# MINIREVIEW

# The Effect of Diabetes Mellitus on Endocrine and Reproductive Function

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*Abstract.* **The adverse effects of diabetes on the circulatory, visual, renal, and peripheral nervous system are commonly recognized and have been extensively studied. The effects of decreased insulin secretion or resistance to insulin action on endocrine glands have not been as carefully documented. Both clinical and animal research have demonstrated that diabetes mellitus is commonly associated with altered thyroid, adrenal and gonadal function. Some of these changes are reversed with insulin replacement therapy, but endocrine function is not always restored to normal even with rigorous glycemic control. Patients with poorly controlled diabetes exhibit basal and stimulated growth hormone (GH) hypersecretion, while patients with good metabolic control still present with diurnal and exercise-induced GH hypersecretion. In contrast, diabetes suppresses GH secretion in the rat. It is unclear why GH secretion is altered, but clinical and experimental evidence exists for diabetes-associated changes in GH-releasing hormone and somatostatin release as well as for changes in the pituitary response to these hypothalamic hormones. The thyroid hormones, $T_3$ and $T_4$, are usually suppressed in both humans and experimental animals with diabetes. This effect of diabetes appears to involve changes in hypothalamic thyrotropin-releasing hormone (TRH) secretion as well as changes in pituitary thyrotropin (TSH) release and direct effects at the level of the thyroid gland. Adrenal cortical function is often enhanced in diabetes, most likely due to alterations in glucocorticoid feedback responses. There is much conflicting data on adrenal medullary function in diabetes; responses to stress and exercise, however, are often abnormal. Finally, male and female reproductive function is often disrupted in diabetes. Data from animal studies suggest that the major cause is altered hypothalamic LHRH secretion secondary to diabetes-induced changes in hypothalamic neurotransmitter metabolism.**

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Diabetes mellitus, whether due to lack of insulin secretion or resistance to insulin action has adverse effects on all organ systems. Although not as extensively documented as pathological changes in the cardiovascular or peripheral nervous system, diabetes mellitus also has profound effects on the neuroendocrine axis. These neuroendocrine effects may potentiate the adverse effects of diabetes on other organ systems and in the case of reproductive function are often of major patient concern. This

review will describe the clinical effects of diabetes on the hypothalamic-pituitary-endocrine gland axis and will review animal studies addressing the mechanisms accounting for altered endocrine function. Most reported animal studies use streptozotocin (STZ) to destroy selectively pancreatic β cells, which is a widely used model of Type I or insulin-dependent diabetes mellitus. It can be argued that some effects of STZ may be due to direct tissue effects or to renal and hepatic cytotoxicity. However, this appears unlikely to be of major importance at least in regard to changes in endocrine function. For example, insulin replacement reverses many of the effects of STZ-induced diabetes (as discussed throughout this review) and *in vitro* exposure of hypothalamic fragments, pituitaries, or testes to STZ does not effect endocrine function (Steger *et al.*, unpublished data). Genetic models of Type I diabetes such as the BB Wistar rat have also been used but there is relatively little data on endocrine or neuroendocrine function in models of Type II or non–insulin-dependent diabetes mellitus.

The reader should be aware that certain reports of the endocrine effects of diabetes appear to be in conflict. However, as is illustrated throughout this review, differences in the severity and duration of the diabetic state often effect reported results. Furthermore, studies of Type I diabetes where insulin replacement is used are often difficult to compare because the degree of glycemic control is not reported, especially when experimental animals are used. Even though insulin replacement initially may reverse endocrine and neuroendocrine abnormalities associated with diabetes, it should be realized that this may not be true over the long term.

