Hypothesis
PGE, Carbohydrate Homeostasis, and Insulin Secretion
A Suggested Resolution of the Controversy

R. PAUL ROBERTSON

SUMMARY

Published information derived from studies of prostaglandins on carbohydrate homeostasis and insulin secretion has been considered somewhat controversial by many investigators. An analysis of the literature published since 1876 suggests that this controversy has its roots in imprecise terminology and overgeneralization of data rather than irreconcilable scientific experiments. The two major sources of confusion have been failure to distinguish glucose-induced acute insulin responses from insulin secretion in general and failure to appreciate that the behavior of indomethacin is not consistent with the effects of other nonsteroidal antiinflammatory drugs (cyclooxygenase inhibitors) on glucose homeostasis and insulin secretion. When acute insulin responses to glucose specifically are examined and data from indomethacin studies are excluded, the available information consistently indicates that prostaglandin E has adverse effects on glucose homeostasis and insulin secretion. DIABETES 32:231–234, March 1983.

Much information about the effects of prostaglandin E (PGE) on carbohydrate tolerance and insulin secretion has been collected. Despite these efforts, the consensus is that this is a complex and controversial area. Two fundamental problems are that PGE has been reported to both inhibit and stimulate insulin secretion and that different inhibitors of PGE synthesis appear to have variable effects on carbohydrate tolerance. However, a major part of the confusion may stem from imprecise terminology and excessive generalization in drawing conclusions rather than irreconcilable experimental data. Consequently, an analysis has been performed of publications dating from 1876 to 1981 that have examined the effects of PGE and nonsteroidal antiinflammatory drugs (cyclooxygenase inhibitors) on circulating glucose and insulin secretion in vitro and in vivo.

From the Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, RG-20 University of Washington, Seattle, Washington 98195. Address reprint requests to Dr. R. Paul Robertson at the above address.
Received for publication 28 July 1982.

METHODS AND RESULTS

A survey of the scientific literature published during the past 105 yr revealed 38 publications in reviewed journals that reported original data and suggested that PGE and/or nonsteroidal antiinflammatory drugs (NSAID) affected carbohydrate tolerance and/or insulin secretion in some fashion. In this analysis the authors' conclusions regarding the effects of PGE and NSAID on the parameters reported were accepted at face value. No attempt was made to evaluate the validity of the conclusions. Consequently, no publication was rejected because of perceived shortcomings in scientific design, methodology, or statistical analysis.

The 38 publications that met these criteria were categorized into two major groups according to their favorable or adverse effects on glucose homeostasis and insulin secretion (Table 1). It was then determined how the publications segregated according to their conclusions about glucose homeostasis when attention was given to the type of NSAID used (Figure 1). Seven publications were found that reported the effects of PGE; in all instances, PGE had only adverse effects on glucose homeostasis. Of the 16 publications reporting the effects of NSAID, 12 reported favorable and 4 reported adverse effects. However, the only drug causing adverse effects was indomethacin and the only drugs causing favorable effects were salicylates and ibuprofen.

The effects of PGE and NSAID on insulin secretion were examined in a similar fashion (Figure 2). Of the seventeen publications reporting the effects of PGE on insulin secretion as a general phenomenon, seven reported favorable (stimulatory) effects while ten reported adverse (inhibitory) effects. However, only five of these seventeen publications reported studies specifically examining glucose-induced acute (first phase) insulin secretion. All five reported inhibition of insulin secretion; one of these indicated that either inhibition or stimulation could be observed depending on the glucose concentration presented to the pancreatic islet. Of the

TABLE 1
Distribution of the 38 references according to their favorable or adverse effects on glucose homeostasis* and insulin secretion†

Glucose homeostasis	
PGE favorable effects	No references
PGE adverse effects	Refs. 1, 2, 3, 4, 5, 6, 7
NSAID favorable effects	Refs. 2, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18
NSAID adverse effects	Refs. 19, 20, 21, 22
Insulin secretion	
General	
PGE favorable effects	Refs. 23, 24, 25, 26, 27, 28, 29
PGE adverse effects	Refs. 1, 2, 3, 4, 5, 6, 7, 25, 30, 31
NSAID favorable effects	Refs. 2, 8, 9, 12, 13, 17, 18, 19, 30, 32, 33, 34
NSAID adverse effects	Refs. 19, 22, 35, 36, 37, 38
Glucose-induced acute insulin response	
PGE favorable effects	Ref. 25
PGE adverse effects	Refs. 1, 2, 4, 6, 25
NSAID favorable effects	Refs. 2, 8, 9, 17, 18, 19, 32
NSAID adverse effects	Refs. 19, 22, 36

