

Invited Commentary

Cardiovascular effects of chronic and acute whey protein ingestion

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Vascular endothelial dysfunction has been associated with various CVD risk factors, including hypertension⁽¹⁾, and is considered an early event in the development of atherosclerosis. Elevated blood pressure (BP) represents a major independent risk factor for CVD⁽²⁾ and is commonly treated pharmacologically by inhibiting angiotensin-converting enzyme (ACE). As ACE is a key enzyme in the regulation of BP, inhibition of its activity prevents the production of the vasoconstrictor angiotensin II from its precursor angiotensin I and removes ACE-mediated inactivation of the vasodilatory molecule bradykinin. Several clinical studies have shown improvement in vascular function in patients prescribed ACE inhibitors⁽³⁾, potentially a result of the pleiotropic effects of ACE inhibitors on the vascular endothelium⁽⁴⁾. Unfortunately, several adverse reactions associated with ACE inhibitors have been reported (i.e. hypotension, cough, fatigue), necessitating the need for alternative therapies.

Increasing interest in the prevention of CVD through the consumption of bioactive dietary compounds as an alternative to pharmacological therapy has led to the discovery of several food-derived peptides possessing ACE-inhibitory activity⁽⁵⁾. Milk is one such example that serves as a rich source of bioactive peptides, including ACE-inhibitory peptides⁽⁶⁾, which have been shown to exert a wide range of biological actions including decreased BP^(7,8) and improved vascular function⁽⁹⁾. The release of these biologically active peptide fragments results from enzymatic hydrolysis occurring either during gastrointestinal digestion or during milk fermentation⁽¹⁰⁾. Whey proteins comprise about 20% of total milk proteins and have a high prevalence of essential amino acids, particularly leucine. The main whey protein constituents in bovine milk are β -lactoglobulin and α -lactalbumin⁽¹¹⁾. The efficient metabolism of whey protein is thought to be a result of its unique heterogeneous group of proteins and a high content of branched-chain amino acids⁽¹²⁾. Specifically, *in vitro* and *in vivo* studies have demonstrated ACE-inhibitory activity of the tripeptides isoleucine-proline-proline (Ile-Pro-Pro) and valine-proline-proline (Val-Pro-Pro) isolated from fermented milk^(13,14). In addition, Sipola *et al.*⁽¹⁵⁾ investigated the dilatory response of rat superior mesenteric arteries incubated with α -lactorphin (Tyr-Gly-Leu-Phe) and β -lactorphin (Tyr-Leu-Leu-Phe), which are released by enzymatic hydrolysis from the whey proteins α -lactalbumin and β -lactoglobulin, respectively. In preparations obtained from hypertensive rats, incubation with both tetrapeptides improved endothelium-dependent relaxation, an

effect abolished by inhibiting NO synthase. In addition, endothelium-independent dilation in hypertensive rats was enhanced in the presence of β -lactorphin, but not in the presence of α -lactorphin. These data suggest that peptides derived from whey proteins have the potential to improve hypertension-induced vascular dysfunction through ACE inhibition and/or NO- and non-NO-mediated pathways.

Promising *in vitro* data have led to investigations seeking to examine the effect of whey proteins on BP and/or vascular function in humans^(16–18). Investigations that have determined the beneficial effects of chronic whey consumption on BP and vascular function^(16,18) in humans have fostered further studies seeking to elucidate whether these beneficial effects can be observed during the acute postprandial period. Recent evidence highlights the importance of the postprandial period as a contributing factor to chronic disease, such as diabetes and atherosclerosis^(19,20). Thus, dietary interventions that potentially mitigate the metabolic disturbances that occur during the postprandial period (i.e. hyperglycaemia, hypertriglycerolaemia) are of great interest in an attempt to restore biological homeostasis. Indeed, a single dose of whey protein was demonstrated to decrease the appearance of plasma TAG and glucose following a breakfast meal in overweight women⁽²¹⁾. Furthermore, as adverse cardiovascular events peak in the early morning hours after waking⁽²²⁾, perhaps due to an increase in BP or blunting of flow-mediated dilation⁽²³⁾, dietary interventions that acutely improve cardiovascular function may be beneficial during this period of increased risk. The measurement of NO-dependent vascular function via conduit artery flow-mediated dilation⁽²⁴⁾ independently predicts adverse cardiovascular events in healthy subjects⁽²³⁾. Therefore, further identification of the impact that whey proteins may acutely exert on the cardiovascular system has both practical and clinical implications.

In this issue of the *British Journal of Nutrition*, Pal & Ellis⁽²⁵⁾ provide insight into this uncertainty by assessing the acute impact of a whey protein isolate on BP, arterial stiffness and inflammatory markers in postmenopausal women, a population particularly susceptible to the development of CVD. Postprandial measurements were taken intermittently for 6 h following consumption of a breakfast meal in conjunction with one of three supplements: 45 g whey protein isolate, 45 g sodium caseinate or a 45 g glucose control. Despite significant time effects over the course of the 6 h postprandial period, there were no significant differences in BP, arterial

stiffness or inflammatory markers between the three groups. The lack of acute effects on cardiovascular measures in this study suggests that the beneficial effects demonstrated previously with whey protein result from habitual intake. Only one other study has investigated the acute cardiovascular effects of a peptide derived from whey protein⁽²⁶⁾. This study non-invasively assessed vascular function before and serially for 2 h following ingestion of 5 g of a hydrolysed peptide derived from whey in young, healthy men and women. Compared with placebo (artificially sweetened water), ingestion of a beverage containing the whey-derived peptide significantly increased brachial artery flow-mediated dilation for up to 90 min postprandially. Furthermore, reactive hyperaemia forearm blood flow, a response primarily independent of NO formation⁽²⁷⁾, increased at 120 min postprandially. These findings suggest that acute ingestion of this whey-derived peptide enhanced vascular function via mechanisms both dependent and independent of NO production. Ongoing work from our laboratory is attempting to determine the effect of this particular whey extract on ageing-induced vascular dysfunction. In addition to its vascular effects, acute whey protein ingestion has the potential to suppress appetite⁽²⁸⁾ and increase protein synthesis following exercise⁽²⁹⁾.

Nutraceuticals hold promise as an adjunct or alternative to pharmaceutical treatment of CVD. Emerging research indicates that whey proteins possess a wide range of biological effects that include improvement in CVD risk factors such as hypertension and vascular dysfunction. Future research is needed to further elucidate the potential health benefits and possible underlying mechanisms (i.e. NO production, ACE inhibition) to acute and chronic whey protein ingestion, particularly in individuals at an increased risk of CVD (i.e. hypertensives, aged, overweight), to identify the unique components of whey responsible and to determine the differing effects of intact and hydrolysed whey proteins. Continued investigation into the potential cardiovascular benefits of acute whey protein ingestion, particularly following a postprandial challenge or as a potential dietary therapy to attenuate early morning cardiovascular events, is warranted.

There is no conflict of interest.

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