Perspectives in Diabetes

Insulin, Prostaglandins, and the Pathogenesis of Hypertension

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Hypertension is associated with hyperinsulinemia in the presence or absence of obesity or glucose intolerance. Physiological concentrations of insulin decrease the catecholamine-induced production of prostaglandin I_2 (PGI_2; prostacyclin) and PGE_2, two potent vasodilators, in adipose tissue, one of the largest organs in the body. This finding suggests that hyperinsulinemia increases peripheral vascular resistance and blood pressure by inhibiting the stimulatory effect of adrenergic agonists (and perhaps other agonists) on the production of PGI_2 and PGE_2 in adipose tissue (and perhaps other tissues). This concept is supported by evidence that PGI_2 and PGE_2 modulate vascular reactivity in states of health and disease. For example, during insulin deficiency, i.e., in diabetic ketoacidosis, PGI_2 and PGE_2 production by adipose tissue are increased, and peripheral vascular resistance and blood pressure are decreased. This hypothesis is also supported by evidence that blood flow through rat and human adipose tissue is decreased in obesity and that insulin decreases the blood flow through adipose tissue in nonobese rats. Thus, insulin may regulate PGI_2 and PGE_2 production by adipose tissue (and possibly other tissues) through a wide range of concentrations with important physiological and clinical consequences. *Diabetes* 40:1223–27, 1991

Hypertension is associated with hyperinsulinemia in the presence or absence of obesity or glucose intolerance (1–4). Physiological concentrations of insulin decrease the catecholamine-induced production of prostaglandin I_2 (PGI_2; prostacyclin) and PGE_2, two potent vasodilators, in adipose tissue (5–8). This suggests that an elevation of the circulating insulin level inhibits the stimulatory effect of adrenergic agonists (and perhaps other agonists) on the production of these vasodilative eicosanoids in adipose tissue (and perhaps other tissues) and thereby increases peripheral vascular resistance and blood pressure (Fig. 1). This perspective reviews information that pertains to this hypothesis and compares it with alternative explanations for the relationship between increased circulating insulin levels and hypertension.

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HYPERINSULINEMIA AND HYPERTENSION

Several studies have demonstrated an association between hyperinsulinemia and hypertension (1–4). In one study of 2475 people, insulin resistance and hyperinsulinemia were present in most hypertensive subjects (1), suggesting that insulin resistance and hyperinsulinemia are common pathophysiological characteristics of obesity, glucose intolerance, and hypertension and may be linked to the increased peripheral vascular resistance of hypertension. Although the prevalence of hypertension is increased in obesity, not all obese individuals are hypertensive. Instead, hypertension correlates with upper-body (central or android) obesity, which in turn is associated with insulin resistance, i.e., diminished sensitivity to the actions of insulin that promote glucose uptake by peripheral tissues such as skeletal muscle (9). The consequent hyperinsulinemia, which is compensatory with regard to glucose homeostasis and perhaps also with regard to regulation of body weight (10), may exert effects on other systems that are not resistant to the action of insulin and lead to deleterious consequences such as hypertension, hypertriglyceridemia, and atherosclerosis (9,11–14). Experimentally, modest hyperinsulinemia causes an increase in blood pressure. The infusion of human insulin into rats at a rate sufficient to raise the plasma insulin level from 180 to 288 pM produces an increase in blood pressure within 3 days (15).

ROLE OF PGI_2 IN BLOOD PRESSURE REGULATION

A considerable amount of evidence supports the view that PGI_2 modulates vascular reactivity and blood pressure in