*A "favorable" effect on glucose homeostasis is defined as one that facilitates maintenance of normoglycemia; an "adverse" effect is one that tends to cause hyperglycemia.
†A "favorable" effect on insulin secretion is defined as one that facilitates stimulation of insulin secretion; an "adverse" effect is one that tends to inhibit insulin secretion.

eighteen publications assessing the effects of NSAID, twelve reported favorable effects while six reported adverse effects on insulin secretion in general. However, only 10 of the 18 publications examined glucose-induced acute insulin secretion. Of these 10, seven reported that NSAID had stimulatory effects while three reported inhibitory effects. In all instances of inhibitory effects, indomethacin was the NSAID used; in all instances of stimulatory effects, the drugs were salicylates or ibuprofen.

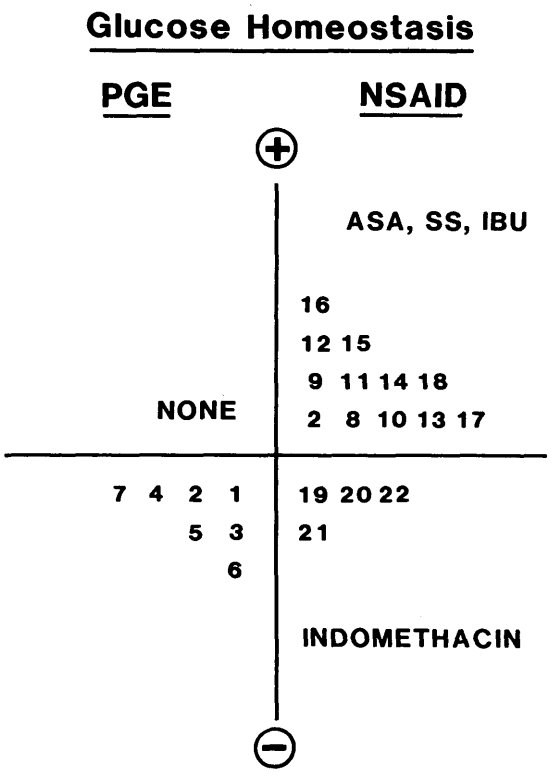

FIGURE 1. The positive (favorable) and/or negative (adverse) effects of PGE and NSAID on glucose homeostasis described in the references given on Table 1. PGE consistently had adverse effects whereas NSAID, with the exception of indomethacin, consistently had favorable effects. (ASA = aspirin; SS = sodium salicylate; IBU = ibuprofen.)

DISCUSSION

This analysis has examined the manner in which the conclusions of 38 publications reporting the effects of PGE and NSAID on glucose homeostasis and insulin secretion distributed themselves into categories of adverse or favorable effects. Consistent trends were observed when indomethacin was considered apart from other nonsteroidal antiinflammatory drugs and when glucose-induced acute (first phase) insulin secretion was considered apart from insulin secretion in general.

PGE has been consistently reported to have adverse effects on glucose homeostasis. Moreover, all NSAID had beneficial effects except indomethacin; all trials with indomethacin demonstrated adverse effects on glucose homeostasis. In no instance did acetylsalicylic acid, sodium salicylate, or ibuprofen cause adverse effects. Thus, one can conclude that PGE diminishes and NSAID as a group enhances glucose homeostasis. It is uncertain why indomethacin has a discordant effect compared with the other NSAID. However, this drug is known to have many pharmacologic effects other than inhibition of cyclooxygenase and therefore may affect glucose homeostasis through a mechanism other than inhibiting PGE synthesis.

When insulin secretion as a general phenomenon was examined, PGE and NSAID as a group had no consistent results. However, appreciation of two major considerations clarifies this issue. First, all studies revealing favorable (stimulatory) effects of PGE on insulin secretion used PGE itself rather than primary secretogogues such as glucose as the stimulus for beta-cell function. This stimulatory effect of PGE itself is presumably mediated by cyclic AMP.[29] None of the reports of favorable effects, except reference 25, studied the effects of PGE on glucose-stimulated insulin secretion specifically (the latter defined here as insulin secretion directly caused by a sudden increase in glucose concentration reaching the pancreatic beta-cell). Secondly, all but two

