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Plasma cytokine response during the postprandial period: a potential causal process in vascular disease?

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Chronic inflammation of the vascular endothelium produces endothelial dysfunction and ultimately atherogenesis. Postprandial hyperlipidaemia is an independent risk factor for cardiovascular disease. Recent studies show that the magnitude of postprandial lipaemia following a single fatty meal is negatively related to vascular function. This is associated with a transient increase in the concentrations of pro-inflammatory cytokines and soluble adhesion molecules and in pro-oxidant activity. One possible interpretation is that repeated exposure of the blood vessel wall to the activities of pro-inflammatory cytokines and pro-oxidants may damage the vascular endothelium and promote atherogenesis. Based on these results, we propose a model of a causal mechanism to explain how consumption of a fatty meal may impair vascular dysfunction.

Vascular dysfunction: cytokines: postprandial: cardiovascular disease

Atherosclerosis has been suggested to be the result of inflammatory processes which cause structural and functional changes to the wall of blood vessels that ultimately lead to endothelial dysfunction and to the development of the atherosclerotic lesion (Ross, 1999). Since inflammation is critical to the development and progression of the atherosclerotic lesion, identification of mechanisms that promote and perpetuate the inflammatory response may provide opportunities to develop protective and therapeutic interventions. There is a growing body of evidence suggesting that exposure to raised concentrations of pro-inflammatory cytokines during the postprandial period may contribute significantly to the aetiology of endothelial dysfunction and vascular disease. The present review summarises these findings in the context of their possible role in the atherosclerotic process.

Endothelial dysfunction: inflammation and atherogenesis

Normal vascular function facilitates dynamic changes in blood flow in response to varying metabolic demands of individual tissues while preventing inappropriate activation of blood coagulation pathways. Insults to the vascular wall initiate and propagate a series of changes to the endothelium which result in impaired regulation of blood flow due to decreased availability of NO, increased blood vessel permeability and adhesiveness, and up-regulation of the activity of pro-coagulant pathways. Such impairment of endothelial function is associated with coronary artery disease (Cox *et al.* 1989; Neunteufl *et al.* 1997) and myocardial infarction (Zeiher *et al.* 1995; Hasdai *et al.* 1997), and is predictive of recurrence of cardiovascular events (Schachinger *et al.* 2000; Suwaidi *et al.* 2000; Perticone *et al.* 2001). One major consequence of endothelial dysfunction is the development of atherosclerotic lesions, which may ultimately lead to the formation of a thrombus that occludes the blood vessel resulting in infarction of the tissue. The magnitude of impairment of endothelial dysfunction is predictive of the progression of atherosclerosis (Schachinger *et al.* 2000).

Chronic inflammation is a critical process in the development of endothelial dysfunction and atherogenesis. Exposure of the vascular endothelium to agents such as peroxidised LDL, free radicals derived from cigarette smoking and homocysteine, and to diseases such as diabetes mellitus, damages the endothelial layer and provokes an inflammatory response. This is reflected in the association between CVD risk factors and impaired endothelium-dependent vasodilation (Vita *et al.* 1990). Persistent exposure to these risk factors produces chronic inflammation characterised by increased endothelial adhesiveness with respect to platelets and leucocytes and the production of pro-inflammatory cytokines (including TNFα, IL-1β and IL-6) and chemokines, which facilitate recruitment of monocytes and T lymphocytes which become resident in the lesion. TNFα, IL-1β and IL-6 up-regulate expression of secretory phospholipase A_2, which promotes the release of inflammatory lipid mediators including eicosanoids, lysophospholipids

Abbreviations: sICAM-1, soluble intercellular adhesion molecule 1; sVCAM-1, soluble vascular cell adhesion molecule 1; TAG, triacylglycerol.

