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Functional Consequences of Streptozotocin-induced Diabetes Mellitus, with Particular Reference to the Cardiovascular System

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I. Introduction

PATIENTS suffering from diabetes mellitus, a disease caused by insulin deficiency or impaired tissue responsiveness to insulin, are particularly prone to disorders of cardiovascular control (Garcia et al., 1974; Jarrett, 1989), including hypertension, atherosclerosis, microangiopathy, congestive heart failure, and autonomic neuropathy. Mortality from cardiovascular disease is almost three times higher in patients with diabetes mellitus than in the general population (Garcia et al., 1974; Jarrett, 1989). Consequently, there has been much interest in the aetiology of cardiovascular disorders associated with this disease, and hence animal models of diabetes mellitus have been developed.

It is now 10 years since the "Proceedings of a Task Force on Animals Appropriate for Studying Diabetes Mellitus and Its Complications" appeared (1982). Since that time, much new information has been published regarding pathophysiology, particularly related to control of cardiovascular function in the rat following treatment with STZ‡ to induce diabetes mellitus; the present review brings together that information and points out important parallels between this animal model and clinical diabetes mellitus.

STZ is an antibiotic extracted from *Streptomyces achromogenes*; structurally it contains a methylnitrosourea group bound to the C2 position of 2-deoxy-D-glucose. Rakieten et al. (1963) were the first to report that STZ, when given intravenously, caused diabetes mellitus in rats and dogs. The action of STZ was further characterised by Junod et al. (1967) who found histological changes in the pancreatic β-cells as soon as 1 h after STZ treatment. Seven to 10 h after STZ treatment, there was massive β-cell degranulation and necrosis, associated with an increase in serum insulin levels and hypoglycaemia. This was followed by prolonged hyperglycaemia (1 to 28 days), which coincided with a reduction in pancreatic insulin levels to <5% of normal values. The diabetogenic effects of STZ were found to be dose dependent (Junod et al., 1969), ranging from a mild diabetes following a dose of 35 mg kg^{-1} to a severe ketotic state, leading to death within 2 to 3 days after a dose of 100 mg kg^{-1}. When treated with intermediate doses of STZ (55 and 65 mg kg^{-1}, i.e., those used in most cardiovascular studies), rats failed to gain weight and developed blood glucose levels 3 to 4 times higher than normal but were able to survive without insulin supplementation and did not develop ketonuria. Histological studies failed to reveal any evidence of a toxic effect of STZ itself on the liver or kidney (Junod et al., 1967), and because rats treated with a high dose of STZ (100 mg kg^{-1}) were able to survive, provided they were given insulin treatment, it was concluded that STZ was selectively toxic for pancreatic β-cells.

Rats treated with STZ display many of the features seen in human subjects with uncontrolled diabetes mellitus, including hyperglycaemia, polydipsia, polyuria, and weight loss (Hebden et al., 1986; Tomlinson et al., 1989c). The following account is an overview of changes that occur in cardiovascular homeostasis in rats following STZ treatment and the many factors (endocrine, renal, hepatic, nervous, cardiac, and vascular) affected by STZ that may underlie these changes. Because abnormalities in the CNS may influence cardiovascular control in STZ-treated rats, the effects of STZ treatment on the CNS have also been considered. Although this is not meant to be a review of human diabetic complications, interesting

‡ Abbreviations: STZ, streptozotocin; AVP, vasopressin; BP, blood pressure; RAS, renin-angiotensin system; ICV, intracerebroventricular; AI, angiotensin I; AII, angiotensin II; ACE, angiotensin-converting enzyme; ACTH, adrenocorticotrophic hormone; ANP, atrial natriuretic peptide; GFR, glomerular filtration rate; TSH, thyroid-stimulating hormone; T_4, thyroxine; T_3, triiodothyronine; HR, heart rate; ATPase, adenosine triphosphatase; VIP, vasoactive intestinal polypeptide; NPY, neuropeptide Y; NGF, nerve growth factor; CNS, central nervous system; mRNA, messenger RNA; 5-HIAA, 5-hydroxyindole acetic acid; GABA, γ-aminobutyric acid; +dP/dt, maximal rate of ventricular pressure development; −dP/dt, maximal rate of decline of ventricular pressure development; EDRF, endothelium-derived relaxing factor.

similarities or differences between cardiovascular control in STZ-treated rats and in patients with diabetes mellitus are highlighted.

In the majority of cases cited in this review, studies were carried out within a few months of STZ treatment and were, therefore, concerned with the effects of relatively acute insulin deficiency. It would, perhaps, be appropriate to compare these STZ-treated rats with newly diagnosed type I diabetic patients, i.e., before insulin treatment has begun, but few cardiovascular studies have been done on this group. Many diabetic patients suffer from chronic insulin deficiency (type I diabetes) or impaired tissue responsiveness to insulin (type II diabetes) and, in addition, may have been receiving insulin treatment, or other hypoglycaemic agents, for many years; such treatment could, itself, lead to long-term complications (Stout, 1979). There have been some studies of the effects of long-term, STZ-induced diabetes, both with and without insulin treatment (Vadlamudi et al., 1982; Willars et al., 1989), but additional experiments using this approach are needed. Nevertheless, investigations of short-term, STZ-induced diabetes can provide valuable information about the underlying pathophysiological changes that lead to chronic diabetic complications and, hence, may be invaluable in the development of treatment strategies, other than insulin therapy, to counteract these changes. Furthermore, a consideration of cardiovascular control in the STZ-treated rat may provide information about the normal physiological role of insulin in the regulation of the cardiovascular system. Many of the studies cited have shown reversal of the effects of STZ by treatment with insulin. However, care has been taken to discuss fully any effects that have been suggested to be due to a direct action of STZ and not to insulin deficiency.

II. Endocrine Systems

A. Vasopressin

Circulating levels of AVP are increased by approximately fourfold in rats treated 6 weeks earlier with STZ (Van Itallie and Fernstrom, 1982). However, increases in plasma AVP occur soon after STZ treatment, becoming significant within 3 days (Vokes and Robertson, 1985), and are dependent on the dose of STZ used (Brooks et al., 1989). Following administration of insulin to STZ-treated rats, plasma AVP concentrations rapidly return toward control levels (i.e., within 2 to 4 h) (Vokes and Robertson, 1985). Furthermore, Brooks et al. (1989) showed that spontaneously diabetic rats maintained on insulin treatment had normal plasma AVP levels, but 24 to 48 h after the withdrawal of insulin plasma AVP had increased dramatically. Thus, it appears that changes in circulating AVP are due to acute effects of insulin deficiency rather than to the long-term effects of diabetes mellitus. Whether or not clearance of AVP from the circulation is altered following STZ treatment is unknown, but it is likely that the elevated circulating levels are due, at least in part, to increased release, because posterior pituitary AVP stores are substantially decreased in STZ-treated rats (Van Itallie and Fernstrom, 1982), and AVP synthesis, measured as incorporation of [^{35}S]cysteine, was increased in the hypothalami of STZ-treated rats, possibly as a compensatory response to increased release (Fernstrom et al., 1990). Moreover, histological changes, including hypertrophy of AVP-containing cell bodies of the hypothalamic paraventricular and supraoptic nuclei and a decrease in AVP-containing neurosecretory granules of the neurohypophysis, have been found in STZ-treated rats (Loesch et al., 1988). These adaptations are similar to those found after water deprivation and are, therefore, consistent with hyperactivity of the hypothalamo-neurohypophyseal system and enhanced AVP release.

The factors responsible for increased release of AVP following STZ treatment are unclear. Normally, the two main stimuli for AVP release are plasma hyperosmolality and hypovolaemia (Verney, 1947). Plasma sodium concentration is believed to be the major determinant of AVP secretion in response to changes in plasma osmolality, but STZ-treated rats are hyponatraemic (Hebden et al., 1986; Tomlinson et al., 1989c) and this would be expected to cause a reduction in plasma AVP levels. It has, therefore, been suggested that STZ-treated rats show enhanced sensitivity to the effects of sodium. However, Van Itallie and Fernstrom (1982) tested osmoreceptor sensitivity to sodium by measuring changes in plasma AVP levels following administration of hypertonic saline to STZ-treated rats and found that, although the relationship of plasma AVP to sodium concentration was shifted to the left compared with that in controls, STZ-treated rats responded to an increase in sodium concentration with an appropriate increase in AVP levels (i.e., there was a resetting but no change in osmoreceptor sensitivity). Normal osmoregulatory control of AVP release in STZ-treated rats has been confirmed by Charlton et al. (1989).

Although plasma osmolality is increased following STZ treatment, this is mainly due to the presence of glucose which, because it is freely able to enter neurones, does not normally stimulate the central osmoreceptor. Recent study of diabetic patients, however, has provided evidence that the osmoreceptor may become sensitive to glucose during diabetes mellitus. Under conditions of insulin deficiency, infusion of dextrose to increase plasma glucose levels of diabetic patients has been found to cause an increase in plasma AVP (Vokes et al., 1987; Grimaldi et al., 1988); whereas under insulin-replete conditions, changes in plasma glucose had no effect on AVP levels (Zerbe et al., 1985; Vokes et al., 1987; Thompson et al., 1988). It was suggested that, unlike most neuronal tissue, cells of the osmoreceptor required insulin to stimulate glucose uptake and, therefore, became

impermeable to glucose during insulin deficiency, allowing hyperglycaemia to exert an effective osmotic stimulus to the release of AVP. In agreement with this hypothesis, Durr et al. (1990) showed that, if plasma tonicity (i.e., taking into account changes in cellular permeability to glucose) was considered instead of plasma osmolality, then patients with diabetic ketoacidosis had no change in sensitivity for AVP release. Another possibility is that unidentified, osmotically effective solutes are present in higher concentrations in the plasma of patients with diabetes mellitus (Hebden et al., 1986).

Blood volume has been found to be reduced in rats 1 week after STZ treatment (Katayama and Lee, 1985; Kikkawa et al., 1986b), probably due to excessive fluid losses caused by osmotic diuresis (Hebden et al., 1986); thus, volume depletion may lead to enhanced AVP release soon after treatment with STZ. However, several weeks after STZ treatment, when fluid intakes and outputs had reached a new steady state, there was no difference in absolute blood volumes of STZ-treated and control rats, and blood volumes relative to body weight were actually increased in the former group (Hostetter et al., 1981; Hebden et al., 1988a). Interpretation of blood volume data is complicated by the nature of body weight loss following STZ treatment. STZ-treated rats display an almost complete loss of white adipose tissue (Geloen et al., 1989), as well as some loss of lean body tissue (muscle, heart, liver), whereas intestinal tissue may actually increase in mass (Pillion et al., 1988). Furthermore, young rats treated with STZ have impaired somatic growth (Sahebjami and Denholm, 1988). Thus, the functional significance of changes in absolute or relative blood volume following STZ treatment is uncertain. Carbonell et al. (1987) tried to overcome this problem by measuring blood volume in STZ-treated rats, along with both age-matched and weight-matched (younger) controls. Twelve weeks after the induction of diabetes mellitus, STZ-treated rats had a contraction in blood volume compared with age-matched controls but blood volume was greater than that in weight-matched controls. It appears, therefore, that several weeks after STZ treatment rats are functionally hypervolaemic, and hence blood volume changes are unlikely to contribute to enhanced AVP release at this time. Interestingly, Brooks et al. (1989) found that spontaneously diabetic rats, which developed hypotension and evidence of blood volume contraction (increased haematocrit), had AVP levels approximately 10-fold higher than those of STZ-treated diabetic rats in which there was no change in BP and a slight decrease in haematocrit. Thus, in circumstances in which volume contraction occurs following STZ treatment, AVP release may be further enhanced.

It is possible that the baroreceptor-mediated control of AVP release is affected during diabetes, independently of changes in blood volume. Both cardiac and sinoaortic baroreceptors exert a tonic influence on AVP release (Bisset and Chowdrey, 1988), and thus in diabetes an inappropriate reduction in baroreceptor firing caused, for example, by neuropathy, could contribute to increased AVP levels. However, because cardiac baroreflex sensitivities are not necessarily reduced in STZ-treated rats (see section IX.C), this seems unlikely. Finally, it is possible that changes within the CNS contribute to altered AVP release (see section VI.D).

Alterations in AVP levels may influence cardiovascular function in STZ-treated rats, either by a direct action on the vasculature or by an effect on renal concentrating mechanisms and fluid handling. Although there is little evidence of any direct vascular effect of AVP on resting BP in either STZ-treated or control rats (Hebden et al., 1987a; Tomlinson et al., 1990a), there is some evidence that AVP may be involved in the maintenance of BP following STZ treatment by favouring blood volume expansion (Tomlinson et al., 1989c, 1990a; see section IX.B). However, STZ-treated rats have been shown to have impaired AVP-mediated BP recovery following pharmacological interruption of the sympathetic nervous system and the RAS (Hebden et al., 1987a; Tomlinson et al., 1990a), and this may be due, in part, to impaired release of AVP in response to hypotension, although reduced vascular reactivity to exogenous AVP has also been found (Buñag et al., 1982; Hebden et al., 1987b; Ramos, 1988).

The BP responses to ICV administration of substances known to release AVP have also been studied (section VI.D). In the absence of drinking water, pressor responses to ICV administration of AII (which are believed to be mediated predominantly by AVP release) were normal in STZ-treated rats (Tomlinson et al., 1990b), although the AVP-mediated pressor response to ICV administration of somatostatin was reduced. Thus, it is possible that AVP release in response to somatostatin was attenuated (Tomlinson et al., 1990c). This observation may be of relevance to the finding of impaired AVP-mediated BP recovery mentioned above, because there is evidence that endogenous CNS somatostatin is involved in AVP release in response to haemorrhage (Brown et al., 1988).

In summary, AVP levels have been found to be increased following STZ treatment, although the exact mechanisms involved have not yet been determined. Alterations in the control of AVP secretion may underlie some abnormal BP responses of STZ-treated rats to stimuli known to elicit AVP release, although other AVP-mediated responses remain apparently normal.

Patients with uncontrolled diabetes mellitus have increased plasma levels of AVP (Vokes and Robertson, 1985), and AVP levels were found to increase when insulin treatment was withdrawn in well-controlled diabetic patients (Vokes et al., 1987). Increased AVP levels in clinical diabetes mellitus may be due to mechanisms similar to those discussed above in STZ-treated rats. In

addition, in patients with ketosis, the occurrence of hypovolaemia and nausea may further stimulate AVP release (Vokes and Robertson, 1985). Furthermore, Fisher et al. (1989) observed an enhancement of hypoglycaemia-induced AVP release in diabetic patients and suggested that this might be a compensatory response to offset impaired glucose counterregulation (i.e., through the hepatic glycogenolytic effects of AVP).

The role of AVP in cardiovascular control in diabetic patients has received little attention. It has, however, been shown that the increase in plasma AVP levels in response to tilting may be impaired in diabetics with autonomic neuropathy (Reid et al., 1989). Thus, diminished AVP responses could contribute to postural hypotension in diabetic patients; in extreme cases in which the renin response to tilt is also diminished, AVP may be crucial in preventing a dramatic decrease in BP (Saad et al., 1988). However, it seems unlikely that the influence of AVP under these conditions is due to a direct vasoconstrictor action because Saad et al. (1988) found that the hypotensive response to a V_1-receptor antagonist did not occur until about 1 h after its administration.

B. Renin-Angiotensin System

Plasma concentrations of several components of the RAS are altered following STZ treatment. Reductions in both plasma renin concentration and plasma renin substrate levels (Funakawa et al., 1983; Ballermann et al., 1984; Ubeda et al., 1988) underlie the decrease in plasma renin activity found in STZ-treated rats (Funakawa et al., 1983; Hayashi et al., 1984; Kigoshi et al., 1986; Kikkawa et al., 1986b; Ubeda et al., 1988). Plasma AII concentrations also may be diminished following STZ treatment (Kigoshi et al., 1986; Kikkawa et al., 1986b). It is apparent that these changes in activity of the RAS are dependent on the time after STZ treatment, because Kikkawa et al. (1986b) found that plasma renin activity and AII concentrations were increased 1 week after STZ treatment, whereas, in animals treated 2 weeks earlier, plasma renin activity was normal but circulating AII levels were elevated. Rats treated with STZ 4 to 8 weeks previously had reduced plasma levels of renin and AII. The time dependence of changes in activity of the RAS following STZ treatment has been attributed in part to changes in blood volume, because Kikkawa et al. (1986b) found that packed cell volume was increased 1 week after STZ treatment, whereas 8 weeks after STZ treatment packed cell volume was reduced. It was suggested that early reduction and later expansion of blood volume caused stimulation and inhibition of the RAS, respectively. Changes in blood volume cannot fully account for altered RAS activity, however, because Katayama and Lee (1985) found no change in plasma renin activity in rats treated 1 week earlier with STZ, despite the fact that plasma volume was reduced in their animals; insulin treatment restored the expected increase in plasma renin activity (Katayama and Lee, 1985). Thus, it appears that insulin lack has an effect on renin release, independently of its effects on plasma volume. It is possible that this impairment of renin release actually contributes to the reduction in blood volume of rats soon after STZ treatment.

Renal renin stores have been found to be unchanged (Funakawa et al., 1983) or diminished (Katayama and Lee, 1985) following STZ treatment. In both studies, basal renin release was attenuated in renal slices taken from STZ-treated rats. This was true whether release was expressed in absolute terms or relative to renal renin content. Impaired renin release in STZ-treated rats (in vivo or in vitro) may be due to diminished endogenous prostaglandin production because STZ-treated rats show reductions in renal papillary synthesis of prostaglandin E_2 and release of prostacyclin from renal medullary slices; both prostanoids usually stimulate renin release (Funakawa et al., 1983; Katayama and Lee, 1985). Because exogenous prostaglandin E_2, which stimulated renin release from control renal slices, had no effect on renin release from renal slices of STZ-treated rats (Katayama and Lee, 1985), it is possible that STZ-treated rats also have reduced responses to endogenous prostaglandins. The absolute increase in renin release following stimulation of renal slices with isoprenaline was also lower in preparations taken from STZ-treated rats than from control rats. However, because relative release was unaltered, this was likely to have been a consequence of diminished stores of renin rather than a specific impairment of β-adrenoceptor-mediated renin release (Katayama and Lee, 1985).

In contrast to the inhibitory effect of STZ treatment on plasma renin activity and AII concentration, plasma levels of ACE are elevated in STZ-treated rats (Valentovic et al., 1987; Hartmann et al., 1988). It has been suggested that increased levels of plasma ACE could result from release of the enzyme from damaged endothelial cells (Porta et al., 1987), although it is also possible that an increase in tissue RAS activity (see below) could cause increased spillover of ACE into the circulation (Campbell, 1987). Levels of ACE in lung tissue from STZ-treated rats tended to be higher than those in control tissue, but this difference was not significant (Valentovic et al., 1987). Increased plasma ACE activity may account for some findings of elevated levels of AII (Kikkawa et al., 1986b), and, hence, of aldosterone (Kikkawa et al., 1986b; Wilkes, 1987) accompanying normal plasma renin activity in STZ-treated rats [conversion of AI to AII in systemic plasma is normally relatively unimportant, because most conversion occurs in the lung circulation (Johnston, 1984); whether or not plasma conversion of AI to AII is relatively more important in STZ-treated than normal rats is unclear].

Hartmann et al. (1988) studied the effects of the ACE inhibitor, lisinopril, on the RAS of STZ-treated rats.

They found that significant inhibition of serum ACE activity required a higher daily dose of lisinopril (5 mg kg^{-1} day^{-1}) in STZ-treated rats than control rats (1 mg kg^{-1} day^{-1}), which was consistent with enhanced ACE activity in the former group. Paradoxically, circulating AII levels were maximally reduced at lower doses of lisinopril in the STZ-treated than the control group. It is possible that this was due to an attenuated increase in renin levels (due to a reduction in negative feedback from AII) following ACE inhibition in the STZ-treated animals (Hartmann et al., 1988).

In addition to changes in peripheral ACE, there is also some indirect evidence from cardiovascular studies that CNS ACE activity may be decreased in STZ-treated rats. Thus, the pressor response to ICV administration of AII, in the absence of drinking water, was found to be normal in STZ-treated rats, whereas the pressor response to ICV AI was attenuated, implying decreased central conversion of AI to AII following STZ treatment (Tomlinson et al., 1990b).

It is now well established that, in addition to the renal and brain RAS, there exist local tissue systems that may be involved in cardiovascular control. Ubeda et al. (1988) showed that tissue renin activity was increased in aortae and adrenals from STZ-treated rats, although plasma renin activity was reduced in these animals. These investigators also found elevated plasma levels of inactive renin in rats treated with STZ and, because both inactive renin and tissue renin activity were decreased following nephrectomy, they suggested that inactive renin secreted by the kidney was taken up locally from plasma and converted to active renin (Ubeda et al., 1988). However, because other workers have shown that extrarenal synthesis of inactive renin may be as important as renal synthesis (Campbell, 1987), it is possible that changes in circulating inactive renin levels following STZ treatment may be the result, rather than the cause, of increased local RAS activity.

Altered RAS activity could affect cardiovascular control in STZ-treated rats through changes in the direct pressor action of AII. It has been shown that STZ-treated rats have impaired AII-mediated BP recovery following ganglion blockade (Hebden et al., 1987a; Tomlinson et al., 1990a); this could be due to impaired release of, and/or reduced vascular reactivity to, AII (Jackson and Carrier, 1983; Hebden et al., 1987a,b; Ramos, 1988; Tomlinson et al., 1990a). The contribution of the RAS to the control of BP is considered in more detail in section IX.B.

In summary, although there is some interstudy variability, plasma renin and AII levels generally have been found to be reduced in STZ-treated rats, whereas plasma ACE activity may be increased. Given the involvement of the RAS in the control of blood volume and BP, via effects on vascular tone and renal sodium handling, the possible consequences of disorders of this system for cardiovascular homeostasis in STZ-treated rats are bound to be complex and at present are little understood.

Changes in RAS activity have also been observed in clinical diabetes mellitus. Plasma renin activity is reduced in diabetic patients with hypertension and neuropathy, possibly due to a number of factors, including plasma volume expansion, destruction of the juxtaglomerular cells, defective synthesis of renin, and impaired catecholamine-stimulated renin release (Christlieb, 1976). In uncontrolled ketotic diabetes mellitus, plasma renin activity may be increased due to hypovolaemia (Christlieb, 1976). Although renin levels may be normal in diabetic patients without hypertension, AII levels have occasionally been found to be reduced (Feldt-Rasmussen et al., 1987; Christiansen et al., 1988), and renin responses to stimulants such as frusemide (Bryer-Ash et al., 1988) may be impaired. As in STZ-treated rats, plasma levels of ACE may be elevated in human diabetic patients (Feldt-Rasmussen et al., 1987).

There is also some evidence for an association between local RASs and the development of microvascular complications, because plasma inactive renin levels (which may have been derived from local RASs) were high in diabetic patients with retinopathy or albuminuria (Luetscher et al., 1985). More specifically, Danser et al. (1989) found that levels of prorenin were higher in vitreous fluid from the eyes of patients with diabetic retinopathy than from the eyes of nondiabetic patients with a detached retina and suggested that, because prorenin levels could not be accounted for by uptake from the plasma, increased activity of a local RAS might be involved in the pathogenesis of diabetic retinopathy. Clearly, the involvement of local RASs in the development of diabetic complications is potentially important and should be studied further both in diabetic patients and in STZ-treated rats.

