Catecholamines released from the sympathochromaffin system produce metabolic changes similar to those of diabetes mellitus. However, increased sympathochromaffin activity does not appear to be a feature of insulin-dependent diabetes mellitus (IDDM), although physiologic catecholamine increments may contribute to short-term metabolic derangements under some conditions. Increased glycemic sensitivity to epinephrine is a feature of IDDM but is the result of the inability to secrete insulin rather than of increased cellular sensitivity to catecholamines. Absolute insulin deficiency results in increased metabolic (glycemic, lipolytic, and ketogenic) sensitivity to catecholamines. More generalized hypersensitivity occurs in diabetic autonomic neuropathy. However, the clinical relevance of these alterations in sensitivity remains to be established. On the other hand, decreased sympathochromaffin activity is common and causes considerable morbidity and some mortality in people with diabetes. In addition to increased sensitivity to catecholamines, decreased sympathochromaffin activity results in the clinical syndromes of postural hypotension, hypoglycemia unawareness, defective glucose counterregulation, or a combination of these. The latter two syndromes cause an increased frequency of severe iatrogenic hypoglycemia, at least during intensive therapy of IDDM. Thus, decreased rather than increased sympathochromaffin activity often complicates IDDM. Clearly, ways to prevent, correct, or compensate for this component of diabetic autonomic neuropathy must be learned before diabetes can be managed effectively and safely in all patients who suffer from the disease until diabetes mellitus is eradicated. Diabetes 38:405–409, 1989

Because of the well-known hyperglycemic actions of epinephrine and norepinephrine, it has long been suspected that catecholamine excess might contribute to the pathophysiology of diabetes mellitus. It is my premise that decreased rather than increased catecholamine release more commonly causes problems that are clinically relevant in people with diabetes. This premise is based on available data in humans, mostly from studies of insulin-dependent diabetes mellitus (IDDM). Non-insulin-dependent diabetes mellitus (NIDDM) has been studied less in this regard.

INCREASED SYMPATHOCHROMAFFIN ACTIVITY

Catecholamines released from the sympathochromaffin (sympathoadrenal) system, i.e., adrenomedullary epinephrine and sympathetic neural norepinephrine, produce metabolic changes that resemble those of diabetes mellitus (1). These catecholamines increase glucose production (glycogenolysis and gluconeogenesis are stimulated) and limit glucose utilization, thus raising the plasma glucose concentration. They also stimulate lipolysis and ketogenesis, thus raising free-fatty acid and ketone body levels. Insulin exerts opposing effects on these processes. Theoretically, therefore, increased sympathochromaffin activity could interact with insulin deficiency to complicate the metabolic abnormalities of diabetes mellitus in the long term, short term, or both.

In the long term, increased sympathochromaffin activity does not appear to be an intrinsic feature of diabetes mellitus. I base this conclusion largely, although not exclusively, on the premise that isotope-derivative (radioenzymatic) measurements of plasma catecholamine concentrations, with appropriate interpretive restraint, provide valid indices of the activity of the sympathochromaffin system in humans (2). Plasma catecholamine levels are elevated, often markedly, in diabetic ketoacidosis (3), and catecholamine responses to exercise are exaggerated in poorly controlled IDDM (3,4), but the levels return to normal with improved metabolic control in both instances. Twenty-four-hour integrated plasma
norepinephrine and epinephrine levels were found to be elevated slightly in patients with mean integrated plasma glucose concentrations of 299 mg/dl (5) but not in those with mean glucose levels of 226 mg/dl (6). In a series of 100 patients with stable nonketotic diabetes, mean basal and posturally stimulated plasma norepinephrine and epinephrine concentrations were normal (7), although subsets of patients with exaggerated or reduced sympathochromaffin responses were identified (7,8). Thus, I agree with Christensen (3), who concluded that “plasma noradrenaline and adrenaline concentrations are normal in patients with short-term diabetes without signs of diabetic neuropathy, provided that metabolic status is reasonably well controlled” and suggested that when found, “elevated catecholamines probably constitute an important compensation to volume depletion and disturbed cell function, thus maintaining vital body functions.”

Nonetheless, the plasma norepinephrine concentration is a relatively insensitive measure of sympathetic neural activity; normal levels do not exclude increased sympathetic activity categorically (2). Therefore, clues that sympathochromaffin activity might be increased in some groups of people with diabetes mellitus, particularly NIDDM (9–13), should not be dismissed.