## Growth Hormone

Growth hormone (GH) hypersecretion is often seen in poorly controlled diabetes (1, 2), but basal GH levels can be normalized with proper metabolic control (3). Patients with well-controlled diabetes still exhibit diurnal and exercise-induced GH hypersecretion (4, 5). Elevated GH levels have received much attention due to the diabetogenic action of GH and the role of GH in mediating certain diabetic complications (6, 7). Despite elevated GH levels, plasma insulin-like growth factor–I (IGF-I) levels are low in insulin-dependent diabetes (8, 9) but not necessarily in patients with non–insulin-dependent diabetes mellitus (10). This difference is apparently due to the fact that insulin is needed for hepatic IGF synthesis and secretion (11).

Interestingly, spontaneous or STZ-induced diabetes suppresses GH synthesis, pituitary GH content and secretion in the rat (12–18). The reduced GH levels in the diabetic rat are reflected by reduced plasma IGF-I levels (15).

It is unclear why GH secretion is altered in diabetes; however, evidence is accumulating that demonstrates several factors may be involved. Clinical studies on the pituitary response to SRIF are equivocal. Schaper *et al.* (19) did not detect any differences in SRIF responses of Type I diabetic males, while, using a different experimental design, Cohen and Abplanalp (20) demonstrated that men with poorly controlled Type I diabetes exhibit resistance to the effects of SRIF. In the latter study, SRIF responsiveness was not restored after 2 weeks of intensive insulin management. Despite the fact that GH is depressed in the diabetic, reductions in pituitary SRIF responses have also been demonstrated in the rat. Thus, primary cultures of pituitary cells from STZ-treated or BB/W-diabetic rats exhibit attenuated GH response to SRIF and reduced [$^{125}$I]-labeled SRIF binding to pituitary membranes (15, 21–23). The reduction in SRIF binding could be secondary to increased SRIF release since SRIF has previously been demonstrated to downregulate the pituitary SRIF receptor (24).

Hypothalamic SRIF content is either unchanged or slightly increased in diabetic rats (25), while hypothalamic SRIF mRNA levels are unaffected (26). Hypothalamic SRIF release into portal blood and from hypothalamic fragments has been reported to be increased in the STZ-diabetic rat but this increase was not seen until several days after GH was already suppressed (16). Opposite effects of diabetes on SRIF release were reported in studies using dispersed rat hypothalamic cells (27). Insulin replacement normalized SRIF release in the former but not in the latter study. Passive immunization of diabetic rats with SRIF antiserum restores GH secretion, suggesting that enhanced SRIF release may mediate the reduction in GH secretion (14), though altered GHRH responses may also be involved (see below). Peripheral secretion of SRIF may also be increased in diabetic animals (28).

Similar studies cannot be done in man but indirect evidence based on pharmacological studies have suggested that SRIF tone may be reduced in certain patients with Type I diabetes (29). Increased interpulse GH levels in diabetics also suggest decreased SRIF tone (30). Exogenous GH does not inhibit GH-releasing hormone (GHRH) response in diabetic patients as it does in normal controls (31, 32), also suggesting that SRIF release may be impaired since this feedback effect of GH probably involves the SRIF axis (33).

Patients with Type I diabetes without diabetic retinopathy (DPR) demonstrate an enhanced GH response to GHRH administration, whereas those with DPR do not (34). The authors suggested that the difference in response between these patient populations might be due to a microvascular disorder involving the pituitary. This report is in partial conflict with a study that demonstrated exaggerated GHRH responses regardless to the degree of metabolic control or the presence of DPR (35). Type II diabetics show an impaired response to GHRH (36), which may be related to the observation that obesity causes a similar impairment in GHRH response (37).

Both increased (22, 38, 39) and decreased (17, 18) GH release in response to GHRH have been reported in diabetic rats. Olchovsky *et al.* (15) demonstrated an absolute decrease in *in vitro* GHRH response in diabetic rats, but this difference was negated when the data were normalized to account for differences in basal GH release. Lack of agree-

ment among these studies may relate to difference in duration and severity of diabetes as well as to the degree of GHRH stimulation. In studies by Ndon *et al.* (17, 18), the suppressed GH response to GHRH was independent of enhanced SRIF tone (17). However, in the spontaneously diabetic BB rat, reduced GHRH responses were reversed by SRIF antiserum, suggesting that increased SRIF tone is responsible for altered GH secretion (18). Hypothalamic GHRH release may be suppressed in diabetic male rats as evidenced by a reduction in hypothalamic GHRH mRNA levels (15) and a reduced GH response to clonidine administration (38). Boujon *et al.* (40) also suggested that GHRH release may be attenuated in the diabetic rat based on the accumulation of axonal GHRH in the median eminence.