There is now increasing interest in the use of ACE inhibitors in the treatment of hypertension in clinical diabetes mellitus, because, although other conventional treatments reduce glucose tolerance, ACE inhibitors may have no effect on, or may even improve, glucose tolerance. If increased activity of the local RAS is shown to play a causative role in the development of microvascular disease during diabetes, ACE inhibitors could possess the further advantage of delaying the appearance of these complications. There is some evidence that ACE inhibitors, such as captopril, which contain sulphydryl groups, may act as scavengers for superoxide radicals (Westlin and Mullane, 1988; Bagchi et al., 1989) although this is still speculative (Kukreja et al., 1990; Mehta et al., 1990; McMurray and Chopra, 1991). Such an action may be particularly beneficial in diabetes mellitus if disorders of endothelial cell function (section VIII.C) give rise to imbalances between production of nitric oxide and of superoxide radicals such that the normal vasodilator, antiaggregatory, and antimitogenic effects of nitric oxide

(Stewart et al., 1988; McCall et al., 1989; Moncada and Higgs, 1990) are impaired.

C. Aldosterone

Plasma aldosterone levels have been found to be temporally related to AII levels following STZ treatment. Thus, plasma aldosterone was elevated in rats 1 and 2 weeks following STZ treatment but was reduced after 4 and 8 weeks (Kikkawa et al., 1986b). Reduced plasma aldosterone levels in rats several weeks after STZ treatment have also been found by other investigators (Hayashi, et al., 1984; Kigoshi et al 1986; Rebuffat et al., 1988a; Ubeda et al., 1988). In contrast, Wilkes (1987) reported increased plasma levels of aldosterone in rats treated 7 to 60 days previously with STZ; however, because data from rats with varying durations of diabetes mellitus were pooled, it is impossible to draw firm conclusions from this result. The direct correlation usually found between aldosterone and AII levels following STZ treatment makes it likely that the changes in aldosterone levels are due, at least in part, to altered AII-stimulated aldosterone release. However, Hayashi et al. (1984) showed that the increase in aldosterone levels in response to exogenous AII, ACTH, or potassium were all attenuated in STZ-treated rats. Similarly, zona glomerulosa cells isolated from STZ-treated rats showed a reduction in sensitivity to AII and in maximum AII-stimulated aldosterone release (Kigoshi et al., 1986), although basal aldosterone release and ACTH-stimulated release were normal. Because Kigoshi et al. (1986) expressed their results in terms of aldosterone production relative to cell number and found that both the number of cells and the width of the zona glomerulosa from STZ-treated rats were diminished, it is possible that the reduction in ACTH-stimulated and basal aldosterone release in vivo (Hayashi et al., 1984) was the result of atrophy of the adrenal zona glomerulosa following STZ treatment. Furthermore, chronic suppression of renin release can lead to down-regulation of adrenal AII receptors, reduced aldosterone biosynthesis, and atrophy of the zona glomerulosa (Kigoshi et al., 1986). It is, therefore, possible that impaired aldosterone secretion was due to chronically low levels of renin.

Rebuffat et al. (1988a) showed that adrenal dysfunction develops in STZ-treated rats, even if the hypothalamo-hypophyseal-adrenal axis and the RAS are pharmacologically interrupted by administration of dexamethasone, captopril, ACTH, and AII. Obviously, the results of this study should be interpreted with caution because administration of such a pharmacological cocktail could have complicated influences on adrenal physiology, but it is possible that STZ treatment has effects on adrenal function independently of changes in RAS activity, perhaps by a direct effect of insulin lack on adrenal tissue (see section II.D). Interestingly, Ubeda et al. (1988) reported increased renin activity in the zona glomerulosa from STZ-treated rats, although the significance of local renin activity for aldosterone production is not known.

In summary, aldosterone levels are reduced several weeks following STZ treatment, partly as a consequence of low circulating concentrations of AII but also because of impaired adrenal responsiveness to AII. The consequences of these abnormalities for BP control in STZ-treated rats have not been addressed, although this topic merits attention, because changes in aldosterone levels will have effects on renal sodium handling and hence on blood volume control.

Clinical diabetes mellitus may also be associated with hypoaldosteronism, with or without hyporeninaemia, particularly when other complications (e.g., hypertension and nephropathy) are present (Christlieb, 1976; De Chatel et al., 1977; Kigoshi et al., 1985). In addition, patients with diabetic ketoacidosis may have increased levels of aldosterone due to volume depletion (Christlieb, 1976). STZ-treated rats may, therefore, be very useful in determining the underlying causes of hypoaldosteronism in clinical diabetes mellitus.

D. Glucocorticoids

In contrast to diminished secretion of aldosterone, there may be enhanced production of other adrenal steroids in STZ-treated rats. De Nicola et al. (1977) found increased basal levels of plasma corticosterone in rats treated 4 weeks earlier with STZ. This change was accompanied by a decrease in pituitary ACTH stores, suggesting that ACTH release from the pituitary was enhanced in STZ-treated animals. Furthermore, rats treated with STZ developed adrenal hypertrophy, and adrenal corticosterone content was increased. Because Kigoshi et al. (1986) found a reduction in the size of the zona glomerulosa of STZ-treated rats (see section II.C), it is probable that the hypertrophy noted by De Nicola et al. (1977) was restricted to the remaining adrenal tissue. Indeed, Rebuffat et al. (1988b) found evidence for hypertrophy of the zona fasiculata in STZ-treated rats; whereas, in rats in which the hypothalamo-hypophyseal-adrenal axis and the RAS were pharmacologically interrupted, STZ treatment caused a reduction in zona fasiculata size that could be reversed by insulin treatment (Rebuffat et al., 1988b). It would, therefore, appear that the direct effect of insulin deficiency is to reduce zona fasiculata size, but, following STZ treatment, zona fasiculata growth may be stimulated by enhanced ACTH release (Rebuffat et al., 1988b).

In other studies, increases or no change in plasma corticosterone levels have been found following STZ treatment (Odedra et al., 1982; Hayashi et al., 1984; Kigoshi et al., 1986; Rebuffat et al., 1988b; Ratner et al., 1991). An explanation for this discrepancy may be provided by the work of Tornello et al. (1981) and Oster et al. (1988), who showed that the circadian rhythm of

STZ-treated rats was shifted such that plasma corticosterone levels peaked during the light period instead of soon after dark (as it does in control rats). Thus, plasma corticosterone levels measured during the day were significantly higher in STZ-treated than control rats, but this difference was not apparent at other times. The studies of De Nicola et al. (1977) and those of Rebuffat et al. (1988b) were carried out in the middle of the light period and that of Ratner et al. (1991) was carried out 2 to 4 h after lights were turned on; no information, however, was given as to the timing of the other three studies cited above. In addition, the level of adrenocortical activity is highly dependent on stress, and this variable has not been controlled for fully during investigations to date.

De Nicola et al. (1977) found that the proportional increase in plasma corticosterone levels in response to stress was similar in STZ-treated and in control rats, but the absolute increase and final levels were greater in the former group. Ratner et al. (1991) observed that STZ-treated rats had elevated basal corticosterone levels and higher levels after stress than did control rats. However, Ratner et al. (1991) suggested that the corticosterone response to stress was reduced in STZ-treated rats because the percentage increase was less than in control rats. Results such as these are obviously difficult to interpret because it is not known whether the absolute or percentage increase is the relevant variable under all conditions. Furthermore, it does not follow that the plasma level of a hormone, such as corticosterone, is a reliable index of its physiological action in all circumstances.

In summary, although there is some evidence for enhanced adrenal function and glucocorticoid output in STZ-treated rats, these data must be interpreted with caution because studies usually have not taken account of the effect of experimental diabetes mellitus on circadian rhythms, or of responses to stress, and their possible influence on plasma steroid levels. Experiments that consider the basal levels of steroids at various times of the day and the relative responses of STZ-treated and control rats to stress more thoroughly are, therefore, needed. The consequences of changes in glucocorticoid levels for cardiovascular control in STZ-treated rats have not been studied experimentally, and although there is evidence that cortisol makes an important contribution to glucose counterregulation in normal subjects (De Feo et al., 1989), its involvement in the pathophysiology of clinical diabetes mellitus remains to be analysed in detail (McMahon et al., 1988).

E. Atrial Natriuretic Peptide

Circulating ANP levels have been found to be increased following STZ treatment (Ortola et al., 1987; Black and Lee, 1989; Hebden et al., 1989; Benigni et al., 1990; Matsubara et al., 1990; Todd et al., 1990), although in another study no change in plasma ANP levels was found (Jackson et al., 1988). It is probable that the increase in ANP levels in STZ-treated rats is due to increased release from the myocardium because there was a reduction in the number of atrial granules in cardiac tissue taken from rats after STZ treatment (Hebden et al., 1989; Todd et al., 1990), and ventricular ANP mRNA levels were increased in STZ-treated rats (Matsubara et al., 1990). Atrial ANP levels were noted to be decreased (Black and Lee, 1989) or unaltered (Matsubara et al., 1990) following STZ treatment, although ventricular ANP levels were found to be increased in the latter study (Matsubara et al., 1990).

The mechanisms underlying increased ANP release are unclear. Matsubara et al. (1990) showed that increased ventricular and plasma ANP levels in STZ-treated rats were associated with elevated ventricular end-diastolic pressure along with expanded blood volume but no change in cardiac contractility. Therefore, Matsubara et al. (1990) suggested that the increased ANP levels were due to increased cardiac filling pressure. However, the observation by Hebden et al. (1989) that right atrial pressure was unaltered in STZ-treated rats in which ANP levels were increased apparently goes against the suggestion that enhanced ANP release occurred as a direct result of volume expansion in their rats. Measurements of atrial distensibility and transmural pressure should be made to rule out the possibility of increased atrial stretch occurring independently of measurable increases in right atrial pressure, particularly because atria from STZ-treated rats have been shown to develop cardiomyopathy (decreased muscular ridges and increased volume of interstitial and connective tissue) (Todd et al., 1990). Indeed, Matsubara et al. (1990) found that, in STZ-treated spontaneously hypertensive rats, ventricular and plasma ANP levels were increased, again in conjunction with elevated ventricular end-diastolic pressure. However, in these rats blood volume was unaltered and ventricular contractility was reduced, implying that the increased ventricular end-diastolic pressure was due to change within the ventricle itself.

Elevated circulating levels of ANP may contribute to the changes in renal function following STZ treatment, because Ortola et al. (1987) reported that administration of an ANP antiserum to STZ-treated rats caused a reduction in GFR, renal plasma flow, and sodium excretion (see section III). However, STZ-treated rats have also been found to show impaired ANP release in response to volume expansion (Hebden et al., 1989), which could have been due to depletion of tissue stores. Renal responsiveness to ANP is also altered following STZ treatment, in association with decreased numbers of renal cortical ANP receptors and impaired GFR and renal plasma flow responses to ANP infusion (Benigni et al., 1990). Furthermore, Patel and Zhang (1990) showed that STZ treatment caused a blunting of the

diuretic and natriuretic responses to ANP in anaesthetised rats. Thus, reduced ANP release and responsiveness to ANP could contribute to impaired renal responses to volume expansion following STZ treatment (Patel and Zhang, 1989).

In summary, STZ treatment results in changes in ANP levels in the heart and plasma and in the actions of ANP which are potentially very important with regard to the interrelations between haemodynamics and volume control.

Plasma ANP levels have also been found to be increased in some human diabetic patients (Trevisan et al., 1990), particularly those with autonomic neuropathy (Kahn et al., 1986; Zoccali et al., 1989) or with poor glycaemic control (Bell et al., 1989). Changes in plasma ANP levels with exercise or postural change have been found to be normal in patients with diabetes mellitus (with or without cardiac autonomic neuropathy) (Donckier et al., 1989). However, in contrast to results in STZ-treated rats showing impaired ANP responses to volume loading (Hebden et al., 1989), De Chatel et al. (1986) found that the increase in plasma ANP levels following a sodium load was enhanced in diabetic patients despite normal resting ANP levels. Similar observations were made by Zoccali et al. (1989) who found that uraemic diabetic patients with autonomic neuropathy had increased plasma ANP levels before dialysis, but when blood volume was reduced by dialysis, ANP levels returned to normal. In contrast, Trevisan et al. (1990) found that the ANP response to volume expansion during euglycaemia was blunted in diabetic patients. However, they suggested that this was due to high plasma levels of insulin in the diabetic patients because elevation of plasma insulin in control subjects also caused blunting of the ANP response to volume expansion. In the study of De Chatel et al. (1986), it was also found that the natriuretic response to volume expansion was impaired in diabetic patients, and it was suggested that this could have been due to a reduction in renal responsiveness to ANP comparable to that seen in STZ-treated rats (Benigni et al., 1990).

The control of ANP release in diabetes mellitus is, therefore, still little understood and, considering the influence of ANP on factors involved in the control of BP more studies should be carried out in both STZ-treated rats and diabetic patients to improve our understanding of this important topic.

F. Thyroid Function

STZ-treated rats are hypothyroid inasmuch as they have reduced hypothalamic and circulating thyroid-releasing hormone levels (Gonzalez et al., 1980; Wilber et al., 1981), decreased plasma and pituitary levels of TSH (Gonzalez et al., 1980; Wilber et al., 1981; Jennings, 1984; Ortiz-Caro et al., 1984; Bestetti et al., 1987), an impaired TSH secretory response to thyroid-releasing hormone (Bestetti et al., 1987), enhanced feedback inhibition of TSH release by T_4 (Gonzalez et al., 1980), reductions in circulating T_4 and T_3 (Berkowitz et al., 1980; Wilber et al., 1981 Dillmann, 1982; Ganguly et al., 1983; Jennings, 1984; Ortiz-Caro et al., 1984; Sundaresan et al., 1984; Ferguson et al., 1985; Ganguly et al., 1986; Bestetti et al., 1987; Takiguchi et al., 1988; Sato et al., 1989), and decreased conversion of T_4 to T_3 in the liver (Jennings, 1984) and kidney (Ferguson et al., 1985). Furthermore, histological changes, consistent with hypersecretion, have been observed in the thyrotrophs of the pituitary and in the thyroid gland of STZ-treated rats (Bestetti et al., 1987). Because rats subjected to food restriction also become hypothyroid, it is possible that altered function of the hypothalamo-pituitary-thyroid axis in STZ-treated rats is due to relative caloric deprivation. However, STZ-treated rats had greater reductions in circulating TSH, T_4, and T_3 than did weight-matched, food-restricted rats (Ortiz-Caro et al., 1984). Moreover, food-restricted rats did not show enhanced T_4 inhibition of TSH release (Gonzalez et al., 1980) or attenuated tissue conversion of T_4 to T_3 (Jennings, 1984; Ferguson et al., 1985). Caloric deprivation is, therefore, only likely to contribute partly to hypothyroidism following STZ treatment.

Hypothyroidism is known to have effects on the cardiovascular system (McDonough et al., 1987), some of which are similar to those found in STZ-treated rats. As discussed below (in section VII), hypothyroidism may contribute to the reduction of cardiac β-adrenoceptor numbers in STZ-treated rats (Sundaresan et al., 1984). In addition, T_3 treatment has been shown to reverse the lengthening of the cardiac action potential following STZ treatment (Legaye et al., 1988). Because hypothyroid rats are bradycardic (McDonough et al., 1987) and the reduction of HR in rats made diabetic with alloxan can be prevented by replacement doses of T_3 (Garber et al., 1983), it is feasible that hypothyroidism contributes, via the mechanisms mentioned above, to STZ-induced bradycardia (see section IX.A).

Hypothyroidism may also be responsible, in part, for changes in contractile function of the heart following STZ treatment (see section VII.B). Dillmann (1982) showed that pharmacological doses of T_3 normalised myosin-ATPase activity in hearts from STZ-treated rats. Thyroid hormone treatment, however, did not prevent defects of sarcoplasmic reticulum calcium transport following STZ treatment (Ganguly et al., 1983). These findings are pertinent to those of Tahiliani and McNeill (1986a) who showed that T_3 treatment only normalised cardiac function of STZ-treated rats if given in conjunction with carnitine (which is believed to improve sarcoplasmic reticulum calcium uptake). Goyal et al. (1987) found that T_3 treatment prevented the development of bradycardia, and the enhanced atrial responses to methoxamine, seen following STZ treatment, but did not alter

the impaired atrial responses to isoprenaline under those conditions. Takiguchi et al. (1989) reported that T_4 treatment reversed the impairment of vasodilator responses to isoprenaline seen in rats treated 8 weeks earlier with STZ but had no effect on impaired responses to noradrenaline, 5-HT, acetylcholine, or isoprenaline 12 weeks after STZ treatment. Hypothyroidism may, therefore, play a role in the early changes in the vasculature following STZ treatment (see section VIII).

In summary, there is now a good deal of evidence that hypothyroidism plays a significant role in disorders of cardiovascular control resulting from STZ treatment. However, the extent to which hypothyroidism is involved is still incompletely defined. Additional, more thorough, studies should be carried out to compare haemodynamics and cardiovascular regulation in STZ-treated rats, hypothyroid rats, and STZ-treated rats following thyroid replacement.

Some studies of patients with diabetes mellitus have shown reduced conversion of T_4 to T_3 (Pittman et al., 1979) and an increased incidence of subclinical thyroid failure (Gray et al., 1980). It is, therefore, important to be aware of the role that might be played by hypothyroidism in the aetiology of cardiovascular disorders associated with diabetes mellitus.

G. Glucagon

Circulating glucagon levels are inappropriately increased following STZ treatment (Williams et al., 1988; Brubaker et al., 1989; Gross et al., 1991). Furthermore, because the administration of a glucagon receptor antagonist lowers blood glucose by 50% in STZ-treated rats, it is possible that circulating glucagon exacerbates hyperglycaemia caused by insulin deficiency in these animals (Johnson et al., 1982). Because pancreatic glucagon stores were found to be unaltered (Brubaker et al., 1989; Gross et al., 1991) and basal glucagon release and glucagon release in response to stimuli such as adenosine, isoprenaline, forskolin, and noradrenaline were reduced (Gross et al., 1991) following STZ treatment, it is feasible that the circulating glucagon derives from extrapancreatic sources (Boros and Keszler, 1989; Brubaker et al., 1989).

Glucagon has many cardiovascular effects. For example, intravenous infusion of glucagon (2 mg kg^{-1} min^{-1}) in rats increased cardiac output and HR and decreased total peripheral resistance (Nichols and Hiley, 1987). Intrasplenic infusion of glucagon (which was believed to mimic more closely the physiological site of delivery of the hormone) only caused changes in cardiac output and total peripheral resistance at higher doses (10 mg kg^{-1} min^{-1}). At the lower dose (2 mg kg^{-1} min^{-1}), the main effect of intrasplenic glucagon was to cause a shift in cardiac output distribution toward the stomach and small intestine, which might indicate vasodilation in these areas and/or vasoconstriction elsewhere.

Intestinal blood flow was found to be increased by 37% in STZ-treated rats (Korthuis et al., 1987) (see section IX.B). This intestinal hyperaemia was apparently related, in part, to humoral factors, because cross-perfusion of control intestinal preparations with blood from diabetic rats caused increases in blood flow and a reduction in vascular resistance (Korthuis et al., 1987). Because glucagon infusion caused a 20% reduction in intestinal vascular resistance (Korthuis et al., 1987) and the administration of glucagon antiserum to STZ-treated rats caused a reduction in blood flow to the stomach, duodenum, and jejunum, but not the ileum and colon (Yrle et al., 1988), it was suggested that high levels of glucagon were responsible for part of the intestinal hyperaemia associated with STZ treatment. Notably, glucagon antiserum also led to a reduction in renal blood flow in diabetic, but not in control, animals (Yrle et al., 1988). Glucagon may, therefore, be involved in enhancing renal as well as intestinal blood flow in STZ-treated rats.

In summary, circulating glucagon levels are elevated following STZ treatment, whereas glucagon release in response to pharmacological stimuli may be attenuated. The usual finding in clinical diabetes mellitus is of reduced glucagon responses to hypoglycaemia (Cryer and Gerich, 1985; Amiel et al., 1988; Gerich, 1988; Gerich and Campbell, 1988). However, glucagon release in response to other stimuli may be enhanced (Amiel et al., 1988). There have been no studies of the possible contribution of glucagon to abnormal cardiovascular regulation in clinical diabetes mellitus.

III. Kidney

STZ has nephrotoxic potential in humans and this raises the possibility that changes in renal function following STZ treatment in rats may be due to a direct effect of the drug rather than to insulin deficiency. However, Evan et al. (1984) "protected" one kidney from direct exposure to STZ by unilaterally occluding the renal hilum before, and for 5 min after, intravenous injection of STZ in rats. The results of this study showed that there were no histological changes in the "unprotected" kidney that were not also present in the protected kidney. Moreover, renal function, as measured by creatinine clearance, urine volume, and urinary protein excretion was similar in STZ-treated rats with one protected kidney and in STZ-treated rats in which this procedure had not been applied (Evan et al., 1984). These authors, therefore, concluded that "investigators need not consider confounding effects of streptozotocin upon the kidney, when using the drug in order to study the effects of diabetes on renal function and structure." Rats treated with STZ do, however, develop changes in renal function, including altered renal haemodynamics and fluid and electrolyte handling, which can be attributed to the development of diabetes mellitus and may be relevant when considering cardiovascular control in these animals.

A. Glomerular Hyperfiltration

Whether anaesthetised or conscious, rats with STZ-induced diabetes mellitus have generally been found to have increased GFR (Carney et al., 1979; Jensen et al., 1981; Wald and Popovtzer, 1984; Khadouri et al., 1987; Bank et al., 1988; Jackson et al., 1988). However, in some studies, rats treated with STZ alone had normal or reduced GFR, whereas GFR was increased in STZ-treated rats given moderate doses of insulin (Hostetter et al., 1981; Craven and De Rubertis, 1989a; Allen et al., 1990; Harvey et al., 1990).

Enhanced total GFR has been found to be associated with elevated single-nephron GFR, renal plasma flow, and glomerular plasma flow rate but nonsignificant increases in ultrafiltration coefficient (Hostetter et al., 1981; Jensen et al., 1981; Bank et al., 1988). The mechanisms behind the increased GFR are unclear. Glucose does cause vasodilation and increases inulin clearance in isolated rat kidneys (Kasiske et al., 1985). Thus, it is possible that hyperglycaemia per se contributes to changes in renal haemodynamics following STZ treatment. Work with anaesthetised dogs has provided evidence that hyperglycaemia may increase renal blood flow and GFR by changing the sensitivity of the tubuloglomerular feedback mechanism (Woods et al., 1987). In addition, tubuloglomerular feedback mechanisms are altered in STZ-treated rats, because renal vascular resistance, measured in the isolated perfused kidney, did not increase at very low perfusion pressures (as it did in control rats) (Mauer et al., 1990), and consequently renal blood flow was maintained at a higher level in STZ-treated than control rats. The alteration in tubuloglomerular feedback may result from ultrastructural changes in the macula densa following STZ treatment (Rasch and Holck, 1988).

STZ-treated rats have been shown to develop renal hypertrophy; both renal weight and protein content have been found to be greater than in control rats 7 days after treatment with STZ (Ku et al., 1986). Because there was a loss of body weight soon after STZ treatment, renal mass per unit body weight was enhanced as early as 4 days after STZ administration (Ku et al., 1986). Seyer-Hansen et al. (1980) carried out morphometric analysis on kidneys from STZ-treated rats and showed that during the first 4 days after STZ treatment renal growth was due to an increase in glomerular size with no change in tubular length or diameter but, subsequently, all three variables were increased. The precise mechanisms behind this renal hypertrophy are unclear. Increased kidney size may occur as an adaptive change in response to enhanced fluid and electrolyte losses due to osmotic diuresis following STZ treatment or as a direct result of hyperglycaemia. The latter effect may be enhanced by AII (Wolf et al., 1991). Interestingly, kidney size in rats subjected to subtotal pancreatectomy, 1 week prior to STZ treatment, was lower than that in rats treated with STZ alone, suggesting a role for glucagon in the development of renal hypertrophy following STZ treatment (Logan and Lee, 1988). It has been proposed that an increased renal action of insulin-like growth factor I (due to increased renal receptors and binding within the kidney) could stimulate renal hypertrophy in diabetic rats (Werner et al., 1990).

