In vivo mitochondrial function in type 2 diabetes mellitus patients before and after treatment with a PPARgamma agonist

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Background: Mitochondrial dysfunction has recently been implicated in (the development of) insulin resistance and type 2 diabetes mellitus [1]. *In vivo* mitochondrial function can be measured with phosphorus magnetic resonance spectroscopy (^{31}P-MRS) by determining the half-time of PCr recovery immediately after exercise [2]. Using this method, we recently observed a decreased *in vivo* mitochondrial function in type 2 diabetic subjects compared to healthy BMI-matched controls [3]. Interestingly, PCr recovery half-time correlated positively with plasma glucose levels in the diabetic patients, revealing that a low mitochondrial function is associated with a more severe diabetic condition. Here, we investigated the effect of a pharmacological intervention (PPARgamma agonist, Rosiglitazone®, GSK) known to improve insulin sensitivity, on *in vivo* mitochondrial function in a group of type 2 diabetic patients.

Methods: Eight overweight subjects (age (y): 62 ± 1.6; BMI (kg/m^2): 29.3 ± 1.1) with type 2 diabetes mellitus discontinued their oral antidiabetic medication two weeks prior to the experiment. Subjects were treated with Rosiglitazone (2 x 4 mg/day) for 8 weeks. Before and after treatment, fasting plasma concentrations of glucose, insulin and free fatty acids (FFA), insulin sensitivity, and *in vivo* mitochondrial function was determined. Insulin sensitivity (glucose infusion rate, GIR) was measured during a hyperinsulinaemic euglycaemic clamp. To investigate *in vivo* mitochondrial function, PCr recovery half-time after exercise was determined by ^{31}P-MRS. The MR measurements were performed on a whole body scanner (1.5T, Intera, Philips, The Netherlands). Non-localized ^{31}P-MRS was performed with a 6 cm surface coil positioned on the vastus lateralis muscle. A time serie of 120 spectra was acquired (TR=4s) during a protocol consisting of 2 minutes of rest, 5 minutes of knee-extension exercise and 5 minutes of recovery from exercise. Exercise was performed inside the magnet with a home-built, non-magnetic exercise device connected to a pulley system. MRS data was fitted with AMARES [4] in the jMRUI 3 software package (http:// www.mrui.uab.es/). The PCr recovery time-course was fitted with a monoexponential curve and the recovery half-time was calculated (MATLAB, The Mathworks. Inc.).

Results: Glucose infusion rate, under hyperinsulinemic euglycemic conditions was increased after the treatment (19.9 ± 2.8 before vs 24.8 ± 2.1 after treatment, p=0.04), indicating improved insulin sensitivity. However, mean PCr recovery half-time, fasting blood glucose, insulin, and FFA levels were unchanged. Mean PCr recovery half-time (s) was 19.9 ± 2.8 and 24.8 ± 2.1 (p=0.20) before and after the treatment respectively. Mean fasting blood glucose level (mmol) was 9.3 ± 0.7 and 8.8 ± 0.7 (p=0.23), mean insulin concentration (mU/l) was 16.1 ± 2.9 and 13.4 ± 1.8 (p=0.20), mean FFA concentration (µmol/l) was 430.6 ± 29.8 and 398.5 ± 41.9 (p=0.53), all before and after the treatment respectively. The individual decrease in fasting plasma insulin levels correlated with the decrease in PCr half-time (R=0.7, p=0.049) (figure 1) and the decrease in fasted plasma glucose tended to correlate with PCr half-time (R=0.6, p=0.077) (figure 2), indicating that subjects in whom plasma insulin and glucose levels decreased most following the Rosiglitazone treatment, were characterized by the most pronounced improvement in mitochondrial function. Changes in PCr half-time did not correlate with changes in insulin sensitivity (R=-0.1, p=0.8).

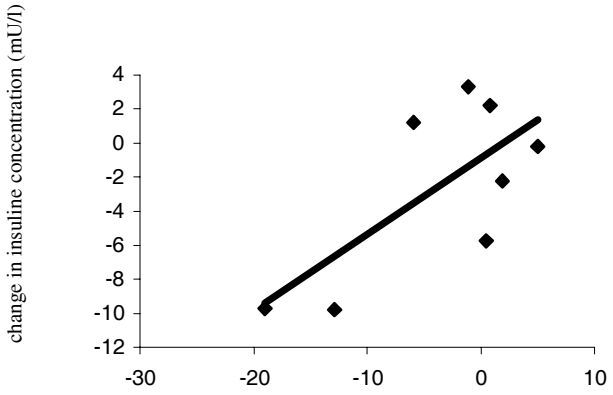

Figure 1 : Correlation of changes in plasma insulin with changes in PCr recovery half-time.

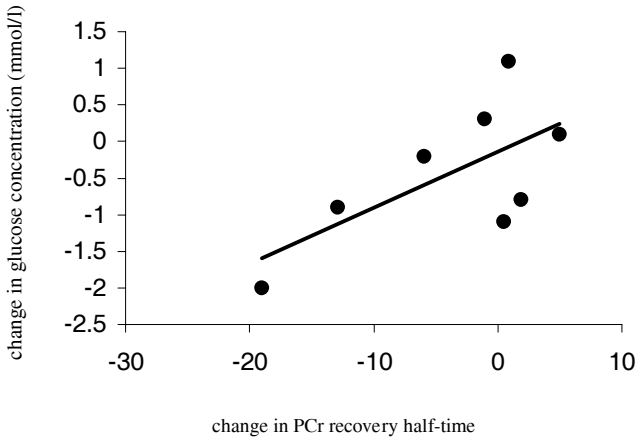

Figure 2 : Correlation of changes in plasma glucose with changes in PCr recovery half-time.

Discussion:

The current intervention with a PPARgamma agonist improved insulin sensitivity, while in vivo mitochondrial function remained unchanged. Furthermore, changes in insulin sensitivity were not correlated with changes in mitochondrial function. These findings suggest that improvements in mitochondrial function are not a prerequisite for an improvement of insulin sensitivity, although these results are very preliminary and, due to the small number of patients, should be interpreted with care. Interestingly, *in vivo* mitochondrial function in the present study improved the most in subjects who showed the largest change in plasma glucose and insulin levels after Rosiglitazone treatment, suggesting that glucose homeostasis may be related to mitochondrial function.

References:

1. Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI (2004), N Engl J Med 350:664-671
2. Kemp GJ, Radda GK (1994), Magn Reson Q 10:43-63
3. Schrauwen-Hinderling VB, Kooi ME, Hesselink MK, et al. (2006), Diabetologia, e-pub ahead of print
4. Vanhamme L, van den Boogaart A, Van Huffel S (1997), J Magn Reson 129:35-43.