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Diabetologia

Letters to the Editor

Increased arachidonic acid incorporation into platelet phospholipids in Type 2 (non-insulin-dependent) diabetes

Dear Sir,

The elegant study by Takahashi et al. [1] clearly demonstrates that the uptake of arachidonic acid (AA) by platelets from Type 2 diabetic patients is significantly increased when compared with control subjects. The authors [1] suggest that this enhanced uptake of AA may account for the increased production of thromboxane A_2 (TXA_2) by such platelets. We agree with this view [2]. However, we feel that certain comments may be relevant.

We have previously shown that the conversion by rat aortic tissue of AA to prostacyclin (PGI_2) is inhibited in the presence of high non-esterified fatty acid (NEFA) concentrations [3]. On the other hand, Takahashi et al. [1] have shown that AA incorporation in diabetic platelets was independent of the plasma NEFA concentrations. These findings, taken in conjunction, therefore suggest the interesting possibility that the raised levels of plasma NEFA concentrations in diabetes, especially if uncontrolled, inhibit vascular PGI_2 synthesis but not platelet TXA_2 release. Such a 'selective' effect would favour the vasoconstrictor and pro-aggregatory actions of TXA_2. This hypothesis, however, requires confirmation by carefully controlled experiments designed to expose both platelets and vascular tissue to identical NEFA concentrations under similar experimental conditions.

The postulated role for NEFA suggested above would be additive to two other 'prothrombotic' actions of these compounds previously proposed by us. Firstly, high NEFA concentrations decrease PGI_2 stability in albumin solutions and plasma [4–6]. Secondly, they inhibit the activity of vascular ADPase, an enzyme which clears pro-aggregatory ADP by converting it to adenosine, a vasodilator and a potent inhibitor of platelet aggregation [7, 8].

Takahashi et al. [1] also show that platelets obtained from diabetic patients with retinopathy incorporated more AA than platelets obtained from patients with no retinopathy. They suggest that this finding may account for the reports of increased TXA_2 release by platelets obtained from diabetic patients with retinopathy. We have recently studied platelet aggregation and TXA_2 release in 76 diabetic patients. Our preliminary findings [9] indicate that platelets from patients without macrovascular complications, or from patients with microvascular pathology only, do not release excessive TXA_2 when stimulated by various aggregating agents. Platelets from patients with disease of larger vessels (e.g. peripheral vascular disease, ischaemic heart disease, cerebral infarcts), on the other hand, release large amounts of TXA_2, especially when vascular pathology is extensive. Several previous studies assessing platelet function in diabetics have not described in detail the incidence of macrovascular disease in their patient populations. Takahashi et al. [1] state that as many as 22% of their diabetic patients had suffered cerebral infarction, while none had myocardial infarction. Did the patients have any other manifestation of macrovascular disease? Does the increased AA incorporation observed in the patients with retinopathy still hold true if those with any concomitant macrovascular disease are not included? If the diabetics with macrovascular disease are grouped together, is their platelet AA incorporation significantly enhanced when compared with platelets obtained from control subjects or from the other diabetics?

Finally, it should be emphasised that accelerated AA uptake by the platelets of diabetic patients may be just one mechanism contributing to increased platelet TXA_2 synthesis and hyperaggregability. Another mechanism which would make available greater amounts of AA for TXA_2 synthesis is increased phospholipase A_2 activity in platelets from diabetic patients [10]. It is also noteworthy that an increase in TXA_2 synthesis correlates significantly with fasting plasma glucose concentrations [11] and platelet function indices correlate with lipid profiles and plasma glucose [12–14]. It is of interest, therefore, that strict metabolic control of diabetes mellitus has also been shown to improve platelet function [12].

Yours sincerely,

D. P. Mikhailidis, J. Y. Jeremy, M. A. Barradas and P. Dandona

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Reply from the authors

Dear Sir,

We are grateful to Dr. Mikhailidis and his colleagues for their comments on our recent paper (Diabetologia 26: 134–137). We are interested in their hypothesis that the high concentrations of plasma non-esterified fatty acids (NEFA) frequently found in diabetic patients might selectively inhibit prostacyclin production, but have no effect on thromboxane A_2 production. As noted, this could explain the high frequency of vascular complications in diabetes. We have demonstrated that the increased arachidonic acid incorporation into platelet phospholipids in Type 2 (non-insulin-dependent) diabetic patients was independent of plasma NEFA concentrations. Furthermore, our preliminary finding has revealed that the increased arachidonic acid uptake into platelets in Type 2 diabetes is also independent of plasma free arachidonic acid concentrations. These results suggest that incorporation of arachidonic acid into platelet phospholipids has a specific regulatory mechanism in comparison with other fatty acids, the incorporation of which is regulated by the plasma concentration of each fatty acid. Our efforts are now focussed on clarifying the mechanisms of accelerated arachidonic acid incorporation into platelet phospholipids in Type 2 diabetes. It has not been well characterized whether the accelerated arachidonic acid uptake into platelets obtained from diabetic patients is correlated with excess thromboxane A_2 liberation from platelets. Thus, further studies are necessary to elucidate the hypothesis which Dr. Mikhailidis et al. have proposed.