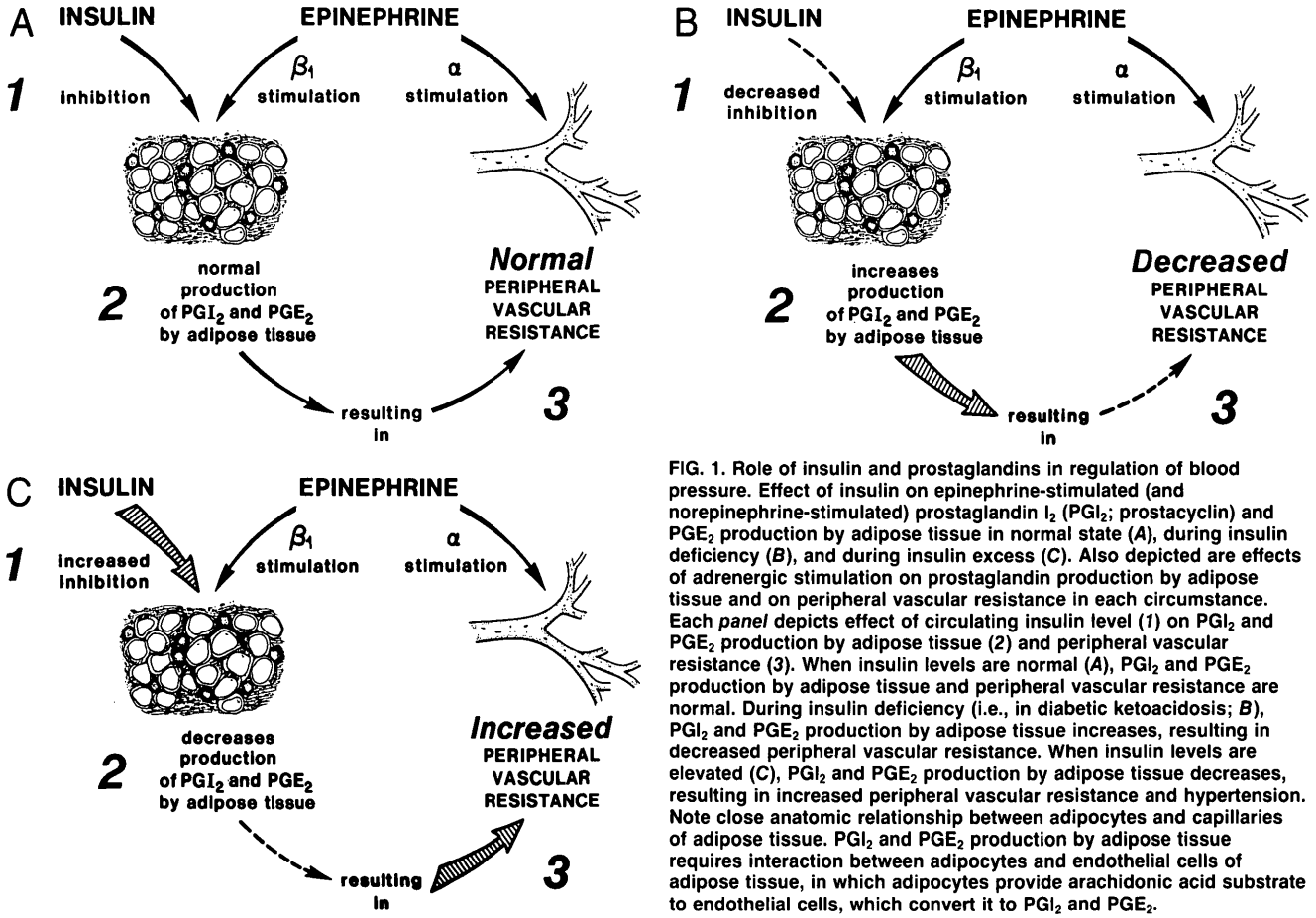

FIG. 1. Role of insulin and prostaglandins in regulation of blood pressure. Effect of insulin on epinephrine-stimulated (and norepinephrine-stimulated) prostaglandin I_2 (PGI_2; prostacyclin) and PGE_2 production by adipose tissue in normal state (*A*), during insulin deficiency (*B*), and during insulin excess (*C*). Also depicted are effects of adrenergic stimulation on prostaglandin production by adipose tissue and on peripheral vascular resistance in each circumstance. Each *panel* depicts effect of circulating insulin level (*1*) on PGI_2 and PGE_2 production by adipose tissue (*2*) and peripheral vascular resistance (*3*). When insulin levels are normal (*A*), PGI_2 and PGE_2 production by adipose tissue and peripheral vascular resistance are normal. During insulin deficiency (i.e., in diabetic ketoacidosis; *B*), PGI_2 and PGE_2 production by adipose tissue increases, resulting in decreased peripheral vascular resistance. When insulin levels are elevated (*C*), PGI_2 and PGE_2 production by adipose tissue decreases, resulting in increased peripheral vascular resistance and hypertension. Note close anatomic relationship between adipocytes and capillaries of adipose tissue. PGI_2 and PGE_2 production by adipose tissue requires interaction between adipocytes and endothelial cells of adipose tissue, in which adipocytes provide arachidonic acid substrate to endothelial cells, which convert it to PGI_2 and PGE_2.

states of health and disease (16). PGE_2 is also a vasodilator but is less potent than PGI_2. PGE_2 probably plays a subsidiary role to PGI_2 in the regulation of vascular tone and blood pressure. Of course, the two agents, which are produced in comparable quantities in adipose tissue in response to epinephrine (17), may produce an additive effect.