Bank et al. (1988) found that GFR was elevated in STZ-treated rats when expressed in absolute terms or when expressed per unit body weight. However, because GFR was unaltered if expressed relative to renal mass, it is possible that an increase in renal mass was responsible for the enhancement of GFR in these animals. Jensen et al. (1981), using micropuncture techniques, showed that renal arteriolar (afferent and efferent) resistance and proximal tubular resistance were both decreased in STZ-treated rats in association with glomerular hyperfiltration. They suggested that this was due to enlargement of the vessels and tubules as a result of renal hypertrophy. Furthermore, there was an increase in glomerular filtration coefficient following STZ treatment which may have been due to enlargement of the glomerulus (Jensen et al., 1981). Renal hypertrophy cannot completely account for the increase in GFR following STZ treatment, however, because GFR was found to be enhanced in one study when renal hypertrophy was absent (Carney et al., 1979).

Circulating or local factors may also mediate glomerular hyperfiltration in STZ-treated rats via renal vasodilation or mesangial cell relaxation (which leads to an increase in glomerular filtration coefficient). Glomerular prostaglandins have been linked to glomerular hyperfiltration because production of vasodilator prostanoids (prostaglandin E_2, prostaglandin F_2, prostacyclin) from isolated glomeruli was elevated, 9 to 23 days (Schambelan et al., 1985) or 9 to 15 days (Craven et al., 1987), after the induction of diabetes mellitus, and indomethacin treatment reversed the enhancement of GFR in rats treated 9 to 15 days earlier with STZ (Craven et al., 1987). It was suggested that elevated levels of prostaglandins led to renal vasodilation and attenuated the contractile response of mesangial cells to AII, thereby producing glomerular hyperfiltration (Craven et al., 1987; Schambelan et al., 1985). Craven et al. (1987), however, found no increase in prostanoid production by glomeruli isolated from rats treated 25 to 28 days earlier with STZ, and there was no effect of indomethacin on GFR at this time. Thus, the dependence of glomerular hyperfiltration on renal prostanoid production may be a feature of acute, STZ-induced diabetes mellitus only. However, Bank et al. (1988) were unable to detect any effect of indomethacin treatment on GFR in rats in which STZ was injected 7 to 10 days earlier.

One difference between the protocols of Bank et al. (1988) and Craven et al. (1987) was that in the former case a single dose of indomethacin was administered and

in the latter case three doses were given during a 24-h period. It may, therefore, be necessary to inhibit prostanoid production for several hours before any effect on glomerular hyperfiltration is observed. In a later study, Craven and De Rubertis (1989a) replicated earlier findings of glomerular hyperfiltration in moderately diabetic rats (i.e., those given STZ and low doses of insulin), associated with increased glomerular production of vasodilator prostanoids. In addition, they observed that STZ-treated rats that were not insulin treated, and which showed a reduction in GFR, had no change in glomerular vasodilator prostanoid production, but biosynthesis of the vasoconstrictor, thromboxane A_2, was increased and glomerular hyperfiltration was reduced by inhibition of thromboxane synthesis. Thus, changes in glomerular eicosanoid production may contribute to the decreased GFR of severe diabetes mellitus as well as to the glomerular hyperfiltration of moderate diabetes mellitus. The effects of STZ treatment on renal prostanoid synthesis are obviously complicated because, as stated before (see section II.B), prostaglandin release from renal papillary and medullary slices from STZ-treated rats is decreased.

Renal kinin activity may also be involved in the changes in renal haemodynamics because, in severely diabetic rats with reductions in GFR and renal plasma flow, tissue kallikrein levels were reduced, whereas in moderately diabetic rats with increased renal plasma flow and GFR, increased levels of kallikrein were found (Harvey et al., 1990). Furthermore, administration of a kallikrein inhibitor to the latter group reduced both renal plasma flow and GFR (Harvey et al., 1990).

Diminished plasma levels of AII have been found in STZ-treated rats (see section II.B). In addition, the normal decline in renal plasma flow and increase in renal vascular resistance in response to AII infusion was blunted in STZ-treated rats (Reineck and Kreisberg, 1983). The contractile response of isolated glomeruli to AII was also diminished following STZ treatment (Kikkawa et al., 1986a). Thus, renal tissue from diabetic rats appeared to exhibit decreased responsiveness to AII. This may have been due, in part, to the decline in AII receptor numbers that has been observed in glomeruli isolated from STZ-treated rats (Ballermann et al., 1984; Wilkes, 1987). However, because Kikkawa et al. (1986a) found an increase in AII receptor density together with diminished contractile responsiveness in glomeruli isolated from STZ-treated rats, some other factors must be involved. As stated before, it has been suggested that increased production of prostanoids may inhibit the renal actions of AII in STZ-treated rats. Furthermore, insulin may play a permissive role in AII-mediated contraction of mesangial cells (Kreisberg, 1982). It is possible, therefore, that reductions in both circulating AII levels and in renal responsiveness to AII contribute to glomerular hyperfiltration in diabetes mellitus. Goldfarb et al. (1991) tested this hypothesis by measuring GFR in the presence and absence of an ACE inhibitor (captopril) at a dose designed to inhibit renal ACE activity without reducing BP. They found that, whereas ACE inhibition caused an increase in GFR in control rats, it produced a small, yet significant, decrease in STZ-treated rats (Goldfarb et al., 1991).

ANP has also been implicated in the development of glomerular hyperfiltration, because plasma levels of this peptide were elevated in STZ-treated rats (Ortola et al., 1987; Black and Lee, 1989; Hebden et al., 1989; Benigni et al., 1990; Matsubara et al., 1990; Todd et al., 1990) (see section II.E), and administration of an ANP antiserum caused GFR to decrease to within normal levels (Ortola et al., 1987). In addition, urinary cyclic guanosine monophosphate levels were increased in STZ-treated rats, implying increased renal stimulation by ANP (Allen et al., 1990). However, it has been found also that impaired release of, and renal responses to, ANP may contribute to a blunted renal response to volume expansion in STZ-treated rats (Hebden et al., 1989; Patel and Zhang, 1989, 1990; Benigni, et al., 1990).

Finally, there is some evidence for involvement of the polyol pathway and phosphoinositide metabolism in the development of glomerular hyperfiltration. Renal aldose reductase activity (Ghahary et al., 1989) and sorbitol levels (Chang et al., 1991) were increased following STZ treatment, whereas glomerular inositol levels and phosphoinositide turnover were reduced (Craven and De Rubertis, 1989b). In addition, galactose feeding (which stimulates flux through the polyol pathway) caused changes in renal haemodynamics similar to those seen in STZ-treated rats (increased GFR and renal plasma flow and reduced afferent arteriolar resistance) (Bank et al., 1989a). In some studies, inhibition of aldose reductase was found to reduce GFR in STZ-treated rats (Goldfarb et al., 1986, 1991; Bank et al., 1989b), although in others no such effect was observed (Daniels and Hostetter, 1989; Chang et al., 1991). In the study of Chang et al. (1991), increases in urinary albumin excretion and glomerular prostaglandin production following STZ treatment were partially prevented by aldose reductase inhibition, despite there being no effect on GFR. Daniels and Hostetter (1989), however, could find no improvement in albuminuria with aldose reductase inhibition in STZ-treated rats. Similarly, equivocal results have been obtained for the effects of STZ-induced diabetes on glomerular structure, because aldose reductase inhibition was found to prevent mesangial cell expansion following STZ treatment (Mauer et al., 1989) but did not prevent the development of glomerular sclerosis 7 months after treatment with STZ (Daniels and Hostetter, 1989).

Goldfarb et al. (1986, 1991) reported that both myoinositol supplementation and aldose reductase inhibition lowered GFR in STZ-treated rats, indicating that glomerular polyol accumulation might exert effects on glomerular haemodynamics via changes in myoinositol me-

tabolism. Similar results were found by Pugliese et al. (1990) who showed that myoinositol treatment reduced, but did not normalise, GFR in STZ-treated rats; the remaining elevation in GFR could be accounted for by renal hypertrophy. However, renal vascular permeability and urinary protein excretion remained high even when renal hypertrophy was taken into account. Other studies failed to show an effect of myoinositol supplementation on GFR in STZ-treated rats (Cohen et al., 1990).

Thus, the role of the polyol pathway and myoinositol metabolism in the development of renal complications in STZ-treated rats remains undetermined. Furthermore, the long-term consequences of inhibiting aldose reductase may be harmful because intracellular sorbitol, along with other organic osmolytes, is important in counteracting the deleterious effects of high concentrations of extracellular solutes in renal tissue. Any reduction in the effectiveness of this mechanism may, therefore, decrease cell viability and, hence, renal function in the long-term (Burg and Kador, 1988; Garcia-Perez and Burg, 1990, 1991).

B. Fluid and Electrolyte Handling

In addition to the derangement in renal haemodynamics, STZ-induced diabetes mellitus is associated with additional changes in renal handling of fluid and electrolytes. There are dramatic increases in the turnover of water, sodium, and potassium soon after STZ treatment (Hebden et al., 1986; Tomlinson et al., 1989c), partly as a result of increased electrolyte intake due to hyperphagia and also because hyperglycaemia leads to osmotic diuresis and, hence, increased fluid and electrolyte losses.

Insulin itself is known to stimulate renal sodium reabsorption (Rostand et al., 1980; De Fronzo, 1981) and potassium excretion (Rossetti et al., 1987). Thus, insulin lack following STZ treatment may potentiate sodium loss due to osmotic diuresis. Other hormonal changes following STZ treatment may also influence renal electrolyte handling. High plasma levels of ANP may contribute to sodium loss following STZ treatment, because administration of an ANP antiserum to STZ-treated rats caused urinary sodium excretion to decline due to a reduction in GFR and fractional excretion of sodium (Ortola et al., 1987). AVP is known to cause natriuresis (Balment et al., 1984); therefore, it is also feasible that high levels of AVP (Van Itallie and Fernstrom, 1982) contribute to sodium loss in STZ-treated rats. Elevated levels of AII and aldosterone could oppose sodium loss soon after the induction of diabetes mellitus at the expense of increasing potassium loss (Kikkawa et al., 1986b), whereas lower levels of these hormones several weeks after STZ treatment may allow the maintenance of potassium balance (Kikkawa et al., 1986b).

Against the background of osmotic diuresis and hormonal alterations, there are adaptive changes within the kidney itself following STZ treatment. Renal sodium-potassium-ATPase activity was enhanced in the renal cortex and medulla within 1 week after STZ treatment (Wald and Popovtzer, 1984; Ku et al., 1986; Cohen et al., 1990); this change has been localised to the proximal convoluted tubule, the medullary thick ascending limb of the loop of Henle, and the collecting tubule (Khadouri et al., 1987) and could be prevented by treatment with myoinositol or aldose reductase inhibitors (Cohen et al., 1990). Proximal tubular sodium-hydrogen exchange has also been found to be enhanced following STZ treatment (El-Seifi et al., 1987). Renal tubular sodium reabsorption was increased within 4 days of STZ treatment, partly as a consequence of glomerular hyperfiltration (and, hence, increased filtered load of sodium) and enhanced glucose-coupled sodium uptake (Wald and Popovtzer, 1984). It is likely, therefore, that stimulation of electrolyte transport systems occurs in the renal tubules of STZ-treated rats as an adaptive change to facilitate an increase in reabsorption and thereby prevent excessive renal losses of electrolytes.

In one study of renal function in anaesthetised animals, it was found that STZ-treated rats showed impaired diuretic and natriuretic responses to volume expansion (Patel and Zhang, 1989). Patel and Zhang (1989) suggested that this was due, in part, to attenuated humoral responses to volume expansion, but a comparison of responses in animals with intact and denervated kidneys showed evidence for a reduction in natriuresis caused by inhibition of renal nerve activity during volume expansion in STZ-treated rats. Interestingly, the defect in the denervated kidney was normalised following acute insulin therapy, whereas that in the intact kidney required chronic insulin treatment for reversal (Patel and Zhang, 1989). It is, therefore, likely that hormonally mediated abnormalities in renal function are the result of short-term insulin deficiency, whereas neural changes might contribute to deranged renal function after longer periods. In additional studies, Zhang and Patel (1991) characterised the renal response to administration of ICV clonidine (an α_2-adrenoceptor), which causes diuresis (believed to be due to AVP release) and natriuresis (believed to be due to sympathoinhibition). They found that both effects were blunted in the STZ-treated rats and that the bradycardia, observed in the control group, was absent in the STZ-treated animals. The authors suggested that STZ-treated rats had impaired AVP release and sympathoinihbition in response to clonidine, although reduced renal responsiveness could not be ruled out (Zhang and Patel, 1991). Thus, it is possible that defects in the CNS control of renal function contribute to the impaired renal responses to volume loading discussed before.

C. Summary

STZ treatment results in changes in renal haemodynamics and electrolyte handling, both of which could

result in changes in cardiovascular control. There is evidence that STZ treatment is associated with renal arteriolar vasodilation that could be due to any combination of hyperglycaemia, altered tubuloglomerular feedback, renal hypertrophy, changes in renal prostanoids or kinins, altered plasma levels of ANP or AII, and altered neural control. Abnormal renal handling of fluid and electrolytes may have consequences for cardiovascular control due to effects on blood volume. We have previously found that Long Evans rats showed evidence of blood volume expansion (reduced haematocrit and hyponatraemia) following STZ treatment but AVP-deficient, Brattleboro rats did not, possibly because of lack of the renal concentrating effect of AVP in the latter group (Tomlinson et al., 1989c). Brattleboro rats also exhibited a greater degree of hypotension following STZ treatment than did Long Evans rats (Tomlinson et al., 1989c, 1990a). Furthermore, Brooks et al., (1989) noted that, although STZ-treated rats were normotensive and had a slight decrease in haematocrit, spontaneously diabetic rats showed a reduction in BP and an increase in haematocrit. Both these results imply that changes in blood volume affect BP following STZ treatment. It is also likely that changes in body fluid and electrolyte balance contribute to the development of hypertension in clinical diabetes mellitus. Indeed, a correlation has been observed between exchangeable body sodium and BP during the very early stages of renal disease in patients with diabetes mellitus (Feldt-Rasmussen et al., 1987).

Nephropathy is frequently observed as a long-term complication of diabetes mellitus. Studies of both STZ-treated rats and patients with diabetes mellitus have provided evidence that early changes in renal haemodynamics may lead to long-term glomerulopathy (O'Donnell et al., 1988; Brown et al., 1982). It is believed that the increase in intraglomerular pressure associated with early diabetes mellitus leads to structural changes in the glomerulus. Experiments with STZ-treated rats have shown that treatments that decrease intraglomerular pressure, such as a low protein diet (Zatz et al., 1985) or ACE inhibitors (Dunn et al., 1986), delay or prevent glomerular damage. Furthermore, hypertension accelerates the development of glomerular damage following STZ treatment (Cooper et al., 1988). Similarly, antihypertensive therapy or ACE inhibition improved renal function (measured by albumin excretion rate) in human patients with diabetes mellitus (Marre et al., 1987; Parving et al., 1987). Aldose reductase inhibition has also been found to reduce GFR in diabetic patients in whom renal damage (assessed by albumninuria) had not yet developed (Pedersen et al., 1991). It is, therefore, likely that the STZ-treated rat will be a useful model for studying the detailed effects of treatments with drugs such as ACE inhibitors, or aldose reductase inhibitors, on renal haemodynamics. However, because glomerular damage in the STZ-treated rat does not exactly mimic that in human patients with diabetes mellitus (O'Donnell et al., 1988), attention should also be paid to those areas of difference and their underlying causes. Because moderate insulin treatment caused an increase in GFR in STZ-treated rats (Jackson et al., 1988; Allen et al., 1990), the effects of various insulin regimens on the development of diabetic glomerulopathy may also be an interesting area of study.

IV. Liver

STZ treatment results in changes in various hepatic enzyme systems that may need to be considered in studies involving quantitation of drug effects in STZ-treated rats. Indeed, Skett and Joels (1985) have reported that degradation of the drugs diazepam, lignocaine, and imipramine was significantly reduced in hepatic tissue taken from rats treated with STZ. The mechanism responsible for the change in hepatic drug metabolism following STZ treatment is not understood. However, MacFarlane and Skett (1986) reported that there was no correlation between either serum glucose or serum triglyceride levels and the reduction in the hepatic metabolism of diazepam following STZ treatment in male rats. The picture was complicated by the observation that abnormalities were present in male, but not in female, rats (Skett and Joels, 1985), a finding consistent with other observations of differential effects of STZ treatment on hepatic enzyme activity in male and female rats (Warren et al., 1983; Zysset and Sommer, 1986). Such observations might be explained by differences in androgenic stimulation of hepatic enzymes because there was no gender difference in the effect of STZ treatment on the hepatic enzyme, aniline hydroxylase, the activity of which is known to be sex independent (Warren et al., 1983).

Many fundamental alterations in hepatic function related to changes in metabolism also occur following STZ treatment. Notably, a reduction in the activity of glycosyltransferases, which are involved in membrane glycoprotein synthesis, has been demonstrated in microsomal fractions prepared from livers of STZ-treated rats (Tepperman et al., 1983). Because a similar phenomenon has been found in the livers of normal rats maintained with a carbohydrate-free diet (Tepperman et al., 1981), it is possible that a decreased metabolic availability of glucose in the diabetic state results in an adaptive decrease in the activity of glycosyltransferases. However, nonenzymatic glycosylation of proteins is increased during diabetes, due to hyperglycaemia, and may contribute to many long-term complications (Zimmerman, 1989).

It has been suggested that an increase in oxidative stress could contribute to tissue damage in diabetes. McLennan et al. (1991) showed that hepatic glutathione levels were normal in well-fed STZ-treated rats but were reduced following food restriction compared with control

rats. Thus, STZ-treated rats may be more susceptible to the development of oxidative stress following starvation.

Hepatic changes relating to altered hormonal systems are also seen following STZ treatment. For example, Jennings (1984) found that conversion of T_4 to T_3 was attenuated in perfused livers isolated from STZ-treated rats and suggested that this abnormality was due to a reduction in activity of hepatic T_4-5′-deiodinase. Also, Singer et al. (1981) reported that glucocorticoid sulphotransferase activity in the liver was approximately doubled within 12 days of STZ treatment.

In summary, STZ treatment clearly results in changes in hepatic metabolism which may, in specific cases (e.g., the decrease in conversion of T_4 to T_3), contribute to the development of cardiovascular disorders. Because changes in drug metabolism also occur following STZ treatment, consideration must be given to possible changes in pharmacokinetics when interpreting results of studies involving administration of drugs to STZ-treated rats. In addition, the studies quoted above highlight areas in which the effects of STZ treatment differ in male and female rats. Because male rats are almost invariably used in cardiovascular studies, it would be of interest to compare the cardiovascular effects of STZ treatment in male and female rats.

Hepatic function has been found to be altered in patients with diabetes mellitus (for examples, see Cairns and Peters, 1983; Gibbons, 1986), but there have been few studies of changes in pharmacokinetics, particularly with regard to possible sex differences in clinical diabetes mellitus.

V. Autonomic Nervous System

Functional and biochemical deficits in the peripheral somatic nervous system in STZ-treated rats have been described in some detail elsewhere (Tomlinson and Mayer, 1984; Greene, 1988; Greene et al., 1990; Kinoshita and Nishimura, 1988; Low et al. 1989; Tomlinson, 1989; Tomlinson et al., 1989a). Although there is evidence that altered relations among sorbitol, phosphoinositides, and Na^+-K^+-ATPase may underlie diabetic complications (Greene et al., 1987), there are observations that indicate other factors must be involved (Tomlinson, 1989; Calcutt et al., 1990; Loy et al., 1990; del Monte et al., 1991). Whatever the nature of the disorder in somatic neurones, it is likely that similar abnormalities occur in autonomic efferent fibres, although the latter may be more resistant to such pathophysiological changes. In addition, disorders of afferent neuronal systems could have important consequences for the reflex control of cardiovascular function.

A. Structural Changes

Monckton and Pehowich (1980) were the first to report degenerative changes in the autonomic nervous system of STZ-treated Wistar rats. These investigators found changes in axons from the sympathetic paravertebral chain within 24 h after STZ treatment; at later times (3 days to 6 weeks), there was widespread degeneration of ganglionic tissue, along with cycles of degeneration and regeneration of axonal tissue and a reduction in axonal calibre. This pattern of change is consistent with a primary lesion in postganglionic fibres. However, Schmidt and Scharp (1982) found no evidence of autonomic neuropathy in the mesenteric nerves of Wistar-Lewis rats 3.5 months after STZ treatment, although they did find histological changes at later times. The pattern of development of autonomic neuropathy may depend on the strain of rat used, because the same workers found that mesenteric axonopathy (although infrequent) was apparent in Sprague-Dawley rats treated 1.5 to 3 months earlier with STZ (Schmidt et al., 1983). It is possible that the degenerative changes seen by Monckton and Pehowich (1980) were transient and, hence, not observed by Schmidt et al. (1983), because the latter did not look for histological changes in their rats at earlier times. Also, because the dose of STZ used by Monckton and Pehowich (1980) (80 mg kg^{-1}) was higher than that used in the studies of Schmidt and coworkers (65 mg kg^{-1}), it is possible that the extent and time of onset of autonomic neuropathy is dependent on the severity of diabetes.

Kniel et al. (1986), using morphometric techniques, found evidence not only for degeneration of sympathetic neurones and Schwann cells in Wistar rats that had been treated with STZ 1 year earlier but also reductions in the cytoplasmic to nuclear ratio and in the size of mitochondria and of the endoplasmic reticulum. Such changes are consistent with decreased neuronal activity. Structural changes in the autonomic nervous system following STZ treatment may be relatively localised because Schmidt et al. (1983) found no evidence of axonopathy in the spleen, bladder, vas deferens, or iris or in the vagus, phrenic, caudal, or sciatic nerves from Sprague-Dawley rats treated 4 to 12 months earlier with STZ, despite the existence of axonopathy in mesenteric nerves of these animals. Furthermore, Schmidt and Plurad (1986) found histological changes in the superior mesenteric ganglia, but not in the superior cervical ganglia, 7 to 15 months after STZ treatment. It has been suggested that the degenerative changes may be localised to the mesenteric innervation because of the marked hypertrophy of gut tissue that occurs following STZ treatment (Schmidt and Cogswell, 1989). However, it is clear this cannot be the sole explanation of the abnormalities because, within the gut, differential changes occur in different neurones (Belai et al., 1988). Furthermore, structural changes have been observed in autonomic fibres in other tissues, such as the pancreas (Tominaga et al., 1987), following STZ treatment.

With regard to the aetiology of neuropathy, it is of interest that the noradrenergic innervation of the vasa nervosum may be selectively damaged following treat-

ment with STZ (Dhital et al., 1986), raising the possibility that disordered control of local blood flow might contribute to neuronal damage. Morphological changes in sympathetic ganglia can be decreased if treatment with an aldose reductase inhibitor is begun soon after the induction of diabetes (Schmidt et al., 1989b). Aldose reductase inhibition, initiated several months after STZ treatment, can also prevent the further development of structural changes in mesenteric nerves but cannot reverse these changes (Schmidt et al., 1991). Pancreatic islet transplantation, however, can both prevent and reverse morphological changes seen in sympathetic ganglia following STZ treatment (Schmidt et al., 1989a).