We have demonstrated that arachidonic acid incorporation was more prominent in diabetic patients with proliferative retinopathy. However, the preliminary findings of Dr. Mikhailidis et al. indicate that excess thromboxane A_2 production from platelets after the addition of various aggregatory agents is well correlated with the existence of macroangiopathy, but not of microangiopathy. Therefore, they have questioned the relationship between arachidonic acid incorporation activity of platelets and macroangiopathy. To begin with, since we have examined arachidonic acid incorporation in the absence of stimulation, it would seem difficult to compare our data directly to that of Dr. Mikhailidis et al. However, we have re-evaluated our data to answer their question. In our patient population, except for the six patients mentioned with cerebral infarction, there were no clinically manifest cases of macroangiopathy, including peripheral arteriosclerotic disease. The arachidonic acid uptake activity of platelets in these six patients was 548 ± 59 ng/60 min per 10^9 platelets, which not only was not significantly different from the value of 577 ± 26 ng/60 min per 10^9 platelets in all diabetic patients examined ($n=27$), but also was not significantly different from the value of 585 ± 30 ng/60 min per 10^9 platelets in patients without macroangiopathy ($n=21$). The arachidonic acid uptake activity in patients with proliferative retinopathy (703 ± 49 ng/60 min per 10^9 platelets; $n=7$) is still significantly higher than that with little or no retinopathy group (525 ± 26 ng/60 min per 10^9 platelets; $n=14$), even if patients with macroangiopathy are excluded.

Yours sincerely,

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Book review

Diabetes education: how to improve patient education. Proc. 2nd European Symposium of Diabetes Education Study Group. J. Ph. Assal, M. Berger, N. Gay and J. Canivet (eds) Amsterdam Oxford Princeton: Excerpta Medica 1983. 329 pp, hardback, US $ 90.50 (Dfl. 235), ISBN 0 444 90338 0

This volume is a collection of papers presented at the Second European Symposium of the Diabetes Education Study Group, Geneva, June 1982 together with selected topics from the Diabetes Education Study Group Workshops.

The question of whether the proceedings of symposia are worth publication was raised in these pages by R. Tattersall [Diabetologia (1983) 24: 463)]. He set down certain criteria for publishing. There must be a coherent theme, ruthless editing, a relatively uniform style and finally the material should not be available elsewhere in a similar form. This work fulfills these recommendations although more ruthless editing would not have come amiss.

Every aspect of patient education is covered from the relatively simple person-to-person encounter to computer-programme learning. Educational objectives and planned educational programmes are given full reign and the successes and failures of different centres are outlined.

Exciting experiments in active participatory learning on the part of the patient are discussed. With a shift away from a primarily didactic form of teaching to problem solving exercises where the patient sets the pace and decides what he or she needs to know. Of course such learning calls for experienced teachers but it may be the only way to stimulate and maintain patient motivation.

Various contributors refer to the work of Jean Piaget who based his theory of learning to a large extent on interaction within the environment. Participatory learning is referred to as 'true learning', as opposed to the 'false learning' of memory work.

Chapter 26 – or is it Paper 26? explores the impact of diabetes on the individual. Comparing the stages of and up to acceptance of the disease with the stages of bereavement as outlined by Dr. Elizabeth Kubler-Ross. If we fail to recognise these stages we may fail miserably in preparing our patients to live with their diabetes.

The thorny issues of patient motivation and compliance are not ignored. There are no perfect answers but the advice is sound and worth following. Evaluation is another matter entirely and I can only echo the words of L. Hornke of the Federal Republic of Germany who states that "a lot of empirical evaluation and research needs to be done in diabetes education".

This book is recommended for physicians, nurses and dieticians who are seriously interested in patient education and not afraid to try something new. The 'meaty' psychology and the minor irritations of repetition and odd spellings might deter some readers, but persevere, it is a unique publication in its field.

Dr. Jean Pirart must have the final word. His paper entitled "What I have to say to a young diabetes specialist after 35 years of experience" is a must for budding diabetologists. The English is quaint but persuasive for all that...

"Diabetology is a wonderful job. But be fully conscious that there often exists a large gap between what should be done and what is actually achieved. Pessimists claim that the patient will understand 50% of what you taught and will apply correctly 25% during the first months of his diabetes. What will remain of your initial message after 10 years will be even more disappointing. ..... Pessimists are wrong. Anyway they never should take care of diabetics. Epidemiologic studies or animal experiments are better jobs for them"

J. Kinson (Birmingham, UK)