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and platelet-activating factor within the plaque (Hurt-Camejo *et al.* 1997; Menschikowski *et al.* 2000). Raised serum secretory phospholipase A_2 activity is associated with vascular dysfunction (Fichtlscherer *et al.* 2004). As the lesion progresses, smooth muscle cells migrate into the region of inflammation resulting in thickening of the vessel wall (Glass & Witztum, 2001). This is associated with further recruitment of macrophages and lymphocytes from the circulation, which produce proteases, cytokines and chemokines that increase the damage to the vessel wall leading to areas of necrotic tissue (Glass & Witztum, 2001). The macrophages also internalise modified LDL particles to form cholesterol-laden 'foam' cells. Together these processes enlarge the lesion, which becomes covered by a fibrous cap that eventually protrudes into the vessel lumen restricting blood flow (Glass & Witztum, 2001). Destabilisation of the fibrous cap releases the contents of the lesion, resulting in the formation of a thrombus which occludes blood flow resulting in infarction of the tissue (Plutzky, 1999).

Postprandial lipaemia and cardiovascular disease

The magnitude of postprandial lipaemia is an independent risk factor for CVD (Ebenbichler *et al.* 1995) and has been suggested to be predictive of risk for myocardial infarction (Stampfer *et al.* 1996). This is of particular importance as man spends the majority of the day in the postprandial state. Patients with CVD exhibit an increased magnitude and duration of the lipaemic response during the postprandial period (Groot *et al.* 1991; Patsch *et al.* 1992; Karpe, 1997). Part of the pro-atherogenic effect of raised postprandial lipaemia may reflect production of large, triacylglycerol (TAG)-rich VLDL particles due to increased flux of fatty acids to the liver. Following removal of TAG by lipoprotein lipase activity, the cholesteryl ester-enriched VLDL remnants are transformed into small dense LDL_3 by the action of hepatic lipase. LDL_3 particles are able to cross the vascular endothelium and accumulate in macrophages, thus depositing cholesterol in the sub-endothelial layer (Carmena *et al.* 2004).

Lipaemia and vascular function

Although chronic repeated postprandial hypertriglyceridaemia contributes to the deposition of cholesterol in the vascular wall, there is evidence that suggests a causal relationship between lipaemia and acute vascular dysfunction. Lundman *et al.* (1997) showed in healthy men that infusion of Intralipid® decreased both flow-mediated (fourfold) and nitroglycerin-induced (twofold) vasodilation. Flow-mediated vasodilation was also decreased in men aged 34 years with chronic hypertriglyceridaemia (Lundman *et al.* 2001). Interestingly, Chowienczyk *et al.* (1997) failed to show an effect of chronic hypertriglyceridaemia on NO-mediated vasodilation in patients with LPL dysfunction. This suggests that TAG hydrolysis and release of fatty acids may be important for the effects of lipaemia on vascular function. This raises the possibility that the magnitude of the effect of lipaemia on vascular function may be determined by the efficiency of entrapment of fatty acids released by LPL activity. This is supported by the observation that in healthy subjects a threefold increase in plasma non-esterified fatty acid concentration due to infusion of Intralipid® and heparin resulted in impaired NO-dependent and -independent vasodilation (de Kreutzenberg *et al.* 2003). Since adipose tissue traps fatty acids relatively inefficiently (Evans *et al.* 2002), individuals with a greater fat mass may be at increased risk of adverse effects of lipaemia on vascular function.

Consumption of a single high-fat meal has been observed by several authors to impair vasodilation. Consumption of a single meal containing 50 g fat produced a significant decrease in flow-mediated vasodilation compared with an isocaloric (3·77 MJ (900 kcal)) fat-free meal (Vogel *et al.* 1997). The change in flow-mediated vasodilation was negatively associated with peak postprandial plasma TAG concentration. Raitakari *et al.* (2000) observed an increase in post-ischaemic hyperaemia, but not flow-mediated dilation, in a mixed group of men and women following meals containing 61 g fat.

The fatty acid composition of the background diet and test meal modifies the change in vascular function during the postprandial period. Marchesi *et al.* (2000) found a decrease in flow-mediated vasodilation following an oral fat challenge in young men who had consumed a diet with monounsaturated:saturated fatty acid = 1 for 4 weeks prior to the study. Vogel *et al.* (2000) investigated the effect of consuming meals containing 50 g of fat provided as rapeseeed oil or olive oil or salmon, or two further meals containing olive oil and antioxidants in healthy men and women. Only the olive oil-containing meal decreased flow-mediated dilation during the postprandial period. This suggests a specific effect of the fatty acids present in olive oil, mainly oleic acid, on vascular function and that this may involve pro-oxidant activities since they were prevented by antioxidant-rich foods. This is a surprising observation as increased intake of olive oil has been reported to have cardioprotective effects (Katan *et al.* 1995).