Even if increased sympathochromaffin activity is not an ongoing feature of diabetes, it is conceivable that physiological increments in catecholamine release might contribute to short-term metabolic derangements, e.g., in diabetic ketoacidosis, during psychological stress, or after hypoglycemia. This suggestion, although plausible, remains to be established. For example, in patients with IDDM, β-adrenergic blockade was found not to delay the development of hyperglycemia and ketosis after insulin withdrawal (14), psychological stress was found not to produce excessive hyperglycemia (15), and the clinical relevance of the Somogyi phenomenon (hyperglycemia caused by counterregulatory, particularly epinephrine, responses to antecedent hypoglycemia) has recently been questioned (16–18), even though catecholamine levels are increased in each of these conditions. Clearly, these findings do not exclude a role for catecholamines in short-term metabolic derangements in diabetes. They do not, however, support such a role.

ALTERED SENSITIVITY TO CATECHOLAMINES

There are reports of altered cardiovascular sensitivity to catecholamines in diabetes. These include decreased myocardial β-adrenergic–receptor densities and adenylate cyclase responsiveness to isoproterenol in hearts from diabetic rats (19), decreased chronotropic sensitivity to isoproterenol in humans with diabetes (20), increased responsiveness to norepinephrine of vessels removed from diabetic animals (21), and increased pressor responses to norepinephrine in humans with diabetes (22). The mechanisms of these cardiovascular alterations are not known.

Altered cellular sensitivity to the metabolic actions of the catecholamines does not appear to be a feature of diabetes mellitus, although sensitivity to catecholamines in vivo is increased with respect to certain actions and more generally in one subset of patients, as summarized below. The evidence from humans on which I base this conclusion is less extensive than that concerning activity of the sympathochromaffin system. Although there are a few reports of studies of other tissues, most investigators studying tissues from humans with diabetes have used circulating cells as models of the status of adrenergic-receptor–effector systems in extravascular catecholamine target tissues despite limitations to this approach (23). We found mononuclear leukocyte β2-adrenergic–receptor densities and antagonist affinities to be normal in metabolically stable patients with IDDM selected for the absence of autonomic neuropathy (24). Adenylate cyclase sensitivity to an agonist was also normal (24). To the extent that these measurements reflect their counterparts in catecholamine target tissues, β1-adrenergic receptors and their linked adenylate cyclase systems appear to be normal in people with uncomplicated IDDM. Note that the glycemic actions of the catecholamines are mediated through β2-adrenergic receptors in people with IDDM (1). Small decrements in platelet α2-adrenergic–receptor densities have been reported in studies in people with diabetes (25), particularly those with autonomic neuropathy (26). Because functional correlates are lacking, the physiologic relevance of these small changes is unknown. Although α2-adrenergic limitation of insulin secretion normally allows the glycemic response to epinephrine and norepinephrine to occur, this mechanism is obviously inoperative in people with IDDM (1).

It is well established that people with IDDM exhibit increased glycemic sensitivity to epinephrine, among other counterregulatory hormones, even when basal insulin levels are sufficient (27). However, this increase is not the result of increased cellular sensitivity to the hormone. Rather, it is the result of the inability to secrete insulin as the plasma glucose concentration rises in response to epinephrine. It can be reproduced in nondiabetic humans by inhibition of the insulin secretory response (1.28). Thus, increased insulin secretion, albeit restrained, normally limits the magnitude of the glycemic response to epinephrine, and the absence of increased insulin levels potentiates the glycemic response in IDDM. Interestingly, the latter mechanism does not apply to the lipolytic and ketogenic sensitivities to epinephrine (28), which are probably not altered in IDDM per se. Although increased free–fatty acid, glycerol, and ketone body responses to the hormone have been reported in IDDM, they are probably the result of elevated levels at baseline (26–30). These responses, in contrast to that of glucose, are similar in IDDM and nondiabetic individuals when baseline levels are similar (A. Avogaro, P.E.C., and D. Bier, unpublished observations), i.e., when basal insulin is sufficient. When insulin is absolutely deficient, however, the lipolytic and ketogenic as well as the glycemic responses to catecholamines are enhanced.

