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OXIDATIVE STRESS AND INFLAMMATION IN THE ENDOTHELIAL DYSFUNCTION OF OBESITY: A ROLE FOR NFκB?

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The study by Kobayasi et al (1) links endothelial dysfunction resulting from high-fat diet-induced obesity to oxidative stress and vascular inflammation that involves a reduction in endogenous antioxidant mechanisms and activation of NFκB. Thus, the reduction of acetylcholine-induced vasorelaxation was associated with reduced vascular expression of eNOS, SOD and IκB but increased expression of TNFα. Blood glucose levels were increased almost 2-fold and blood pressure was elevated in response to a high-fat diet.

Although it is well-established that diabetes and obesity are conditions of oxidative stress that predispose to cardiovascular disease, the use of antioxidant therapies to prevent or delay the onset of cardiovascular complications has been disappointing (2). Moreover, the epidemic increase in obesity and metabolic syndrome predates an overwhelming increase in cardiovascular disease without the advent of effective therapies. The results of the current study suggest that anti-inflammatory strategies that target NFκB in addition to antioxidant therapy may provide a potential avenue for investigation as both SOD and inhibition of NFκB with sodium salicylate corrected the defect in endothelium-dependent vasorelaxation in mice maintained on a high-fat diet for 16 weeks. It would have been of interest to address the effect of antioxidant treatment in vivo on endothelial function and the levels of inflammatory markers, especially in light of a recent study showing that tempol treatment of WKY and SHR rats maintained on a high-fat diet prevented endothelial dysfunction (3). Similarly, it would be of interest to determine whether in vivo treatment with sodium salicylate prevents or reverses endothelial dysfunction and the associated oxidative stress and inflammation in this model. Thus, the sequence of events leading to the development of endothelial dysfunction as it relates to activation of NFκB, inflammation and oxidative stress has not been elucidated. As the authors discuss, NFκB regulates transcription of genes for inflammatory cytokines but, in turn, may, also, be activated by cytokines such as TNFα, which was increased in obese mice compared to lean mice. For example, DOCA-salt induced-hypertension in the rat was associated with increased renal NFκB activity, which was reduced by an inhibitor of TNFα (4).

A puzzling aspect of this study is the immediacy of the reversal of endothelial dysfunction by sodium salicylate, which was used as an inhibitor of NFκB. Thus, aortic rings from mice maintained on a high-fat diet were incubated with sodium salicylate for 60 minutes, which was sufficient to restore vasorelaxant responses to acetylcholine (1). It is difficult to envisage how inhibition/removal of a transcription factor would affect downstream events so rapidly unless the effects of sodium salicylate do not only relate to inhibition of NFκB. The results with SOD, which does not enter cells unless conjugated to polyethylene glycol, suggest that extracellular superoxide interacts with endothelium-derived nitric oxide, presumably in the sub-endothelial

space, to reduce its bioavailability at the vascular smooth muscle. As SOD and sodium salicylate produce essentially similar effects in correcting the response to acetylcholine in the aortae from obese mice, the possibility that sodium salicylate reduces superoxide levels either directly or indirectly should be considered.

An alternative explanation for the effect of sodium salicylate to correct the impaired endothelium-dependent vascular responses of aortic rings from mice fed a high-fat diet may relate to inhibition of cyclo-oxygenase as the endothelium can produce contracting factors such as prostaglandin endoperoxides and thromboxane A₂ (5). Although this is an unlikely possibility given the relative lack of potency of sodium salicylate as an inhibitor of cyclo-oxygenase, it was used at a high concentration, 5mM, in this study. The authors cite studies that indicate that the effect of salicylate is unrelated to inhibition of cyclo-oxygenase, a possibility that would have been excluded if indomethacin, for example, was without effect on relaxant responses. Thus, Traupe et al (2001) reported increased cyclo-oxygenase-dependent contractile responses to acetylcholine and increased vascular expression of thromboxane receptors in mice made obese by high dietary fat (6). Moreover, oxidative stress has been shown to increase COX-2 expression in a number of cell types including endothelial cells (7) and vascular smooth muscle cells (8) and salicylate has been reported to inhibit COX-2 expression (9), perhaps an effect via inhibition of NFκB. However, in order to clarify the contribution of NFκB in the endothelial dysfunction associated with obesity, the use of selective inhibitors should be employed.

