E. Ferrannini

Rosiglitazone and lipid metabolism

Received: 26 November 2004 / Accepted: 26 November 2004 / Published online: 29 December 2004
© Springer-Verlag 2004

Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear receptors (subtypes so far identified: PPAR γ , PPAR α , and PPAR δ) which act as transcription factors regulating a large number of genes involved in glucose and lipid metabolism [1]. Agents that bind to and activate PPARs are in clinical use or development for the treatment of hyperglycaemia (PPAR γ agonists), hypertriglyceridaemia (PPAR α agonists) or both (dual and pan PPAR agonists). PPAR γ agonists include both thiazolidinedione and non-thiazolidinedione compounds of varying specificity and affinity, and fibrates are typical PPAR α agonists. Of the two thiazolidinediones currently on the market, rosiglitazone is a more specific and potent PPAR γ agonist than pioglitazone, which also displays some PPAR α agonist activity [2]. Both agents enhance the sensitivity of glucose metabolism to insulin in patients with type 2 diabetes, thereby lowering plasma glucose concentrations within a few weeks of treatment. Studies with the euglycaemic–hyperinsulinaemic clamp have shown that both agents increase insulin-mediated glucose uptake at the whole-body level, and that this mostly reflects skeletal muscle glucose uptake [3]. A recent study of rosiglitazone, which combined the clamp technique with ^{18}F -deoxyglucose and positron-emitting tomography, also showed enhanced glucose uptake in both the visceral and subcutaneous adipose tissue of diabetic patients [4]. Long-term use of both thiazolidinediones is associated with decreased abdominal visceral adipose tissue mass and weight gain due to an expansion of the subcutaneous fat mass [3]. PPAR γ expression is abundant in adipose tissue and scanty in skeletal muscle [1], and the paradox that agents which target receptors mainly expressed in adipose tissue have their major effect upon the insulin sensitivity of skeletal muscle has required a lot of explanation. Many experts believe that the sequence of events starts with differentiation of pre-adipocytes into mature, small, insu-

lin-sensitive adipocytes, which are more active in clearing NEFA from the circulation; the resulting decrease in plasma NEFA reduces competition with glucose for uptake by skeletal muscle, thereby enhancing insulin-mediated glucose uptake [3]. However, this simple model lacks empirical support, given that the reduction of circulating NEFA by thiazolidinediones has been minimal or absent in several human studies. A report by Tan and colleagues in this issue of *Diabetologia* [5] sets forth to test, indeed to challenge, this paradigm.

Tan and colleagues used a cross-over design to randomise diet-treated patients with type 2 diabetes to full-dose rosiglitazone or placebo for a period of 12 weeks. Timed measurements of glucose and lipid variables were then made in relation to a mixed meal. Given the complexity of the remainder of the experimental protocol, it may be useful to outline what was being measured. By threading indwelling cannulae into a heated hand vein (to obtain arterialisated blood), a deep forearm vein (to sample venous efflux from predominantly muscle tissue) and the superficial epigastric vein (draining abdominal subcutaneous fat), and by measuring blood flow through these regions, the investigators were able to calculate the net substrate balance across insulin's two main target tissues, skeletal muscle and fat. Combined triglyceride, NEFA and glycerol balances were obtained, making it possible to estimate the total transcapillary NEFA flux in and out of tissues, the rate of intravascular triglyceride lipolysis (or rate of action of lipoprotein lipase) and the rate of adipose tissue lipolysis (reflecting the rate of action of hormone-sensitive lipase). Since the lipid fraction of the mixed meal was labelled with carbon, it was also possible to measure the tracer enrichment of circulating NEFA and triglycerides. Finally, needle biopsy of muscle and adipose tissue provided a means to measure the expression of several PPAR γ -responsive genes.

The results can be recapitulated as follows. As expected, glucose clearance in skeletal muscle was enhanced by rosiglitazone over the postprandial period. In the fasting state, circulating NEFA and triglyceride levels were unaffected by rosiglitazone, but NEFA release from

E. Ferrannini (✉)
Department of Internal Medicine and CNR, Institute of Clinical
Physiology, University of Pisa School of Medicine,
56100 Pisa, Italy

adipose tissue was increased, due to increased tissue lipolysis; muscle NEFA uptake was also increased. These coupled effects may reflect the fall in circulating insulin levels. In contrast, plasma NEFA and triglycerides both fell during the late postprandial period, and none of the measured regional lipid fluxes could account for this.