Two reports have demonstrated a relationship between lipoprotein profile and vascular function. The postprandial decrease in flow-mediated dilation was positively associated with the concentration of cholesterol-rich remnant-like lipoprotein particles in both healthy volunteers (Wilmink *et al.* 2001) and patients with moderate hypertriglyceridaemia (Maggi *et al.* 2004). While this may reflect a direct effect of remnant particles on the vascular endothelium, it is also possible that the concentration of remnant particles is a proxy measure for LPL activity.

Lipid peroxidation and vascular dysfunction

As indicated by Vogel *et al.* (2000), oxidant damage appears to be an important mechanism by which postprandial lipaemia alters vascular and endothelial function. However, only one study has investigated directly the effect of an oral pro-oxidant lipid challenge on vascular function. Consumption of a meal containing 65 g fat used repeatedly in deep fat frying, and so presumably rich in lipid hydroperoxides, produced a sevenfold decrease in endothelium-dependent flow-mediated dilation, while no effect was found with the same amount of unused cooking fat (Williams *et al.* 1999). The magnitude of change in plasma TAG concentration following consumption of a high-fat (53 g) meal by men and women aged 56 years was negatively associated with flow-mediated dilation, but was positively related to phorbol myristoyl acetate-induced superoxide anion production by neutrophils *in vitro* (Bae *et al.* 2001). No associations were found between hypertriglyceridaemia, vascular function and leucocyte activation following a low-fat (3 g) meal. This suggests that priming of superoxide production by leucocytes by exposure to raised TAG concentration may represent a mechanism leading to endothelial damage and vascular dysfunction.

A causal association between pro-oxidant activity and vascular dysfunction is further supported by several reports of amelioration of the negative effect of an oral lipid load by consumption of antioxidants. Plotnick *et al.* (1997) showed in healthy individuals that consumption of 1 g vitamin C and 33 mg (800 IU) vitamin E prior to ingestion of a high-fat (50 g) meal prevented the 40 % reduction in flow-mediated endothelium-dependent vasodilation that occurred in the absence of the antioxidants. This is supported by the observation that consumption of vegetables providing 184 mg vitamin C, 20 mg vitamin E, 15 mg β-carotene and 9·2 g fibre partially ameliorated the impaired vasodilatory response to L-arginine when healthy subjects consumed a high-fat meal (50 g fat, 58 g carbohydrate; Esposito *et al.* 2003*a*). There was no effect of consuming a meal containing 144 g carbohydrate and 17 g fat on the effect of L-arginine on postprandial vasoreactivity. Consumption of red wine has been suggested to be cardioprotective because of the presence of antioxidant phenolics and its consumption may explain the paradox of a high-fat diet and low prevalence of CVD in the French population (Frankel *et al.* 1993). However, there was no effect of consuming red wine (3 ml/kg body weight) compared with an isocaloric control beverage on the postprandial decrease in flow-mediated dilation following consumption of a high-fat meal (0·8 g/kg body weight; Djousse *et al.* 1999). Unfortunately, the authors did not disclose the amount and type of antioxidant phenolic compounds present in the wine, and so it is possible that higher intakes may produce a beneficial effect. Wilmink *et al.* (2000) showed that supplementation of healthy young adults with 10 mg folic acid/d for 14 d prevented the rise in urinary malondialdehyde excretion and the decrease in flow-mediated dilation following a high-fat meal, although nitroglycerin-mediated endothelium-dependent vasodilation was not altered. However, the mechanism of folic acid action is unclear. Folic acid increases NO production by promoting the regeneration of tetrahydrobiopterin, which is required for NO synthase activity (Wever *et al.* 1997; Verhaar *et al.* 1998). However, this does not explain the decrease in whole-body malondialdehyde excretion.

