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Inhibition by Indomethacin of the Glycemic Response to Arginine in Man (40754)[1]

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Although reports implicate the prostaglandins (PGs) in insulin secretion (1–5), little has been published regarding the effects of PGs on glucagon secretion and action. Studies in rats indicate that certain PGs stimulate glucagon (3, 5), and a recent paper (6) suggests that pretreatment with indomethacin, a potent inhibitor of PG synthesis (7), blocks the glycemic response to glucagon in rats and that PGE_1 partially restores this response. Indomethacin has also been shown to inhibit glucagon secretion in isolated guinea pig islets (8). The present study was undertaken to investigate its effect in therapeutic doses on glucagon secretion and action in man.

Subjects and methods. In eight normal volunteers (100.5 ± 2.6% of ideal body weight) we evaluated the plasma glucagon, glucose, and serum insulin responses to arginine infusion before and after 3 days of indomethacin administration. Each subject ate a balanced diet containing at least 250 g of carbohydrate daily. All studies were performed in the outpatient facilities of the Metabolic Research Unit after an overnight fast. An indwelling i.v. needle was inserted in each arm, one for infusion of arginine and the other for sampling. Thirty minutes of bed rest were allowed before obtaining samples for glucose, insulin, and glucagon determinations.

During the control experiment, baseline samples were obtained at −20, −10, and 0 min. Arginine (20 g Arginine–HCl) was then infused at a constant rate over 30 min, and samples were obtained at min 10, 20, and 30. Additional samples were drawn at 45 and 60 min.

The subjects were then instructed to take indomethacin (25 mg, q.i.d.) with food for 3 days prior to the second arginine infusion. (This dose of indomethacin has previously been shown to inhibit PG secretion markedly (9).) On the day of the repeat study, the subjects took an additional 25 mg indomethacin, but otherwise fasted. Arginine infusion with sampling as described above was again performed. At 0 min an additional sample was taken for serum indomethacin determination.

Serum insulin, plasma glucagon, plasma glucose (10), and serum indomethacin (11) values were determined by previously described methods.

Plasma glucose, insulin, and glucagon were plotted as a function of time for each subject in the control and indomethacin studies. Statistical evaluation was performed using paired t testing and standard linear regression analysis.

Results. The mean (±SEM) indomethacin level at the beginning of the second arginine infusion was 0.258 ± 0.045 μg/ml (range: 0.090 to 0.465 μg/ml). Although one subject experienced mild anorexia while taking indomethacin, there was no detectable change in weight in the subjects after 3 days of this drug.

Glucose, insulin, and glucagon responses to arginine during the control study and indomethacin treatment are shown in Fig. 1.

Basal glucose, insulin, and glucagon levels were unaffected by indomethacin, which also had no significant effect on maximal arginine-stimulated plasma glucagon (304 ± 27 vs 322 ± 40 pg/ml in the control study). However, indomethacin significantly decreased the maximal plasma glucose level (87 ± 5 vs 96 ± 2 mg/dl; $P < 0.02$) and the maximal serum insulin level (26 ± 4 vs 44 ± 5 μU/ml; $P < 0.005$). There was no statistically significant correlation between the serum indomethacin level and percentage of inhibition of maximal glucose

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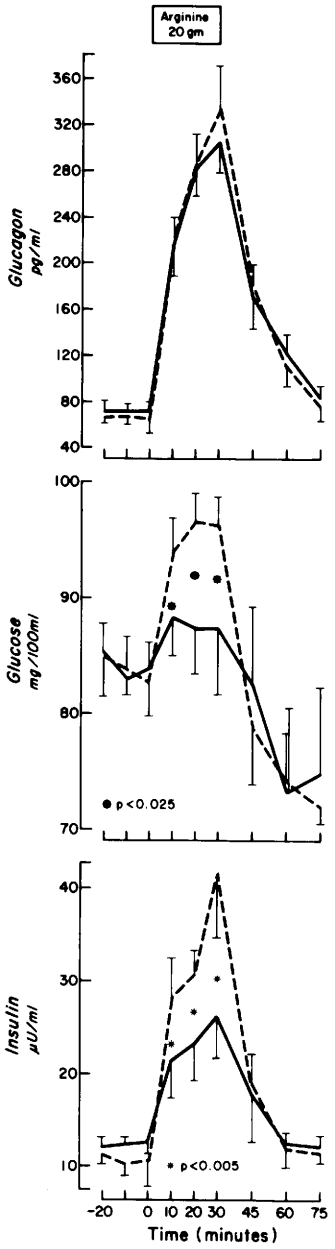

