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Metformin severely impairs *in vivo* muscle oxidative capacity in a rat model of type 2 diabetes

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Objective: To investigate the effects of metformin on *in vivo* and *in vitro* skeletal muscle mitochondrial function in Zucker diabetic fatty (ZDF) rats using ³¹P magnetic resonance spectroscopy (MRS) and high-resolution respirometry (HRR), respectively.

Methods: 12-week old healthy (*fa/+*) and diabetic (*fa/fa*) ZDF rats were treated with metformin (0, 30, 100 or 300 mg/kg body weight/day) for 15 days by oral gavage. At day 14, *in vivo* ³¹P MRS was performed on the *tibialis anterior* (TA) muscle to measure PCr recovery. At day 15, animals were killed and TA muscles were excised for *in vitro* HRR measurements.

Results: Metformin treatment decreased PCr recovery rates in a dose-dependent manner in both healthy *fa/+* and diabetic *fa/fa* rats. Whereas, the clinical dose of 30 mg/kg/day had no significant effect, PCr recovery rates were ~22% and ~47% decreased at 100 and 300 mg/kg/day. HRR measurements showed a similar, but less pronounced effect of metformin on *in vitro* mitochondrial function.

Conclusion: Metformin treatment impairs *in vivo* skeletal muscle oxidative capacity in rats in a dose-dependent manner. ***This research was funded by a VIDI grant from the Netherlands Organisation for Scientific Research (NWO).***