It is of clinical significance that endothelial dysfunction, considered an early indicator for the development of cardiovascular disease of multiple etiologies including obesity and diabetes (10,11), can be acutely reversed after 16 weeks of a high-fat diet. Similarly, a recent study by Ketonen et al (2010) found that caloric restriction reversed endothelial dysfunction in mice fed a high-fat diet for up to 150 days and this effect was associated with a reduction of vascular oxidative stress. This group, also, reported that the impairment in endothelium-dependent vasorelaxation after 8 months of a high-fat diet, which was associated with increased production of pro-inflammatory cytokines, was corrected upon removal of periadventitial fat or by reducing oxidative stress (13). This study supports the results of Kobayasi et al. (1) implicating oxidative stress and inflammation in endothelial dysfunction but indicates that periadventitial fat is the source of both the oxidative stress and vascular inflammation. Importantly, both studies indicate a lack of irreversible changes even after 8 months of a high-fat diet, indicating that corrective measures may be implemented long after the appearance of endothelial dysfunction. Presumably, restoration of normal vascular function would occur if the high-fat diet is replaced by a standard murine diet.

The present study (1) confirms the results of other studies showing that obesity is a condition of oxidative stress associated with vascular inflammation and impaired vasorelaxant responses to acetylcholine (12,14). The major new findings relate to the potential contribution of activation of NFκB, supporting the findings of Pierce et al. (2009) in obese humans in which a putative inhibitor of NFκB improved flow-mediated dilation and reduced oxidative stress. The results of these studies should provide the impetus for studies to elucidate the contribution of NFκB to endothelial dysfunction and for long-term animal studies of inhibitors of NFκB, alone and in combination with antioxidants, on the development of cardiovascular and renal disease associated with obesity, metabolic syndrome and diabetes.

References

1. Kobayasi, Renata; Akamine, Eliana H.; Davel, Ana P.; Rodrigues, Maria A.; Carvalho, Carla R.; Rossoni, Luciana Venturini. Oxidative stress and inflammatory mediators contribute to endothelial dysfunction in high-fat diet-induced obesity in mice. *J Hyperten*. 2010 in press.

2. Maxwell, S; Greig, L. Anti-oxidants – a protective role in cardiovascular disease? *Expert Opin Pharmacother* 2001;2:1737–1750.
3. Knight SF, Yuan J, Roy S, Imig JD. Simvastatin and tempol protect against endothelial dysfunction and renal injury in a model of obesity and hypertension. *Am J Physiol renal Physiol* 2010;298:F86–F94. [PubMed: 19906952]
4. Elmarakby AA, Quigley JE, Imig JD, Pollock JS, Pollock DM. TNF-alpha inhibition reduces renal injury in DOCA-salt hypertensive rats. *Am J Physiol Regul Integr Comp Physiol* 2008;294:R76–R83. [PubMed: 17989143]
5. Furchgott RF, Vanhoutte PM. Endothelium-derived relaxing and contracting factors. *FASEB J* 1989;3:2007–2018. [PubMed: 2545495]
6. Traupe T, Lang M, Goettsch W, Munter K, Morawietz H, Vetter W, Barton M. Obesity increases prostanoid-mediated vasoconstriction and vascular thromboxane receptor gene expression. *J Hypertens* 2002;20:2239–2245. [PubMed: 12409963]
7. Cosentino F, Eto M, De Paolis P, van der Loo B, Bachschmid M, Ullrich V, Kouroedov A, Delli Gatti C, Joch H, Volpe M, Lüscher TF. High glucose causes upregulation of cyclooxygenase-2 and alters prostanoid profile in human endothelial cells: role of protein kinase C and reactive oxygen species. *Circulation* 2003;107:1017–1023. [PubMed: 12600916]
8. Shi Y, Vanhoutte PM. Oxidative stress and COX cause hyper-responsiveness in vascular smooth muscle of the femoral artery from diabetic rats. *Br J Pharmacol* 2008;154:639–651. [PubMed: 18414395]
9. Wu KK. Aspirin and other cyclooxygenase inhibitors: new therapeutic insights. *Semin Vasc Med* 2003;3:107–112. [PubMed: 15199473]
10. Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. *J Clin Invest* 1996;97:2601–2610. [PubMed: 8647954]
11. Ding H, Triggle CR. Endothelial dysfunction in diabetes: multiple targets for treatment. *Pflugers Arch* 2010;459:977–994. [PubMed: 20238124]
12. Ketonen J, Pilvi T, Mervaala E. Caloric restriction reverses high-fat diet-induced endothelial dysfunction and vascular superoxide production in C57B1/6 mice. *Heart Vessels* 2010;25:254–262. [PubMed: 20512454]
13. Ketonen J, Shi J, Martonen E, Mervaala E. Periadventitial adipose tissue promotes endothelial dysfunction via oxidative stress in diet-induced obese C57B1/6 mice. *Circ J*. 2010 Epub ahead of print.
14. Elmarakby AA, Imig JD. Obesity is the major contributor to vascular dysfunction and inflammation in high-fat diet hypertensive rats. *Clin Sci* 2010;118:291–301. [PubMed: 19728860]
15. Pierce GL, Lesniewski LA, Lawson BR, Beske SD, Seals DR. NF- κ B activation contributes to vascular endothelial dysfunction via oxidative stress in overweight/obese middle-aged and older humans. *Circulation* 2009;119:1284–1292. [PubMed: 19237660]