B. Biochemical and Functional Changes

1. Noradrenergic and cholinergic neurotransmission. Despite the relatively localised histological changes in the autonomic nervous system of STZ-treated rats, more widespread biochemical changes may occur. Thus, Schmidt and Plurad (1986) found a reduction in dopamine-β-hydroxylase activity in superior cervical ganglia from STZ-treated rats, although activity of this enzyme was unaltered in superior mesenteric ganglia. In a later study, Schmidt et al. (1989b) found increased sorbitol levels in superior cervical, superior mesenteric, and coeliac ganglia from STZ-treated rats, together with decreased myoinositol levels in the superior cervical ganglia. Reductions in myoinositol levels and in sodium-potassium-ATPase activity in superior cervical ganglia from STZ-treated rats (preventable by treatment with an aldose reductase inhibitor) were also observed by Greene and Mackway (1986). These observations suggest that disorders of the polyol pathway may contribute to autonomic neuropathy following STZ treatment. Indeed, as discussed before, Schmidt et al. (1989b) showed that aldose reductase inhibition reduced, but did not normalise, neuroaxonal dystrophy in superior mesenteric ganglia from STZ-treated rats.

Buñag et al. (1982) measured the splanchnic nerve firing rate in anaesthetised rats and found no difference between control and STZ-treated rats under resting conditions, although the increase in sympathetic efferent nerve activity following electrical stimulation of the hypothalamus was attenuated in the latter group. This result appears to contrast with that of Berkowitz et al. (1980) who found that serum dopamine-β-hydroxylase activity was increased fivefold in STZ-treated rats and suggested that sympathetic activity may have been enhanced in these animals. However, it is now known that the half-life of dopamine-β-hydroxylase is lengthened in STZ-treated rats (Hurst et al., 1982; Munoz et al., 1984), due to competition of high levels of glucose with dopamine-β-hydroxylase for clearance at its catabolic site (Munoz et al., 1984). Thus, serum dopamine-β-hydroxylase cannot be used as a reliable index of sympathetic nervous system activity in diabetic rats.

Head and Berkowitz (1979a,b) found that plasma levels of noradrenaline and dopamine were increased 16 weeks after STZ treatment, along with increased tissue levels of noradrenaline and dopamine in the renal artery, vena cava, heart, and aorta and of adrenaline in the renal artery and aorta. No changes in tissue catecholamine levels were found in mesenteric arteries or veins following STZ treatment (Head and Berkowitz, 1979a,b). Later studies also showed increases in noradrenaline levels in the heart, skin, adrenal, kidney, ileum, vas deferens, spleen, and plasma following STZ treatment (Paulson and Light, 1981; Fushimi et al., 1984; Lucas and Qirbi, 1989). In addition, Lucas and Qirbi (1989) observed elevated adrenal adrenaline content following STZ treatment. The effects of STZ on plasma and tissue noradrenaline levels appear to be dependent on the severity and duration of diabetes, because Fushimi et al. (1984) saw no change in noradrenaline levels 2 weeks after STZ or when a low dose of STZ (35 compared with 80 mg kg^{-1}) was used. Furthermore, Jobidon et al. (1985) found no change in plasma or cardiac noradrenaline levels after treatment with 45 mg kg^{-1} STZ.

Obviously, tissue or plasma noradrenaline levels alone provide little information about sympathetic nervous system activity because they depend on a number of factors, including rates of synthesis, uptake, and release of noradrenaline by the tissues. Indeed, lung uptake and metabolism of noradrenaline is increased in STZ-treated rats (McKee and Bryan, 1990). For this reason, Ganguly et al. (1986, 1987) made detailed studies of noradrenaline metabolism in cardiac tissue from STZ-treated rats. They found that not only was cardiac noradrenaline content increased following STZ treatment but also noradrenaline turnover, uptake, synthesis, and release were increased (Ganguly et al., 1986, 1987). The difference in noradrenaline turnover between control and STZ-treated rats was abolished following treatment with the ganglion blocker, pentolinium, indicating that the increase in noradrenaline turnover in STZ-treated rats may have been due to enhanced sympathetic nerve activity. The results of Ganguly et al. (1987) are in agreement with those of Lucas and Qirbi (1989) who found enhanced noradrenaline turnover in the ventricle, ileum, and vas deferens of STZ-treated rats but disagree with those of Yoshida et al. (1985, 1987) who obtained evidence for reduced noradrenaline turnover in interscapular brown adipose tissue, heart, and pancreas from STZ-treated rats. In both the latter studies, the alterations in noradrenaline turnover were partially prevented by aldose reductase inhibition.

Ganguly et al. (1987) also noted that STZ-treated rats did not respond to cold stress with an increase in cardiac noradrenaline turnover. Thus, although basal sympathetic nerve activity may have been high in these animals, they appeared to be unable to respond to stress with a further increase in sympathetic activity. In con-

trast, increases in urinary adrenaline and noradrenaline during cold exposure were found to be enhanced in STZ-treated rats (Bellush and Henley, 1990). There may, therefore, be regional differences in the effects of STZ treatment on sympathetic responses to stress.

Functional studies have shown deranged autonomic control of a number of systems following STZ treatment. Tomlinson et al. (1982) found that vasa deferentia from long-term (6 months) diabetic rats had an attenuated response to field stimulation of noradrenergic nerves, enhanced responsiveness to exogenous noradrenaline, but no change in contractility in response to potassium chloride. These changes, which are consistent with autonomic denervation, were accompanied by histological abnormalities in nerve terminals of the vasa deferentia. Similar results were later obtained by Longhurst et al. (1989).

Changes in bladder function following treatment with STZ clearly depend on experimental conditions (Kolta et al., 1985; Longhurst and Belis, 1986; Paro and Prosdocimi, 1987; Santicioli et al., 1987; Kudlacz et al., 1988, 1989; Latifpour et al., 1989; Lee and Wong, 1989; Maggi et al., 1989), with increases and decreases being described in different protocols. Some of the confusion may arise because STZ treatment results in an increase in bladder capacity and mass (Longhurst et al., 1990).

In the gastrointestinal system, loss of noradrenergic innervation has been suggested to contribute to the decreased rate of intestinal fluid and electrolyte absorption of STZ-treated rats (Chang et al., 1985). Impaired cholinergic neurotransmission has also been seen in the small intestine following STZ treatment (Nowak et al., 1990) but, as elsewhere, the details of the changes occurring in the functional responsiveness of gastrointestinal systems to autonomic stimulation depends on the study considered and the region investigated (Tominaga et al., 1987; Belai et al., 1988; Hoyle et al., 1988; Kamata et al., 1988; Liu et al., 1988; Anderson et al., 1989; Lucas and Sardar, 1991).

Noradrenergic nerve function has been shown to be impaired in the cardiovascular system. For example, contractile responses to electrical field stimulation and tyramine were attenuated in caudal arteries from rats treated 8 weeks earlier with STZ (Hart et al., 1988). Furthermore, Sato et al. (1989) found that left atria isolated from STZ-treated rats showed greater attenuation of contractile responses to transmural stimulation than to noradrenaline, implying that noradrenaline release during nerve stimulation may have been reduced in this tissue. These results were confirmed by Hashimoto et al. (1990) who also showed that aldose reductase inhibitors improved the responses to transmural nerve stimulation but not those to noradrenaline and suggested that the former was due to a beneficial effect of aldose reductase inhibitors on cardiac neuropathy.

There is also evidence for changes in parasympathetic control of the heart in STZ-treated rats. There may be an early increase in vagal nerve activity followed by a decrease, due to neuropathy, because Chang and Lund (1986) measured baroreflex sensitivities in STZ-treated rats and found that 12 and 24 weeks after STZ treatment baroreflex sensitivities were increased, whereas 48 weeks after STZ there was a reduction in baroreflex sensitivity. These authors suggested that the changes that they observed were due to altered vagal activity (see section VII.C.3).

2. Peptidergic mechanisms. In addition to changes in noradrenergic and cholinergic autonomic neuronal biochemistry and function, there are also changes in various neuropeptides following STZ treatment.

MacLean (1987) observed that, 3 months after STZ treatment, substance P and somatostatin transport in the vagus nerve was increased. Thus, because these neuropeptides are located in sensory nerves, it is feasible that afferent dysfunction occurs and affects cardiovascular reflexes in STZ-treated animals. In another study of long-term (11 month) STZ-induced diabetes mellitus, substance P levels were decreased in sciatic nerve and in lumbar dorsal root ganglia (Willars et al., 1989). A reduction in VIP content of sciatic nerves from STZ-treated rats has also been found (Noda et al., 1990). Because VIP in the sciatic nerve is contained in autonomic and sensory neurones, and the reduction in VIP content was concomitant with a slowing of nerve conduction velocity, it was suggested that impaired control of the neuronal microvasculature by VIP could contribute to neuropathy.

Altered neuropeptide levels have also been found in gut tissue from STZ-treated rats. Belai et al. (1988) found increased tissue levels of VIP, and an increased density of VIP immunoreactive nerve fibres, in the proximal colon, 8 weeks after STZ treatment, although they were reduced again after 16 weeks. However, substance P levels were increased at that time. Whereas there was a reduction in the density of nerve fibres containing calcitonin gene-related peptide 8 weeks after STZ treatment, these changes were not apparent after 25 weeks. No changes in NPY levels or fibre distribution were found. An early increase and later normalisation of noradrenaline levels was also found in association with enlarged varicosities in fibres staining for dopamine-β-hydroxylase. Based on these observations and previous results showing impaired release of VIP during electrical stimulation of the ileum from STZ-treated rats (Belai et al., 1987), it was suggested that the pattern of change seen in VIP and noradrenaline levels was due to accumulation in degenerating nerves (Belai et al., 1988).

Functional studies have also shown impaired responses to electrical stimulation of nonadrenergic, noncholinergic inhibitory nerves (possibly containing VIP) in the gastric fundus of STZ-treated rats (D'Amato and Curro, 1990), although other results were suggestive of an en-

hancement in nonadrenergic, noncholinergic (in this case, possibly purinergic) transmission (Belai et al., 1991a). The situation is further complicated when the exact location of the nerves involved is considered. Belai and Burnstock (1990) showed that, following STZ treatment, the change in pattern of innervation of the myenteric plexus in the ileum was similar to that found in the proximal colon (Belai et al., 1988), but the changes in the submucous plexus differed. For example, in the ileal submucous plexus, NPY levels were increased and VIP levels increased and remained high, with no evidence for degenerative changes in VIP-containing neurones (Belai and Burnstock, 1990). These changes could contribute to altered peptidergic control of intestinal fluid absorption and, hence, influence overall fluid balance following STZ treatment. However, Schmidt et al. (1988) could find no evidence of abnormalities of the peptidergic (VIP, bombesin, substance P, NPY, or somatostatin) innervation of the small intestine in rats treated with STZ 12 to 18 months earlier. Furthermore, Belai et al. (1991b) could find no evidence of neural degeneration or altered neurotransmitter levels in the distal colon. Differences in the effects of STZ treatment on the innervation of the proximal and distal colon may reflect the different functions and origin of innervation of the two regions (Belai et al., 1991b).

Inconsistent changes in neuropeptide levels have been found in other tissues from STZ-treated rats. The density of NPY- and VIP-containing fibres was increased in prostate glands from STZ-treated rats (Crowe et al., 1987), and there was an increase in substance P immunoreactivity in the iris (Tomlinson et al., 1989b). However, there was a reduction in NPY immunoreactivity in the parotid gland (Sharkey et al., 1989) following STZ treatment. In none of these studies was any change found in nerves associated with blood vessels. However, Lagnado et al. (1987) did find a reduction in VIP-immunoreactive fibre density in perivascular nerves of cerebral blood vessels from STZ-treated rats, although no changes in NPY fibres were found. Furthermore, Karanth et al. (1990) observed enhanced VIP immunoreactivity, but unaltered NPY immunoreactivity, around blood vessels in the skin of rats treated with STZ. Thus, it is possible that altered neuropeptide levels might affect local blood flow control in the cerebral and skin circulations following STZ treatment. Crowe et al. (1983) found a reduction in VIP immunoreactive nerves in erectile tissue and around blood vessels in the penis of STZ-treated rats and suggested that this could contribute to impotence during diabetes.,

Recently, it was reported that NGF production may be impaired following administration of STZ, because there was a reduction in NGF content of some sympathetically innervated tissues (e.g., salivary gland and cardiac ventricles) a few weeks after STZ treatment (Hellweg and Hartung, 1990). At later times, NGF content was increased in most sympathetically innervated tissues (Hellweg and Hartung, 1990), consistent with the earlier findings that retrograde neuronal transport of NGF was reduced following STZ treatment (Schmidt et al., 1983, 1986). Indeed, Hellweg and Hartung (1990) found a reduction in sciatic nerve and superior cervical ganglion NGF content. Thus, it is feasible that disorders of production and transport of this peptide could contribute to autonomic neuropathy in diabetes mellitus. Elsewhere, attention has been drawn to the structural similarities between NGF and insulin and the possible interactions between these molecules (Bennett, 1983). In this context, it is intriguing that acute in vitro treatment with insulin can reverse abnormalities of the peptidergic innervation of the gut from rats treated with STZ (Burnstock et al., 1988). In addition, it is striking that treatment with capsaicin, which destroys sensory nerve fibres that are dependent on NGF, induces abnormalities of cardiovascular regulation (Bennett and Gardiner, 1984; Gardiner et al., 1989) that are similar to those seen following treatment with STZ (Hebden et al., 1987a).

C. Summary

There is evidence for widespread changes in autonomic nervous system function in STZ-treated rats. Although studies designed to measure noradrenaline turnover have produced conflicting results, most functional studies have shown impaired sympathetic responses in STZ-treated rats. As suggested by Belai et al. (1988), it is possible that some findings of increased noradrenaline levels may be related to early neuronal degeneration. Altered autonomic nervous system activity may affect cardiovascular control in STZ-treated rats, via influences on HR and cardiac contractility and/or on vasomotor tone (these possibilities are considered in more detail in section IX).

Autonomic neuropathy is a common complication of clinical diabetes mellitus and may be responsible for many changes in cardiovascular function, including tachycardia, a reduction in beat to beat variation in HR, abnormal responses to the Valsalva manoeuvre, orthostatic hypotension, abnormal BP and HR responses to exercise, impaired baroreflexes, and disordered thermoregulation (Hosking et al., 1978; Bennett, 1983; Bennett and Gardiner, 1988; Scott et al., 1988). The degree of autonomic neuropathy is dependent on the duration of diabetes (Bergstrom et al., 1987), but subclinical autonomic neuropathy may be present at the time of diagnosis (Ziegler et al., 1986). Apart from the cardiovascular consequences of autonomic neuropathy that may be directly life threatening [e.g., postural hypotension, cardiac arrhythmias, and cardiorespiratory arrest (Bennett, 1983)], the metabolic sequelae are the most troublesome. Thus, defective glucoregulation and unawareness of hypoglycaemia are dependent, in part, on sympathoadrenal dysfunction and, possibly, on impaired vagal control of

the pancreas (Hilsted et al., 1982; Gerich, 1988; Gerich and Campbell, 1988). However, the extent to which defective hypothalamic activation of glucoregulatory mechanisms in patients with insulin-dependent diabetes mellitus contributes to their abnormal glucoregulation (Frier et al., 1988) remains to be established.

Strict glycaemic control does not appear to improve autonomic neuronal function; indeed, it may further impair glucoregulation (Gerich, 1988) and render patients prone to hypothermia (Scott et al., 1988). However, pancreatic transplantation does seem to be effective in halting the development of neuropathy (Kennedy et al., 1990), as is true in STZ-treated rats (Schmidt et al., 1989a). Because there is evidence that disorders of the polyol pathway are involved in the development of autonomic neuropathy following STZ treatment, there have been several recent clinical trials concerning the effects of inhibiting aldose reductase on autonomic neuronal function of diabetic patients. However, improvements in autonomic function have been neither impressive nor consistent (Martyn et al., 1987; Raskin and Rosenstock, 1987; Gill et al. 1990). Thus, it has been suggested that either the polyol pathway is not as important in the development of human diabetic neuropathy as it is in the rat or aldose reductase inhibitors will have to be given prophylactically to prevent overt changes in autonomic function (Martyn et al., 1987; Raskin and Rosenstock, 1987). However, as mentioned in section III.A), it is not clear how long-term treatment with aldose reductase inhibitors would affect renal function.

It has recently been reported that patients with type II diabetes mellitus and neuropathy had lower serum levels of NGF than controls and that NGF levels correlated with reductions in motor nerve conduction velocity (Faradji and Sotelo, 1990). Administration of orally active, nonpeptide analogues of NGF might, therefore, be one possible future treatment for diabetic neuropathy, although it may be very difficult to control the action of exogenous NGF.

VI. Central Nervous System

A. Insulin and the Central Nervous System

Insulin and insulin-binding sites are widely distributed within the CNS (Unger et al., 1991). Originally, it was thought that insulin receptors within the CNS were localised to the brain vasculature and to areas accessible from the peripheral circulation because, when labeled insulin was given intravenously, only brain microvessels and circumventricular organs that lack a blood-brain barrier (i.e., area postrema, arcuate nucleus, and median eminence) showed insulin binding (Van Houten and Posner, 1981). However, more recent studies using the technique of in vitro autoradiography have shown labeling of insulin-specific binding sites in several areas within the CNS that are inaccessible from the peripheral circulation (olfactory bulb and the preoptic suprachiasmatic, paraventricular, and periventricular nuclei of the hypothalamus) (Corp et al., 1986).

Insulin levels in the rat brain are apparently not directly dependent on plasma insulin levels because Havrankova et al. (1981) found that whole brain insulin content and insulin receptor numbers in several brain regions (olfactory bulb, diencephalon, cerebral cortex, brainstem, cerebellum) were unaltered even 4 weeks after STZ treatment, despite markedly reduced levels of circulating insulin. This, together with the existence of insulin receptors which are apparently inaccessible to plasma insulin (Corp et al., 1986), indicates that there may be insulin within the CNS with functions separate from those of circulating insulin. However, the origin of insulin in the brain is still debatable. Some studies have suggested that insulin in the CNS is derived from plasma insulin (through uptake by the circumventricular organs or via transport across the blood-brain barrier) (Baskin et al., 1987; see above), but it is likely that insulin is synthesised within the CNS itself because insulin mRNA has been localised in the periventricular hypothalamus by in situ hybridisation (Young, 1986). Furthermore, Schechter et al. (1988) showed that 3 to 5% of cultured rabbit neurones were immunoreactive for insulin and a similar proportion were labeled by insulin complementary DNA probes. Glial cells, however, showed no labeling with either technique. Thus, it appears probable that insulin is synthesized in a subpopulation of CNS neurones and from these may gain access to the CSF and thereby to other brain areas. The relative contributions of local synthesis, and of uptake of plasma insulin, to the CNS insulin pool remain to be determined (Unger et al., 1991).

Insulin is likely to have diverse actions within the CNS; it has been shown to increase glucose uptake across the blood-brain barrier and in specific brain regions (e.g., the hypothalamus), and there is evidence that insulin may play a role in brain development (Baskin et al., 1987; Unger et al., 1991). Insulin may also have a neuromodulatory role within the CNS because it is released from cultured neuronal cells or synaptosomes under depolarizing conditions and is known to inhibit cell firing and to modulate synaptic activity (Baskin et al., 1987; Unger et al., 1991), as well as stimulating phosphoinositide turnover in cerebral cortex (Catalan et al., 1991). Moreover, insulin is involved in the control of body weight and of food intake through actions within the CNS (Baskin et al., 1987; Unger et al., 1991); insulin may also stimulate thirst (Spitz, 1975).

Insulin acting on the CNS has also been implicated in the development of hypertension (Landsberg, 1986). However, it was shown recently that insulin, injected into the lateral cerebral ventricle of anaesthetised rats, caused a decrease in BP, HR, and renal sympathetic nerve activity (Nishimura et al., 1991). The effect was greater when the same dose was injected into the ventro-

medial hypothalamus. Because hypothalamic and plasma levels of digoxin-like immunoreactivity were decreased following ICV administration of insulin, the authors suggested that the action of insulin may have been due to enhanced sodium-potassium-ATPase activity (Nishimura et al., 1991).

It should be stressed that the STZ-treated rat is a model of pancreatic insulin deficiency. Brain insulin and insulin receptor levels have been found to be unaltered in rats 4 weeks after STZ treatment (Havrankova et al., 1981). Any effect of STZ-induced diabetes on the CNS could, therefore, simply be attributable to a lack of circulating insulin and to the secondary effects of this deficiency.

B. Structural Changes

Long-term, STZ-induced diabetes mellitus in rats can result in structural changes within the CNS. Jakobsen et al. (1987b) studied the brains of rats that had been treated with STZ 1 year previously and maintained with low-dose insulin treatment to prevent excessive body weight loss. These investigators found that brain weight and neocortical volume were reduced in the STZ-treated animals, in association with a loss of neocortical neurones. It was suggested that the latter may have been due to a direct effect of lack of circulating insulin or to metabolic factors such as hypoglycaemic episodes, sorbitol accumulation, or myoinositol depletion. Alternatively, cerebral damage may have been the result of vascular changes, because the total length of the neocortical capillary network was disproportionately reduced relative to the decrease in cortical volume following STZ treatment (Jakobsen et al., 1987b). This reduction could account partially for the decrease in cerebral blood flow observed in rats after STZ treatment (Mooradian, 1987; Lass et al., 1989; Pardridge et al., 1990). However, in one study of STZ-treated rats, brain blood volume was unaltered, despite decreased cerebral blood flow (Pardridge et al., 1990). In another, reductions in regional blood flow were found in some areas of brains taken from rats treated with STZ, but no decrease in the density of perfused capillaries was found in those areas (Knudsen et al., 1991). Thus, humoral as well as structural factors may affect cerebral blood flow in STZ-treated rats (see section VIII.C).

There also are changes in blood-brain barrier function in STZ-treated rats that could affect transport of substances into the brain and, hence, influence brain development and activity. Choi et al. (1989) described increases in blood-brain glucose transporter mRNA in STZ-treated rats. However, the concentration of glucose transporters in capillaries isolated from the brains of STZ-treated rats was decreased (Pardridge et al., 1990), and there have been reports of either no change or a down-regulation in glucose transport (Mooradian, 1988; Choi et al., 1989; Jakobsen et al., 1990). Lorenzi et al. (1986) found an apparent increase in blood-brain barrier permeability to inulin, but not to sucrose or horseradish peroxidase, in selected brain areas (mediobasal hypothalamus, mediodorsal hypothalamus, and periaquaductal grey) of rats treated 4 weeks earlier with STZ. Mayhan (1990) showed that blood-brain barrier permeability to albumin was not significantly greater in STZ-treated than control rats, although leaky sites were found in the microvasculature of the former but not of the latter group. However, following acute hypertension, the number of leaky sites was similar in control and STZ-treated animals, indicating that STZ treatment did not cause an increase in blood-brain barrier susceptibility to damage under these conditions (Mayhan, 1990).

Blood-brain barrier permeability to sodium and potassium in cortical tissue was reduced 2 weeks after STZ treatment (Knudsen et al., 1986; Jakobsen et al., 1987a), and permeability to chloride and sucrose remained unaltered. It was suggested that these changes in blood-brain barrier permeability to electrolytes could eventually lead to structural changes within the cortex of STZ-treated rats (Knudsen et al., 1986). Interestingly, treatment with myoinositol normalised the decreased sodium permeability of the blood-brain barrier in STZ-treated rats (Knudsen et al., 1989).

STZ-treated rats may also develop more localised histological changes within the CNS that are related to specific functional alterations. Thus, ultrastructural changes in the AVP- and oxytocin-containing cells of the hypothalamic paraventricular and supraoptic nuclei and in the neurohypophysis of rats 8 weeks after STZ treatment have been noted (Loesch et al., 1988) and are consistent with the proposed increase in AVP release in rats following STZ treatment (Van Itallie and Fernstrom, 1982; see section II.A). Degenerative changes have also been noted in luteinising hormone-releasing hormone-containing neurones of the arcuate nucleus and median eminence in rats treated 4 weeks earlier with STZ, concomitantly with defective luteinising hormone release in response to naloxone (Bestetti et al., 1985, 1989). Bestetti et al. (1989) also observed degenerative changes in axons of the medial basal hypothalamus associated with a reduction in the basal release of thyroid-releasing hormone in vitro.