PGI_2 is produced locally in blood vessels (16). It is the principal product of arachidonic acid in all arteries and veins tested (18) and is also produced by capillary endothelium (19). PGI_2 is also produced by cultured human, bovine, and porcine endothelial cells, cultured human and bovine vascular smooth muscle cells, and other cells (20–28).

Catecholamines and other pressors stimulate PGI_2 production in humans (29,30). Angiotensin II stimulates PGI_2 production by cultured endothelial cells (23), stimulates the production of PGI_2 and other prostaglandins in various tissues (31), and appears to release PGI_2 into the circulation in animals (32,33) and humans (34).

Inhibition of PGI_2 production enhances vascular responsiveness to vasoconstrictors. Indomethacin, an inhibitor of prostaglandin synthesis, prevents the appearance of a PGI_2-like substance into the circulation and increases the pressor response to angiotensin II in dogs (33). Indomethacin also enhances the pressor response to the intravenous infusion of angiotensin II in humans (35) and causes an increase in blood pressure in animals (36–38) and humans (39–41) under various circumstances.

Rats that are genetically susceptible to salt-induced hypertension exhibit impaired generation of vascular PGI_2 (and increased generation of vascular thromboxane A_2) compared with appropriate control animals (42).

PGI_2 modifies vascular resistance and blood pressure in several disease states. The infusion of PGI_2 at low rates, e.g., 5–10 ng · kg^{-1} · min^{-1}, in healthy subjects produces tachycardia, hypotension, decreased peripheral vascular resistance, nausea, vomiting, and, occasionally, abdominal pain (43–46). This suggests the possibility that increased endogenous PGI_2 production produces similar effects in certain disorders. This appears to be the case.

Direct hemodynamic evidence indicates that the decreased peripheral vascular resistance observed in diabetic ketoacidosis (DKA), despite profound volume depletion (which ordinarily causes increased peripheral vascular resistance), is a result of the vasodilative effects of increased PGI_2 (and possibly PGE_2) production by adipose tissue as a consequence of insulin deficiency (47; Fig. 1*B*). Treatment with insulin decreases the increased PGI_2 and PGE_2 production and increases the peripheral vascular resistance toward a normal level (47). Increased PGI_2 and PGE_2 production by adipose tissue in DKA may also account for the nausea, vomiting, and abdominal pain that occur in this disorder, because the PGI_2 infusion rate that decreases vascular resistance and blood pressure in humans also causes nausea, vomiting, and, occasionally, abdominal pain (43–46).

The permissive effect of glucocorticoids on vascular tone and blood pressure, i.e., the enhancement of vascular responsiveness to pressors such as catecholamines without

necessarily having an effect when given alone, may be mediated by the ability of these agents to inhibit PGI_2 production by vascular endothelium and perhaps other cells (16). The inhibition of PGI_2 production by glucocorticoids may explain, at least in part, the hypertension of Cushing's syndrome (16). Conversely, the production of PGI_2 may be raised in Addison's disease and other states of glucocorticoid deficiency (16). Patients with untreated Addison's disease typically have tachycardia, hypotension, nausea, vomiting, and abdominal pain. Thus, increased PGI_2 production may also explain many of the cardiovascular and gastrointestinal features of Addison's disease (16).

In short, PGI_2 and PGE_2 production are inhibited by glucocorticoids and by insulin, possibly at different anatomic locations. When there is a deficiency of either hormone, the production of these vasodilative prostaglandins increases, causing decreased peripheral vascular resistance and hypotension and possibly nausea, vomiting, and abdominal pain. Thus, certain similarities in the clinical features of adrenal insufficiency and DKA may reflect the role of increased prostaglandin production in the pathogenesis of both disorders. When the level of either hormone is excessive, the production of vasodilative prostaglandins decreases, causing increased peripheral vascular resistance and hypertension.