Overall, these studies suggest that exposure of the vascular endothelium to a fat-rich meal impairs vascular function by a mechanism involving the generation of pro-oxidant agents. The production and action of NO is the main determinant of the flow-mediated dilation response (Joannides *et al.* 1995). Hypercholesterolaemia results in increased production of superoxide radicals by the vascular endothelium, which may lead to impaired production and increased degradation of NO (Ohara *et al.* 1993). This is consistent with studies showing impaired whole-body NO production in hyperlipidaemic subjects (Wever *et al.* 1997). However, while peroxidised lipids derived from a meal represent a potential insult to the vascular endothelium, the extent to which peroxidation of circulating lipids contributes to impaired vascular function is unclear. Bae *et al.* (2003) showed that although vitamin E prevented the impairment of vascular function following a high-fat meal, there was no difference in serum malondialdehyde concentration between high-fat meals with or without vitamin E and a low-fat meal. This suggests that vitamin E may not be acting by preventing peroxidation of circulating lipids. Thus it is possible that additional mechanisms which promote oxidative damage to the vascular endothelium may be important. Furthermore, consumption of a meal containing 30 g fat increased the proportion of platelets expressing P-selectin and activated platelet integrin glycoprotein IIb-IIa, of platelet–monocyte aggregates and of monocytes expressing TNFα and IL-1β, which is consistent with promotion of changes to haemostatic and inflammatory processes associated with CVD (Hyson *et al.* 2002).

Postprandial changes to concentrations of circulating cytokines and soluble adhesion molecules

Pro-inflammatory cytokines such as TNFα promote the production of superoxide and H_2O_2 by a range of cell types including macrophages, endothelial cells and fibroblasts (Thannickal & Fanburg, 2000). Stimulation of the vascular wall to produce these reactive oxygen species may result in tissue damage and impairment of vascular function by inhibiting the action of NO. Thus an increase in the concentrations of specific pro-inflammatory cytokines in the bloodstream during the postprandial period and during hyperglycaemia may lead to oxidative damage to the vascular endothelium.

Nappo *et al.* (2002) compared the effect of feeding a high-fat meal (50 g fat, 50 g carbohydrate) with or without vitamin E (533 mg (800 IU)) and vitamin C (1 g) and a high carbohydrate meal (144 g carbohydrate, 17 g fat) on the concentrations of circulating cytokines and soluble adhesion molecules in healthy subjects and patients with type 2 diabetes mellitus. In the healthy individuals, there were significant increases in the concentrations of the pro-inflammatory cytokines TNFα (56 %) and IL-6 (75 %) and of the soluble adhesion molecules soluble intercellular adhesion molecule 1 (sICAM-1; 40 %) and soluble vascular cell adhesion molecule 1 (sVCAM-1; 29 %) in plasma after the high-fat, but not the high-carbohydrate meal. Raised concentrations of soluble adhesion molecules are associated with increased CVD risk (Hwang *et al.* 1997; Morisaki *et al.* 1997; Ridker *et al.* 1998; Rohde *et al.* 1998) and are thought to reflect damage to the vascular endothelium. Thus these data suggest acute damage to the vascular endothelium after a meal. The change in plasma TAG concentration was positively correlated with the change in TNFα concentration after the meal. A similar pattern was observed in the diabetic patients, although the concentrations of the cytokines were consistently higher than in healthy subjects and there were significant, although smaller, increases in the concentrations of the pro-inflammatory cytokines and soluble adhesion molecules following the high-carbohydrate meal. The postprandial increase in these cytokines following the high-fat meal was prevented by addition of antioxidant vitamins. This suggests that consumption of a meal results in an increase in circulating pro-inflammatory cytokines and adhesion molecules which is dependent upon the fat and antioxidant content of the meal and the ability of individuals to regulate glucose homeostasis. Consumption of a high-fat meal was associated with an increase in IL-18 and a decrease in adiponectin concentration while there was no effect on plasma IL-8 in healthy subjects and patients with type 2 diabetes (Esposito *et al.* 2003*b*). However, IL-18 concentration decreased after consumption of a high-carbohydrate, high-fibre meal. The concentrations of TNFα, IL-6 and IL-10 after a high-fat (50 g) meal were greater in patients with adult-onset growth hormone deficiency syndrome than in healthy subjects (Twickler *et al.* 2003). Ceriello *et al.* (2004) investigated the effect of simvastatin on the postprandial increase in the plasma concentrations of sICAM-1, sVCAM-1, soluble E-selectin and nitrotyrosine in healthy subjects and patients with type 2 diabetes mellitus. Subjects were fed a

