gorgun, C. Z., Tong, Q., Uysal, K. T., Brown, K. K., Harrington, W. W., Oliver, W. R., Jr., Wilson, T. M., Kliwer, S. A., and Hotamisligil, G. S. (2000) J. Biol. Chem. 275, 23681–23687.
9. McTernan, C. L., McTernan, P. G., Harte, A. L., Levick, P. L., Barnett, A. H., and Kumar, S. (2002) Lancet 359, 46–47
10. Savage, D. B., Sewter, C. P., Kienk, E. S., Segal, D. G., Vidal-Puig, A., Considine, R. V., and O’Rahilly, S. (2001) Diabetes 50, 2199–2202
11. Nagase, I., and Smith, U. (2001) Biochem. Biophys. Res. Commun. 285, 561–564
12. Fukui, Y., and Motoujima, K. (2002) Diabetes Obes. Metab. 4, 342–345
13. Fujita, H., Fujishima, H., Morii, T., Koshimura, J., Narita, T., Kakei, M., and Ito, S. (2002) Biochem. Biophys. Res. Commun. 298, 345–349
14. Rajala, M. W., Obici, S., Scherer, P. E., and Rossetti, L. (2003) J. Clin. Invest. 111, 225–230
15. Pravenec, M., Zidek, V., Šimáková, M., Kren, V., Krenová, D., Horký, K., Jakbymová, M., Míková, B., Kázdová, L., Aitman, T. J., Churchill, P. C., Webb, R. C., Hingarh, N. H., Yang, V., Wang, J., St. Lezin, E. M., and Kurtz, T. W. (1999) J. Clin. Invest. 103, 1651–1657
16. Aitman, T. J., Glazier, A. M., Wallace, C. A., Cooper, L. D., Norsworthy, P. J., Wahid, F. N., Al-Majali, K. M., Trembling, P. M., Mann, C. J., Shoulders, C. C., Graf, D., St. Lezin, E., Kurtz, T. W., Kren, V., Pravenec, M., Ibrahimi, A., Abumrad, N. A., Stanton, L. W., and Scott, J. (1999) Nat. Genet. 21, 76–83
17. Pravenec, M., Landa, V., Zidek, V., Musilová, A., Kren, V., Kázdová, L., Aitman, T. J., Glazier, A. M., Ibrahimi, A., Abumrad, N. A., Qi, N., Wang, J., St. Lezin, E. M., and Kurtz, T. W. (2002) J. Biol. Chem. 277, 48501–48507
18. Charreau, B., Menoret, S., Tessson, L., Soulilou, J.-P., and Anegen, I. (1997) Rat Genome 3, 125–132
19. Muller, P. Y., Janovjak, H., Miserez, A. R., and Dobbie, Z. (2002) BioTechniques 32, 1372–1379
20. Muller, P. Y., Janovjak, H., Miserez, A. R., and Dobbie, Z. (2002) BioTechniques 33, 514
21. Vranić, A., Poledne, R., Fáby, P., and Kazdová, L. (1978) Metabolism 27, 885–888
22. Qi, N., Kázdová, L., Zidek, V., Landa, V., Kren, V., Pershadsingh, H. A., St. Lezin, E., Abumrad, N. A., Pravenec, M., and Kurtz, T. W. (2002) J. Biol. Chem. 277, 48501–48507
23. Moon, B., Kwan, J. J., Duddy, N., Sweeney, G., and Begum, N. (2003) Am. J. Physiol. 285, E106–E115
24. Janke, J., Engeli, S., Gorzelniak, K., Luft, F. C., and Sharma, A. M. (2002) Obes. Res. 10, 1–5
25. Hotamisligil, G. S. (2003) J. Clin. Invest. 111, 173–174
26. Reaven, G. M., Ho, H., and Hoffman, B. B. (1990) Horm. Metab. Res. 22, 363–365
27. Reaven, G. M. (1991) Am. J. Med. 90, 7S–12S
28. Reaven, G. M. (1988) Diabetes 37, 1595–1667
29. Grundy, S. M. (1999) Am. J. Cardiol. 83, 23S–29S
30. DeFronzo, R. A., and Ferrannini, E. (1991) Diabetes Care 14, 173–194
31. Boden, G. (2002) Curr. Opin. Clin. Nutr. Metab. Care 5, 545–549
32. Kraegen, E. W., Cooney, G. J., Ye, J. M., Thompson, A. L., and Furler, S. M. (2001) Exp. Clin. Endocrinol. Diabetes 109, Suppl. 2, S189–S201
33. Kelley, D. E., and Goodpaster, B. H. (2001) Diabetes Care 24, 933–941
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J. Biol. Chem. 2003, 278:45209-45215.
doi: 10.1074/jbc.M304869200 originally published online August 27, 2003

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