FIG. 1. Mean glucagon, glucose, and insulin responses (mean ± SEM) to i.v. arginine in eight normal subjects before (– – –) and after (——) indomethacin treatment.

($r = 0.004$; $P > 0.05$) or insulin ($r = 0.4$; $P > 0.05$) levels.

Discussion. This study, a direct application to man of work recently reported in the rat (6), suggests that, although glucagon secretion is not affected by indomethacin at this dosage, its glycemic action—as assessed by the response to i.v. arginine (12)—is partially inhibited.

Prostaglandins may modulate the action of certain tropic hormones, possibly via an effect on adenyl cyclase (13, 14). Reduction of PG synthesis might therefore affect processes such as glucagon-stimulated glycogenolysis. The report that exogenous PGE_1 partially reverses indomethacin's inhibition of the glycemic response to glucagon in rats (6) supports this interpretation of the observed effect of this drug. Another intriguing possibility is that indomethacin impairs glucagon's action by altering the hepatic glucagon receptor in some manner unrelated to inhibition of PG synthesis.

An alternate explanation for the above findings is depletion of liver glycogen secondary to anorexia or inhibition of glycogen synthesis or gluconeogenesis. Lack of significant anorexia, change in weight, or a difference between basal glucose, insulin, or glucagon levels (15, 16) during indomethacin treatment makes glycogen depletion secondary to anorexia unlikely. Indomethacin has been reported to uncouple oxidative phosphorylation *in vitro* and *in vivo* (17) and could thereby inhibit adenosine triphosphate-dependent processes such as glycogen synthesis, gluconeogenesis, and glycogenolysis. However, tissue levels of indomethacin obtained in these animal experiments were far in excess of the modest therapeutic concentrations achieved in the present study. Furthermore, in the rat model (6), normal liver glycogen stores were retained during indomethacin treatment.

The reduction in stimulated plasma glucose levels during indomethacin treatment might be explained by augmented peripheral glucose uptake. However, the lack of effect of indomethacin on the fasting glucose level, coupled with the report (18) that treatment of normal volunteers with 100 mg of indomethacin did not increase the hypoglycemic effect of exogenous insulin, makes this explanation unlikely.

There is conflicting evidence regarding direct effects of indomethacin on the islet cell: It has been reported by different investigators to stimulate insulin secretion di-

rectly (19) and to inhibit glucose-stimulated insulin release (13). However, the lowered glucose levels during indomethacin treatment may contribute to the decreased insulin response (20) observed in the present study.

The effect of indomethacin observed in the present study conflicts with the report that acetylsalicylic acid augments the insulin response to arginine without decreasing the glucose response (21). Such discrepancy suggests that the observed metabolic changes during treatment with one or both drugs are unrelated to PG inhibition. The different effect of the two upon the variables studied suggests the need for a comprehensive definition of their respective impacts on carbohydrate metabolism, since these may have clinical relevance.

Summary. We investigated the effect of indomethacin on the glucagon, glucose, and insulin responses to arginine in eight normal subjects. Glucagon secretion was not affected, but glucose and insulin responses were significantly decreased. Although inhibition of hepatic glycogenolysis is a possible reason for this effect, hepatic glycogen depletion and augmented peripheral glucose utilization are other explanations to be considered.

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