C. Neurotransmitter Systems

In addition to overt structural changes in the CNS following STZ treatment, there are perturbations in several neurotransmitter systems that may influence CNS control of the cardiovascular system. It has been suggested that STZ has effects on brain neurotransmitter systems independently of its diabetogenic action, because ICV injections of STZ had effects at doses lower than those needed to produce diabetes when given systemically (Lackovic and Salkovic, 1990). However, the changes in neurotransmitters seen were not identical

with those following systemic STZ administration; moreover, in the latter case, many of the observed changes in the CNS can be reversed by systemic insulin treatment. It is, therefore, likely that the changes described below are due to diabetes mellitus and not to a direct CNS effect of STZ.

1. Noradrenaline. Elevated noradrenaline levels have been found in the forebrain (Trulson and Himmel, 1985), thalamus, hypothalamus, medulla, and midbrain (Bitar et al., 1986) and in the whole brain (Lackovic et al., 1990) of STZ-treated rats. Furthermore, noradrenaline turnover (determined by the rate of decrease of noradrenaline levels following inhibition of tyrosine hydroxylase by α-methyl-*p*-tyrosine) (Trulson and Himmel, 1985; Steger and Kienast, 1990) and levels of the major metabolite of noradrenaline, 3-methoxy-4-hydroxyphenylglycolsulphate (Trulson and Himmel, 1985; Bitar and De Souza, 1990), were decreased in various forebrain areas of rats following treatment with STZ. In addition, homovanillic acid levels were decreased in whole brains from STZ-treated rats (Lackovic et al., 1990). Moreover, α_1-adrenoceptor numbers were increased in the hypothalamus, medulla, and midbrain of STZ-treated rats (Bitar et al., 1986), and β_1-adrenoceptor numbers were increased in the anterior and lateral hypothalamus, ventroposterior thalamus, and basolateral amygdala (Bitar and De Souza, 1990). These results are consistent with a reduction in neuronal turnover and release of noradrenaline following STZ treatment, leading to elevated levels of stored noradrenaline and, hence, compensatory up-regulation of α_1- and β_1-adrenoceptors. However, no change in cerebrocortical α_2-adrenoceptor function (assessed by inhibition of noradrenaline release with an α_2-adrenoceptor agonist; Drukarch et al., 1989) or β_2-adrenoceptor numbers (Bitar and De Souza, 1990) have been detected in STZ-treated rats. Furthermore, enhanced brain levels of noradrenaline have not been found in all studies following STZ treatment. Thus, Chu et al. (1986) observed elevated levels of noradrenaline only in the corpus striatum of STZ-treated rats; brainstem noradrenaline levels were unaltered and hypothalamic levels were decreased following STZ treatment. It is possible that inconsistencies between studies may arise because changes in noradrenaline levels are relatively localised within the CNS, and the sensitivity of techniques used to measure noradrenaline levels is limited. Indeed, Bitar et al. (1987a) found that increased hypothalamic noradrenaline levels were localised to discrete regions, namely, the median eminence, supraoptic nucleus, and paraventricular nucleus; levels were normal in the ventromedial hypothalamus and suprachiasmatic nucleus.

An alternative explanation for the discrepancies between studies was provided by the work of Glanville and Anderson (1986) who showed that, whereas in the fasted state, accumulation of the major metabolite of noradrenaline was similar in hypothalami from STZ-treated and control rats, noradrenaline metabolite accumulation was significantly lower in the former group following the ingestion of a carbohydrate meal. Thus, it may be necessary to consider the prandial status of animals when comparing studies with regard to hypothalamic noradrenaline metabolism.

2. Dopamine. As with noradrenaline, there is evidence for a reduction in the turnover of dopamine in brains from STZ-treated rats. Concentrations of the dopamine metabolite, dihydroxyphenylacetic acid, were reduced in the striatum (Kwok and Juorio, 1986; Shimomura et al., 1988) and in the thalamus, medulla, midbrain, hypothalamus, and pons (Bitar et al., 1986) of rats treated with STZ, although dopamine levels were normal (Bitar et al., 1986; Kwok and Juorio, 1986; Shimomura et al., 1988) or elevated (Lackovic et al., 1990). Dopamine turnover (measured by the rate of decrease in dopamine levels following inhibition of tyrosine hydroxylase with α-methyl-*p*-tyrosine) was found to be decreased in the median eminence and mediobasal hypothalamus of STZ-treated rats (Steger and Kienast, 1990). Furthermore, dopamine synthesis within the striatum and the limbic forebrain was shown to be reduced following STZ treatment (Trulson and Himmel, 1983), whereas dopamine receptor number was increased in these brain regions (Lozovsky et al., 1981; Trulson and Himmel, 1983). These results are consistent with reduced activity of the dopaminergic neuronal system.

3. 5-Hydroxytryptamine. In addition to the reduction in turnover of catecholamines following STZ treatment, synthesis and turnover of the indoleamine, 5-HT, have been found to be lower in brains from STZ-treated rats than in brains from control animals (Trulson et al., 1986); no change in 5-HT levels or in the levels of the 5-HT metabolite, 5-HIAA, were found. Several other investigators have also reported a lack of effect of STZ treatment on brain 5-HT and 5-HIAA levels (MacKenzie and Trulson, 1978; Mello et al., 1988). Kwok and Juorio (1987), however, found that 5-HT and 5-HIAA levels were reduced in the striatum of STZ-treated rats, and Bitar et al. (1986, 1987a) observed reduced levels of 5-HIAA in the hypothalamus (suprachiasmatic nucleus, supraoptic nucleus, and ventromedial hypothalamus), thalamus, medulla, midbrain, cortex, cerebellum, olfactory bulb, and pons of STZ-treated rats. In contrast, 5-HT levels were increased in the cortex and remained unaltered in the other brain regions studied (thalamus, medulla, midbrain, hypothalamus, cerebellum, olfactory bulb, hippocampus, and pons). Changes in 5-HT and 5-HIAA levels following STZ treatment may, therefore, be localised to discrete brain regions and may not be apparent when whole brain levels are measured, although Lackovic et al. (1990) reported elevated 5-HT levels in whole brain accompanied by reduced levels of 5-HIAA at 12, but not at 2, weeks following STZ treatment. Thus,

time-dependent changes may also account for some discrepancies between studies.

As with catecholamine turnover, it appears that 5-HT levels and turnover may be affected by nutritional status of the animals prior to measurement. Mello et al. (1988) showed that, although STZ-treated rats had unaltered brain 5-HT, 5-HIAA, and 5-hydroxytryptophan (a 5-HT precursor) levels in the fed state, brain levels of all three substances were greater in STZ-treated rats following fasting than in fed controls, although no comparison was made in this study between fasted control and fasted STZ-treated rats. Crandall and Fernstrom (1980) found that 5-HT levels were similar in brains from fasted STZ-treated and fasted control rats, whereas 5-HIAA levels were reduced in the former group. Furthermore, the normal increase in brain 5-HT and 5-HIAA in response to glucose ingestion was absent in STZ-treated animals. Disturbances in the metabolism of 5-HT in the hypothalamus in response to immobilisation stress have also been found following treatment with STZ (Chaouloff et al., 1989).

4. Adrenaline. Brain levels of adrenaline have been seen to be affected differentially by STZ treatment, depending on the brain area studied. Chu et al. (1986) found reduced hypothalamic adrenaline levels, normal brainstem adrenaline levels, and elevated levels of adrenaline in the striatum of STZ-treated rats compared with controls. Other studies have shown enhanced phenylethanolamine-N-methyl-transferase (the enzyme that converts noradrenaline to adrenaline), activity in the brainstem of STZ-treated rats with no concomitant change in hypothalamic phenylethanolamine-N-methyl-transferase activity (Fischer and Stewart, 1986). However, at present the relationship between changes in phenylethanolamine-N-methyl-transferase activity and adrenaline levels is unclear.

5. Acetylcholine. Blood-brain barrier choline transport has been found to be impaired following STZ treatment (Mooradian, 1987), and it was suggested that this could lead to changes in cholinergic mechanisms within the CNS. However, Bitar et al. (1986) measured choline acetyltransferase as a marker of presynaptic cholinergic neurone activity and reported that this was unaltered in several brain areas (including cortex) following STZ treatment. Thus, the effects of STZ on cholinergic neurotransmission remain unresolved.

6. Hypothalamic neuropeptides. There is, at present, much interest in the role of neuropeptides as central neuromodulators, and it is becoming increasingly apparent that neuropeptides are involved in functions such as glucoregulation (Froham, 1983), ingestive behaviour (Levine et al., 1986), and cardiovascular regulation (Gardiner and Bennett, 1989), all of which are affected by diabetes mellitus. Studies of some central neuropeptide levels have been done in STZ-treated rats. Forman et al. (1985, 1986) showed that hypothalamic β-endorphin levels were reduced following STZ treatment but suggested that this reduction was due to a generalised inhibition of hypothalamic protein synthesis, because hypothalamic protein content was lower in STZ-treated rats than in control animals and, consequently, β-endorphin concentrations, expressed per unit weight of protein, were similar in the two groups. Locatelli et al. (1986), however, found a decrease in hypothalamic β-endorphin concentrations (expressed per unit weight of protein) in rats following STZ treatment. Because hypothalamic β-endorphin levels of control rats in the latter study were 10-fold higher than those found by Forman et al. (1985), it is possible that the discrepancy between these two studies was methodological in origin.

In an extensive study by Williams et al. (1988) of STZ-treated rats, levels of NPY, neurotensin, calcitonin gene-related peptide, neurokinin A, bombesin, galanin, neuromedin B, substance P, somatostatin, and VIP were measured in hypothalami. One day after STZ treatment, neurotensin levels were elevated, 2 weeks later calcitonin gene-related peptide levels were increased, and after 4 weeks neurokinin A and NPY levels were elevated. The levels of the other six peptides studied were unaltered. The most striking changes were found in NPY levels; this observation is interesting in light of the known actions of NPY to stimulate food and water intake (Morley et al., 1987) and raises the possibility that increased hypothalamic levels of NPY could contribute to the hyperphagia and polydipsia of STZ-treated rats. Consistent with this proposition, changes in NPY levels were later found to be localised to areas involved in the control of food and fluid intake (paraventricular, medial preoptic and arcuate nuclei, and the ventromedial and lateral hypothalamus) with no change in the anterior hypothalamus or lateral preoptic and supraoptic nuclei (Williams et al., 1989). Similar results were found by Abe et al. (1991) who showed that NPY levels were increased in the paraventricular nucleus, arcuate nucleus, and ventromedial hypothalamus but not in the lateral hypothalamus and suprachiasmatic nucleus of STZ-treated rats. However, increased levels of NPY were seen in the medial preoptic, suprachiasmatic, paraventricular, and arcuate nuclei, median eminence, ventromedial area, and dorsomedial area of the hypothalamus by Sahu et al. (1990). In addition, in response to potassium chloride, NPY release from medial basal-preoptic areas isolated from STZ-treated rats was increased (Sahu et al., 1990).

D. Central Nervous Control of the Cardiovascular System

As yet, there has been little work done on central aspects of cardiovascular control following STZ treatment. The neurotransmitter studies reviewed above should, however, initiate a great deal of interest in this area because catecholamines (Brody et al., 1984; Gardiner and Bennett, 1990), 5-HT (Kuhn et al., 1980), and

neuropeptides (Gardiner and Bennett, 1989) have all been implicated in the central control of the cardiovascular system. Biochemical studies have shown that hexokinase (a marker of metabolic activity) levels were increased in the paraventricular nucleus and in the medial and commissural divisions of the nucleus of the solitary tract in rats treated with STZ (Krukoff and Patel, 1990). Krukoff and Patel (1990) suggested that these changes were related to increased AVP release and altered cardiovascular regulation, respectively. However, the nucleus of the solitary tract not only receives afferents concerned with cardiovascular regulation but also visceral afferent fibres and taste fibres. Thus, increased activity in these systems could have contributed to the changes observed by Krukoff and Patel (1990).

Buñag et al. (1982) studied the cardiovascular effects of electrically stimulating the hypothalamus of conscious rats. The pressor response to such stimulation was impaired in STZ-treated rats relative to controls, whereas the tachycardic and behavioural responses were unaltered. It was suggested that the abnormality was within the CNS, because the increase in sympathetic outflow following electrical stimulation of the hypothalamus of anaesthetised STZ-treated rats was less than that of controls. Furthermore, there were no differences in the pressor responses of STZ-treated rats to intravenous noradrenaline or tyramine, implying that the defect was not peripheral in origin (Buñag et al., 1982). These results should be interpreted with caution, however, because it is by no means certain that the response to hypothalamic stimulation was entirely due to increased sympathetic activity. Whether or not the findings of Buñag et al. (1982) are related to the altered hypothalamic neurotransmitter turnover discussed above is unclear.

Trimarchi et al. (1987) found that stimulation of central GABAergic mechanisms with ICV administration of muscimol (a GABA receptor agonist) or ethanolamine-O-sulphate (which inhibits GABA breakdown) caused greater hypotensive and bradycardic responses in STZ-treated than control rats. In a parallel experiment, it was also shown that hypothalamic and brainstem GABA concentrations were reduced in rats following STZ treatment. No differences were found, however, in the hypotensive or bradycardic response of STZ-treated and control rats to another depressor substance, dopamine, injected into a lateral cerebral ventricle (Trimarchi et al., 1987). Zhang and Patel (1991) found no difference in the hypotensive response to ICV administration of clonidine in STZ-treated and control rats, although they did find evidence of a reduction in clonidine-induced sympathoinhibition in the former group.

In our laboratory we have studied the cardiovascular effects of substances that elicit pressor responses when injected ICV. We found normal BP responses to ICV AII in STZ-treated rats, when drinking responses were prevented by denying the animals access to water (Tomlinson et al., 1990b). Under those conditions, pressor responses to ICV AII are believed to be predominantly due to the release of AVP (Haack and Mohring, 1978; Harland et al., 1988; Unger et al., 1985), although there may also be some involvement of the sympathetic nervous system (Unger et al., 1985). However, STZ-treated rats showed a reduction in the pressor response to ICV somatostatin, which is also believed to be due to AVP release (see section II.A; Brown, 1988; Tomlinson et al., 1990c). This is consistent with results from others showing that depletion of endogenous brain somatostatin with cysteamine attenuated haemorrhage-induced AVP release but had no effect on the increase in plasma AVP caused by ICV injections of AII (Brown et al., 1988).

These findings suggest that central somatostatin pathways may be involved in the release of AVP in response to haemorrhage but not in response to ICV AII. STZ-treated rats have been shown to have normal hypothalamic levels of somatostatin (Williams et al., 1988), somatostatin mRNA (Papachistou et al. 1989), and somatostatin synthesis (Fernstrom et al., 1990), and thus our results suggest that cardiovascular reponses to the release of endogenous somatostatin might be impaired following STZ treatment. Interestingly, adenohypophyseal cells from STZ-treated rats have reduced sensitivity to the inhibition of growth hormone secretion by somatostatin in vitro (Sheppard et al., 1989; Olchovsky et al., 1990). It is possible, therefore, that a deficiency in AVP release in response to endogenous somatostatin could contribute to the impaired AVP-mediated BP recovery seen following ganglion blockade in STZ-treated rats (see section II.A; Tomlinson et al., 1990c).

Despite impaired pressor responses to ICV somatostatin in STZ-treated rats, bradycardic responses remained intact (Tomlinson et al., 1990c). One possible explanation for these results is an involvement of GABAergic pathways, because ICV somatostatin has been shown to reduce autonomic nerve firing via GABAergic mechanisms (Tonoue et al., 1985), and the administration of GABA attenuates AVP release in response to ICV somatostatin (Brown and Carver-Moore, 1990). Thus, enhanced responses to GABA within the CNS of STZ-treated rats (Trimarchi et al., 1987) could feasibly reduce AVP release while contributing to a bradycardia (due to sympathoinhibition) following administration of ICV somatostatin.

In contrast to the results with somatostatin, STZ-treated rats showed impaired bradycardic reponses to ICV AII in the absence of drinking water (Tomlinson et al., 1990b). This was not due to a reduction in baseline baroreflex sensitivity in STZ-treated rats but could have been due to an effect of STZ treatment on the interaction between AII and the CNS mechanisms involved in the control of HR (Tomlinson et al., 1990b). When drinking was allowed following ICV administration of AII, control

rats but not STZ-treated rats showed an enhancement in the systolic BP response and a tachycardia, indicating that sympathetic activation may have been impaired in the STZ-treated group (Tomlinson et al., 1990b). Furthermore, ICV administration of AII during peripheral V_1-receptor antagonism caused a greater sympathetically mediated pressor response in control than STZ-treated rats (Tomlinson et al., 1990b). However, this finding differed from results obtained using substance P, which causes a sympathetically mediated pressor response when administered ICV (Unger et al., 1985), because this peptide had similar effects in control and STZ-treated rats (Tomlinson et al., 1990c).

The central pathways involved in the responses to ICV administration of substance P seem to include cholinergic but not noradrenergic neurones, because the pressor response is attenuated by depletion of brain acetylcholine levels or by ICV pretreatment with a nicotinic receptor antagonist (Trimarchi et al., 1986) but is unaffected by depletion of periventricular noradrenergic systems with ICV administration of 6-hydroxydopamine (Badoer et al., 1988). Conversely, the response to ICV AII is totally abolished by pretreatment with ICV 6-hydroxydopamine (Bellin et al., 1987). The findings of normal pressor responses to ICV substance P but reduced sympathetically mediated responses to ICV AII may, therefore, be consistent with reports of reduced forebrain noradrenaline turnover (Trulson and Himmel, 1985), but no change in choline acetyltransferase activity (Bitar et al., 1986) in the brains of STZ-treated rats, and could indicate that impaired sympathoadrenal effects associated with ICV AII may be specific to that stimulus.

It is notable that drinking responses to ICV administration of AII were found to be enhanced in STZ-treated rats, possibly related to the polydipsia seen in these animals (Hebden et al., 1986; Tomlinson et al., 1989c). Evidence was also found for a reduction in central conversion of AI to AII, because the pressor response to AI, in contrast to that to AII, was attenuated in STZ-treated rats (Tomlinson et al., 1990b). This provides evidence, albeit indirect, for a reduction in CNS ACE activity following STZ treatment.

E. Summary

STZ treatment results in changes in the structure and biochemistry of the CNS, which in the past have received little attention but are now being studied more thoroughly. There have, however, been very few studies attempting to relate CNS disorders with changes in physiological function (e.g., cardiovascular regulation, thermoregulation, pain perception, reproductive function, memory, and behaviour), despite ample evidence to suggest that these would reveal interesting results.

Although peripheral neuropathy is well recognised as a complication of clinical diabetes mellitus, the role of central neuropathy in the pathophysiology of this disease is less well understood. However, apart from the immediate and life-threatening effects of acute hypoglycaemia and hyperglycaemia, diabetic patients may be subject to long-term mild hyperglycaemia, unusual swings in blood glucose levels, and other secondary complications of diabetes mellitus that may damage the CNS (Mooradian, 1988). Thus, CNS dysfunction may result from cerebrovascular accident, hypertension, peripheral and autonomic neuropathy, altered cerebral electrolyte content and brain metabolism, changes in neurotransmitters, and altered blood-brain barrier function (Mooradian, 1988). Although the effects of these factors (with the exception of cerebrovascular accident) are likely to be difficult to detect, there is evidence for an impairment in cognitive function in subjects with diabetes mellitus (Mooradian, 1988), and changes in brain monoamine levels similar to, although not identical with, the pattern of change seen in STZ-treated rats (increased noradrenaline, 5-HT, and dopamine in localised regions). Given the difficulties in testing CNS control of physiological functions (such as cardiovascular control) in patients, it is possible that CNS involvement in the complications of diabetes mellitus has been underestimated. In any event, the STZ-treated rat is likely to be particularly useful in determining the effects of diabetes mellitus on brain metabolism, neurotransmitter systems, electrolyte content, and blood-brain barrier function.

VII. Myocardium

STZ treatment causes changes in the intrinsic chronotropic and inotropic properties of the heart and in cardiac adrenoceptor and cholinoceptor populations.

A. Chronotropic Function

The rate of spontaneously beating atria from STZ-treated rats has been shown to be slower than that of atria from control rats (Foy and Lucas, 1978; Jackson et al., 1986; Reid and Lieu, 1991; Yu and McNeill, 1991) as has that of perfused heart preparations (Li et al., 1989; Nicholl et al., 1991). This reduction in spontaneous beating rate may depend on changes in the electrical properties of cardiac tissue from STZ-treated rats, because the duration of the cardiac action potential, measured in atrial or ventricular tissue, was lengthened following STZ treatment (Nordin et al., 1985; Legaye et al., 1988). Myocardial calcium metabolism was also altered following STZ treatment, the uptake of calcium by the sarcoplasmic reticulum being reduced in STZ-treated rats (Ganguly et al., 1983; Lopaschuk et al., 1983) concomitantly with depressed sarcoplasmic reticulum calcium-ATPase activity (Ganguly et al., 1983). Similarly, calcium uptake, calcium-ATPase (Heyliger et al., 1987; Makino et al., 1987), sodium-calcium exchange (Makino et al., 1987), sodium-potassium-ATPase activity (Pierce and Dhalla, 1983), and sodium-hydrogen exchange (Pierce et al., 1990) of sarcolemmal membranes from STZ-treated rats were all diminished. Binding studies

have shown either no change (Yu and McNeill, 1991) or an increase (Nishio et al., 1990) in voltage-sensitive calcium channels in crude membrane extracts of ventricular tissue from STZ-treated rats. However, in the latter study, verapamil failed to displace binding (unlike in control rats), indicating that there may have been a qualitative change in the calcium channels. It is, therefore, possible that changes in calcium metabolism and/or the metabolism of other ions contribute to the altered electrical properties of cardiac tissue isolated from STZ-treated rats (Nordin et al., 1985; Legaye et al., 1988). Moreover, STZ-treated rats showed a reduced sensitivity to the arrhythmogenic effects of ouabain which could be attributable to alterations in ion transport, particularly sodium-calcium exchange (Navaratnam and Khatter, 1989; Khatter and Agbanyo, 1990). Altered myocardial metabolism may also affect the spontaneous beating rate of hearts isolated from STZ-treated rats, because Nicholl et al. (1991) showed that the rate returned to control values if glucose oxidation was improved by the addition of dichloroacetate to the perfusion medium.

B. Inotropic Function

Cardiac contractility and relaxation, represented by +dP/dt and −dP/dt, respectively, and peak ventricular pressure development, were all reduced in hearts isolated from STZ-treated rats (Penpargkul et al., 1980; Vadlamudi et al., 1982; Heyliger et al., 1986; Rodgers, 1986; Rodrigues et al., 1986, 1990), particularly at higher filling pressures. Similar changes in contractile properties of the heart have also been found in vivo in both anaesthetised (Dowell et al., 1986; Paulson et al., 1986) and in conscious (Carbonell et al., 1987; Litwin et al., 1990) STZ-treated rats. Litwin et al. (1990) studied diastolic function in detail. They found that hearts from STZ-treated rats were dilated but that myocardial wall stiffness was unaltered such that there was an overall reduction in "chamber stiffness," i.e., a shift in the exponential pressure/volume relationship for the passively expanded ventricle. This decrease in stiffness was compensated for in vivo by an increase in end-diastolic pressure. Thus, the "operating stiffness" was similar in control and STZ-treated rats. Changes in myocardial contractility were manifest as reductions in cardiac output (both in aortic and coronary flow) in hearts isolated from STZ-treated rats (Penpargkul et al., 1980; Paulson et al., 1987; Li et al., 1989).

