Exploring the Promise of Resveratrol: Where Do We Go From Here?

Jill P. Crandall and Nir Barzilai

Resveratrol (3,5,4'-trihydroxystilbene), a plant-derived polyphenol and activator of the mammalian sirtuin, SIRT1, has demonstrated promising effects on glucose metabolism in rodent models (1). However, despite the widespread use of resveratrol as a nutritional supplement and the many health claims made on its behalf, data from human studies are extremely limited. Here, we explore why, in contrast to many studies in mammalian models, the article by Poulsen et al. (2) in this issue of *Diabetes* reports that chronic high doses of resveratrol have no demonstrable metabolic effects.

Interest in resveratrol has skyrocketed in recent years, initially from its association with the health benefits of red wine (the "French paradox") and its in vitro anticancer activity (3). Subsequent reports demonstrated that it activates sirtuins and extends the life span of lower organisms ("calorie restriction mimetic"), including rodents (4). Studies in vitro show that resveratrol enhances insulin-stimulated glucose uptake in skeletal muscle, liver, and adipocytes (5,6) and stimulates insulin secretion via inhibition of β-cell K_{ATP} channels (7). These observations have been confirmed in vivo in several animal models, including aging, diet-induced obesity, and diabetic (*db/db*) mice (4,8–10). Importantly, key metabolic effects of resveratrol can be monitored in relevant tissues (muscle, fat, and liver), thus providing critical insight into mechanisms. These effects include increased mitochondrial biogenesis and oxidative phosphorylation, increased SIRT1, AMP kinase and PGC-1α activation, and decreased inflammatory markers in tissues.

Available data from human resveratrol studies have largely been limited to short-term pharmacokinetic or toxicology studies. However, recently a few studies exploring the cardiometabolic effects of resveratrol have been published (11–13). Timmers et al. (11) reported improvement in a variety of metabolic parameters in a small group of obese middle-aged men treated with resveratrol (150 mg/day) for 30 days. These included increased metabolic rate, improved insulin sensitivity, and reductions in hepatic fat and markers of inflammation. In skeletal muscle, mitochondrial function was increased, as were activated AMPK and levels of SIRT1 and PGC-1α. Another study (12) reported improved glucose tolerance and insulin sensitivity in older adults with impaired glucose tolerance (IGT) at doses of 1,000–2,000 mg/day for 4 weeks. These human studies, in a wide range of doses, have been consistent with observations from animal models in showing the positive effects of resveratrol on glucose metabolism.

In the study by Poulsen et al. (2), obese men (mean age ~35 years) were treated with resveratrol 1,500 mg/day or placebo for 4 weeks. Surprisingly, a comprehensive and scientifically rigorous set of procedures designed to assess effects on in vivo insulin sensitivity, energy expenditure, and body composition and on in vitro analysis of tissues, including gene expression, AMPK phosphorylation, inflammation, and oxidative stress, failed to show any evidence of an effect. This study has a number of strengths, including the performance of a wide array of metabolic tests, application of "gold standard" methodology (euglycemic clamp, gene arrays, NMR spectroscopy, etc.), and the selection of a moderate-to-high resveratrol dose that would be most likely to demonstrate benefit, if such exists. However, the failure of these exhaustive tests to detect even a hint of resveratrol effect suggests the possibility of one or more fundamental limitations in the study design. First, evidence suggests that resveratrol works in metabolically compromised states (4,8–10). The relatively young subjects in this study were obese, but were not selected on the basis of glucose intolerance and, according to HOMA-IR (a test with known limitations), were at most mildly insulin resistant. As pointed out by the authors, these individuals may have been "too metabolically healthy" to benefit from resveratrol. Other studies in young lean (14) or nonobese middle-aged subjects with normal glucose tolerance (15) also failed to demonstrate significant metabolic effects of low-to-moderate resveratrol doses. Likewise, studies in lean rodents treated with resveratrol have also failed to detect any benefit on metabolism or life span with resveratrol (16,17). Second, questions remain about the quality and bioavailability of resveratrol. Commercially available resveratrol preparations, considered as food supplements, are not subject to the regulatory oversight required for pharmaceuticals. In a separate pilot study, the authors provide evidence that the resveratrol preparation used in their study can be absorbed and detected in the plasma following oral administration, but plasma levels were not measured during the main study. The presence of urinary resveratrol metabolites provides reassurance that some resveratrol was consumed, but in the presence of overwhelmingly negative results, specific quantification of plasma levels would be helpful. Lastly, since resveratrol is rapidly cleared from plasma and has a $t_{1/2}$ of ~2.5 h (18), it is possible that the metabolic tests were performed too long after the last resveratrol administration, resulting in lack of effect or possibly even a "rebound" worsening of metabolic parameters.

From the Diabetes Research and Training Center and Institute for Aging Research, Albert Einstein College of Medicine, Bronx, New York.
Corresponding author: Jill P. Crandall, jill.crandall@einstein.yu.edu.
DOI: 10.2337/db12-1788

See accompanying original article, p. 1186.

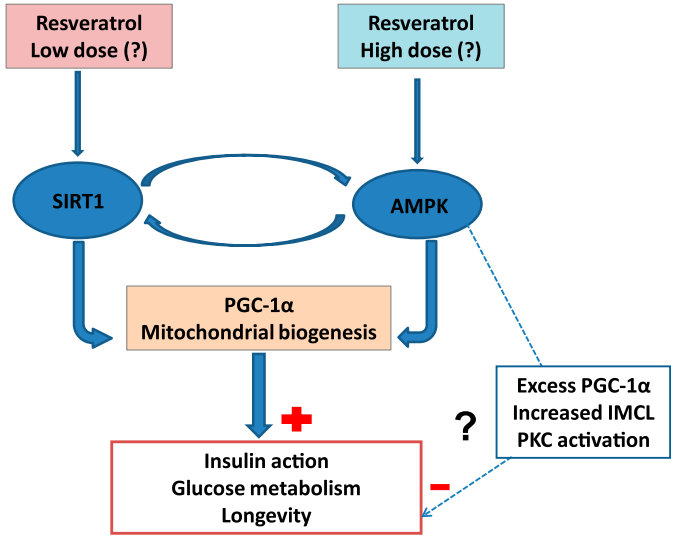

FIG. 1. Potential mechanisms for low- vs. high-dose resveratrol. IMCL, intramyocellular lipids; PKC, protein kinase C.