The observation is novel in two respects. First, it shows that pure PPAR γ activation does have lipid-lowering effects in its own right, and that these can be uncovered by a physiological stimulus such as a mixed meal. Second, humans spend more than two-thirds of their lives in the fed state, and the fall in postprandial lipaemia induced by rosiglitazone is likely to have long-term implications for vascular function. The mechanisms underlying these effects remain elusive. Since NEFA exchange was unaltered across subcutaneous fat or skeletal muscle, rosiglitazone must have suppressed NEFA release from unmeasured fat depots. Visceral fat is the obvious suspect here, both by exclusion of other sources and because thiazolidinediones are known to affect visceral fat volume. Although this appears plausible, quantitative issues must also be considered. How large are the visceral fat depots? Estimates obtained with the use of multiscan magnetic resonance imaging [6] indicate that visceral fat in the whole abdomen (from the upper edge of the liver to the pelvis) may amount to 10–15% of total body fat. Even with the addition of intrathoracic visceral fat [6], this is a small amount of fat to account for the major effect of rosiglitazone upon NEFA release. The reduction in visceral fat reported with long-term use of this drug is of the order of ~200 g [4]. However, the study of Tan and colleagues does offer one clue, in that rosiglitazone treatment was associated with reduced appearance of labelled palmitate (ingested with the meal) in circulating NEFA, implying that the rate of NEFA spillover from chylomicron-triglycerides was decreased. Could this be due to actions on intestinal lipid absorption? Or to a change in apoprotein distribution and/or chylomicron handling? Intriguing possibilities, and amenable to experimental testing.

The effects of rosiglitazone on late postprandial triglyceride levels were probably linked to the effects on NEFA; they too imply an unmeasured dimension. Since the drug did not affect triglyceride removal by subcutaneous fat or skeletal muscle, and remnants of triglyceride-rich lipoproteins did not change (they would have fallen if the liver had taken up more), the postprandial fall in plasma triglyceride must reflect decreased hepatic secretion of triglyceride-rich lipoproteins. NEFA is the substrate for these particles, and it is conceivable that the reduced flux of NEFA to the liver resulted in reduced packaging and export of triglyceride-rich lipoproteins. Since the presumed reduction in NEFA release from visceral fat depots would primarily impact upon the liver, this interpretation

receives collateral support from the observation that rosiglitazone decreases intrahepatic fat [6], the immediate precursor pool for triglyceride-rich lipoproteins. Interestingly, this would bring the liver, which some now view as a primary site of thiazolidinedione action on glucose metabolism [7, 8], into much greater prominence.

What about changes in the pattern of gene expression? A novel finding in the study by Tan and colleagues is that rosiglitazone augmented the expression of hexokinase II, an early committed step for glucose metabolism in skeletal muscle. As the authors rightly point out, it is difficult to decide whether this was a direct action of the drug or an indirect effect mediated by chronic reduction in NEFA concentrations.

Does this new information contribute to our understanding of type 2 diabetes? It does, in more than one way, for we learn more of adipose tissue biology and of its role in glucose homeostasis and inter-organ lipid exchange, and we also hear more of complex cross-talk within the abdomen (gut, fat, liver). Does this new information advance therapeutic understanding? Yes, in that it draws attention to the postprandial lipaemia in which we all swim happily for most of the day. Do thiazolidinediones meet our needs in the treatment of type 2 diabetes? Hardly the case at present, but they do open up a fascinating new world of possibilities [3]. To keep mind and eyes wide open is the least we can do.

Reference

- Berger J, Moller D (2002) The mechanisms of action of PPARs. *Annu Rev Med* 53:409–435
- Sakamoto J, Kimura H, Moriyama S et al (2000) Activation of human peroxisome proliferator-activated receptor (PPAR) subtypes by pioglitazone. *Biochem Biophys Res Commun* 278:704–711
- Yki-Järvinen H (2004) Thiazolidinediones. *N Engl J Med* 351:1106–1118
- Virtanen KA, Hällsten K, Parkkola R et al (2003) Differential effects of rosiglitazone and metformin on adipose tissue distribution and glucose uptake in type 2 diabetic subjects. *J Clin Endocrinol Metab* 52:283–290
- Tan GD, Fielding BA, Currie JM et al (2005) The effects of rosiglitazone on fatty acid and triglyceride metabolism in type 2 diabetes. *Diabetologia* 48 DOI 10.1007/s00125-004-1619-9
- Tiikkainen M, Hakkinen AM, Korshenninnikova E et al (2004) Effects of rosiglitazone and metformin on liver fat content, hepatic insulin resistance, insulin clearance, and gene expression in adipose tissue in patients with type 2 diabetes. *Diabetes* 53:2169–2176
- Sironi AM, Vichi S, Gastaldelli A et al (1997) Effects of troglitazone on insulin action and cardiovascular risk factors in patients with non-insulin-dependent diabetes. *Clin Pharmacol Ther* 62:194–202
- Tonelli J, Li W, Kishore P et al (2004) Mechanisms of early insulin-sensitizing effects of thiazolidinediones in type 2 diabetes. *Diabetes* 53:1621–1629