Cholinergic muscarinic receptor stimulation suppresses GH and GH responses to GHRH in normal and diabetic patients, whereas sensitivity to blockade is reduced in diabetic patients possibly due to increased cholinergic tone (32, 41). This suggestion could account for the decreased SRIF release associated with diabetes since SRIF is under chronic cholinergic inhibition (2).

## Effects of Diabetes Mellitus on the Hypothalamic-Pituitary-Thyroid Axis

Diabetes mellitus in humans and experimental animals is often associated with hypofunction of the hypothalamic-pituitary-thyroid axis. Insulin-dependent diabetic patients frequently have clinical or subclinical hypothyroidism (42–45). The thyroid glands of diabetic patients were noted to have an increased incidence of fibrosis, calcification, and nodularity at autopsy when compared with the normal population (46). Animal models of diabetes mellitus, using either alloxan or STZ, are associated with hypofunction of the thyroid axis (47–53). It is unclear, however, whether the primary defect involves the hypothalamus, pituitary, or the thyroid gland.

Several investigators have demonstrated that diabetes mellitus alters the function of the hypothalamus thereby causing decreased thyrotropin-releasing hormone (TRH) secretion that ultimately leads to thyroid hypofunction. Wilber *et al.* (48) determined that, as early as 72 hr postinjection of STZ, Sprague-Dawley rats had significantly lower mean serum thyroxine ($T_4$), triiodothyronine ($T_3$), and thyroid-stimulating hormone (TSH) when compared with controls. The decreased TSH level was associated with a 46% decline in circulating TRH in the same animals, although the hypothalamic TRH content was not significantly different between the two groups. Mitsuma and colleagues (51) showed that, in addition to decreased serum $T_3$, $T_4$, and TSH, diabetic Wistar rats had a significantly decreased hypothalamic immunoreactive TRH content at 2 and 4 weeks post STZ injection. Furthermore, plasma immunoreactive TRH and TSH levels in response to cold stimulus (4°C) were also significantly decreased in diabetic rats compared with controls.

Moreover, several investigators demonstrated that the decreased TRH levels of diabetic rats were due to decreased secretion rather than an absolute decrease in TRH content (54, 55). Bestetti's group (53, 54) showed that *in vitro* basal secretion of immunoreactive TRH was significantly decreased from the medial basal hypothalamus (MBH) of Sprague-Dawley rats 1 month after induction of diabetes with STZ. However, $K^+$ stimulated TRH release was significantly increased in diabetic rats compared with control rats. The total immunoreactive TRH was also increased in the MBH of STZ diabetic rats following $K^+$ stimulation compared with controls. Similarly, Rondeel *et al.* (55) demonstrated that, despite a normal TRH content in the hypothalami of STZ-diabetic Wistar rats, *in vitro* release of TRH was significantly decreased in diabetic hypothalami compared with controls.

Several studies have correlated the morphologic alteration in the hypothalamus of diabetic rats with decreased TRH release. Using light and electron microscopy, Bestetti and colleagues (56) demonstrated that STZ-diabetic Wistar rats had a significantly increased glycogen accumulation in the neuronal perikarya, tanycytes, and glial cells around the arcuate nucleus particularly in the basal region compared to normal rats. Neurons in the diabetic rat arcuate nucleus had fragmented endoplasmic reticulum and loss of organelles with irregularity of the nuclei and cell outlines indicating cellular damage. The tanycytes were hypertrophic. Ultrastructurally, the tanycytes lost the apical processes, had a decreased number of organelles, and had an increased nuclear to cytoplasmic ratio (56). According to the study of Hefco *et al.* (57), the TRH necessary for TSH secretion is released from the median eminence-arcuate nucleus area. The activity of this nucleus depends on intact connections with the anterior hypothalamus. Therefore, these ultrastructural alterations around the arcuate nucleus in the Wistar rat may be responsible for the observed decreased secretion of TRH.