The many challenges to the translation of resveratrol's promising preclinical data to careful human studies were recently reviewed (19) and include issues related to dosing, toxicity, drug interactions, lack of the U.S. Food and Drug Administration (FDA) oversight, and inadequate funding. Despite initial enthusiasm, resveratrol has largely been abandoned by the pharmaceutical industry, although the reasons (scientific vs. economic) have not been made public and results of some completed clinical trials were never published. In this context, a well-done but ultimately negative study can be highly informative and can advance the field. One lesson from this experience is that future studies should be conducted in subjects with a defined metabolic defect, particularly the patient population for which the compound might have clinical utility. The issue of appropriate resveratrol dose also requires additional study. Doses used in animal (5–500 mg/kg/day) and human studies (5–5,000 mg/day) have varied widely, and not enough is known about the dose-response relationship. Price et al. (20) recently demonstrated that different doses of resveratrol can elicit different responses, with lower resveratrol doses (~30 mg/kg/day) increasing SIRT1-dependent AMPK phosphorylation and higher doses (~300 mg/kg/day) working via a SIRT1-independent mechanism (Fig. 1). Whether this has relevance to the so far inconsistent findings in human resveratrol studies needs to be explored. Other unknown factors that may affect resveratrol efficacy, such as role of race, sex, and age, also need further study. We predict that in metabolically compromised individuals (e.g., insulin resistance or aging) effects of resveratrol may be seen in numerous tissues and will be associated with clinically apparent metabolic benefits.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov 2006;5:493–506
2. Poulsen MM, Vestergaard PF, Clasen BF, et al. High-dose resveratrol supplementation in obese men: an investigator-initiated, randomized, placebo-controlled clinical trial of substrate metabolism, insulin sensitivity, and body composition. Diabetes 2013;62:1186–1195
3. Jang M, Cai L, Udeani GO, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science 1997;275:218–220
4. Barger JL, Kayo T, Vann JM, et al. A low dose of dietary resveratrol partially mimics caloric restriction and retards aging parameters in mice. PLoS ONE 2008;3:e2264
5. Sun C, Zhang F, Ge X, et al. SIRT1 improves insulin sensitivity under insulin-resistant conditions by repressing PTP1B. Cell Metab 2007;6:307–319
6. Breen DM, Sanli T, Giacca A, Tsiani E. Stimulation of muscle cell glucose uptake by resveratrol through sirtuins and AMPK. Biochem Biophys Res Commun 2008;374:117–122
7. Chen WP, Chi TC, Chuang LM, Su MJ. Resveratrol enhances insulin secretion by blocking K(ATP) and K(V) channels of beta cells. Eur J Pharmacol 2007;568:269–277
8. Do GM, Jung UJ, Park HJ, et al. Resveratrol ameliorates diabetes-related metabolic changes via activation of AMP-activated protein kinase and its downstream targets in db/db mice. Mol Nutr Food Res 2012;56:1282–1291
9. Um JH, Park SJ, Kang H, et al. AMP-activated protein kinase-deficient mice are resistant to the metabolic effects of resveratrol. Diabetes 2010;59:554–563
10. Baur JA, Pearson KJ, Price NL, et al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 2006;444:337–342
11. Timmers S, Konings E, Bilet L, et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metab 2011;14:612–622
12. Brasnyó P, Molnár GA, Mohás M, et al. Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. Br J Nutr 2011;106:383–389
13. Crandall JP, Oram V, Trandafirescu G, et al. Pilot study of resveratrol in older adults with impaired glucose tolerance. J Gerontol A Biol Sci Med Sci 2012;67:1307–1312
14. Ghanim H, Sia CL, Abuaysheh S, et al. An antiinflammatory and reactive oxygen species suppressive effects of an extract of *Polygonum cuspidatum* containing resveratrol. J Clin Endocrinol Metab 2010;95:E1–E8
15. Yoshino J, Conte C, Fontana L, et al. Resveratrol supplementation does not improve metabolic function in nonobese women with normal glucose tolerance. Cell Metab 2012;16:658–664
16. Turrens JF, Lariccia J, Nair MG. Resveratrol has no effect on lipoprotein profile and does not prevent peroxidation of serum lipids in normal rats. Free Radic Res 1997;27:557–562
17. Miller RA, Harrison DE, Astle CM, et al. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. J Gerontol A Biol Sci Med Sci 2011;66:191–201
18. la Porte C, Voduc N, Zhang G, et al. Steady-state pharmacokinetics and tolerability of trans-resveratrol 2000 mg twice daily with food, quercetin and alcohol (ethanol) in healthy human subjects. Clin Pharmacokinet 2010;49:449–454
19. Smoliga JM, Vang O, Baur JA. Challenges of translating basic research into therapeutics: resveratrol as an example. J Gerontol A Biol Sci Med Sci 2012;67:158–167
20. Price NL, Gomes AP, Ling AJ, et al. SIRT1 is required for AMPK activation and the beneficial effects of resveratrol on mitochondrial function. Cell Metab 2012;15:675–690