ROLE OF PROSTAGLANDIN PRODUCTION BY ADIPOSE TISSUE IN THE PATHOGENESIS OF HYPERTENSION

Adipose tissue is one of the largest organs in the body. It weighs ~11.8 kg in a nonobese young woman and ~4.8 kg in a nonobese young man (48). The contribution of adipose tissue to total body mass is even greater in obesity and in nonobese individuals as they age (49). As noted above, hypertension correlates with upper-body obesity, i.e., with an increase in the size of the abdominal adipose depot.

Enlarged adipose tissue mass may contribute to increased peripheral vascular resistance in obesity. Blood flow through human adipose tissue measured by the clearance rate of radioactive xenon decreases significantly with increasing thickness of the fatty tissue (50). Blood flow through adipose tissue is also decreased in obese Zucker rats (51). Of course, the increase in peripheral vascular resistance in hypertension may also occur in other tissues such as skeletal muscle, but there is no direct evidence to support this possibility (49).

PGI_2 and PGE_2 play important roles in the normal function of adipose tissue and are produced in comparable quantities by adipose tissue (17). Catecholamine-stimulated PGI_2 and PGE_2 production by adipose tissue involves a cooperative interaction between the adipocyte and the endothelial cell of adipose tissue (17,52). Neither cell alone produces PGI_2 or PGE_2 in response to epinephrine. The presence of both cell types is required for the production of PGI_2 and PGE_2 (17,52). The adipocyte provides the arachidonic acid substrate to the endothelial cell, which utilizes the arachidonic acid to produce PGI_2 and PGE_2 (17,52). Although insulin inhibits PGI_2 and PGE_2 production by adipose tissue, the cellular site of action is not known.

One of the major physiological functions of endogenous prostaglandins in adipose tissue is the regulation of the local blood flow (53,54). Both PGE_2 and PGI_2 are potent vasodilators in most vascular beds (55). The functional vasodilation of adipose tissue that accompanies lipolysis is due at least in part to the vasodilative effect of these prostaglandins (53,56). This concept is supported by evidence that the functional vasodilation is abolished by indomethacin and aspirin (53). Reincorporation of free fatty acids released during triglyceride lipolysis is a mechanism for regulation of the net rate of triglyceride breakdown in adipose tissue (57–59). The functional vasodilation of adipose tissue appears to provide a mechanism for the rapid removal of free fatty acids from adipose tissue and their rapid delivery to the systemic circulation. In this way, the functional vasodilation of adipose tissue may increase the efficiency of the lipolytic process and minimize the activity of a futile cycle of triglyceride lipolysis and reesterification of free fatty acids into neutral lipids.

PGI_2, a potent lipolytic substance, and PGE_2, a potent antilipolytic substance, provide a mechanism for the coordinate control of catecholamine-stimulated lipolysis in adipose tissue (17). Of course, epinephrine stimulates lipolysis in the absence of PGE_2 and PGI_2, e.g., in isolated adipocytes. However, when adipocytes are mixed with endothelial cells or intact adipose tissue, epinephrine also stimulates the production of PGE_2 and PGI_2 during the activation of lipolysis (17,52). When both prostaglandins are produced, there appears to be no net effect on the rate of lipolysis (17). Thus, production of PGI_2 and PGE_2 may increase the efficiency of the lipolytic process by their vasodilative effects, whereas concurrent production of both a lipolytic and an antilipolytic prostaglandin prevents any alteration of the lipolytic cascade per se. It is possible that, in some circumstances, PGI_2 and PGE_2 production by adipose tissue is dissociated and that the ensuing imbalance alters the rate of hormone-stimulated lipolysis.

Insulin decreases prostaglandin production and blood flow in adipose tissue. Insulin in physiological concentrations inhibits catecholamine-stimulated PGI_2 production (5–7) and PGE_2 production (5,8) by adipose tissue in vitro (6,7) and in vivo (5,8). Infusion of insulin into lean Zucker rats produces a significant reduction in blood flow to the retroperitoneal, inguinal, and mesenteric fat depots but does not reduce blood flow to any nonadipose organ studied (60). After a meal, rat adipose tissue blood flow decreases in inverse relation to the circulating insulin levels (61). A glucose infusion sufficient to increase the circulating insulin level also decreases adipose tissue blood flow (62). Therefore, hyperinsulinemia may decrease the rate of blood flow and the efficiency of lipolysis in adipose tissue and increase systemic blood pressure by decreasing PGI_2 and PGE_2 production in adipose tissue (Fig. 1*C*).