Because rats are relatively resistant to atherosclerosis, alterations in cardiac function following STZ treatment are believed to be due to cardiomyopathy, but the underlying biochemical changes are still incompletely understood. Treatment with STZ resulted in a decrease in cardiac myosin-ATPase activity, due to a shift from the more active V_1 myosin isoenzyme to the less active V_3 form (Malhotra et al., 1981; Dillmann, 1982). Because contractile function is thought to be related to myosin-ATPase activity, it is possible that this shift contributed to the diminished cardiac contractility of STZ-treated rats. Recently, Popovich et al. (1989) found that cardiac creatine kinase activity and mRNA levels were reduced following STZ treatment, and they pointed out that this abnormality could limit availability of substrate for myosin-ATPase. The depression of myosin-ATPase could also, in part, be the result of hypothyroidism (see section II.F) because chronic administration of T_3 to rats following STZ treatment prevented the reduction in myosin-ATPase activity and the shift in isoenzyme distribution (Dillmann, 1982). This effect, however, required plasma T_3 concentrations to be increased to supranormal levels. Furthermore, impaired cardiac contractility in STZ-treated rats was not improved by a similar T_3 treatment regimen (Tahiliani and McNeill, 1984).

Changes in cardiac calcium metabolism (see above) may also underlie impaired contractile functioning. Because removal of calcium from myocardial cytoplasm is believed to facilitate cardiac relaxation, it is possible that depression of calcium transport by both the sarcoplasmic reticulum and sarcolemma could lead to impaired cardiac relaxation (Penpargkul et al., 1980; Heyliger et al., 1986; Rodgers, 1986; Rodrigues, et al., 1986). It has also been suggested that reduced calcium uptake by the sarcoplasmic reticulum could lead to diminished calcium stores within this organelle and, hence, to impaired calcium release, with consequent reductions in cardiac contractility (Tahiliani and McNeill, 1986c). Indeed, Bouchard and Bose (1991) found evidence for a reduction in sarcoplasmic reticulum calcium stores and decreased fractional release of calcium during stimulation in STZ-treated rats. Furthermore, limited removal of calcium from cytoplasm by the sarcolemma may lead to intracellular calcium overload and contribute to the further development of diabetic cardiomyopathy (Makino et al., 1987), as may changes in the transport of other ions, such as the reduction in sarcolemmal sodium-hydrogen exchange, which could affect the control of intracellular pH (Pierce et al., 1990).

Diabetes mellitus is associated with changes in myocardial metabolism, in particular, a shift from glucose to fat metabolism (Lopaschuk, 1989). Hence, rats treated with STZ have increased plasma levels of triacylglycerides, cholesterol (Heyliger et al., 1986; Rodrigues et al., 1986; Paulson et al., 1987; Xiang et al., 1988), free fatty acids, and phospholipids (Rodrigues et al., 1986) and increased cardiac triacylglycerol and cholesterol content (Heyliger et al., 1986; Xiang et al., 1988). Changes in the phospholipid content of sarcolemmal membranes from ventricular tissue of STZ-treated rats have also been found, together with an increase in the cholesterol to phospholipid ratio (Makino et al., 1987). In contrast, there was a reduced cholesterol to phospholipid ratio in sarcoplasmic reticular membranes of cardiac ventricular tissue isolated from rats treated with STZ, due to an

increase in the phospholipid content (Ganguly et al., 1983). Phospholipids are important regulators of many membrane enzymes, and the cholesterol to phospholipid ratio is an indicator of membrane fluidity; this in turn affects enzyme function. Thus, altered phospholipid composition and cholesterol to phospholipid ratio following STZ treatment could underlie changes in membrane enzyme function (Ganguly et al., 1983; Pierce and Dhalla, 1983; Makino et al., 1987).

An important influence of fat metabolism on diabetic cardiomyopathy is evident from the observation that the depressed function of hearts isolated from STZ-treated rats was worsened if the perfusion medium contained high levels of free fatty acids, representative of those in diabetic plasma (Paulson et al., 1987). Furthermore, treatments that lower blood lipids, such as exercise (Paulson et al., 1987), hydralazine (Rodrigues et al., 1986), choline and methionine (Heyliger et al., 1986), carnitine (Rodrigues et al., 1990), or myoinositol (Xiang et al., 1988) were all effective in improving cardiac function (assessed by +dP/dt and −dP/dt) in STZ-treated rats. It is by no means certain, however, that other consequences of these treatments [e.g., enhanced thyroid function (Rodrigues et al., 1986)] did not also contribute to improvements in cardiac function. Increased fatty acid levels may also contribute to the increased susceptibility of hearts from STZ-treated rats to ischaemic damage (Lopaschuk and Spafford, 1989).

It is probable that increased fatty acid metabolism reduces cardiac contractility via a detrimental effect on cardiac glucose metabolism. Thus, although inclusion of insulin and/or increased levels of glucose in the perfusion medium did not improve contractile function of hearts isolated from STZ-treated rats (Penpargkul et al., 1980; Tahiliani and McNeill, 1986b), enhancement of glucose oxidation with dichloroacetate normalised contractile function (Nicholl et al., 1991).

Recently, much work has focused on the role of the polyol pathway and of myoinositol in the complications of diabetes mellitus (Raskin and Rosenstock, 1987), including cardiomyopathy (Nakada and Kwee, 1989). Cameron et al. (1989) showed that, in cardiac tissue taken from STZ-treated rats, the rates of contraction and relaxation could be increased toward normal by treatment with inhibitors of aldose reductase. These authors suggested that this could have been due to a direct effect on mobilisation of intracellular calcium stores but ruled out a link with myoinositol, because free myoinositol levels were unaltered in cardiac tissue from the STZ-treated rats in their study. However, others have found that the incorporation of radioactively labeled myoinositol into phosphoinositides was reduced in cardiac tissue from STZ-treated rats, but could be improved by aldose reductase inhibition, and suggested that a reduction in phosphoinositide turnover might also influence cardiac calcium metabolism following STZ treatment (Bergh et al., 1988). In contrast, myoinositol treatment did not improve sarcoplasmic reticulum calcium uptake of hearts isolated from STZ-treated rats, although cardiac function was improved by this treatment (Xiang and McNeill, 1990). Insulin replacement is the most effective treatment for preventing changes in cardiac function following STZ-treatment (Tahiliani and McNeill, 1984; Carbonell et al., 1987). Thus, cardiac complications seen in diabetic rats are likely to depend on multiple factors associated with insulin deficiency.

C. Cardiac Autonomic Receptors

In addition to changes in the contractile machinery of the myocardium, there is much evidence for changes in cardiac autonomic receptor function and/or numbers following STZ treatment.

1. β-Adrenoceptors. Savarese and Berkowitz (1979) were the first to report a decrease (28%) in the number of cardiac β-adrenoceptors 8 weeks after STZ treatment with no change in β-adrenoceptor affinity. It was suggested that this reduction in receptor number might have contributed to the bradycardia also seen in their animals (Savarese and Berkowitz, 1979). Since that time, there have been several reports of diminished cardiac β-adrenoceptor numbers, with no change in affinity, in cardiac tissue taken from rats 2 to 10 weeks after treatment with STZ (Heyliger et al., 1982; Williams et al., 1983; Sundaresan et al., 1984; Atkins et al., 1985; Bitar et al., 1987b; Nishio et al., 1988; Sato et al., 1989). It is likely that these changes develop gradually, because Gøtzsche (1983) found no change in cardiac β-adrenoceptor numbers 8 days after STZ treatment, and Latifpour and McNeill (1984) found a small, nonsignificant decrease in β-adrenoceptor numbers 3 months after STZ treatment but a significant decrease after 6 months. However, it is notable that there appears to be no consistency with regard to the time of onset of changes in β-adrenoceptor numbers in different studies. Neither is there a clear relationship between these changes and the time of onset of bradycardia, which may occur within 4 days of STZ-treatment (Tomlinson et al., 1989c).

Alterations in β-adrenoceptor numbers appear to be relatively restricted to cardiac tissue because no change occurred in the β-adrenoceptor populations of lung membranes from rats treated with STZ (Latifpour and McNeill, 1984). In a study using refinement of earlier approaches, Kashiwagi et al. (1989) measured concentrations of cell surface and total cell β-adrenoceptors of cardiac myocytes 10 weeks after STZ treatment. Although there was a 41% reduction in cell surface-binding sites, there was no difference between STZ-treated and control rats in total cell receptor concentration, suggesting abnormalities in β-adrenoceptor recycling.

In addition to effects on β-adrenoceptor number, STZ treatment may also lead to uncoupling of the β-adrenoceptor from second messenger systems. Gøtzsche (1983)

found that, in cardiac tissue taken 8 days after treatment with STZ, β-adrenoceptor number was unaltered, but cyclic adenosine monophosphate (cAMP) accumulation in response to the β-adrenoceptor agonist, isoprenaline, was diminished. In contrast, Atkins et al. (1985) found that cyclic adenosine monophosphate accumulation in response to isoprenaline was normal in cardiac tissue taken from rats treated 2 weeks previously with STZ, but was impaired 4 weeks after STZ treatment. In that study, there was a similar reduction in β-adrenoceptor number at both times. Because no change in basal cyclic adenosine monophosphate production (Gøtzsche, 1983; Atkins et al., 1985; Nishio et al., 1988) was found following STZ treatment, it was suggested that the defect was in the coupling of β-adrenoceptors to adenylate cyclase. This might have been due to changes in regulatory guanosine triphosphate-binding proteins (Nishio et al., 1988) because there was evidence for an increase in G_i proteins (i.e., those that inhibit adenylate cyclase) in cardiac tissue from STZ-treated rats. Isolated papillary muscle and ventricular tissue from STZ-treated rats also showed attenuated contractile responses to isoprenaline (Heyliger et al., 1982; Yu and McNeill, 1991). Diminished atrial responses to isoprenaline and noradrenaline were also observed following STZ treatment (Goyal et al., 1987; Sato et al., 1989).

In contrast to all the studies noted above, Austin and Chess-Williams (1991) found enhanced responsiveness of isolated papillary muscles and atria from STZ-treated rats to isoprenaline and forskolin and an increase in β-adrenoceptor number. The major difference in methodology was that Austin and Chess-Williams (1991) used female rats in their study: male rats were used in all of the other studies with the exceptions of those of Gøtzsche (1983) and Goyal et al. (1987). Because sex differences are known to occur in various cardiovascular responses mediated by the noradrenergic system (Altura and Altura, 1977; Freedman et al., 1987), it is possible that STZ treatment has different effects in male and female rats (see section IV).

There are several reasons why cardiac adrenoceptor function may be altered following STZ treatment. Although it is possible that enhanced turnover of catecholamines in the myocardium (see section V.B.1) could contribute to adrenoceptor down-regulation, there is much controversy about the effect of STZ on cardiac noradrenaline turnover. Furthermore, when cardiac noradrenaline content and β-adrenoceptor numbers were measured in the same study (Atkins et al., 1985), no change in the former was found at a time when the latter was reduced.

Hypothyroidism following STZ treatment also has been suggested to contribute to the diminished number of cardiac β-adrenoceptors (see section II.F), because rats that had been thyroidectomised prior to STZ treatment developed no further reduction in β-adrenoceptor numbers after STZ treatment (Sundaresan et al., 1984), and administration of T_4 to intact rats following STZ treatment prevented the decrease in cardiac β-adrenoceptor numbers (Sundaresan et al., 1984). The role of hypothyroidism is, however, contentious because reductions in plasma thyroid hormone levels are not temporally related to changes in cardiac β-adrenoceptors, and an insulin regimen that reversed the effects of STZ on cardiac β-adrenoceptors had no effect on plasma thyroid hormone levels (Nishio et al., 1988). Furthermore, Goyal et al. (1987) found that T_3 treatment, at a dose that prevented the development of bradycardia, did not prevent the impairment in atrial chronotropic or inotropic responses to isoprenaline following STZ treatment.

In summary, although there is some consistency among studies in showing reductions in β-adrenoceptor numbers and impaired coupling to second messenger systems and contractile responses, the time course of these changes and the relationships between them are not clear. There have been no comparable studies of the β-adrenoceptors in the vasculature of STZ-treated rats.

2. α-Adrenoceptors. A reduction in cardiac α-adrenoceptor number with no change in affinity occurs following STZ treatment (Heyliger et al., 1982; Williams et al., 1983; Latifpour and McNeill, 1984; Bitar et al., 1987b). The responsiveness of STZ-treated rats to α-adrenoceptor agents may depend on the tissue used because, although the contractility of isolated papillary muscle to the α_1-adrenoceptor agonist, methoxamine, was attenuated following STZ treatment (Heyliger et al., 1982), the α_1-adrenoceptor-mediated chronotropic and inotropic responses of atria or ventricles isolated from STZ-treated rats were enhanced (Canga and Sterin-Borda, 1986; Jackson et al., 1986; Goyal et al., 1987; Xiang and McNeill, 1991; Yu and McNeill, 1991). Discrepancies between the effects of STZ treatment on α-adrenoceptor numbers and responsiveness to α-adrenoceptor agonists may arise because of changes in the activity of second messenger systems. Indeed, it was found that atrial calcium turnover in response to α-adrenoceptor stimulation was enhanced (Jackson et al., 1986), and there were increased atrial and ventricular contractile responses to calcium (Yu and McNeill, 1991) following STZ treatment. Furthermore, inositol (1,4,5) trisphosphate production in response to noradrenaline was enhanced in ventricular tissue isolated from STZ-treated rats (Xiang and McNeill, 1991). In the study by Jackson et al. (1986), phenylephrine in the presence or absence of the β-adrenoceptor antagonist, timolol, was used to assess chronotropic responses. These authors observed that the response to phenylephrine alone was inhibited by timolol to a lesser extent in tissue from STZ-treated rats than in control animals and suggested that, whereas α-adrenoceptor stimulation is normally of little importance in the control of HR, following STZ treatment this may

become increasingly important due to a diminished contribution from β-adrenoceptor stimulation.

Changes in myocardial eicosanoid production have been suggested to underlie altered α-adrenoceptor function in STZ-treated rats. Canga et al. (1985) found that atrial tissue isolated from STZ-treated rats showed an enhanced contractile response to arachidonate in association with a switch from prostacylin production (predominant in control atria) to thromboxane B_2 production. They also observed that the response to arachidonate was attenuated by inhibitors of prostacyclin production in atria from control rats but not from STZ-treated rats and that inhibitors of thromboxane production reduced the response in atria from the latter but not from the former. Similar results were obtained when the effects of prostacyclin and thromboxane inhibitors on the contractile response of atria to methoxamine were studied (Canga and Sterin-Borda, 1986). These findings led to the suggestion that a switch from prostacyclin production to thromboxane B_2 production could underlie the reduced α-adrenoceptor numbers and enhanced sensitivity to α-adrenoceptor stimulation found in atrial tissue from STZ-treated rats. The results of these studies must be interpreted with caution, however, because a very high dose of STZ (100 mg kg^{-1}) was used and rats were studied only 72 h after treatment, although similar results have been obtained recently with lower doses of STZ (Wald et al., 1989). As with cardiac β-adrenoceptors, hypothyroidism may contribute to changes in α-adrenoceptor function, because Goyal et al. (1987) found that T_3 treatment prevented the enhancement in atrial responses to methoxamine seen following STZ treatment. In addition to changes in autonomic neuronal function, prostaglandin production, and hypothyroidism, there are a number of other factors that may be responsible for the abnormalities in cardiac α-adrenoceptor mechanisms, such as changes in cardiac membrane fluidity, and/or nonenzymatic glycosylation of proteins that occur during hyperglycaemia.

3. Cholinoceptors. Cardiac muscarinic receptors are also affected by STZ treatment. Carrier and Aronstam (1987) found a decrease (34%) in muscarinic receptor number in atria from rats treated with STZ 8 to 10 weeks earlier. Similarly, Kofo-Abayomi and Lucas (1987) showed that atrial muscarinic receptor number was reduced (with no change in affinity) 6 weeks after STZ treatment. At this early time, changes in muscarinic receptors appeared to be limited to the atria because there were no reductions apparent in whole heart (Williams et al., 1983) or ventricles (Carrier et al., 1984), although Latifpour and McNeill (1984) found a decrease in ventricular muscarinic receptor numbers in rats 6 months after treatment with STZ.

Functional changes in cardiac cholinergic mechanisms may also occur following STZ treatment. Vadlamudi and McNeill (1983) saw no change in the negative inotropic effect (as measured by the reduction in +dP/dt) of the muscarinic agonist, carbachol, in the perfused heart isolated from rats treated 7 and 30 days previously with STZ, whereas after 100 days there was a reduction in cardiac sensitivity to carbachol. In contrast, at 180 and 300 days after STZ treatment, sensitivity to the negative inotropic effects of carbachol had increased. It was suggested that at this later time the increased carbachol sensitivity was due to the development of parasympathetic neuropathy (see section V) and consequent denervation supersensitivity. In the earlier stages following STZ treatment, it is possible that enhanced vagal activity could lead to muscarinic receptor down-regulation. Evidence in favour of this proposition was provided by Kofo-Abayomi and Lucas (1988) who found that, whereas atria isolated from rats 6 weeks after STZ treatment were less sensitive than control tissue to the negative inotropic effects of exogenous acetylcholine, the response to transmural nerve stimulation in the presence of the β-adrenoceptor antagonist, propranolol, was greater in atria from STZ-treated rats than from control rats. This raises the possibility that release of acetylcholine during transmural stimulation was enhanced in STZ-treated animals, consistent with the finding that myocardial acetylcholine and choline concentrations and choline acetyltransferase activity were increased 8 weeks after STZ treatment (Akiyama et al., 1989).

The negative chronotropic effects of muscarinic agonists have also been investigated. Carrier and Aronstam (1987) found that atria isolated from rats treated with STZ 8 to 10 weeks previously showed enhanced negative chronotropic responses to acetylcholine, carbamylcholine, and bethanechol, whereas the negative inotropic responses to these muscarinic agonists were unaltered. Similarly, Li et al. (1989) showed that the negative chronotropic effects of the cholinergic agent, methacholine, were enhanced 6 to 52 weeks after STZ treatment. Because muscarinic receptor number was found to be decreased in the study of Carrier and Aronstam (1987), it was suggested that the coupling of muscarinic receptors to transduction mechanisms involved in the negative chronotropic effects was altered following STZ treatment. However, more recently, Aronstam and Carrier (1989) observed that there was a decreased proportion of cholinoceptors in the high-affinity state. Bergh et al. (1988) found that myoinositol-1-phosphate release from cardiac tissue following muscarinic receptor stimulation with carbachol was unaltered following STZ treatment, which suggests that no change in coupling to phosphoinositide breakdown had occurred. It is possible, however, that coupling of cholinergic receptors to adenylate cyclase is altered in STZ-treated rats, because the content of G_i proteins in cardiac tissue has been found to be increased following STZ treatment (Nishio et al., 1988). It is noteworthy that, in other tissues (adipose tissue and hepatocytes), evidence has been found for a reduction in

G_i protein content and activity (Gawler et al., 1987; Green and Johnson, 1991) following STZ treatment.

D. Summary

It is now well established that STZ-treated rats have defects in the intrinsic electrical and contractile properties of the heart and in adrenoceptor and cholinoceptor populations; these effects may lead to impaired cardiac function.

It has long been known that patients with diabetes mellitus have an increased risk of mortality from cardiac failure that cannot simply be explained in terms of other risk factors (atherosclerosis, hyperlipidaemia, or hypertension) (Kannel et al., 1974). Pathological and physiological studies have provided evidence for cardiomyopathy in clinical diabetes mellitus (Fein and Sonnenblick 1985; Crepaldi and Nosadini, 1988; Jarrett, 1989; Zarich and Nesto, 1989) that may be manifest as impaired ventricular function, even before clinical signs of cardiac failure develop. Evidence for diminished left ventricular contractility, prolonged relaxation, and impaired ventricular filling has been found in diabetic patients (Fein and Sonnenblick 1985; Crepaldi and Nosadini, 1988). As with STZ-treated rats, these changes become more apparent with increased cardiac load, such as during exercise (Vered et al., 1984; Zola et al., 1986). Although impaired cardiac function in diabetic patients is likely to depend on a number of factors including atherosclerosis, microangiopathy, and autonomic neuropathy, there is also direct evidence for myopathic changes in cardiac myocytes (Gøtzsche, 1986).

Because it is virtually impossible to examine myocardial cell function in diabetic patients soon after the onset of the disease, studies in STZ-treated rats are vital to discover what biochemical changes in cardiac tissue might underlie cardiomyopathy. From the experimental data reviewed here, it is clear that more detailed investigations of changes in calcium handling and their causes could provide information that might be useful in the control of diabetic cardiomyopathy. In addition, new areas of study should include the role of regulatory G proteins and the polyol pathway in the further development of diabetic cardiac complications.

VIII. Vasculature

STZ treatment results in changes in vascular reactivity to both vasoconstrictor and vasodilator agents. Altered vascular reactivity might be due to changes in vascular smooth muscle contractility and/or in endothelial cell function; these are considered separately below. Unfortunately, because of the methodological difficulties involved, there have been no reported receptor-binding studies in the vasculature from STZ-treated rats.

A. In Vitro Studies of Vascular Smooth Muscle Function

1. Vasoconstrictor mechanisms. Because interesting regional differences in vascular reactivity (possibly of physiological relevance) have been observed in STZ-treated rats, the following sections consider different preparations separately.

a. AORTA. The aorta is a large conduit vessel and as such may not provide a suitable model for studying changes in vascular reactivity that would be of the greatest functional relevance in terms of the control of blood flow or BP. In spite of this, most studies of the effects of STZ treatment on vascular reactivity have been carried out using aortic tissue. Although these investigations have failed to produce consistent results, they do illustrate methodological considerations that must be taken into account when assessing the effects of STZ treatment on vascular reactivity.

Aortae from STZ-treated rats have been found to show attenuated maximal contractile responses to noradrenaline, phenylephrine, methoxamine, 5-HT, calcium, and potassium (Pfaffman et al., 1982; Ramanadham et al., 1984; Oyama et al., 1986; Head et al., 1987a; Wakabayashi et al., 1987), although no changes in sensitivity (ED_{50} values) to noradrenaline, methoxamine, or 5-HT were found in those studies (Ramanadham et al., 1984; Head et al., 1987a). In contrast, others have observed increased maximal contractile responses to noradrenaline or methoxamine in aortic tissue from STZ-treated rats (Owen and Carrier, 1980; Scarborough and Carrier, 1984; MacLeod, 1985; Harris and MacLeod, 1988; Legan, 1989; Abebe et al., 1990), with no change (Scarborough and Carrier, 1984; MacLeod, 1985; Abebe et al., 1990) or an increase in sensitivity (Owen and Carrier, 1980; Harris and MacLeod, 1988; Legan, 1989). Enhanced responses to 5-HT following STZ treatment were also seen in one study (Legan, 1989). However, this enhancement was not the result of a generalised increase in contractility because responses to potassium (Legan, 1989) or calcium (MacLeod, 1985) were unaltered. Hebden et al. (1988b) reported that responses to AVP, methoxamine, or potassium chloride were all normal in aortae from rats treated with STZ 3 weeks previously.

Various explanations have been put forward to account for the differences between results. The method of expressing data has varied between studies, contractile force being expressed in absolute terms or relative to tissue weight, protein content, or cross-sectional area. Because aortic wet weight (Scarborough and Carrier, 1984; Oyama et al., 1986; Head et al., 1987a; Mulhern and Docherty, 1989) and cross-sectional area (MacLeod, 1985; Harris and MacLeod, 1988) were found to be reduced following STZ treatment, the expression of results in relative or absolute terms could lead to differing conclusions being drawn about the effects of STZ treatment on vascular contractility. Indeed, Mulhern and Docherty (1989) showed that contractile responses of aortic tissue from STZ-treated rats to noradrenaline, 5-HT, and potassium were enhanced when expressed relative to tissue weight but not when expressed in absolute

terms. This cannot account entirely for the discrepancies among studies, however, because others have found impaired contractile responses to noradrenaline and 5-HT when the results were expressed relative to tissue weight (Head et al., 1987a). Furthermore, Mulhern and Docherty (1989) did not find the selective increase in contractile responses to noradrenaline and 5-HT that was observed by others (MacLeod, 1985; Legan, 1989).

