Contractile Activity and Prostacyclin Generation in Isolated Coronary Arteries from Diabetic Dogs

Dear Sir,

Sterin-Borda et al. [1] have demonstrated that prostacyclin (PGI_2) increased the tension in coronary arteries obtained from pancreatectomised diabetic dogs whereas it caused relaxation in arteries from non-diabetic animals. This altered response to PGI_2 in vessels from diabetic animals was associated with enhanced PGI_2 production.

These findings are of considerable interest, but should be interpreted with caution since: (1) normal, rather than sham operated, animals were used for comparison. We have previously shown [2] that surgery alone (laparotomy only; laparotomy + dissection around blood vessels) in rats, results in a significant elevation of blood vessel PGI_2 production; (2) total pancreatectomy removes more than insulin production alone; (3) no data regarding PGI_2 production by vessels obtained from insulin-treated pancreatectomised dogs were presented.

Nevertheless, altered vascular responses by diabetic vessels are in accord with our observations of diabetic patients [3, 4]. We found that 60% of diabetic patients studied did not respond to a carbon dioxide challenge with the increase in cerebral blood flow observed in normal subjects. In about 30% of the diabetic patients, carbon dioxide actually induced a fall in cerebral blood flow. Similar abnormalities in cutaneous vascular reactivity have been reported in diabetic children [5]. We have therefore suggested that abnormal vascular reactivity is a complication of diabetes, distinct from classical micro- or macrovascular disease [6]. The presence of abnormal vascular reactivity in diabetes has been shown to be unrelated to age, duration, time of onset or presence of other vascular complications of diabetes [7]. The mechanism underlying this abnormal vascular reactivity could involve an altered response of vascular smooth muscle to PGI_2.

Sterin-Borda et al. [1] attributed the enhanced PGI_2 synthesis in vessels from diabetic dogs to increased substrate availability following post-pancreatectomy lipolysis. However, we have shown that elevated non-esterified fatty acid concentrations, which are likely to occur in uncontrolled diabetic patients, result in a marked inhibition of PGI_2 production by rat aortic rings [8]. Similarly, the addition of progressively higher concentrations of non-esterified fatty acids to plasma and human serum albumin (the plasma protein to which PGI_2 probably binds and is thus stabilised), results in an acceleration of the rate of decay of PGI_2 [9, 10]. Lipolysis may thus inhibit PGI_2 production and accelerate PGI_2 decay. The effect of enhanced lipolysis is thus likely to be complex as far as the synthesis, decay and bioavailability of PGI_2 are concerned.

In the present paper [1], the authors do not consider their previous finding [11] that inhibitors of prostaglandin synthesis abolish the PGI_2-induced increase in tension in vessels obtained from pancreatectomised dogs. They had attributed this finding to the inhibition of synthesis of a thromboxane A_2-like substance in arteries from diabetic animals. However, since the production of thromboxane A_2 involves an initial pathway in common with PGI_2, we would expect that post-pancreatectomy lipolysis would exert an inhibitory effect on thromboxane A_2 synthesis.

The current status of PGI_2 production, and indeed that of other vasoactive prostaglandins in diabetes, remains unclear. One possible explanation of the conflicting reports is that diabetes involves a multiplicity of continually changing plasma metabolic profiles. Each variable making up this profile may influence PGI_2 synthesis in a different fashion. For example, in our experiments in vitro, clinically unacceptable plasma glucose concentrations (15–30 mmol/l) were stimulatory, whereas high concentrations of ketone bodies had no effect on PGI_2 synthesis [8]. Non-esterified fatty acids, as mentioned above, were markedly inhibitory.

Clearly, the relationship of diabetes mellitus with prostaglandin metabolism and vascular abnormalities requires further investigation.

Yours sincerely,

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References

1. Sterin-Borda L, Borda ES, Gimeno MF, Lazzari MA, del Castillo E, Gimeno AL (1982) Contractile activity and prostacyclin generation in isolated coronary arteries from diabetic dogs. Diabetologia 22: 56–59
2. Hamilton G, Rosza I, Hutton R, Chow FPR, Dandona P, Hobbs KEF (1981) Portal vein prostacyclin activity in experimental portal hypertension in rats. Clin Sci 60: 327–329
3. Dandona P, James IM, Newbury PA, Woollard ML, Beckett AG (1978) Cerebral blood flow in diabetes mellitus: evidence of abnormal cerebrovascular reactivity. Br Med J 2: 325–326
4. Dandona P, James IM, Woolard ML, Newbury P, Beckett AG (1979) Instability of cerebral blood flow in insulin-dependent diabetics. Lancet 2: 1203–1206
5. Ewald U, Tuvemot T, Rooth G (1981) Early reduction of vascular reactivity in diabetic children detected by transcutaneous oxygen electrode. Lancet 1: 1287–1288
6. Dandona P, James IM, Beckett AG (1980) Vascular reactivity in diabetes. Lancet 2: 694
7. Georgiadis E, Dandona P, Hughes R, Morris R, Woolard ML, Beckett AG, James IM (1981) Cerebral blood flow in patients with diabetic feet. Diabetologia 21: 274 (Abstract)
8. Jeremy JY, Mikhailidis DP, Dandona P (1982) Simulating the diabetic environment modifies prostacyclin synthesis in vitro in the rat. Diabetologia 22: 388 (Abstract)
9. Mikhailidis DP, Mikhailidis AM, Dandona P (1982) The effect of human plasma proteins on the stabilisation of the platelet anti-aggregatory activity of prostacyclin. Ann Clin Biochem (in press)
10. Mikhailidis DP, Mikhailidis AM, Dandona P (1981) Plasma non-esterified fatty acid levels and atherogenesis in diabetes mellitus. Diabetologia 21: 499–500
11. Sterin-Borda L, Gimeno M, Borda E, del Castillo E, Gimeno AL (1981) Prostacyclin (PGI_2) and U-46619 stimulate coronary arteries from diabetic dogs and their action is influenced by inhibitors of prostaglandin biosynthesis. Prostaglandins 22: 267–278

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