Brown adipose tissue transplantation ameliorates polycystic ovary syndrome

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Edited by R. Michael Roberts, University of Missouri–Columbia, Columbia, MO, and approved January 21, 2016 (received for review November 24, 2015)

Polycystic ovary syndrome (PCOS), which is characterized by anovulation, hyperandrogenism, and polycystic ovaries, is a complex endocrinopathy. Because the cause of PCOS at the molecular level is largely unknown, there is no cure or specific treatment for PCOS. Here, we show that transplantation of brown adipose tissue (BAT) reversed anovulation, hyperandrogenism, and polycystic ovaries in a dehydroepiandrosterone (DHEA)-induced PCOS rat. BAT transplantation into a PCOS rat significantly stabilized menstrual irregularity and improved systemic insulin sensitivity up to a normal level, which was not shown in a sham-operated or muscle-transplanted PCOS rat. Moreover, BAT transplantation, not sham operation or muscle transplantation, surprisingly improved fertility in PCOS rats. Interestingly, BAT transplantation activated endogenous BAT and thereby increased the circulating level of adiponectin, which plays a prominent role in whole-body energy metabolism and ovarian physiology. Consistent with BAT transplantation, administration of adiponectin protein dramatically rescued DHEA-induced PCOS phenotypes. These results highlight that endogenous BAT activity is closely related to the development of PCOS phenotypes and that BAT activation might be a promising therapeutic option for the treatment of PCOS.

brown adipose tissue | transplantation | ameliorates | PCOS | adiponectin

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Significance

In the current study, we show that brown adipose tissue (BAT) activity is dramatically reduced in a dehydroepiandrosterone (DHEA)-induced polycystic ovary syndrome (PCOS) rat when compared with a normal control rat. Importantly, the key features of PCOS (such as insulin resistance and irregular estrous cycle) are alleviated after BAT transplantation. Mechanistically, transplanted BAT enhances endogenous BAT activity and thereby increases the circulating adiponectin level, which was lower in both the PCOS patient and PCOS rat model. Furthermore, exogenous adiponectin protein administration recapitulates beneficial effects from BAT transplantation in a PCOS rat. Taken together, these data highlight the important role of BAT in the development of PCOS and that BAT-induced adiponectin might open up a new way in the treatment of PCOS.

Author contributions: X.Y., T.H., H. Zhao, Y.H., H.W., H.J.L., W.J., and Z.-J.C. designed research; X.Y., T.H., H. Zhao, Y.H., R.Y., J.L., C.Z., H. Zhang, G.W., H. Zhou, M.D., J.Z., Q.L., and H.J.L. performed research; Q.L. contributed new reagents/analytic tools; X.Y., T.H., Y.H., R.Y., J.L., C.Z., H. Zhang, G.W., H. Zhou, M.D., J.Z., H.W., H.J.L., and W.J. analyzed data; and X.Y., T.H., H. Zhao, H.J.L., W.J., and Z.-J.C. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1523236113/-/DCSupplemental.

