Letter to the Editor

Acetylsalicylic acid and glucose metabolism in man: is there a role for prostaglandins?

Dear Sir,

A recent paper by Bratusch-Marrain et al. [1] claims that acetylsalicylic acid impairs tissue sensitivity to insulin in healthy subjects and in Type 2 (non-insulin-dependent) diabetic patients. Moreover, the augmenting effect of acetylsalicylic acid on insulin levels has been interpreted as the result of reduced insulin clearance rate rather than increased secretion [1].

The suspicion that salicylate could produce an inhibitory effect on insulin-stimulated glucose uptake arose in the last decade, when it was seen that the augmentation of glucose-induced insulin responses in normal subjects after salicylate treatment was not associated with increased glucose utilization rates [2]. Later, we demonstrated that, in the absence of B-cell function in Type 1 (insulin-dependent) diabetic patients, salicylate treatment tended to increase rather than decrease glucose values [3, 4]. The finding supports the concept of a peripheral action of the compound opposing the effect of insulin. The analysis of glucose turnover in normal man during an infusion of salicylate [5] shows the association of increased insulin levels (glucagon unchanged) with low rates of glucose clearance and uptake. Thus, an effect of the impairment of tissue sensitivity to insulin by salicylate was already documented early in this decade.

With regard to the second point of the paper, it must be kept in mind that the possibility that salicylate compounds may also impair hepatic insulin extraction had been proposed by Ratzmann et al. [6] in 1982. However, Prince et al. [7], as well as our group [8], found no alteration in the C-peptide-insulin relationship after either glucose or arginine administration in both normal subjects and Type 2 diabetic patients.

The problem is to relate the metabolic effects of salicylate in man with the presumed inhibition of endogenous prostaglandin synthesis. Prostaglandins of the E series have been shown to stimulate glucose uptake *in vitro* [9], and prostaglandin inhibitors to depress mitochondrial pyruvate dehydrogenase activity in adipocytes, an effect which is reversed by exogenous prostaglandin E₂ [10]. On the other hand, the infusion of exogenous prostaglandins (E₁ or E₂) may counteract the potentiating effect of salicylate on glucose-induced insulin secretion in both healthy subjects [11] and in Type 2 diabetic patients [12]. These data seem to indicate that a possible mechanism by which salicylate compounds exert their multiple metabolic effects in man may be related to inhibition of endogenous prostaglandin E₁ or E₂ synthesis.

References

1. Bratusch-Marrain PR, Vierhapper H, Komjati M, Waldhäusl WK (1985) Acetyl-salicylic acid impairs insulin-mediated glucose utilization and reduces insulin clearance in healthy and non-insulin-dependent diabetic man. *Diabetologia* 28: 671-676

2. Giugliano D, Torella R, Siniscalchi N, Improta L, D'Onofrio F (1978) The effect of acetylsalicylic acid on insulin response to glucose and arginine in normal man. *Diabetologia* 14: 359-362
3. Giugliano D, Luyckx AS, Lefebvre PJ (1980) Effects of acetylsalicylic acid on blood glucose, plasma FFA, glycerol, 3-hydroxybutyrate, alanine, C-peptide, glucagon and growth hormone responses to arginine in insulin-dependent diabetics. *Diabet Metab* 6: 39-46
4. Giugliano D, Passariello N, Torella R, Cerciello T, Varricchio M, Sgambato S (1981) Effects of acetylsalicylic acid on plasma glucose, free fatty acids, betahydroxybutyrate, glucagon and C-peptide responses to salbutamol in insulin-dependent diabetic subjects. *Acta Diabetol Lat* 18: 27-36
5. Giugliano D, Saccà L, Scognamiglio G, Ungaro B, Torella R (1982) Influence of acetylsalicylic acid on glucose turnover in normal man. *Diabet Metab* 8: 279-282
6. Ratzmann KP, Besch W, Witt S, Schulz B (1982) Discrepant effect of the prostaglandin synthesis inhibitor acetylsalicylic acid on insulin and C-peptide response to glucose in man. *Horm Metab Res* 14: 508-512
7. Prince RL, Larkins RG, Alford FP (1981) The effect of acetylsalicylic acid on plasma glucose and the response of glucose-regulatory hormones to intravenous glucose and arginine in insulin-treated diabetics and normal subjects. *Metabolism* 30: 293-298
8. Giugliano D, Cacciapuotì F, Varricchio M (1979) Acetylsalicylic acid augments insulin and C-peptide responses to arginine in diabetes mellitus. *Prostaglandins Med* 2: 109-110
9. Olefsky JM (1977) Interaction between insulin receptors and glucose transport. *Biochem Biophys Res Commun* 75: 271-276
10. Begum N, Tepperman HM, Tepperman J (1985) Studies on the possible involvement of prostaglandins in insulin generation of pyruvate dehydrogenase activator. *Diabetes* 34: 29-37
11. Giugliano D, Di Pinto P, Torella R, Frascolla N, Saccomanno F, Passariello N, D'Onofrio F (1983) A role for endogenous prostaglandin E in the biphasic pattern of insulin release in humans. *Am J Physiol* 245: E591-E597
12. Giugliano D, Cerciello A, Saccomanno F, Quatraro A, Paolisso G, D'Onofrio F (1985) Effects of salicylate, tolbutamide and prostaglandin E₂ on insulin responses to glucose in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 61: 160-166

Yours sincerely

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