The presence or absence of a functional vascular endothelium has also been proposed to contribute to discrepancies among studies. Harris and MacLeod (1988) reported an enhancement in contractile responses of aortae from STZ-treated rats to noradrenaline and methoxamine in the presence, but not in the absence, of an intact endothelium. This contrasts with the results of Mulhern and Docherty (1989), who found that removal of the endothelium did not affect the differential responsiveness of aortae from STZ-treated and control rats, and the findings of Scarborough and Carrier (1984), who saw no enhancement in the contractile responses of aortae from STZ-treated rats to methoxamine in the presence of an intact endothelium. Although integrity of the vascular endothelium may not provide a simple explanation for discrepancies among studies, there is much evidence for alterations in endothelial cell function following STZ treatment (see section VIII.C). It is, therefore, necessary to consider endothelial function when comparisons are made between vascular reactivity of tissue isolated from control and STZ-treated rats.

The composition of bathing media is another aspect of methodology that has varied in different studies of vascular reactivity. Some investigators have included β-adrenoceptor antagonists and catecholamine uptake inhibitors in the medium (Harris and MacLeod, 1988; Mulhern and Docherty, 1989), whereas in the other studies cited above they were not included. Although there is no straightforward relationship between the presence or absence of β-adrenoceptor antagonists and uptake inhibitors and the results obtained (i.e., decreased or increased vascular reactivity in STZ-treated rats), there is some evidence for a decrease in β-adrenoceptor-mediated vasodilation (Kamata et al., 1989a) and an increase in noradrenaline uptake in vascular tissue from STZ-treated rats (Hart et al., 1988) which could interfere with interpretation of results from experiments in which β-adrenoceptor antagonists and uptake blockers were not included.

Overall, aortic preparations from STZ-treated rats have been observed to show either a generalised reduction in contractility or a specific enhancement of responses to some vasoconstrictors. The mechanisms behind these changes are unclear, but in the former case there may have been a defect in the contractile machinery, perhaps due to disruption of contractile proteins; in the latter case, specific receptor and second messenger systems may have been altered.

Scarborough and Carrier (1984) suggested that the increased reactivity to noradrenaline that they observed in aortae isolated from STZ-treated rats was due to changes in handling of extracellular calcium. They observed that contractile responses to noradrenaline or the selective α_2-adrenoceptor agonist, clonidine, were enhanced in aortae from STZ-treated rats and were inhibited by the calcium channel blocker, nifedipine, to a greater extent than those of control tissue. In contrast, contractile responses to the selective α_1-adrenoceptor agonists, methoxamine and phenylephrine, were unaltered following STZ treatment (Scarborough and Carrier, 1984), suggesting that, following STZ treatment, influx of extracellular calcium (mediated by stimulation of α_2-adrenoceptors) was enhanced but that there was no effect on the mobilisation of intracellular calcium stores (mediated by stimulation of α_1-adrenoceptors). Similar results were obtained by Legan (1989) who found enhanced responses to noradrenaline, but no changes in phenylephrine-mediated contractions, in aortae from STZ-treated rats. In that study, it also was observed that the increase in phosphatidylinositol turnover following noradrenaline or phenylephrine stimulation was impaired in aortic tissue from STZ-treated rats, providing further evidence that changes in intracellular calcium mobilisation did not mediate the enhanced responsiveness to noradrenaline. The situation is obviously not that simple, however, because, as stated above, others have shown enhanced responses to α_1-adrenoceptor agonists. Indeed, Abebe et al. (1990), using yohimbine and prazosin to antagonise contractile responses to noradrenaline, stated that these responses were mediated by α_1-adrenoceptors in both control and STZ-treated rats. In addition, they agreed that the enhanced contractile responses of aortae from STZ-treated rats to noradrenaline were, for the most part, dependent on extracellular calcium. However, Abebe et al. (1990) also noticed that, at maximal concentrations of noradrenaline in calcium-free medium (when contraction is dependent on release of calcium from intracellular stores), the responses of aortae from STZ-treated rats were enhanced relative to controls. Thus, under these conditions, mobilisation of intracellular calcium stores also may be increased following STZ treatment. This is consistent with some observations [but contrasting with those of Legan (1989)] of enhanced inositol phosphate production following stimulation with noradrenaline in aortae from STZ-treated rats (Head et al., 1987b; Abebe and MacLeod, 1990).

b. MESENTERIC VESSELS. Isolated mesenteric arteries from STZ-treated rats showed enhanced maximal contractile responses to noradrenaline (MacLeod, 1985; Agrawal and McNeill, 1987a,b; Harris and MacLeod, 1988; White and Carrier, 1988, 1990), to the α_1-adrenoceptor agonists, methoxamine and phenylephrine (Agrawal and McNeill, 1987a,b; Harris and MacLeod, 1988; White and Carrier, 1988), to the α_2-adrenoceptor ago-

nists, clonidine and guanabenz (Agrawal and McNeill, 1987a,b; White and Carrier, 1988), to 5-HT, and to potassium (Agrawal and McNeill, 1987a,b; White and Carrier, 1990), with no change in the affinities for these agonists (Agrawal and McNeill, 1987a,b; Harris and MacLeod, 1988; White and Carrier, 1988, 1990). As with aortae, it was suggested that increased contractility of mesenteric arteries from STZ-treated rats was due to an increased sensitivity to extracellular calcium, because the contractile responses to calcium channel activation or to calcium were also enhanced (Agrawal and McNeill, 1987a; White and Carrier, 1990). Furthermore, in the absence of extracellular calcium, there were no differences in the contractile responses of mesenteric arteries from STZ-treated and control rats to α-adrenoceptor agonists (White and Carrier, 1988, 1990). In addition, mesenteric arteries from STZ-treated rats showed enhanced contractile responses to stimulation of protein kinase C with phorbol esters (Abebe and MacLeod, 1990; White and Carrier, 1990) in the absence, but not in the presence, of nifedipine or verapamil (Abebe and MacLeod, 1990). Inhibition of protein kinase C abolished the enhanced responsiveness of mesenteric arteries from STZ-treated rats to noradrenaline, implying that α_1-adrenoceptor-linked mechanisms mediated the increased responsiveness in this tissue (Abebe and MacLeod, 1990). Interestingly, the latter finding was also observed in aortae from STZ-treated rats, but in this tissue the response to phorbol esters was unaltered (Abebe and MacLeod, 1990). Thus, in aortae the alterations in the transduction mechanisms may be restricted to the earlier steps, whereas in mesenteric arteries later stages of the transduction process may also be involved. This could explain why responses to potassium were increased in the latter but not the former tissue.

Agrawal and McNeill (1987b) suggested that changes in eicosanoid synthesis might contribute to the enhanced responses of arteries from STZ-treated rats because, in the presence of indomethacin, there were no differences in the maximal contractile responses of mesenteric arteries from control or STZ-treated rats. As with studies using aortic tissue, there is disagreement regarding the involvement of the vascular endothelium. For example, Harris and MacLeod (1988) noted that aortae and mesenteric arteries isolated from STZ-treated rats only displayed increased contractile responsiveness to noradrenaline if the endothelium was left intact, whereas White and Carrier (1988) found that contractile responses of mesenteric arteries from STZ-treated rats were enhanced in the presence and in the absence of the endothelium.

In contrast to the observations of enhanced responses of mesenteric arteries from STZ-treated rats, studies using perfused mesenteric vascular beds have shown diminished responses to vasoconstrictors following STZ treatment. Reductions in the maximal contractile response to noradrenaline and 5-HT (Takiguchi et al., 1989) and in the sensitivity to noradrenaline (Longhurst and Head, 1986; Korthuis et al., 1987) were found. These results highlight the dangers of using large blood vessels to assess changes that may be of functional relevance to the control of blood flow through individual vascular beds following STZ treatment.

c. OTHER VESSELS. In general, in agreement with the work on mesenteric arteries, other vascular tissues from STZ-treated rats have shown enhanced responsiveness to noradrenaline. Bhardwaj and Moore (1988) saw increases in the maximal contractile response and in the sensitivity to noradrenaline of isolated perfused kidneys from STZ-treated rats. In that study, indomethacin was included in the medium, so possible effects of changes in eicosanoid production on the reactivity of the renal vasculature (see section III.A) would have been masked. Quilley and McGiff (1990) showed an increase in the contractile response of isolated kidneys from STZ-treated rats to low doses of phenylephrine, although the maximal response was unaffected. It was also observed that the vasoconstrictor response to arachidonic acid was enhanced because of increases in production of, and responsiveness to, endoperoxides in tissue isolated from STZ-treated rats (Quilley and McGiff, 1990). However, Sarubbi et al. (1989) found that indomethacin did not affect significantly the depressed vasoconstrictor responses to AVP or AII of kidneys from rats treated with STZ.

Increases in contractility and sensitivity to noradrenaline were observed in the isolated perfused hindquarters (Friedman, 1989) and in the caudal artery (Ramanadham et al., 1984) of STZ-treated rats. Ramanadham et al. (1984) suggested that the enhanced responsiveness that they observed was due to denervation supersensitivity following neuropathy (see section V), because they found a reduction in catecholamine content of caudal arteries from STZ-treated rats, and contractile responses to potassium were unaltered. However, Hart et al. (1988), despite finding clear evidence of impaired neuronal function (reduced noradrenaline content and contractile responses to transmural nerve stimulation and tyramine), saw no change in the sensitivity to noradrenaline, and a decrease in the maximum contractile response to noradrenaline, of caudal arteries of STZ-treated rats.

Recently, there have been some reports of experiments utilising smaller resistance vessels. For example, Morff (1990) studied cremasteric muscle arterioles in vivo and found no change in the sensitivity of larger arterioles to noradrenaline, although sensitivity of smaller vessels was reduced in STZ-treated rats. Such results emphasise the need to consider changes in all areas of the circulation following STZ treatment. Intrinsic properties of the microvasculature may also be altered following STZ treatment because myogenic contraction was delayed in arterioles from STZ-treated rats, although the mechanism for this is unknown (Hill et al., 1990).

2. Vasodilator mechanisms. Aortic rings prepared from rats with STZ-induced diabetes mellitus showed reduced relaxation to acetylcholine, adenosine diphosphate, histamine, and the calcium ionophore, A23187, but not to sodium nitroprusside, glyceryl trinitrate, papaverine, or ANP (Oyama et al., 1986; Pieper and Gross, 1988; Kamata et al., 1989b). Classically, these results would be taken to indicate a selective impairment of "endothelium-dependent" vasorelaxation. However, there is now evidence that diminished nitric oxide production by endothelial cells (see section VIII.C) causes supersensitivity to organic nitrates (Moncada et al., 1991b; Gardiner et al., 1991a); thus, no change (Oyama et al., 1986; Bhardwaj and Moore, 1988; Takiguchi et al., 1988; Kamata et al., 1989b) or a reduction in sensitivity to nitroprusside (Hill et al., 1990) may indicate an abnormality of guanylate cyclase-mediated vasorelaxation. Furthermore, in other studies, acetylcholine-induced relaxation of noradrenaline-contracted aortic rings from STZ-treated rats has been found to be normal (Head et al., 1987a; Wakabayashi et al., 1987; Harris and MacLeod, 1988; Mulhern and Docherty, 1989). Thus, there is no consensus regarding abnormalities of these vasodilator mechanisms in STZ-treated rats. However, it is apparent that, even under normal conditions, the mechanisms involved in classical endothelium-dependent vasodilator processes may be more complex than previously suspected (Gardiner et al., 1990c, 1991a). Vasodilation in response to isoprenaline has been reported to be impaired in the aorta (Kamata et al., 1989a), mesenteric vascular bed (Takiguchi et al., 1988), and pancreatic vascular bed (Gross et al., 1991) of STZ-treated rats. Vasodilation in response to forskolin was also attenuated in pancreatic vascular beds from STZ-treated rats (Gross et al., 1991). Thus, as in cardiac tissue (see section VII.C.1), there may be a reduction in β-adrenoceptor-mediated responses in vascular tissue following STZ treatment. It is noteworthy that β-adrenoceptor-mediated vasodilation (Gardiner et al., 1991a,b) and cardiac β-adrenoceptor-mediated effects (Gardiner et al., 1991b) may be transduced, in part, by nitric oxide.

Local autoregulation of the vasculature also may be abnormal following STZ treatment because vasodilator responses to adenosine in the perfused pancreatic preparation (Gross et al., 1989) and to prostanoids (prostacyclin and prostaglandin E_2) in cremasteric muscle arterioles (Hill and Larkins, 1989b; Hill et al., 1990) were reduced. The extent to which changes in endothelium-mediated relaxation following STZ treatment (see section VIII.C) may also affect autoregulation is unknown.

B. In Vivo Studies of Vascular Smooth Muscle Function

The response of the vasculature in vivo to various vasoactive agents has been measured following STZ treatment. Hayashi et al. (1983) found that conscious rats treated 1 week previously with STZ showed a diminished pressor response to noradrenaline compared with control rats, although 4 weeks after STZ treatment responses were normal. Ramos (1988) found impaired responsiveness to noradrenaline 3 and 6 weeks after STZ, but normal responses were found 12 weeks after STZ treatment. Because both of these studies were carried out in rats with intact baroreflexes, it is not certain whether the decreased pressor response was straightforwardly due to a reduction in vascular sensitivity to noradrenaline. However, Jackson and Carrier (1983) performed similar studies in both intact and ganglion-blocked rats and found that the response of STZ-treated rats to noradrenaline remained attenuated even in the absence of baroreflexes. This was confirmed by Hebden et al. (1987b) who found impaired responses to the α_1-adrenoceptor agonist, methoxamine, in both intact and ganglion-blocked STZ-treated rats. Furthermore, Lucas (1985) showed that the diminished pressor response of pithed STZ-treated rats to noradrenaline was due to abnormal changes in total peripheral resistance, because there was no change in cardiac output following noradrenaline infusion. The work of Lucas (1985) also revealed interesting differences in the regional responses to noradrenaline; for example, noradrenaline-induced vasoconstrictions were reduced in the intestine, kidneys, and skin of STZ-treated rats but enhanced in vessels of the leg muscle and tail. These results accord with some of the in vitro studies cited above showing impaired responses of mesenteric vasculature from STZ-treated rats to noradrenaline (Longhurst and Head, 1986; Korthuis et al., 1987; Takiguchi et al., 1989) but enhanced responses in the perfused hindquarters (Friedman, 1989) and caudal artery (Ramanadham et al., 1984).

Pressor responses to AVP (Buñag et al., 1982; Hebden et al., 1987b; Ramos, 1988) and AII (Jackson and Carrier, 1983; Hebden et al., 1987b; Ramos, 1988), and depressor responses to isoprenaline (Foy and Lucas, 1976; Jobidon et al., 1989) have also been found to be attenuated following STZ treatment. Depressor responses to arachidonic acid infusion were reduced following STZ treatment, possibly due to a shift from vasodilator to vasoconstrictor prostanoid production (Law and King, 1990). In recent studies, the depressor response to glyceryl trinitrate was found to be unaltered in conscious (Kiff et al., 1991b), or decreased in anaesthetised (Bucala et al., 1991), STZ-treated rats. In the study of Kiff et al. (1991b), depressor responses to acetylcholine and bradykinin were also normal in conscious, STZ-treated rats, whereas Bucala et al. (1991) found a diminished hypotensive response to acetylcholine. There is no obvious explanation for the disparities between these results, especially because Bucala et al. (1991) produced evidence that the abnormalities in their STZ-treated rats were due to advanced glycosylation end products, i.e., effects that should be apparent under all experimental conditions.

Generally, in vivo, STZ-treated rats have a reduced total peripheral resistance and increased regional blood flows (Carbonell et al., 1987). However, blood flow in various vascular beds is affected differentially and may be related to the regional variations in altered vascular contractility discussed above, as well as to factors such as intestinal hypertrophy (Kiff et al., 1991a,b). These will be discussed in more detail in section IX.B.

C. In Vitro and in Vivo Studies of Endothelial Function

Under normal conditions, vascular smooth muscle responses to various stimuli may be influenced by endothelial cell function (Furchgott and Vanhoutte, 1989), both by the release of EDRFs and endothelium-derived contracting factors. There is now compelling evidence that nitric oxide produced from L-arginine is the major EDRF and probably the endogenous activator of cyclic guanosine monophosphate formation in many cell types (Moncada et al., 1988a,b, 1989, 1991a; Moncada and Higgs, 1990). L-Arginine and nitric oxide may be of major importance in the diabetic state, because L-arginine also has profound effects on insulin and glucagon secretion (Moncada et al., 1989), and nitric oxide is involved in controlling cell replication (Garg and Hassid, 1989). In addition to effects on vascular reactivity in diabetes mellitus, disorders of endothelial cell function appear to contribute to increased vascular permeability, altered haemostasis, aberrant angiogenesis, changes in the local production of ACE, and so on (Porta et al., 1987; Lorenzi and Cagliero, 1991).

There is now much evidence for alterations in endothelium-dependent vasodilation following STZ treatment. For example, Oyama et al. (1986), investigating aortic rings from rats treated previously with STZ, found significant reductions in the relaxations to acetylcholine and histamine. There was no change in the response to sodium nitroprusside, and scanning electron microscopy indicated that the endothelial cell surface structure was normal in STZ-treated rats. Oyama et al. (1986) considered that these results were best accounted for by "metabolic changes in EDRF," although they thought EDRF was probably produced from arachidonic acid (see below). These results differ from those of others (Head et al., 1987a; Wakabayashi et al., 1987; Mulhern and Docherty, 1989) who found no change in relaxation in response to acetylcholine in aortae from STZ-treated rats. However, the results of Oyama et al. (1986) were confirmed by Kamata et al. (1989b) who also showed decreased basal and acetylcholine-stimulated cyclic guanosine monophosphate production in aortic strips from STZ-treated rats. Because the relaxant responses to ANP and sodium nitroprusside were unchanged in this study, it is likely that the attenuated responses to acetylcholine were due to decreased production of nitric oxide from the endothelium of STZ-treated rats. In contrast, Harris and MacLeod (1988) found no change in either basal or acetylcholine-stimulated cyclic guanosine monophosphate production in aortae from STZ treated rats, although elevated glucose levels have been found to impair endothelium-dependent relaxation in rabbit aortae (Tesfamariam et al., 1991).

As with vascular smooth muscle contractility, it is feasible that endothelial cell function in different vascular beds does not change uniformly after STZ treatment. For example, Bhardwaj and Moore (1988) suggested that EDRF release in response to acetylcholine was increased in isolated perfused kidneys from STZ-treated rats. They excluded hyperresponsiveness to EDRF because sodium nitroprusside (which produces nitric oxide) had the same effect in control kidneys and in those from STZ-treated rats. Similarly, White and Carrier (1986) found enhanced relaxation elicited by histamine in the superior mesenteric artery isolated from rats treated with STZ. In contrast to the enhanced responses seen in visceral vasculature (White and Carrier, 1986; Bhardwaj and Moore, 1988), Mayhan and coworkers (Mayhan, 1989; Mayhan et al., 1991) found clear evidence of impaired vasodilator responses to endothelium-dependent stimuli (acetylcholine, 5-HT, and adenosine) in cerebral arterioles in vivo in STZ-treated rats. Such conflicting reports will only be resolved when experiments that investigate, simultaneously, endothelial cell integrity in various vascular beds are carried out.

The mechanisms underlying altered endothelium-dependent relaxation following STZ treatment are incompletely understood. Increased production of vasoconstrictor prostaglandins (see later) might oppose endothelium-dependent relaxation in STZ-treated rats. In addition, there may be changes in the production and/or breakdown of nitric oxide itself. It has been suggested that the products of nonenzymatic glycosylation quench nitric oxide both in vitro and in vivo (Bucala et al., 1991). Recently, there has been a great deal of interest in the role of free radicals in the pathogenesis of the complications of diabetes mellitus (Baynes, 1991). Oxygen-derived free radicals enhance the breakdown of nitric oxide (Stewart et al., 1988; McCall et al., 1989). Thus, it is feasible that the dynamics of the nitric oxide system are different in STZ-treated and control rats. Indeed, STZ-treated rats were more susceptible than control rats to inhibition of endothelium-dependent relaxation following exposure to a free radical-generating system (Pieper and Gross, 1988) and showed increased vasodilation when free radicals were removed with superoxide dismutase (Langenstroer and Pieper, 1990). Recently, Hattori et al. (1991) reported that peak relaxations to acetylcholine, histamine, or adenosine diphosphate were not different in noradrenaline-preconstricted rings of thoracic aortae from control and STZ-treated rats, but the responses were more transient in the latter. Pretreatment with superoxide dismutase enhanced peak relaxations, and durations of relaxant responses, in both

groups, but under those conditions the responses in preparations from STZ-treated rats were not different from those of control animals. In aortae with the endothelial cells removed, nitric oxide caused peak relaxations that were similar in both groups, but, once again, the response was more transient in the preparations from STZ-treated rats. This relaxant response was prolonged in the presence of superoxide dismutase. Hence, these findings are entirely consistent with those of Pieper and Gross (1988) and Langenstroer and Pieper (1990).

Depressor responses to acetylcholine have either been found to be attenuated in anaesthetised or pithed STZ-treated rats (Foy and Lucas, 1976; Bucala et al., 1991) or unaltered in conscious STZ-treated rats (Kiff et al., 1991b). However, Kiff et al. (1991a) showed that the pressor response to inhibition of nitric oxide production with N^G-nitro-L-arginine methyl ester was attenuated in STZ-treated rats. Simultaneous haemodynamic measurements showed that in response to N^G-nitro-L-arginine methyl ester the hindquarter vasoconstriction was impaired in STZ-treated rats, although the decreases in renal and mesenteric vascular conductances were similar to those in control rats. In another study, Kiff et al. (1991b) found that, despite similar depressor responses, STZ-treated rats failed to show the hindquarter vasodilation that was observed in control rats in response to bradykinin. Because hindquarter vasodilator responses to bradykinin are particularly dependent on nitric oxide production (Gardiner et al., 1990c), these observations, together with that of resting hindquarter vasoconstriction in STZ-treated rats (Kiff et al., 1991a,b), point to impaired production and/or responsiveness to nitric oxide in the hindquarter vascular bed of the STZ-treated rat. However, recent observations (Gardiner et al., 1991c) indicate that a component of the normal hindquarter vasodilator response to bradykinin is mediated by β_2-adrenoceptors, and the effects of the latter are transduced, in part, by nitric oxide. Thus, it is feasible that impaired adrenal medullary adrenaline release (or action) in response to bradykinin could contribute to the impaired hindquarter vasodilator response to this peptide in STZ-treated rats.

A recent report from Lash and Bohlen (1991) indicates that iontophoretic application of acetylcholine onto the intestinal arterioles in adult rats, treated either 8 to 11 days or 7 to 8 weeks previously with STZ, evoked diminished vasodilator responses. However, in all other respects, including vasodilator responses to bradykinin or sodium nitroprusside, diabetic rats appeared normal. Clearly, methodological differences could account for the apparent contradiction between these results and those of Kiff et al. (1991a,b).

Although STZ itself may cause nitric oxide-mediated vasodilation (Thomas and Ramwell, 1989), this is not likely to have influenced results obtained in STZ-treated rats because the half-life of STZ in vivo is short, and STZ at a concentration of 50 mM was without effect in the isolated perfused kidney (Bhardwaj and Moore, 1988).

