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COMMENT ON CHONDRONIKOLA ET AL.

Brown Adipose Tissue Improves Whole-Body Glucose Homeostasis and Insulin Sensitivity in Humans. Diabetes 2014;63:4089–4099

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e-LETTERS – COMMENTS AND RESPONSES

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In this interesting article by Chondronikola et al. (1), the measurements of adipose tissue mitochondrial respiration are reported. The authors use a study by López et al. (2) as a reference for details of the used methods. A list of the substrates used for mitochondrial respiration (octanoyl-carnitine, pyruvate, glutamate, malate, ADP, succinate, and oligomycin) is given. In the results (see Fig. 6*G*), they report data on the "uncoupled mitochondrial respiration" (1). There are several problematic issues here. First, in the study by López et al. (2), mitochondrial respiration was not measured and therefore there is no description of the method. Second, basic information about the handling of the biopsies is missing (e.g., time from sampling to measurement, buffer composition). Third, temperature and oxygen concentration during the measurements are important confounders, but this information is not given. Fourth, the sequence of substrate addition and the respiratory data from the mentioned substrates are not reported. Fifth, "uncoupled" respiration is reported, but none of the substrates are uncoupling agents, so at what time in the sequence was it performed and which uncoupler was used?

If we assume that the uncoupler was added at the end of the sequence of the mentioned substrates, then it followed a composite mixture of substrates for complex I and II, with complex V inhibited by oligomycin. Did the authors check if the presence of oligomycin before the addition of the uncoupler affected the respiratory rate? In our hands, this is the case. It is unfortunate that the description of the methods and the necessary control experiments are limited to the extent that the experiments cannot be replicated.

A total of 10 and 50 mg of adipose tissue was used for brown adipose tissue (BAT) and white adipose tissue respiratory analyses, respectively. However, without the measurement of the mitochondrial content per mg tissue, no conclusions can be made regarding the intrinsic mitochondrial respiration (3). It is not a surprise that respiration increases with increased mitochondrial content.

In the article and supplementary data, individual gene expression is reported from three BAT^{+} and one BAT^{-} subjects (see Fig. 6*F*, *H*, and *I* and Supplementary Figs. 3–6); however, the subjects were not identified. These data are expressed relative to "fold of ctrl BAT," but this is not explained (1). What is the "ctrl" condition? It cannot be the thermoneutral (TN) condition because the same unit is used in Fig. 6*F* as in Fig. 6*H* and *I*. Further, the data are shown as mean ± SD, and statistical differences are indicated by asterisks. How can the authors perform a statistical test of $n = 1$ and report data with a standard deviation? The authors describe that they used paired analysis for comparisons between TN and cold exposure (CE). They state that a "one-sample *t* test was used to evaluate whether CE induced changes in the various metabolic measurements

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compared with TN" (1). It is not clear if this covers the gene expression data, but nevertheless a one-sample *t* test compares the mean with a predefined value, and here paired CN vs. TN conditions are compared, and it remains unclear precisely which data were analyzed with which methods.

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