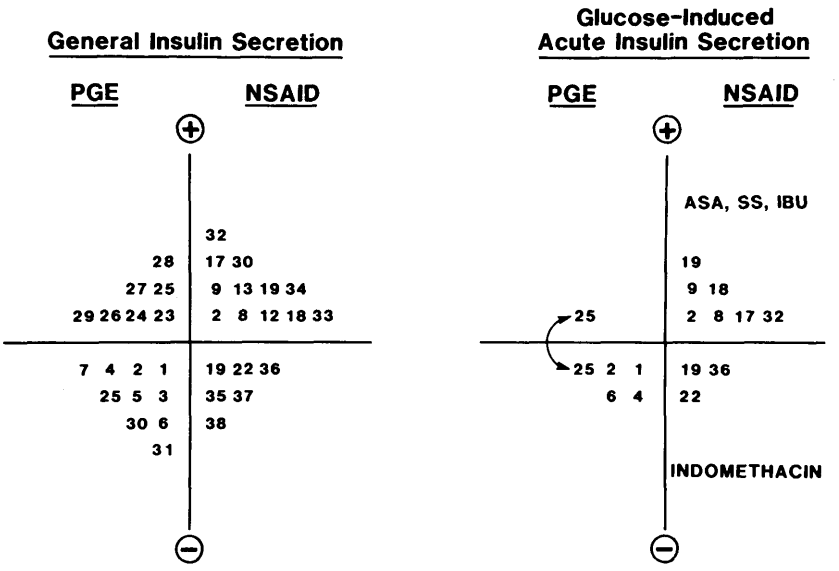

FIGURE 2. The positive (favorable) and/or negative (adverse) effects of PGE and NSAID on insulin secretion described in the references given in Table 1. Left panel: No clear pattern emerged when insulin secretion as a general phenomenon was considered. Right panel: However, when glucose-induced insulin secretion specifically was studied, PGE was consistently an inhibitor of insulin secretion whereas NSAID, with the exception of indomethacin, consistently augmented insulin secretion. The linkage of the two references 25 by an arrow indicates that this reference reported that PGE had stimulatory effects on acute insulin secretion in the presence of a low glucose concentration, whereas in the presence of a high glucose concentration PGE had inhibitory effects. (ASA = aspirin; SS = sodium salicylate; IBU = ibuprofen.)

publications[35,38] reporting an inhibitory effect of NSAID on insulin secretion studied indomethacin, whereas only one of the studies[13] that demonstrated a favorable effect used indomethacin. These findings indicate that glucose-stimulated insulin responses should be analyzed separately from insulin secretion as a general phenomenon and again indicate that the behavior of indomethacin is not necessarily always consistent with other drugs in the NSAID group such as acetylsalicylic acid, sodium salicylate, and ibuprofen.

All studies of glucose-induced acute insulin responses reported adverse effects of PGE. Interestingly, reference 25 demonstrated that either an adverse or a favorable effect could be elicited depending on the glucose concentrations used in the experiments. In this study, low glucose concentrations favored enhancement while high glucose concentrations favored inhibition of insulin responses by PGE. This biphasic behavior of PGE is consistent with the effects of PGE in other tissues where it can operate as a partial agonist/antagonist. The only NSAID found to inhibit glucose-induced acute insulin responses was indomethacin. All other NSAID augmented acute insulin responses, an effect never seen with indomethacin. Thus, inhibition of acute insulin responses by indomethacin probably explains this drug's deleterious effect on glucose homeostasis described above. The mechanism of action of this adverse effect on beta-cell function is probably not related to inhibition of PGE synthesis and may be related to actions unrelated to cyclooxygenase inhibition such as interruption of calcium flux[39] or inhibition of cyclic-AMP-dependent protein kinase.[40]

In conclusion, the following statements appear valid: (1) Experiments using PGE have demonstrated only deleterious effects on glucose homeostasis whereas all NSAID, except indomethacin, improved glucose homeostasis. (2) If no distinction is made between glucose-induced acute (first phase) insulin secretion and insulin secretion as a general phenomenon, PGE itself has been shown to both stimulate and inhibit insulin secretion. Virtually all NSAID other than indomethacin augmented insulin secretion as a general phenomenon, whereas indomethacin usually inhibited it. (3) When glucose-induced acute insulin responses specifically are considered, PGE consistently inhibited insulin secretion, whereas NSAID excluding indomethacin consistently augmented insulin secretion.

It appears that the current controversy in this area of investigation is primarily due to a failure to both precisely define terminology relative to insulin secretion and to appreciate that indomethacin behaves discordantly as a member of the group of nonsteroidal antiinflammatory drugs. The challenge for the future is to ascertain the implications of the observations that have been reported for our understanding of normal physiology and pathophysiology of insulin secretion and glucose homeostasis. With specific regard to pathophysiology, the studies that have focused on glucose-induced acute insulin responses seem particularly relevant, since it is this phase of insulin secretion that is universally defective in diabetic patients with hyperglycemia.[41]

REFERENCES

[1] Robertson, R. P., Gavareski, D. J., Porte, D., and Bierman, E. L.: Inhibition of *in vivo* insulin secretion by prostaglandin E_1. J. Clin. Invest. *54*:310–15, 1974.