The neurochemical basis for altered TRH secretion in diabetic rats has not been extensively studied. Experiments by Morley *et al.* (58) in normal rats suggest that activation of the serotonergic system is inhibitory to the secretion of TSH primarily by central inhibition of TRH release, as there was a strong inverse correlation between serotonin levels and hypothalamic TRH content. On the other hand, Henley and Belush (59) found that although both STZ-diabetic and hypothyroid rats have hypofunction of the hypothalamic-pituitary-thyroid axis, in diabetic rats the brainstem serotonin turnover is decreased, while in hypothyroid rats serotonin turnover is increased. Thus, Henley and Bellush (59) suggest that an altered serotonin turnover in the brainstem of diabetic rats play a role in the hypofunction of the hypothalamic-pituitary-thyroid axis in a different mechanism compared with that observed in nondiabetic hypothyroid rats. However, the changes in hypothalamic serotonin metabolism observed in the diabetic rat could also be related to alterations in the release of other pituitary hormones.

In contrast to these studies implicating hypothalamic

mechanisms, others have shown that diabetes mellitus alters pituitary function leading to decreased TSH secretion independent of any TRH effects. Rossi *et al.* (60) used the reverse hemolytic plaque assay to demonstrate a decreased *in vitro* TSH secretion in thyrotrophs of diabetic rats compared with controls. Moreover Chamras and Hershman (61) demonstrated that STZ-diabetic Sprague-Dawley pituitary thyrotrophs *in vitro* showed significantly decreased basal TSH secretion after 48 hr of culture in comparison to thyrotrophs isolated from nondiabetic controls. Intracellular TSH content in diabetic thyrotrophs was decreased by 45% compared with controls and TRH-induced TSH secretion in diabetic thyrotrophs was 30% lower than controls. Similar to other experiments using diabetic animal models, the plasma TSH, $T_4$, and $T_3$ levels were decreased. Bestetti *et al.* (53) also demonstrated that diabetic pituitary glands were significantly lighter in weight than controls. Moreover, the Type II thyrotrophs (which were more strongly positive for TSH) were greater in number than type I thyrotrophs, and this distribution of the different thyrotroph cells was opposite that of control thyrotrophs.

Other investigators have found inherent defects in the thyroid gland of diabetics leading to hypothyroidism. Jolin and Gonzales (49) demonstrated that STZ-diabetic Wistar rats had a decreased *in vivo* and *in vitro* iodide uptake, decreased thyroid/serum [I-] ratio and gland organic iodide formation suggesting an inherent depression of thyroid function independent of a concomitantly observed decrease in plasma TSH. Ortiz-Caro and Jolin (62) demonstrated that compared with control rats, diabetic Wistar rats had a significantly decreased metabolic clearance rate (MCR) and fractional disappearance rates (K) of $T_4$ and $T_3$. The production rates of $T_4$ and $T_3$ were also significantly reduced in diabetic rats compared with controls.

Chopra *et al.* (50) showed that 1 week duration of STZ-induced diabetes in rats was associated with decreased outer ring monodeiodination of $T_4$ and $T_3$, and $3'5'T_2$ to $3'$-$T_1$ and inner ring monodeiodination of $T_3$ and $3,5T_2$, both in the absence and presence of a thiol donor (dithiothreitol). This data suggested that, in diabetes mellitus, the activity of a single monodeiodinase enzyme was decreased. Furthermore, the investigators suggested that this may be responsible for the documented low $T_3$ syndrome observed in IDDM patients (43) as well as in *in vitro* studies of liver slices from STZ-diabetic rats (63).