Patients with IDDM complicated by autonomic neuropathy exhibit increased sensitivity to various β-adrenergic actions of epinephrine compared with patients without this complication (30). These actions include hemodynamic (heart rate, vasodilation, and thus blood pressure) and metabolic (glucose concentration and rate of appearance; free–fatty acid, glycerol, and lactate levels; and oxygen consumption) responses to the hormone. The mechanism of this increased sensitivity has not been established. It is reasonable to attribute it provisionally to derangement hypersensitivity resulting from decreased sympathochromaffin function. Upregulation of target-tissue adrenergic receptors might occur in
this setting, but this has not been demonstrated in such patients. Indeed, mononuclear leukocyte β2-adrenergic receptors and platelet α2-adrenergic receptors have been found to be normal in patients with diabetic autonomic neuropathy (A. Deijgaard, S. Liggert, N. Christensen, P.E.C., and J. Hilsted, unpublished observations).

In summary, increased sympathochromaffin activity does not appear to be an ongoing feature of diabetes mellitus. People with IDDM exhibit increased glycemic sensitivity to catecholamines even when basal insulin levels are sufficient, increased metabolic sensitivity to catecholamines when insulin levels are low, and more generalized increased tissue sensitivity to catecholamines in the presence of autonomic neuropathy. Thus, it is reasonable to postulate that physiological activation of the sympathochromaffin system might result in short-term metabolic deterioration, although compelling evidence that this is clinically relevant is lacking.

**DECREASED SYMPATHOCHROMAFFIN ACTIVITY**

Decreased sympathochromaffin activity, although not a universal finding and therefore not an intrinsic feature of diabetes mellitus, is common. It causes considerable morbidity and some mortality in people with diabetes. In addition to increased tissue sensitivity to catecholamines, manifestations of sympathochromaffin hypofunction include the clinical syndromes of postural hypotension due to classic autonomic (in this case sympathetic) neuropathy, hypoglycemia unawareness, and defective glucose counterregulation, all viewed reasonably as components of diabetic autonomic neuropathy.

Postural hypotension due to sympathetic neural failure is a well-known feature of diabetic autonomic neuropathy and therefore is the classic example of clinically relevant sympathochromaffin hypofunction. Plasma norepinephrine concentrations (31), appearance rates (32), and production rates (32) are reduced in patients with postural hypotension due to diabetic autonomic (sympathetic) neuropathy, probably as the result of sympathetic postganglionic lesions analogous to that of diabetic peripheral (somatic) neuropathy, although the precise mechanisms of these lesions remain a matter of debate (34,35). Sympathetic neuropathy is, of course, linked closely with parasympathetic neuropathy. Whether the result of autonomic neuropathy per se, other complications of diabetes that are common at this stage of the disease, or both, the presence of diabetic autonomic neuropathy indicates a bad prognosis. In one series, 50% of affected patients died within 2.5 yr (36).

Note that postural hypotension is not invariably the result of sympathetic neural failure even in people with diabetes. Although many patients with postural hypotension have reduced plasma norepinephrine responses to standing (hypoadrenergic postural hypotension) that are indicative of sympathetic hypofunction (7,34), others have exaggerated norepinephrine responses (hyperadrenergic postural hypotension; 7). The latter are a reflection of compensatory increases in the magnitude of the sympathetic response in patients with other causes of postural hypotension, e.g., decreased intravascular volume (8).

The clinical syndrome of hypoglycemia unawareness in people with diabetes is probably also the result of sympathochromaffin hypofunction (37–39). Affected individuals no longer have the neurogenic (adrenergic) symptoms (e.g., sweating, palpitations, hunger, weakness) that previously warned of developing hypoglycemia. Thus, neuroglycopenic manifestations are the first evidence of hypoglycemia and, because they impair brain function, often preclude self-treatment with food to prevent progression to even more severe hypoglycemia. Although the issue has not, to my knowledge, been studied prospectively, hypoglycemia unawareness probably increases the frequency of severe iatrogenic hypoglycemia. The frequency of the syndrome has not been precisely defined, but it appears to be common in IDDM (38). Hypoglycemia unawareness is associated with reduced plasma epinephrine responses to experimental hypoglycemia in IDDM (37,38). If this is viewed as a marker for hypofunction of the entire sympathochromaffin system, including its sympathetic neural and adrenomedullary components, the clinical syndrome could plausibly be attributed to sympathochromaffin hypofunction. There is disagreement, however (39).

Defective glucose counterregulation, a newly recognized risk factor for severe iatrogenic hypoglycemia in people with IDDM, is a third clinical syndrome attributable to sympathochromaffin hypofunction (40,41). It is associated with and best attributed to combined deficiencies of the glucagon and epinephrine secretory responses to plasma glucose decrements (39). As demonstrated in prospective studies, the risk of severe iatrogenic hypoglycemia is increased >25-fold, at least during intensive therapy of IDDM, in patients with defective glucose counterregulation (40,41).