high-fat meal (75 g) or glucose (75 g) or a combination of a high-fat meal and glucose before and after receiving simvastatin. Both the high-fat meal and glucose alone resulted in increased concentrations of soluble adhesion molecules and nitrotyrosine in controls and diabetic subjects. Combination of the high-fat meal with glucose produced a greater overall increase in these markers. Simvastatin treatment (40 mg/d) reduced the increase in soluble adhesion molecules and nitrotyrosine after 3–6 d and 3 months, although decreased circulating lipid concentrations were observed only after 3 months. The reduction in the postprandial increase in concentrations of soluble adhesion molecules was attributed to a reduction in oxidative damage to the vascular endothelium rather than to the effect of simvastatin on plasma lipid concentrations. Importantly, the results of this study indicate that the insult to the vascular endothelium during the postprandial period was not simply due to oxidation of circulating lipids derived from a meal, since glucose alone produced increases in soluble adhesion molecules and nitrotyrosine. However, other studies failed to find an effect of high-carbohydrate meals on the postprandial change in concentrations of soluble adhesion molecules and pro-inflammatory cytokines (Nappo *et al.* 2002; Esposito *et al.* 2003*b*). Since similar amounts of carbohydrate (50 g) and glucose (75 g) were consumed, one possibility is that in the studies which did not observe an effect on soluble adhesion molecule and pro-inflammatory cytokine concentrations, the carbohydrate was primarily in the complex form rather than monosaccharide. If so, the magnitude of the change in pro-inflammatory cytokine and soluble adhesion molecule concentrations may be determined by the glycaemic response and the associated dynamic changes to lipid and carbohydrate metabolism following a meal.

Effect of hyperglycaemia on concentrations of circulating cytokines and soluble adhesion molecules

The observation that glucose alone increases the concentrations of soluble adhesion molecules after a meal is supported by studies involving short-term induction of hyperglycaemia. Maintenance of hyperglycaemia at 15 mmol/l for 2 h produced an increase in the concentration of sICAM-1, but not of sVCAM-1 at 1 h which returned to baseline by 2 h in healthy subjects (Marfella *et al.* 2000). A similar pattern was observed for plasma TNFα and IL-18 concentrations (Esposito *et al.* 2002*a*). This suggests that induction of hyperglycaemia produces an acute increase in some pro-inflammatory cytokines and soluble adhesion molecules. These data also imply that changes in the regulation of carbohydrate metabolism rather than steady-state glucose and insulin concentrations may be the main determinant of the pro-inflammatory cytokine and soluble adhesion molecule responses. However, the physiological relevance of these studies is questionable as the concentration at which blood glucose was 'clamped' is far in excess of that produced even transiently in healthy individuals after a meal. Thus the contribution of such effects to the initiation of pro-inflammatory cytokine and soluble adhesion molecule responses may be small under postprandial conditions. The increases in sICAM-1 (Marfella *et al.* 2000) and TNFα and IL-18 (Esposito *et al.* 2002*a*) were greater in patients with type 2 diabetes than in controls. Intravenous injection of three glucose pulses (each 0·33 g/kg) produced increases in TNFα and IL-18 that were prevented by infusion of glutathione (Esposito *et al.* 2002*a*). This suggests that the increase in circulating TNFα and IL-18 is related to oxidative damage induced by hyperglycaemia.

Hyperglycaemia induces TNFα release from monocytic cells by increasing the production of reactive oxygen species, leading to activation of NF-κB (Guha *et al.* 2000). This is due to an increase in the cellular NADH:NAD^+, which decreases the availability of NAD^+ for other pathways (Ushio-Fukai *et al.* 1996; Cosentino *et al.* 1997; Ido *et al.* 1997) and altered redox balance due to increased flux through the sorbitol pathway (Ido *et al.* 1997). Kirwan *et al.* (2001) showed that persistent hyperglycaemia at 10 mmol/l resulted in greater *ex vivo* TNFα production in lipopolysaccharide-stimulated peripheral blood mononuclear cells compared with baseline. In addition, TNFα production was greater in older subjects (67 years) than in younger individuals (22 years), which may reflect a decrease in insulin sensitivity in older subjects. The magnitude of TNFα production was positively related to fat mass and abdominal fat, which was also suggested to reflect impaired insulin sensitivity. In an earlier study, the production of TNFα by blood mononuclear cells taken from healthy women and stimulated with lipopolysacchide was significantly correlated with both age and BMI (Yaqoob *et al.* 1999).