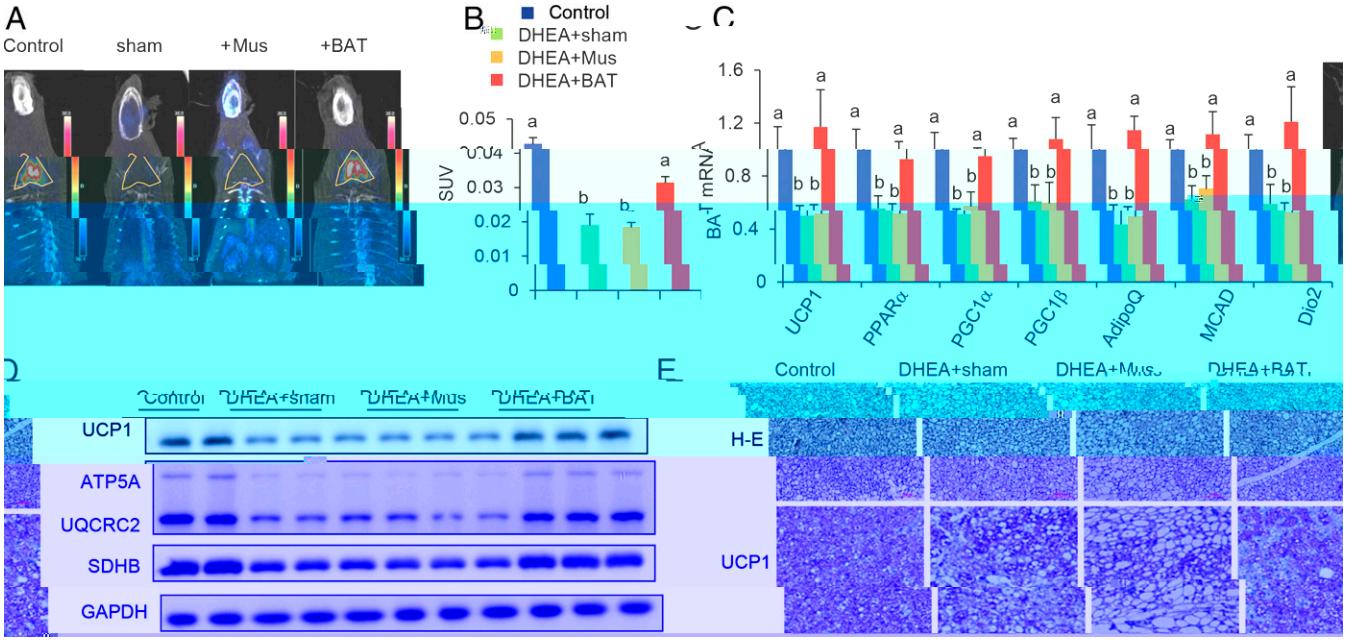

Fig. 1. BAT transplantation reverses PCOS BAT activity. BAT activity was assessed at the end of the experiment (3 wk after tissue transplantation) by using PET-CT. BAT transplantation could significantly increase endogenous BAT activity in the DHEA+BAT group compared with the DHEA+sham or DHEA+Mus groups (*A*). Yellow triangle indicates the anatomical site of the interscapular BAT. The activity of brown adipose tissue, expressed as the standard uptake values (SUVs), dramatically decreased in the DHEA+sham and DHEA+Mus groups compared with the control and BAT transplantation groups (*B*). Furthermore, BAT transplantation could significantly increase BAT-specific marker gene expression (*C*) and OXPHOS protein expression (*D*), as well as UCP1 expression (*E*), compared with the DHEA+sham or DHEA+Mus groups. Data were analyzed by one-way ANOVA with Tukey's post hoc test. n = 8–10 per group. Different lowercase letters indicate significant differences among groups (One-way ANOVA, with Tukey's post hoc test, $P < 0.05$).

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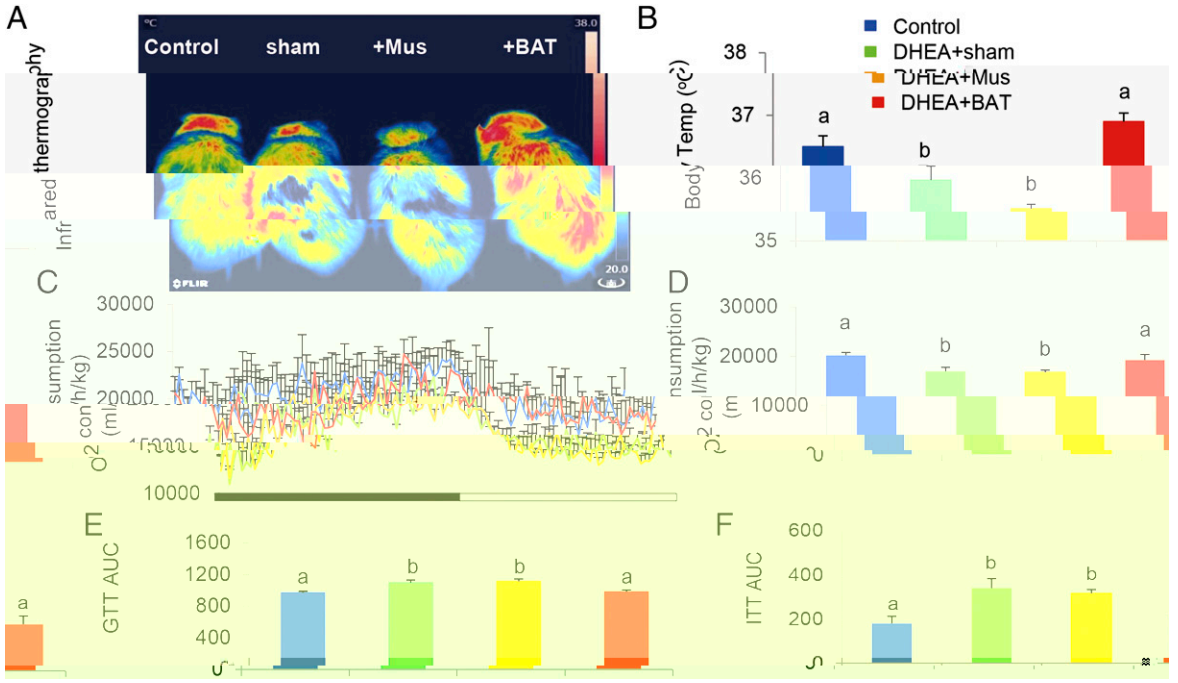

Fig. 2. BAT transplantation reverses PCOS metabolic abnormality. An infrared thermal image demonstrates that cold exposure significantly reduced body temperature of the DHEA+sham and DHEA+Mus groups whereas BAT transplantation significantly reversed DHEA-induced body temperature reduction (*A* and *B*). In addition, BAT transplantation significantly increased whole-body energy expenditure compared with the DHEA+sham or DHEA+Mus groups (*C* and *D*). Moreover, results from a glucose tolerance test (*E*) and insulin tolerance test (*F*) showed that BAT transplantation significantly reversed DHEA-induced glucose intolerance. Data were analyzed by one-way ANOVA with Tukey's post hoc test. n = 8–10 per group. (*A* and *B*) $P < 0.05$. Different lowercase letters indicate significant differences among groups (One-way ANOVA, with Tukey's post hoc test, $P < 0.05$).