Risk factors for severe hypoglycemia in IDDM include relative or absolute insulin excess (39). Clearly, defective glucose counterregulation, probably operative in concert with hypoglycemia unawareness, must be added to the list of risk factors. Although the relative contribution of these disorders of sympathochromaffin hypofunction, vis-à-vis that of insulin excess, remains to be defined, it appears to be substantial (39). In addition to the morbidity of iatrogenic hypoglycemia, sufferers at times by virtually all people with IDDM, it has been estimated that hypoglycemia causes ~4% of deaths among people with IDDM practicing conventional therapy and, in a few patients, 9% of deaths in those practicing intensive therapy (39). Clearly, these could be underestimates.

Both sympathetic postganglionic neurons and the chromaffin cells that constitute the adrenal medulla synthesize and release catecholamines, among other products, in response to central nervous system activation of sympathetic preganglionic cholinergic neurons (42). They are derived embryologically from a common neuroectodermal stem cell (42). Both contain the biosynthetic enzymes that lead to the formation of norepinephrine and release that catecholamine. Chromaffin cells also synthesize epinephrine, and the adrenal medullae are its predominant source in humans, at least in adults (2). The sympathochromaffin system is a classic neuroendocrine system (43). Its sympathetic postganglionic neurons release norepinephrine in direct relation to target cells, and the catecholamine functions primarily as a neurotransmitter, whereas its adrenal medulla release epinephrine into the circulation to function as a hormone. Thus, the adrenal medullae are most reasonably conceptualized as sympathetic postganglionic neurons without axons and...
therefore as an integral component of the autonomic nervous system. As summarized above, deficient adrenomedullary epinephrine secretory responses contribute to the development of hypoglycemia in many patients with IDDM. Furthermore, deficient epinephrine (and pancreatic polypeptide) responses to hypoglycemia identify patients at high risk for future development of classic diabetic autonomic neuropathy (44). These considerations suggest that adrenomedullary hypofunction, like sympathetic neural hypofunction, resulting from diabetes mellitus is a feature of diabetic autonomic neuropathy. That does not imply that the pathogenesis of the adrenomedullary defect is necessarily the same as that of the sympathetic neural defect, or that they must occur in the same individual.

Pending the prevention or cure of diabetes mellitus, ways to prevent, correct, or compensate for sympathochromaffin hypofunction must be learned for diabetes to be managed both effectively and safely in all people who suffer from the disease. Presumably, the development and application of perfect insulin-delivery systems would prevent this complication, among others, although this remains to be proved. Certainly, it would minimize the risk of hypoglycemia. Insight into the precise causes of sympathetic neural and adrenomedullary hypofunction would probably contribute to the prevention or correction of these complications and should be pursued. However, attempts to prevent, correct, or compensate for these deficits need not await such insight. People suffer from diabetes mellitus and its complications now. While support should continue for a broad range of basic research that might clarify the mechanisms of the complications of diabetes and ultimately eliminate the disease for future generations, the more applied end of the research spectrum for those who live with diabetes mellitus today should not be ignored.

The role of altered sympathochromaffin activity in the pathophysiology of IDDM, as I currently see it, is summarized in Fig. 1. Altered sympathochromaffin activity does not appear to be an intrinsic feature of the disease. There is a strong conceptual basis for the hypothesis that physiologic increments in sympathochromaffin activity contribute to short-term metabolic derangements (e.g., hyperglycemia and ketosis) in diabetes mellitus. The inability to increase insulin secretion as the plasma glucose concentration rises (relative insulin deficiency) results in increased glycemic (but not lipolytic or ketogenic) sensitivity to catecholamines, absolute insulin deficiency results in increased metabolic (glycemic, lipolytic, and ketogenic) sensitivity to catecholamines, and autonomic neuropathy results in increased hemodynamic and metabolic sensitivity to catecholamines. However, compelling evidence of the clinical relevance of these alterations in sensitivity is lacking. On the other hand, it is clear that decreased sympathochromaffin activity is common and causes considerable morbidity and some mortality. It results in postural hypotension, hypoglycemia unawareness, defective glucose counterregulation, or a combination of these clinical syndromes. The postural hypotension can cause syncope, whereas the other syndromes contribute to an increased frequency to severe iatrogenic hypoglycemia, at least during intensive therapy of IDDM. Thus, decreased rather than increased sympathochromaffin activity commonly complicates IDDM.

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