Concentrations of circulating cytokines and soluble adhesion molecules and adiposity

Elevated concentrations of pro-inflammatory cytokines and soluble adhesion molecules have been reported in obese subjects. Obese women (BMI 36 kg/m^2) had a twofold greater concentration of circulating IL-18 than women of normal weight (24 kg/m^2; Esposito *et al.* 2002*b*). Women with BMI of 37 kg/m^2 had raised TNFα, IL-6, P-selectin, sICAM-1 and sVCAM-1 concentrations compared with controls (BMI 24 kg/m^2; Ziccardi *et al.* 2002). TNFα and IL-6 concentrations were positively related to visceral obesity. Weight loss resulting in a decrease in BMI from 36 to 32 kg/m^2 was accompanied by a 40 % decrease in circulating IL-18 concentration (Esposito *et al.* 2002*b*), while a decrease in BMI from 37 to 33 kg/m^2 resulted in significant decreases in concentrations of TNFα (31 %), IL-6 (47 %), P-selectin (30 %), sICAM-1 (26 %) and sVCAM-1 (17 %; Ziccardi *et al.* 2002). These changes in circulating pro-inflammatory cytokines and soluble adhesion molecules were associated with improved vascular function. These reports suggest that even modest weight reduction may produce dramatic positive changes in circulating pro-inflammatory cytokine and soluble adhesion molecule concentrations, which are directly associated with improved vascular function. Furthermore, it has been suggested that weight loss is more important than glycaemic control in regulating sICAM-1, endothelin-1 and E-selectin concentrations (Pontiroli *et al.* 2004).

A model for the causal relationship between postprandial cytokine response and vascular dysfunction

In summary, consumption of a fatty meal results in impaired vascular function and increased concentrations of pro-inflammatory cytokines and soluble adhesion molecules. It appears that oxidative damage to the endothelium and/or to leucocytes, and dynamic changes to the regulation of carbohydrate metabolism, may contribute to the pro-inflammatory cytokine and soluble adhesion molecule responses, and to vascular dysfunction.

The causal process that links these observations has not been defined. However, development of a model may be useful for

designing investigations to identify the underlying mechanism. It may be useful to assume that the consumption of a meal is the initiating event and the end point is endothelial damage (which is probably reflected in the rise in soluble adhesion molecule concentrations) and dysfunction leading to altered control of blood flow. The order of the intervening steps of oxidative damage and cytokine release is less clear, and this may depend upon the type of tissue and on the time point after the meal.

A mechanistic model to summarise the current literature is presented in Fig. 1. Initially, consumption of a fatty meal results in the secretion of pro-inflammatory cytokines into the circulation. The source of the pro-inflammatory cytokines leading to this systemic increase is not known, but adipose tissue is a likely candidate. Adipose tissue secretes TNFα, IL-1β and IL-6, probably primarily from resident macrophage populations (Wellen & Hotamisligil, 2003). This is supported by the observations that (i) the circulating pro-inflammatory cytokine concentrations are higher in obese individuals (Esposito *et al.* 2002*b*; Giugliano *et al.* 2004), who have a greater number of macrophages in their adipose tissue (Weisberg *et al.* 2003; Wellen & Hotamisligil, 2003) that produce TNFα (Fain *et al.* 2004), and (ii) the pro-inflammatory cytokine concentrations decrease following weight loss. How a fatty meal may induce an increase in macrophage pro-inflammatory cytokine production is unclear. It is possible that exposure to increased free fatty acid and/or glucose concentrations results in oxidative damage to the tissue producing an inflammatory response. The greater magnitude of the pro-inflammatory cytokine response in individuals with type 2 diabetes mellitus may reflect an additional effect of raised postprandial glucose concentration compared with healthy subjects. Furthermore, the greater pro-inflammatory cytokine response in obese individuals and the ameliorating effect of weight loss (Esposito *et al.* 2002*b*; Giugliano *et al.* 2004) also suggest that adipose tissue may be the primary source of pro-inflammatory cytokines in the postprandial period. This does not exclude a direct local up-regulation of pro-inflammatory cytokine production by the vascular endothelium following a meal and it is possible that this could raise circulating pro-inflammatory cytokine concentrations. However, this does not explain the effects of obesity and weight reduction on postprandial circulating pro-inflammatory cytokine concentrations.