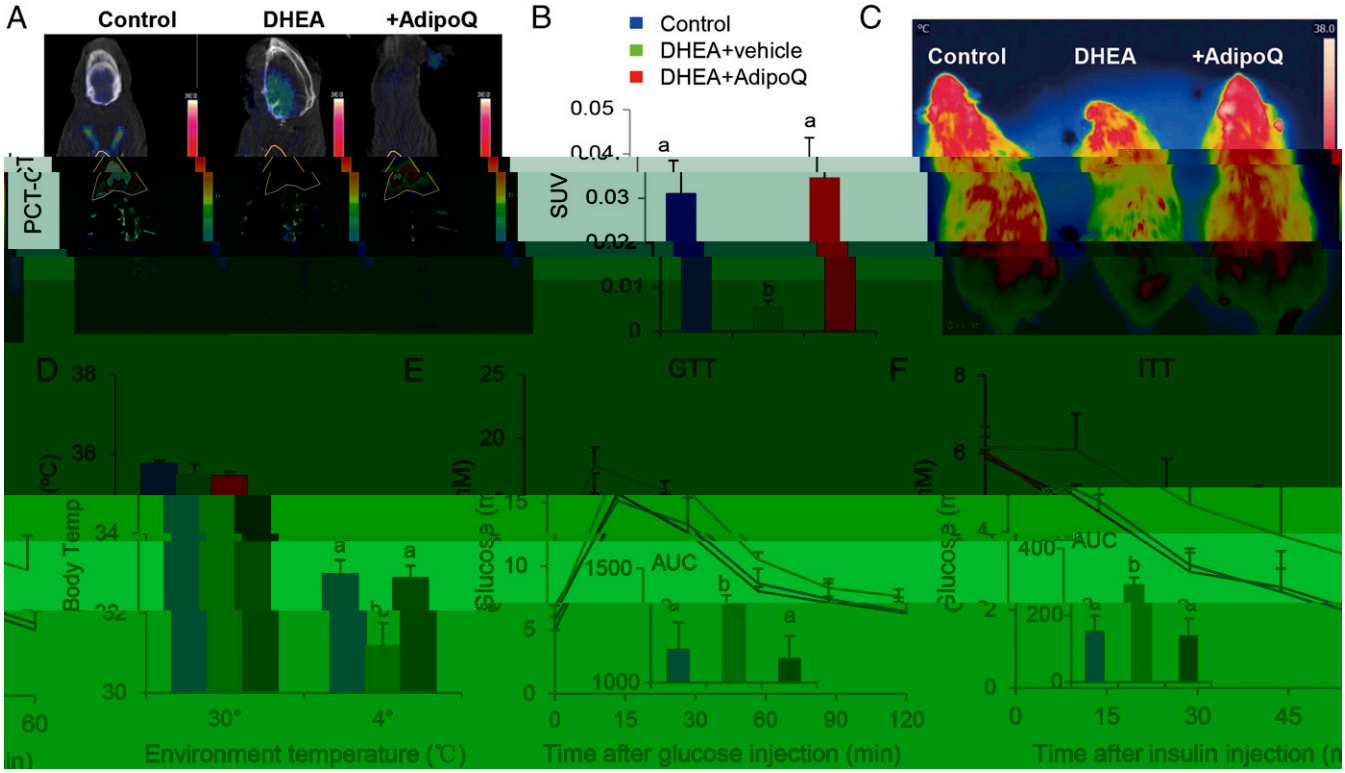

Fig. 4. Adiponectin recapitulates the beneficial effects of BAT transplantation. Adiponectin treatment could significantly increase endogenous BAT activity compared with DHEA groups as evidenced by PET-CT (*A* and *B*). Moreover, Infrared thermal images demonstrated that adiponectin treatment significantly reversed DHEA-mediated body temperature reduction (*C* and *D*). A glucose tolerance test (*E*) and insulin tolerance test (*F*) showed that adiponectin treatment significantly improved DHEA -induced insulin resistance (inner graph indicating area under the curve of GTT and ITT, respectively). Data were analyzed by one-way ANOVA with Tukey's post hoc test; $n = 6$ per group. Different lowercase letters indicate significant differences among groups (One-way ANOVA, with Tukey's post hoc test, $P < 0.05$).

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ACKNOWLEDGMENTS. This work was supported by Ministry of Science and Technology of China Grant 2012CB944701 (to W.J.), Strategic Priority Research Program Grant XDB13030000 (to W.J.), Key Research Program