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Supplementing exercise: translational considerations for nutraceutical and lifestyle interventions

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Ageing is the primary risk factor for cardiovascular diseases (CVD). With the unprecedented increase in the ageing population, the need for effective interventions and an understanding of their mechanism(s) of action is of utmost biomedical importance. Exercise elicits beneficial effects on cardiovascular health in older adults and is an important lifestyle intervention for the primary prevention of CVD. Preclinical studies suggest that the polyphenol resveratrol, a caloric restriction mimetic, potentiates the beneficial effects of exercise and may be a novel intervention for CVD prevention. Recently, Gliemann *et al.* (2013) conducted a translational investigation to assess the efficacy of concomitant resveratrol and exercise training for improving multiple markers of cardiovascular health including exercise capacity, functional performance and vascular function in older adults, as well as the mechanisms involved therein.

Gliemann *et al.* (2013) randomized older (60- to 72-year-old) sedentary men into two groups matched for aerobic capacity and clinical characteristics. Both groups underwent 8 weeks of exercise training with either placebo or resveratrol supplementation (250 mg *trans*-resveratrol per day). Resveratrol supplementation with exercise did not provide synergistic benefits on the outcomes assessed compared with exercise alone and blunted exercise-induced improvements in some outcomes. Specifically, while percentage body fat decreased and functional performance increased in both groups, the resveratrol group failed to achieve significant reductions in mean arterial pressure and exhibited a significantly smaller increase in maximal oxygen uptake. Subjects randomized to the resveratrol and exercise group also exhibited increased muscle expression of the procoagulant and vasoconstrictor protein, thromboxane. In contrast to the authors' hypothesis, skeletal muscle expression of the central metabolic regulator sirtuin-1 (SIRT1) did not change across the intervention period in either group.

The findings by Gliemann *et al.* (2013) suggest that in contrast to select evidence from preclinical studies, concomitant resveratrol supplementation and exercise training do not have synergistic effects to improve markers of cardiovascular health in humans. This contradiction highlights two important issues, i.e. the importance of effective clinical translation of preclinical findings to humans and the importance of hormesis in the maintenance of human health.

The importance of clinical translation

While rodent models play a vital role in identifying and testing potential therapeutic agents, as well as understanding their mechanisms of action, translation of findings to humans is irreplaceable, due to increased variation in physiology compared with murine models, necessitating clinical trials to determine efficacy. This point has been well established for pharmaceutical agents, for which failure rates for proof-of-concept trials in humans are reported at 60–70% (Schäfer & Kolkhof, 2008). More recently, similar findings have been extended to a number of natural food-based compounds in select disease settings. Ultimately, it is in the human population that the success or failure of an intervention must be determined.

In the process of determining efficacy, careful consideration of the dose, duration and frequency of a given intervention is essential to translational study designs if there is to be any reasonable expectation of similar outcomes in humans. In particular, differences in metabolic rates between rodents and humans lead to a potential obstacle for the translation of resveratrol as, like other polyphenols, it has exhibited poor bioavailability in humans due to rapid metabolism in the liver. Of relevance to the present investigation, the additive benefits of resveratrol and exercise in rats may occur through a SIRT1-dependent mechanism, as these interventions synergistically increase activation of SIRT1 in this model (Hart *et al.* 2013). In the study by Gliemann *et al.* (2013), resveratrol supplementation in combination with exercise did not lead to an upregulation of muscle SIRT1 protein expression, but SIRT1 activity was not assessed. It seems possible that the dose, frequency and/or duration of resveratrol supplementation in the study by Gliemann *et al.* (2013) were not high enough to activate sirtuin signalling in humans. Indeed, the dose used by Gliemann *et al.* (2013) was over 10 times lower than that used in previous preclinical studies, and the intervention was 2 weeks shorter than that incorporated by Hart *et al.* (2013), despite substantial differences in lifespan. The reasoning for such a relatively low dosage and short duration is not discussed.

Another important consideration for effective translational research is the preclinical models used to build the hypotheses under investigation. Hart *et al.* (2013) demonstrated synergistic effects of exercise and resveratrol supplementation in rats bred for high running capacity. However, more recently, Ringholm *et al.* (2013) showed that concomitant resveratrol supplementation and exercise do not elicit beneficial effects in wild-type mice above those observed with exercise alone. These findings emphasize that different rodent models can lead to divergent outcomes and that consideration of the preclinical models used may prevent failure of translation to human populations.

The importance of hormesis

In the study by Gliemann *et al.* (2013), resveratrol mitigated some exercise-induced adaptations, an outcome exhibited in multiple studies with antioxidant supplementation and exercise. Previous studies have demonstrated that antioxidant consumption blunts exercise-induced improvements in a number of cardiovascular-related outcomes including increased endothelium-dependent dilatation and insulin sensitivity, decreased blood pressure and upregulation of endogenous antioxidants. Hormesis is defined as an adaptive response to an optimal level of stress resulting in overall beneficial protective outcomes (Mattson, 2008). In the context of exercise, beneficial responses may be induced by a hormetic action of reactive oxidative species. Increases in the levels of reactive oxidative species upregulate stress-resistance pathways that

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promote improved metabolic signalling, endogenous antioxidants and reduction of inflammation, among other favourable outcomes. As resveratrol has been reported directly to scavenge reactive oxygen species and upregulate endogenous antioxidants (Wang *et al.* 2012), it is possible that the antioxidant effects of resveratrol mitigated the beneficial effects of exercise by blocking its hormetic action. Evidence for the ability of resveratrol to blunt exercise-induced reactive oxygen species signalling in pre-clinical models is inconsistent, arguing for further investigation of this potential effect, especially in humans. As exercise and resveratrol alone have been shown to improve parameters of cardiovascular health in older adults, this study highlights the necessity of investigating the interactions between lifestyle and nutraceutical interventions.

In conclusion, this study demonstrates the importance of translating promising therapeutic interventions to humans and the need to consider hormesis in the conceptual development of effective interventions for the prevention of CVD. Future research should explore promising nutraceutical interventions alone and in combination with healthy lifestyle behaviours with known cardiovascular benefits in order to optimize the development of impactful interventions.

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