Increase in Activity During Calorie Restriction Requires Sirt1

Danica Chen,[1] Andrew D. Steele,[1,2] Susan Lindquist,[2] Leonard Guarente[1]*

Sir2 (silent information regulator 2) is a nicotinamide adenine dinucleotide (NAD)–dependent deacetylase that is required for longevity due to calorie restriction in the budding yeast *Saccharomyces cerevisiae* and in the fruit fly *Drosophila melanogaster* (*1*, *2*). In mammals, calorie restriction induces a complex pattern of physiological and behavioral changes, such as a reduction in blood glucose, triglycerides, and growth factors, and an increase in movement and foraging activity (*3*–*6*). Here we report that the mammalian Sir2 ortholog, Sirt1, is required for one of these phenotypes, the increase in physical activity.

To address a possible role in calorie restriction for Sirt1, we measured the food intake of wild-type and knockout (KO) mice lacking functional Sirt1 that were fed ad libitum [wild type: 4.26 ± 0.43 grams of chow per day (g/day); KO: 4.08 ± 0.72 g/day chow]. The food allotment for all the restricted mice was adjusted to 60% of the ad libitum values, and food was administered once daily.

Consistent with earlier reports, we observed a large increase in physical activity in wild-type mice after 9 months of calorie restriction (*4*–*6*). Five separate measurements of movement in the home cage—distance traveled, hanging in a cuddled position, hanging in a vertical position, jumping, and walking—showed this increase (Fig. 1A). We observed either no increase or greatly reduced increases in these activities in the knockout mice on the calorie-restriction regimen. We also determined motor capacity in wild-type and knockout mice by measuring their ability to stay on an accelerating treadmill or rotarod. The knockout mice performed better than wild-type mice in these assays (Fig. 1B), suggesting that the failure of the knockout mice to increase their physical activity during calorie restriction was not caused by a reduced capacity for movement.

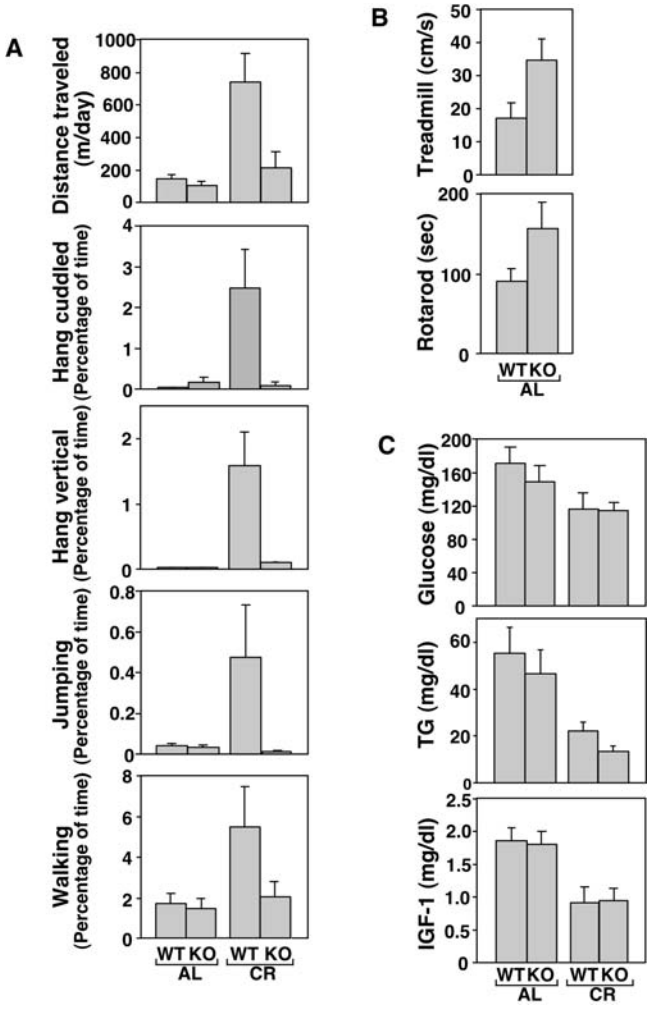

Fig. 1. The physiological and behavioral changes of calorie restriction in wild-type and Sirt1 knockout mice. (**A**) Calorie restriction increases physical activity of wild-type (WT) but not Sirt1 knockout (KO) mice. Five parameters of movement were recorded of Sirt1 knockout and wild-type mice fed ad libitum (AL) or calorie restricted (CR). (**B**) Sirt1 knockout mice do not have reduced movement. The motor capacity of mice was tested in treadmill and rotarod assays. (**C**) Calorie restriciton induces comparable physiological changes in wild-type and knockout mice. Blood glucose, TG, and IGF1 were reduced comparably by calorie restriction in wild-type and knockout mice. Body weights were also reduced by calorie restriction [37.8 ± 3.8 g (AL) to 19.9 ± 1.9 g (CR) for WT mice; 18.29 ± 2.7 g (AL) to 15.4 ± 1.4 g (CR) for KO mice].

The inability of knockout mice to respond to calorie restriction was also not due to them experiencing a lower degree of food restriction. Serum levels of glucose, triglycerides (TG), and insulin-like growth factor 1 (IGF1) were reduced comparably in both wild-type and knockout mice (Fig. 1C), indicating that the regimen exerted expected effects on these physiological parameters and that Sirt1 was not required for these changes.

Our findings suggest that a parameter of mammalian calorie restriction, up-regulation of physical activity, requires the gene that codes for Sirt1. The molecular mechanism for this increase in physical activity is not known. It is possible that calorie restriction triggers changes in brain regions that govern physical activity and that Sirt1 is a regulator of this pathway. It will be of interest to determine whether Sirt1 mediates other effects of calorie restriction in mammals, such as the extension of life span.

References and Notes

1. S. J. Lin, P. A. Defossez, L. Guarente, *Science* **289**, 2126 (2000).
2. B. Rogina, S. L. Helfand, *Proc. Natl. Acad. Sci. U.S.A.* **101**, 15998 (2004).
3. R. Weindruch, R. L. Walford, *The Retardation of Aging and Disease by Dietary Restriction* (Thomas, Springfield, IL, 1988).
4. J. L. Weed, M. A. Lane, G. S. Roth, D. L. Speer, D. K. Ingram, *Physiol. Behav.* **62**, 97 (1997).
5. R. J. McCarter *et al.*, *Aging* (*Milano*) **9**, 73 (1997).
6. J. O. Holloszy, K. B. Schechtman, *J. Appl. Physiol.* **70**, 1529 (1991).
7. L.G. is founder, consultant, stock holder, and board member of Elixir Pharmaceuticals, Inc., a company that develops therapeutics to treat age-related diseases. S.L. is founder, consultant, and stock holder for FoldRX Pharmaceuticals, Inc., a company that develops therapies for diseases of protein misfolding and amyloidosis.

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Materials and Methods

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[1]Department of Biology, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA. [2]Whitehead Institute for Biomedical Research, 9 Cambridge Center, Cambridge, MA 02142, USA.

*To whom correspondence should be addressed. E-mail: leng@mit.edu