Nitric oxide is not the only vasoactive factor synthesised by endothelial cells; both vasodilator and vasoconstrictor eicosanoids are produced, but the former do not appear to contribute to relaxation evoked by acetylcholine in aortic preparations from STZ-treated rats (Oyama et al., 1986). However, Mayhan et al. (1991) found that the impairment in endothelium-dependent vasodilator responses of cerebral arterioles from STZ-treated rats to acetylcholine and adenosine could be reversed with indomethacin or a thromboxane A_2 antagonist. Although there is evidence for altered eicosanoid activity in vascular tissues from STZ-treated rats (Myers et al., 1985; Fujii et al., 1986), such studies, and those concerned with circulating eicosanoid levels (Axelrod et al., 1986), do not localise the problem to endothelial cells.

It is now known that endothelial cells also produce peptides, such as endothelin, that have potent direct vascular effects (Yanagisawa et al., 1988; Inoue et al., 1989) and also stimulate release of EDRF and eicosanoids (De Nucci et al., 1988). The regional haemodynamic effects of the different endothelins and of the related sarafotoxins involve complex interactions among several mechanisms in vivo in conscious rats (Gardiner et al., 1990a,b); hence, there are several ways in which the endothelins could be involved in cardiovascular disorders in clinical diabetes mellitus and following STZ treatment.

Recent studies have shown that plasma endothelin levels are elevated in rats following STZ treatment and that endothelin release from isolated mesenteric arteries is increased (Takeda et al., 1991). However, endothelin-binding sites on cardiac membranes from STZ-treated rats appear to be reduced (Nayler et al., 1989). Inotropic and chronotropic responses to endothelin were similar in atria isolated from STZ-treated and control rats, as was the inhibition of responses to noradrenaline by endothelin (Reid and Lieu, 1991), but endothelin attenuated atrial responses to transmural nerve stimulation to a lesser extent in the former than in the latter group (Reid and Lieu, 1991). The pressor response to endothelin in vivo was similar in STZ-treated and control rats, although the underlying haemodynamic changes differed in that STZ-treated rats showed a greater decrease in renal and mesenteric conductances and, hence, by inference, a greater decrease in cardiac output than control rats (Kiff et al., 1991a). In addition to effects on the vasculature and the heart, endothelin may have indirect effects on altered cardiovascular control following STZ treatment via an action the kidney (Brenner et al., 1989).

D. Summary

Although there is much controversy, studies of vascular reactivity in STZ-treated rats have revealed changes

in both vasoconstrictor and vasodilator responses. Those results obtained from large vessels in vitro are difficult to extrapolate to function in vivo, because in the latter case other factors, such as the release of vasoactive agents and/or the structure of the vascular bed, may also influence the results. In addition, STZ-treated rats have increased plasma glucose levels and osmolality (Hebden et al., 1986), both of which may cause vasodilation (Korthuis et al., 1987; Friedman, 1989). It is, therefore, surprising that, in all the in vitro studies (cited above) of vascular reactivity using isolated vessels, a similar bathing medium was used for control tissue and for tissue from STZ-treated rats. More interesting and relevant results might have been obtained had the composition of the bathing medium been adjusted to represent the extracellular fluid of the animals from which the tissues were obtained. Indeed, this could explain the difference between results obtained for noradrenaline reactivity using isolated mesenteric arteries or perfused mesenteric vascular beds, because Korthuis et al. (1987) suggested that the decreased reactivity to noradrenaline that they observed in mesenteric vascular beds from STZ-treated rats was due to an inhibitory influence of hyperglycaemia or hyperglucagonaemia.

Patients with diabetes mellitus develop disorders of the vasculature, including macroangiopathy and microangiopathy (see Kastrup, 1988; Jarrett, 1989), both of which may contribute to other long-term complications, such as cardiac failure, hypertension, retinopathy, neuropathy, and nephropathy (Crepaldi and Nosadini, 1988; Kastrup, 1988). STZ-treated rats do not provide a good model for the factors contributing to macroangiopathy because rats are relatively resistant to the development of atherosclerosis. Furthermore, it is possible that long-term insulin treatment, rather than the primary insulin deficiency, leads to atherosclerosis in diabetic patients (Stout, 1979). However, STZ-treated rats given deoxycorticosterone acetate develop atherosclerosis associated with hypertension and increased plasma lipid and cholesterol levels (greater than those in rats treated with STZ alone). This model may, therefore, be useful in the study of the development of atherosclerosis during diabetes mellitus (Hebden et al., 1990).

Microangiopathy is believed to be due to factors such as basement membrane thickening and increased vascular permeability (Williamson et al., 1990), but changes in local haemodynamics may also be apparent before, or concomitant with, the development of clinical microangiopathy (Kastrup, 1988; Williamson et al., 1990). Tooke (1986) suggested that, initially, microvascular overperfusion and capillary hypertension could lead to basement membrane thickening which, in turn, might cause impaired vasodilation, although "defective release of, or response to, vasoactive mediators are alternative, largely uninvestigated hypotheses in man" (Tooke, 1986). Hence, STZ-treated rats could prove very useful in studying the potential effects of vasoactive agents on the microvascular circulation in diabetes mellitus. Indeed, vascular permeability (measured by albumin escape) has been shown to be increased as soon as 1 day after STZ treatment. Thus, changes in Starling forces within the capillaries of STZ-treated rats occur long before structural changes (Tucker, 1990).

There is now good evidence that endothelial function is impaired in patients with diabetes mellitus (Porta et al., 1987; Stout, 1987; Jensen et al., 1989) in a manner similar to that in STZ-treated rats. Thus, STZ-treated rats may provide a model for the study of the underlying causes of endothelial cell damage in diabetes mellitus and a means of assessing the contribution of endothelial cells to the vascular abnormalities of diabetes mellitus. It will be of great interest to discover whether there are disorders of L-arginine metabolism in STZ-treated rats and in clinical diabetes mellitus, because these could account for disordered endothelial cell replication and abnormal interaction with platelets. Furthermore, because the L-arginine to nitric oxide pathway is involved in many processes, including neutrophil chemotaxis and normal macrophage function (Moncada et al., 1989, 1991a; Moncada and Higgs, 1990), a generalised disorder of this pathway could have extensive implications in diabetes mellitus. Similarly, the role of enhanced free radical production in the development of diabetic complications awaits further clarification.

Recent observations indicate that plasma endothelin levels are markedly elevated in clinical diabetes mellitus, as has been found in STZ-treated rats, and, hence, this peptide could exacerbate vascular disease in clinical diabetes mellitus (Takahashi et al., 1990). In the study by Takahashi et al. (1990), plasma from control subjects showed no peak corresponding to endothelin-1, whereas plasma from diabetic patients did show such a peak on high-performance liquid chromatography analysis. However, in both groups, the biggest peak was detected in the void volume. Takahashi et al. (1990) suggested that this peak might correspond to a precursor molecule of endothelin-1. Presumably, this molecule was detected in their radioimmunoassay because control subjects had measurable endothelin levels in their plasma (540 ± 50 fmol $liter^{-1}$). The fact that high-performance liquid chromatography analysis of plasma from diabetic patients did show a peak corresponding to endothelin-1 indicates that the elevated endothelin levels detected by radioimmunoassay (type I diabetics, 2090 ± 280 fmol $liter^{-1}$; type II diabetics, 1840 ± 130 fmol $liter^{-1}$) were partly attributable to endothelin-1, but the contribution of proendothelin to the difference in plasma levels between control and diabetic patients is not clear. However, Tsunoda et al. (1991) recently examined this question using a specific sandwich enzyme immunoassay for human endothelin-1 [1–21] and human proendothelin-1 [1–38]. They found no difference in plasma endothelin-1 levels between con-

trol subjects and patients with type II diabetes mellitus (both had levels of approximately 600 fmol liter^{-1}), but the mean plasma proendothelin-1 level in diabetic patients was 1011 fmol liter^{-1}, whereas in control subjects it was 773 fmol liter^{-1}. Tsunoda et al. (1991) suggested that these findings were evidence for suppressed endothelin-converting enzyme activity in their diabetic patients, but it is also feasible that endothelial cell damage resulted in leaching of proendothelin-1 into plasma. As mentioned before, it is possible that a component of the elevated plasma endothelin levels detected in diabetic patients by Takahashi et al. (1990) was due to proendothelin-1, but their high-performance liquid chromatography finding of endothelin-1 in plasma from diabetic patients, but not from control subjects, is difficult to reconcile with the observations of Tsunoda et al. (1991).

The role of endothelins and their interactions with nitric oxide in cardiovascular disorders in diabetes mellitus remain to be established.

IX. Integrated Cardiovascular Function

Of the many cardiovascular variables of interest in any study of the control of the cardiovascular system, BP and HR are the most easily measured and, consequently, have received the most attention in investigations of cardiovascular control in STZ-treated rats. However, it is clear that BP and HR alone cannot provide an adequate basis for the assessment of cardiovascular status, and further studies involving full haemodynamic assessment in conscious STZ-treated rats (Kiff et al., 1991a,b) are required.

A. Heart Rate

Bradycardia has frequently been reported in STZ-treated rats (Pfaffman, 1980; Buñag et al., 1982; Jackson and Carrier, 1983; Chang and Lund, 1986; Rodrigues et al., 1986; Carbonell et al., 1987; Hebden et al., 1987a,b, 1988a; Kusaka et al., 1987; Akiyama et al., 1989; Jobidon et al., 1989; Tomlinson et al., 1989c, 1990a,b,c; Yamamoto and Nakai, 1990), although this has not always been observed (Kawashima et al., 1978). Bradycardia appears rapidly after STZ treatment, with daily measurements showing that HR is significantly reduced as soon as 4 days after STZ (Tomlinson et al., 1989c). In the short-term, it is possible that bradycardia results from an increase in vagal activity and/or enhanced sensitivity to the chronotropic effects of acetylcholine (see section VII.C.3). Studies in vitro showed no effect of atropine on spontaneous beating rate of hearts isolated from control or STZ-treated rats (Li et al., 1989) but, surprisingly, there have been no reports concerning the in vivo effect of atropine on HR in rats treated with STZ. Reduced sympathetic stimulation may also contribute to bradycardia (see sections V and VII). Although studies using ganglion blockade failed to provide evidence for a reduction in neural drive to the heart 3 to 4 weeks after STZ treatment (Hebden et al., 1987a; Tomlinson et al., 1990a), chronic (1 month) treatment of STZ-treated rats with propranolol reduced HR to a lesser extent than in control rats (Fein et al., 1991). In addition, the level of HR following ganglion blockade was lower in STZ-treated than control rats, indicating that the intrinsic rate of beating was reduced following STZ treatment (Hebden et al., 1987a; Tomlinson et al., 1990a). This effect may have been due to the changes in cardiac electrical properties and calcium handling or myocardial metabolism (see section VII.A).

B. Blood Pressure

Kawashima et al. (1978) were the first to report that rats treated with STZ became hypertensive. Since that time, many other authors have observed increased BP in STZ-treated rats (Buñag et al., 1982; Funakawa et al., 1983; Hayashi et al., 1983; Katayama and Lee, 1985; Rodrigues et al., 1986; Hartmann et al., 1988; Ramos, 1988; Fein et al., 1991; Takeda et al., 1991). However, BP has also been found to be reduced (Kohler et al., 1980; Pfaffman, 1980; Jackson and Carrier, 1983; Chang and Lund, 1986; Kusaka et al., 1987; Hebden et al., 1987a,b, 1988a; Jobidon et al., 1989; Tomlinson et al., 1989c, 1990a,b,c; Yamamoto and Nakai, 1990) or unaltered (Rodgers, 1986; Ganguly et al., 1987; Yamamoto, 1988; Akiyama et al., 1989) following treatment with STZ. The reason for these discrepancies is not related to differences in dose of STZ, time after treatment, or strain of rat used.

Kusaka et al. (1987) suggested that "STZ-induced hypertension" was an artifact of the indirect BP recording technique of tail cuff plethysmography that was used by all but two (Buñag et al., 1982; Hayashi et al., 1983) of the groups cited above who found STZ-treated rats to be hypertensive. In some studies (Kusaka et al., 1987; Yamamoto, 1988), BP was measured in the same rats both indirectly and directly via an arterial cannula. It was found that, although BP of STZ-treated rats was higher than that of control rats when measured indirectly, directly measured BP was unchanged or lower in STZ-treated than in control rats. Kusaka et al. (1987) suggested that emaciation of the tails of STZ-treated rats caused the need for a greater tail cuff pressure to compress the caudal artery, thus leading to spuriously increased BP values. This proposition was supported by the observation that the discrepancy between directly and indirectly measured systolic BP was greater in STZ-treated than in control animals (Yamamoto, 1988). Furthermore, whereas we found no change in BP following STZ treatment using the tail cuff method, we have consistently observed reductions in BP using direct recording techniques (Tomlinson et al., 1989c, 1990a,b,c).

There have been two studies in which BP was measured directly in STZ-treated rats and was found to be increased. Buñag et al. (1982) observed that, although diastolic BP was increased in their STZ-treated animals,

there was no increase in either systolic or mean BP when measured through a cannula in the femoral artery. Hayashi et al. (1983) found an increase in mean BP measured in the carotid artery of STZ-treated rats but did not report values for systolic or diastolic BP. Thus, there have been no reported cases of systolic hypertension from intraarterial recordings in STZ-treated rats.

Interestingly, Ramos (1988) (who measured BP indirectly) reported that maintaining STZ-treated rats with a low salt diet ameliorated the development of hypertension. In that study, the development of hypertension in STZ-treated rats was also prevented by daily treatment with an ACE inhibitor or with an α-adrenoceptor antagonist. All three of these treatments also lowered BP in control rats, although to a lesser degree than in the STZ-treated animals. There are two possible interpretations of these results: (*a*) STZ treatment can induce hypertension which is maintained by the RAS and the sympathetic nervous system. Differences among studies could then be accounted for by differing degrees of activation of these two systems or by differing salt intakes among studies (unfortunately, in no case has dietary salt intake actually been reported); (*b*) the observed hypertension is an artifact of the recording technique. Although the results of Ramos (1988) showed a greater dependency of BP on the RAS and sympathetic nervous system in STZ-treated compared with control rats, no conclusions can be drawn about the absolute levels of BP in these animals.

The involvement of the autonomic nervous system in the regulation of BP following STZ treatment is unclear. Hebden et al. (1987a) showed that the decrease in systolic BP following ganglion blockade in the presence of captopril (to eliminate any pressor contribution from the RAS) was 12 mm Hg greater in control than in STZ-treated rats. This difference was similar in magnitude to the degree of systolic hypotension seen in STZ-treated animals (13 mm Hg) under basal conditions. It is, therefore, possible that reduced sympathetic activity may contribute to systolic hypotension following STZ treatment. In contrast, acute sympathetic nervous system blockade with propranolol and phentolamine caused a greater decline in BP of rats treated 12 (but not 3 or 6) weeks earlier with STZ compared with control rats (Ramos, 1988). Furthermore, daily treatment of STZ-treated rats with the α_1-adrenoceptor antagonist, prazosin, prevented the increase in indirectly measured BP seen in these animals following STZ treatment (Ramos, 1988). As stated before, these results show only that the STZ-treated rats in the study of Ramos (1988) had an increased dependency on the sympathetic nervous system for BP maintenance but do not show (contrary to the author's claim) that activation of the sympathetic nervous system caused the development of hypertension in these animals. In another study, treatment of STZ-treated rats with propranolol for 1 month had no effect on BP (Fein et al., 1991).

As discussed in sections II.B and III, changes in activity of the RAS may contribute to disorders of cardiovascular regulation following STZ treatment, via effects on body sodium handling and/or through a direct vasoconstrictor effect. Acute administration of the ACE inhibitor, captopril, caused a smaller decrease in BP in control rats than in rats treated with STZ 3 weeks previously but not in those treated 6 or 12 weeks previously (Ramos, 1988). Chronic daily treatment with ACE inhibitors has also been shown to prevent or reverse the apparent increase in BP (measured indirectly) seen following STZ treatment (Hartmann et al., 1988; Ramos, 1988); control rats responded to chronic ACE inhibition with a decrease in BP (Ramos, 1988) but to a lesser degree. Thus, STZ-treated rats in those studies showed increased dependency on the RAS for BP maintenance.

The possible role of the RAS in the maintenance of BP in the face of STZ-induced hypotension was investigated by Hebden et al. (1987a) who found no immediate effect of the ACE inhibitor, captopril, on BP of STZ-treated rats that were hypotensive (measured directly). However, 1 h after ACE inhibition, BP had declined in STZ-treated but not in control rats. It is tempting to speculate that this delayed hypotensive response was related to inhibition of an enhanced local vascular tissue RAS activity (Ubeda et al., 1988) (see section II.B). Alternatively, captopril may have been having an effect on renal function during this time to cause volume depletion in the STZ-treated animals. Another interesting possibility is that captopril, via a free radical-scavenging action (McMurray and Chopra, 1991), preferentially increased nitric oxide levels in the STZ-treated rats. However, as mentioned earlier, a specific interaction between nitric oxide and captopril, in vivo, remains speculative.

Unlike effects mediated by the autonomic nervous system or the RAS, there is little evidence for an acute, direct influence of the other major pressor system, AVP, on resting BP in STZ-treated rats. Administration of an antagonist of the vascular (V_1-receptor-mediated) effects of AVP had no effect on BP of STZ-treated rats that were hypotensive (Hebden et al., 1987a; Tomlinson et al., 1990a); nor was there any effect in STZ-treated rats in which BP (measured indirectly) was found to be increased (Ramos, 1988). It is possible, however, that AVP exerts chronic effects on BP control, either by influencing cardiovascular mechanisms or through its antidiuretic actions on the kidney. We have addressed this problem by comparing BP in control, Long Evans and in AVP-deficient Brattleboro rats and have found evidence for some involvement of AVP in maintaining blood volume and supporting BP after STZ treatment (Tomlinson et al., 1989c, 1990a). However, Ramos (1988) found no difference between the effects of STZ on BP (measured indirectly) in Brattleboro and in Wistar rats

(although this strain is not the correct control for Brattleboro rats).

There have been few studies of the haemodynamic changes underlying the effects of STZ on BP. In one study, using rats that were hypotensive following STZ treatment, Carbonell et al. (1987) found that there was reduced cardiac contractility, HR, and total peripheral resistance, together with a relative increase in blood volume, stroke volume, and cardiac output. Similarly, Yamamoto and Nakai (1990) observed hypotension, reduced total peripheral resistance, and increased cardiac index in conscious STZ-treated rats. The reduction in total peripheral resistance would appear, from other studies, to have been due to a number of factors such as renal and gastrointestinal hypertrophy, hyperglycaemia, hyperosmolality, changes in humoral factors such as ANP and glucagon, and abnormalities in vascular reactivity and endothelial function (see relevant sections above). These effects appear to differ between vascular beds, as demonstrated in vivo by Hill and Larkins (1989a) who compared regional blood flows in various vascular beds 4 weeks after STZ and found an increase in intestinal blood flow, whereas flows to other abdominal and to thoracic organs and the brain were maintained, and those to skin and muscle was reduced. The increase in intestinal blood flow was reduced when rats were kept on a restricted diet (to prevent an increase in intestinal mass) following STZ treatment, although blood flow to skin and muscle remained reduced (Hill and Larkins, 1989a), indicating that the effects of STZ to cause hypoperfusion of the latter vascular beds was due to something other than a vascular "steal" phenomenon. Anaesthetised rats were used in this study (Hill and Larkins, 1989a), and anaesthesia interferes with cardiovascular regulation. However, work using conscious, chronically instrumented rats has shown increased renal and mesenteric blood flow and decreased hindquarter blood flow following STZ treatment (Kiff et al., 1991a,b), along with evidence for the latter being mediated by a decrease in nitric oxide production and/or responsiveness (see section VIII.C).

The study of Carbonell et al. (1987) also showed that extracardiac factors (which act to increase venous return) compensated for impaired cardiac contractility and, hence, maintained cardiac output in STZ-treated rats. In addition, Dowell et al. (1986) found that, during volume expansion, changes in stroke index (stroke volume/unit body weight) were enhanced in STZ-treated rats. This was in contrast to the work of Paulson et al. (1987) who found that the stroke volume response to increased filling pressure was diminished in hearts from STZ-treated rats. The contribution of increased venous return to the maintenance of cardiac output and BP following STZ-treatment still, therefore, remains to be resolved. Unfortunately, there have been no studies of haemodynamics by authors who have found rats to be hypertensive, because such studies might help to resolve the discrepancies reported above.

C. Baroreflexes

In addition to changes in resting BP and HR, cardiac baroreflex sensitivities have been found to be altered in STZ-treated rats. Buñag et al. (1982) showed that, under urethane anaesthesia, STZ-treated rats had a greater HR response to a given increase in BP, elicited by bolus doses of AVP or noradrenaline, than did control rats. Similarly, under pentobarbital anaesthesia, STZ-treated rats were found to have enhanced cardiac baroreflex sensitivities (determined by administering graded doses of isoprenaline and relating steady-state BP to HR) (Dowell et al., 1986). However, the results of these studies must be interpreted with caution because both urethane and pentobarbital anaesthesia have effects on the baroreflex control of HR (Stornetta et al., 1987). Furthermore, isoprenaline, noradrenaline, and AVP have cardiac effects.

Jackson and Carrier (1983) found that cardiac baroreflex sensitivities to graded bolus doses of noradrenaline or AII were enhanced in conscious STZ-treated rats. This is partly in agreement with the work of Hebden et al. (1987b) who found that STZ-treated rats had increased cardiac baroreflex sensitivities to graded doses of methoxamine but not to graded doses of AVP or AII. In those studies, it was also suggested that the baroreflex control of the vasculature was impaired in STZ-treated rats because pressor responses to AII and AVP were normal in intact STZ-treated rats but were lower than in control rats following ganglion blockade (Hebden et al., 1987b). However, another explanation for this reduction in baroreflex buffering following STZ treatment may be that, although HR responses to doses of AVP and AII were normal in STZ-treated rats, cardiac output responses were reduced because STZ treatment is known to have differential effects on cardiac parasympathetic and sympathetic innervation (see section VII.C).

Using a different method to assess cardiac baroreflex sensitivities, Chang and Lund (1986) found that the slope of the relation between pulse interval and systolic BP during an infusion of phenylephrine was steeper in conscious, STZ-treated rats than in controls. Similarly, in STZ-treated rats, we (Tomlinson et al., 1990b) found enhanced baroreflex sensitivities when these were measured as the slope of the relationship between pulse interval and mean BP (Gardiner and Bennett, 1986) during infusions of methoxamine [with the doses adjusted to allow for the decreased sensitivity of STZ-treated rats to methoxamine (Hebden et al., 1987b)].

Interestingly, Chang and Lund (1986) also measured baroreflex sensitivity after longer durations of diabetes and found it to be reduced. These authors suggested that the changes were due to alterations in vagal function over time (see section VII.C.3), although it is also possi-

ble that CNS changes (see section VI) could have contributed. Finally, there has only been one study of baroreflex sensitivity to a depressor stimulus, and in that case no effect of STZ treatment was observed (Tomlinson et al., 1990b).

D. Summary

One of the major controversies in studies concerning cardiovascular control in STZ-treated rats is whether these animals are hypertensive or hypotensive. However, a thorough review of the literature reveals convincing evidence that STZ-induced hypertension is an artifact and that, in the majority of cases in which BP has been measured directly, hypotension has been found.

The study of integrated cardiovascular control in conscious, STZ-treated rats has barely begun. Little is known of the control of regional circulations in this model or of the ways in which the factors considered in this review might influence them. However, techniques are available for assessing the control of regional haemodynamics in vivo, and application of these techniques to the study of integrated cardiovascular function in STZ-treated rats, along with the use of new pharmacological compounds, should provide important basic scientific information relevant to our understanding of the factors contributing to disordered cardiovascular regulation in patients with diabetes mellitus (Bennett, 1983; Bennett and Gardiner, 1988).

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