[2] Robertson, R. P., and Chen, M.: A role for prostaglandin E in defective insulin secretion and carbohydrate intolerance in diabetes mellitus. J. Clin. Invest. *60*:747–53, 1977.

[3] D'Onofrio, F., Torella, R., Giugliano, D., Improta, L., and Grazioli, A.: Effects of vaso-inactive doses of PGA_1 and PGE_1 on insulin secretion in the rat. Pharmacol. Res. Commun. *9*:427–36, 1977.

[4] Giugliano, D., and Torella, R.: Prostaglandin E_1 inhibits glucose-induced insulin secretion in man. Prostaglandins Med. *1*:165–66, 1978.

[5] Giugliano, D., Torella, R., Sgambato, S., and D'Onofrio, F.: Effects of α- and β-adrenergic inhibition and somatostatin on plasma glucose, free fatty acids, insulin, glucagon, and growth hormone responses to prostaglandin E_1 in man. J. Clin. Endocrinol. Metab. *48*:302–308, 1979.

[6] Konturek, S. J., Mikós, E. M., Król, R., Wierzbicki, Z., and Dobrzanska, M.: Effect of methylated prostaglandin E_2 analogue on insulin secretion in man. Prostaglandins *15*:591–602, 1978.

[7] Sacca, L., Perez, G., Rengo, F., Pascucci, L., and Condorelli, M.: Reduction of circulating insulin levels during the infusion of different prostaglandins in the rat. Acta Endocrinol. *79*:266–74, 1975.

[8] Giugliano, D.: Acetylsalicylic acid in diabetes. Lancet *1*:560, 1981.

[9] Field, J. B., Boyle, C., and Remer, A.: Effect of salicylate infusion on plasma-insulin and glucose tolerance in healthy persons and mild diabetics. Lancet *1*:1191–94, 1967.

[10] Ebstein, N.: Zur therapie des diabetes mellitus, insbesondere uber die anwendung des salicylsauren natrons bei demselben. Berl. Klin. Woschenschr. *13*:337–40, 1876.

[11] Williamson, R. T., and Lond, M. D.: On the treatment of glycosuria and diabetes mellitus with sodium salicylate. Br. Med. J. *1*:760–62, 1901.

[12] Torella, R., Giugliano, D., Siniscalchio, N., Sgambato, S., and D'Onofrio, D.: Influence of acetylsalicylic acid on plasma glucose, insulin, glucagon, and growth hormone levels following tolbutamide stimulation in man. Metabolism *28*:887–89, 1979.

[13] Luyckx, A. S., Deliege, M., Jardon-Jeghers, Cl., and Lefebvre, P. J.: Insulin, prostaglandin E_2 and glucagon release by human insulinoma tissue incubated *in vitro*. Influence of indomethacin. Diabete Metab. *7*:13–17, 1981.

[14] Cotton, E. K., and Fahlberg, V. I.: Hypoglycemia with salicylate poisoning. Am. J. Dis. Child. *108*:171–73, 1964.

[15] Limbeck, G. A., Ruvalcaba, R. H., Samols, E., and Kelley, V. C.: Salicylates and hypoglycemia. Am. J. Dis. Child. *109*:165–67, 1965.

[16] Hecht, A., and Goldner, M. G.: Reappraisal of the hypoglycemic action of acetylsalicylate. Metabolism *8*:418–28, 1959.

[17] Prince, R. L., Larkins, R. G., and Alford, F. P.: 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*:293–98, 1981.

[18] Micossi, P., Pontiroli, A. E., Baron, S. H., Tamayo, R. C., Lengel, F., Bevilacqua, M., Raggi, U., Norbiato, G., and Foa, P. P.: Aspirin stimulates insulin and glucagon secretion and increases glucose tolerance in normal and diabetic subjects. Diabetes *27*:1196–1204, 1978.

[19] Chen, M., and Robertson, R. P.: Effects of prostaglandin synthesis inhibitors on human insulin secretion and carbohydrate tolerance. Prostaglandins *18*:557–67, 1979.

[20] Syvälahti, E.: The levels of serum growth hormone and immunoreactive insulin after administration of antipyretic analgetics. Acta Pharmacol. Toxicol. *37*:336–44, 1975.

