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COMMENTARY

Lipoic acid supplementation and endothelial function

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Endothelial dysfunction is caused by all the recognized cardiovascular risk factors and has been implicated in the complex processes leading to the initiation and progression of atherosclerosis. Short-term treatment with lipoic acid is shown in the current issue of the *British Journal of Pharmacology* to improve endothelial function of aortic rings of old rats. The age-related decrease in phosphorylation of nitric oxide synthase and Akt was improved by lipoic acid supplementation. The improved phosphorylation status may have been due to reduced activity of the phosphatase PPA2, associated with decreased levels of endothelial ceramide induced by lipoic acid. Neutral sphingomyelinase activity was also reduced by lipoic acid, which was due, at least in part, to increased glutathione levels in endothelial cells. The favourable antioxidant, anti-inflammatory, metabolic and endothelial effects of lipoic acid shown in rodents, in this and other recently published studies, warrant further assessment of its potential role for prevention and treatment of cardiovascular diseases.
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Endothelial dysfunction predisposes to the initiation and progression of atherosclerosis, and its multiple devastating clinical consequences, including myocardial infarction, stroke and death. All the recognized cardiovascular risk factors, smoking, dyslipidemia, diabetes and hypertension, have been shown to cause endothelial dysfunction. Classes of medications that provide major clinical cardiovascular benefits, such as statins and angiotensin-converting enzyme inhibitors, have also been shown to improve endothelium-dependent vasorelaxation. The residual cardiovascular risk of patients with coronary artery disease, despite chronic treatment with these highly useful drugs, entirely justifies the search for additional therapeutic approaches to be administered in addition to standard care. Intensely investigated pharmacological targets include oxidative stress and inflammatory pathways (Tardif, 2006; Moubayed *et al*., 2007).

In this issue of the journal, Smith *et al*. (2008) report the effects of the antioxidant lipoic acid on endothelial function in Fischer 344 × Brown Norway rats that are typically used in aging studies. Lipoic acid is shown in this study to improve, but not completely normalize, acetylcholine-induced vasorelaxation of aortic rings of old rats. Smith *et al*. also show that lipoic acid supplementation improves age-related decrease in phosphorylation of nitric oxide synthase and Akt. The improved phosphorylation status may have been due to reduced activity of the phosphatase PPA2, associated with decreased levels of endothelial ceramide induced by lipoic acid. Although there may be more than one pharmacological mechanism underlying reduced ceramide levels (such as potential changes in *de novo* synthesis), lipoic acid also reduced neutral sphingomyelinase activity in old rats. While the activity of endothelial ceramidase is reported by the authors not to be altered by age or lipoic acid, the enzyme ceramide synthase responsible for *de novo* synthesis of ceramide was not evaluated in this study. The lipoic acid-induced reduction in neutral sphingomyelinase activity by 30% was probably due, at least in part, to increased glutathione levels in endothelial cells, as supplementation with glutathione monoethylester also reduced this activity by 25%. Old rats treated with lipoic acid had higher levels of reduced glutathione and a trend for a higher glutathione redox ratio compared with untreated animals of similar age. As observed with lipoic acid, administration of glutathione monoethylester also restored partially the age-related loss in phosphorylation of nitric oxide synthase and Akt.

The short duration of treatment is a limitation of the current study, as acknowledged by the authors. Nevertheless, the improved endothelial function induced by 24 h of therapy may in part explain the anti-atherosclerotic effects of lipoic acid after more prolonged supplementation in genetically modified mice models (Zhang *et al*., 2008). An important question not entirely resolved by the current study is the mechanism of action of lipoic acid, and particularly to what degree its antioxidant properties

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mediated the beneficial effect on endothelial function. The assessment of oxidative stress was indeed very limited in this study. Furthermore, lipoic acid has been shown in other animal studies to have anti-inflammatory effects such as the ability to reduce adhesion molecules and chemokines, to lower serum triglycerides and to activate the phosphoinositide 3-kinase/Akt-signalling pathway leading to reduced activation of nuclear factor-kappa B, a key proinflammatory transcription factor (Zhang and Frei, 2001; Zhang *et al*., 2007). Lipoic acid has also been reported to have 'anti-obesity' effects in genetically modified mice (Zhang *et al*., 2008), but weight changes were not reported in the current study probably due to the short duration of treatment.

The most important question, however, is what these recent findings with lipoic acid in preclinical studies can mean ultimately for primary and secondary prevention of cardiovascular diseases in the clinical setting. Although oxidative stress and inflammation are involved in the atherosclerotic process, much remains to be learned about the clinical effects of medications with antioxidant and/or anti-inflammatory properties in patients with coronary heart disease. Atherosclerosis is now indeed understood to be a chronic inflammatory disease characterized by excess accumulation of monocyte-derived macrophages within the arterial wall (Ross, 1999). However, the protective cardiovascular effects of medications primarily targeting inflammatory pathways remain to be demonstrated in patients (Moubayed *et al*., 2007). Compelling evidence also points to oxidative stress as an important trigger in the complex chain of events leading to the initiation and progression of atherosclerosis (Kunsch and Medford, 1999). While prospective epidemiological studies have supported a protective role for antioxidant vitamins in cardiovascular diseases, results of randomized clinical trials have been disappointing (Tardif, 2006). There are however potentially important problems associated with the use of these vitamins, which include their potential pro-oxidant effects (Bowry *et al*., 1992). This may explain the worsening of endothelium-dependent vasodilation with high-dose α-tocopherol (Keaney *et al*., 1994), and the negative results of the vitamin arms of several clinical trials. Observations made with antioxidant vitamins cannot however be directly extrapolated to lipoic acid supplementation.

Clinical evaluation of other chain-breaking antioxidants demonstrates the complex process that lipoic acid should undergo before being used clinically for cardiovascular protection. The synthetic antioxidant probucol has been shown to reduce post-angioplasty re-stenosis (Tardif *et al*., 1997), but its effects on carotid and femoral atherosclerosis have been conflicting ((Tardif, 2006). The antioxidant succinobucol (AGI-1067), a probucol derivative (Tardif *et al*., 2003), was recently shown to reduce the composite of hard atherosclerosis-related outcomes (cardiovascular death, myocardial infarction and stroke) in a clinical trial (ARISE) of more than 6000 patients with a recent acute coronary syndrome, but the finding for this pre-specified secondary endpoint will require confirmation because the antioxidant did not alter the incidence of the combined primary endpoint that also included unstable angina and coronary revascularization (Tardif *et al*., unpublished data). The path to full clinical validation of the favourable results obtained experimentally with lipoic acid will be long and include determination of the minimal dosage required to induce vascular, metabolic and/or anti-inflammatory effects in patients, as well as demonstration of safety and tolerability of pharmacological doses.

In summary, the favourable antioxidant, anti-inflammatory, metabolic and endothelial effects of lipoic acid in rodents warrant further assessment of its potential role for prevention and treatment of cardiovascular diseases.

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