Insulin may regulate prostaglandin production in adipose tissue through a wide range of concentrations with important physiological and clinical consequences. As indicated above, during insulin deficiency, i.e., in DKA, PGI_2 and PGE_2 production by adipose tissue is increased, and peripheral vascular resistance and blood pressure are decreased (47; Fig. 1*B*). Conversely, hyperinsulinemia may decrease PGI_2 and PGE_2 production by adipose tissue. This could contribute to the hypertension associated with hyperinsulinemia and could decrease the efficiency of lipolysis (Fig. 1*C*).

It may be argued that systemic production of PGI_2 is so

low that its inhibition by insulin is not likely to engender hypertension. In fact, the basal total-body production of PGI_2 in nonobese humans is small, <100 pg · kg^{-1} · min^{-1} (63). However, the production rate increases in response to catecholamines and angiotensin II in animals and humans (see above). Also, the basal or stimulated production rate has not been measured in obesity, especially upper-body obesity, and may be higher in obese than in nonobese subjects. Furthermore, increased or decreased PGI_2 or PGE_2 production in the vascular bed of a specific organ such as adipose tissue may not be detected by methods that assess total-body production rates.

ALTERNATIVE MECHANISMS BY WHICH INSULIN MAY CAUSE HYPERTENSION

Several mechanisms have been proposed by which hyperinsulinemia may cause hypertension (9,11–14). First, by virtue of its ability to promote renal tubular reabsorption of sodium, insulin causes an increase in total-body sodium and extracellular fluid volume so that higher renal (and therefore arterial) perfusion pressures are necessary to maintain sodium balance (9,11). Second, insulin increases sympathetic nervous system activity in humans (64), and resistance to the action of insulin on the sympathetic nervous system does not appear to develop in obese subjects (9,14). The increased sympathetic activity may then contribute to hypertension by increasing sodium reabsorption, cardiac output, and peripheral vascular resistance (9,64). Third, insulin stimulates the activity of the Na^+-H^+ exchanger, which is linked to Ca^{2+} exchange (11). Intracellular accumulation of Na^+ and Ca^{2+} presumed to enhance the sensitivity of vascular smooth muscle to the pressor effects of norepinephrine, angiotensin II, and volume expansion. Fourth, insulin may cause vascular hypertrophy, thereby increasing peripheral vascular resistance (11).

These mechanisms may or may not explain the ability of hyperinsulinemia to cause hypertension. Although evidence can be marshaled in support of each of these proposed mechanisms, none of them is established beyond doubt, and serious reservations may be raised about each of them. For example, it is not established unequivocally that the ability of insulin to cause renal tubular sodium reabsorption increases blood pressure. In one carefully controlled study, the ability of insulin to cause proximal renal tubular sodium reabsorption did not raise blood pressure in healthy subjects or patients with insulin-dependent diabetes mellitus (65). Furthermore, total-body sodium content is increased to a comparable degree in normotensive and hypertensive patients with diabetes mellitus so that increased total-body sodium may contribute to the development of hypertension in susceptible individuals but is not sufficient to explain the relationship between hyperinsulinemia and hypertension (12,65). Similarly, the physiological relevance of insulin's ability to stimulate sympathetic nervous system activity is open to question, because the circulating insulin level that stimulates sympathetic nervous system activity as measured by the circulating norepinephrine level is not usually attained even in obesity (64). The data used to support a role for the Na^+-H^+ exchanger as a mediator of the hypertensive effect of insulin were not obtained in vascular tissue of patients with hypertension. Although the Na^+-H^+ exchanger is a useful marker for hypertension, its role in the pathogenesis of hypertension has not been proven. Finally, the ability of insulin to stimulate vascular hypertrophy does not necessarily translate into increased peripheral vascular resistance. Nevertheless, our hypothesis and the alternative hypotheses proposed previously are not mutually exclusive. In fact, the several proposed mechanisms may be additive or synergistic.

CONCLUSIONS

The inhibitory effect of insulin on catecholamine-induced PGI_2 and PGE_2 production by adipose tissue (and possibly other tissues) can explain the association between hyperinsulinemia and hypertension. This concept is already supported by diverse experimental and clinical findings. Further tests of this hypothesis should include studies of the effects of hyperinsulinemia on blood flow and vascular resistance in adipose tissue (and other vascular beds) and on PGI_2 and PGE_2 production by adipose tissue (and other vascular beds) in normotensive and hypertensive subjects with and without obesity and glucose intolerance.

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