[21] Syvälahti, E. K. G.: The effect of indomethacin on serum growth hormone, immunoreactive insulin, and blood glucose levels of young adult males. Int. J. Clin. Pharmacol. *10*:111–16, 1974.

[22] Widström, A.: Influence of indomethacin on glucose-induced insulin response in normal man—role of prostaglandins in the rapid insulin release? Horm. Metab. Res. *9*:172–75, 1977.

[23] Pek, S., Tai, T.-Y., Elster, A., and Fajans, S. S.: Stimulation by prostaglandin E_2 of glucagon and insulin release from isolated rat pancreas. Prostaglandins *10*:493–502, 1975.

[24] Pek, S., Tai, T.-Y., and Elster, A.: Stimulatory effects of prostaglandins E_1, E_2, and F_2-alpha on glucagon and insulin release in vitro. Diabetes *27*:801–809, 1978.

[25] Burr, I. M., and Sharp, R.: Effects of prostaglandin E_1 and of epinephrine on the dynamics of insulin release *in vitro*. Endocrinology *94*:835–39, 1974.

[26] Lefebvre, P. J., and Luyckx, A. S.: Stimulation of insulin secretion after prostaglandin PGE_1 in the anesthetized dog. Biochem. Pharmacol. *22*:1773–79, 1973.

[27] Bressler, R., Vargas-Cordon, M., and Lebovitz, H. E.: Tranylcypromine: a potent insulin secretagogue and hypoglycemic agent. Diabetes *17*:617–24, 1968.

[28] Schusdziarra, W., Rouiller, D., Harris, V., Wasada, T., and Unger, R. H.: Effect of prostaglandin E_2 upon release of pancreatic somatostatin-like immunoreactivity. Life Sci. *28*:2099–2102, 1981.

[29] Johnson, D. F., Fujimoto, W. F., and Williams, R. H.: Enhanced release of insulin by prostaglandins in isolated pancreatic islets. Diabetes *22*:658–63, 1973.

[30] Metz, S. A., Robertson, R. P., and Fujimoto, W. Y.: Inhibition of prostaglandin E synthesis augments glucose-induced insulin secretion in cultured pancreas. Diabetes *30*:551–57, 1981.

[31] Dodi, G., Santoro, M. G., and Jaffe, B. M.: Effect of a synthetic analogue of PGE_2 on exocrine and endocrine pancreatic function in the rat. Surgery *83*:206–13, 1978.

[32] Giugliano, D., Torella, R., Siniscalchi, N., Improta, L., and D'Onofrio, F.: The effect of acetylsalicylic acid on insulin response to glucose and arginine in normal man. Diabetologia *14*:359–62, 1978.

[33] Hyams, D. E., Howard, A. N., Evans, I. E., and Davison, S. H. H.: The effect of 3-methyl salicylic (O-cresotinic) acid on plasma insulin and glucose tolerance in diabetic and non-diabetic subjects. Diabetologia *7*:94–101, 1971.

[34] Reid, J., MacDougall, A., and Andrews, M. M.: Aspirin and diabetes mellitus. Br. Med. J. *2*:1071–74, 1957.

[35] Vik-Mo, H., Hove, K., and Mjøs, O. D.: Effects of sodium salicylate on plasma insulin concentration and fatty acid turnover in dogs. Acta Physiol. Scand. *103*:113–19, 1978.

[36] Topol, E., and Brodows, R. G.: Effects of indomethacin on acute insulin release in man. Diabetes *29*:379–82, 1980.

[37] Schmitt, J. K., Davis, J. L., Lorenzi, M., Benet, L. Z., Burns, A., and Karam, J. H.: Inhibition by indomethacin of the glycemic response to arginine in man. Proc. Soc. Exp. Med. Biol. *163*:237–39, 1980.

[38] Arnold, M. A., and Fernstrom, J. D.: Salicylate reduces serum insulin concentrations in the rat. Life Sci. *19*:813–18, 1976.

[39] Radomirov, R., and Petkov, V.: Indomethacin and aspirin influences on the contractile effects of prostaglandin E_1 on guinea pig ileum at different Ca^{++} concentration. Med. Pharmacol. *30*:775–77, 1977.

[40] Kantor, H. S., and Hampton, M.: Indomethacin in submicromolar concentrations inhibits cyclic AMP-dependent protein kinase. Nature *276*:841–43, 1978.

[41] Brunzell, J. D., Robertson, R. P., Lerner, R. L., Hazzard, W. R., Ensinck, J. W., Bierman, E. L., and Porte, D., Jr.: Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance test. J. Clin. Endocrinol. Metab. *42*:222–29, 1976.