TNFα up-regulates production of superoxide and H_2O_2 by endothelial cells and by leucocytes (Fain *et al.* 2004). Thus the increase in circulating pro-inflammatory cytokines, including TNFα, during the postprandial period may induce local production of reactive oxygen species in the vascular endothelium and sub-endothelial layer, leading to an inflammatory response and oxidative damage to the tissue. This may alter the activity of effector systems that are associated with altered vascular function. Pro-inflammatory cytokines induce secretory phospholipase A_2 secretion, which increases production of pro-inflammatory lipid mediators (Menschikowski *et al.* 2000) that perpetuate the inflammatory response, including reactive oxygen species, leading to further damage to the vascular endothelium, which is indicated by the postprandial increase in the concentrations of circulating soluble adhesion molecules. Increased superoxide decreases NO production and increases its degradation. Overall, the effect of increased production of superoxide would be to impair vasodilation. If so, this model provides a mechanism to explain how raised concentrations of pro-inflammatory cytokines in blood after a meal impair NO-mediated vascular function. This also suggests one mechanism by which obesity may increase risk of vascular dysfunction and CVD. However, it is not intended that this model should be regarded as the sole explanation for this disease process, but may represent an important mechanism in the pathological process. In addition, because of a lack of experimental evidence, this model cannot be readily extended to explain any effects of a meal on NO-independent, endothelium-dependent vasodilation.

Conclusion

There is a clear need for further studies on the association between changes in macronutrient metabolism during the postprandial period, the pro-inflammatory cytokine response and vascular dysfunction, including detailed analysis of the effects of meal composition, the time of day at which the meal is consumed (Burdge *et al.* 2003) and the age, gender and health status of the

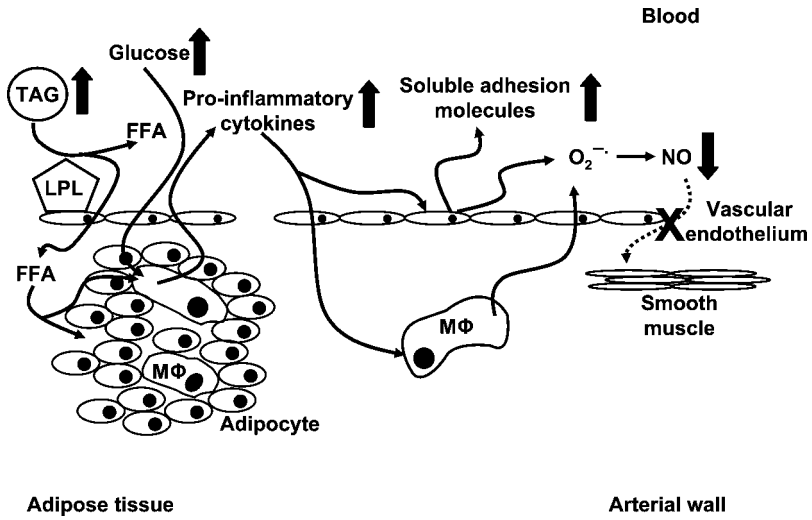

Fig. 1. Schematic model of the possible relationship between postprandial change in macronutrient concentration, pro-inflammatory cytokine secretion and altered vascular function. A detailed description of the proposed mechanism is provided on p. 5-6. TAG, triacylglycerol; LPL, lipoprotein lipase; FFA, free fatty acids; Mϕ, macrophage; NO, nitric oxide.

individual. Such investigations may ultimately lead to the formulation of dietary recommendations to limit the postprandial inflammatory response and ameliorate CVD risk.

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