Furthermore, Bagchi *et al.* (64) determined that the thyroidal response to TSH in diabetic mice was decreased, as indicated by a decreased formation of protein bound [$^{127}$I]- and [$^{131}$I]-labeled iodothronines and decreased rate of hydrolysis of labeled thyroglobulin. In this experiment, the generation of cAMP was greater in diabetic mice than in controls. However, the release of $T_4$ and $T_3$ was significantly decreased in diabetic thyroid cells in response to TSH. This led the investigators to suggest that the decreased $T_4$ and $T_3$ response to TSH occurs after the generation of the second messenger in diabetic thyroid cells. Bestetti *et al.* (53) described the thyroid gland of diabetic rats to have epithelial cells that had flattened rough endoplasmic reticulum, decreased colloid, and follicular cells that had scanty exocytotic apical and endocytotic vesicles, as well as a decreased amount of immunoreactive thyroglobulin when compared with normal controls.

It appears that all three levels of the axis were affected by the metabolic alterations of diabetes. Nevertheless, diabetic patients recover from the hypothyroid state with insulin treatment (44, 64). However the diabetic state may have been produced in animal models, treatment with insulin either *in vivo* or *in vitro* also seemed to correct the hypothyroid state. Ortiz-Caro *et al.* (65) showed that administration of 6 U insulin/100 g body wt for 12 days in STZ-diabetic rats restored the normal TSH secretion pattern that was previously completely suppressed. Insulin treatment also reversed the decreased metabolic clearance rate and fractional disappearance rates of $T_4$ and $T_3$ in STZ-diabetic rats (62); as well as increased the iodide uptake in the thyroid gland of the diabetic rat (49).

It is unclear how insulin treatment corrects the hypofunction of the hypothalamic-pituitary-thyroid axis, as some investigators have demonstrated that hyperglycemia *per se* was not responsible for the hypothyroid state in diabetes mellitus. Boado *et al.* (66) showed that rats treated with β-hydroxybutyric acid (βHB), but not those treated with $NH_4Cl$ to induce systemic acidosis, had significantly decreased pituitary content and plasma TSH levels. Nevertheless, the thyroid hormone levels in βHB acidotic rats were similar to those in untreated controls. The TSH response to TRH was similar in long- and short-term duration of STZ diabetes and in βHB acidotic rats. Furthermore, Chamras and Hershman (16) showed that preincubation of pituitary thyrotrophs with 25 nM glucose did not impair basal TRH-stimulated TSH release. Rondeel *et al.* (55) demonstrated that increasing glucose concentration from 10 to 30 n*M* did not affect the *in vitro* TRH release from hypothalami of normal rats.

## Adrenal Cortical Function

Diabetic patients, even with good glycemic control, demonstrate elevated levels of plasma cortisol and ACTH both before and after dexamethasone suppression tests (67, 68). The severity of the disruption of the HPA axis is significantly correlated with the duration of the diabetic state and degree of metabolic control.

Plasma corticosterone levels are also generally elevated in the diabetic rat but often not until several weeks after experimental induction of diabetes with STZ or alloxan (69–71). It is important to note that plasma corticosterone and ACTH levels are not consistently elevated in single blood samples from diabetic rats but are seen in serial samples. Urinary corticosterone levels and adrenal weights are consistently elevated in diabetic rats (71). Thymus weights, which are reduced by corticosterone treatment, are also reduced in diabetic rats. Thymus weights in adrenalec-

tomized diabetic rats did not differ from those in adrenalectomized controls. The circadian periodicity of corticosterone release is also altered in the STZ-treated rat (72). Diabetes-related changes in corticosterone concentrations do not appear to be due to altered metabolic clearance based on studies with labeled corticosterone (73).

Diabetic rats maintain the ability to increment further corticosterone levels in response to stress or exercise (71, 73, 74; Herron and Steger, unpublished). In fact, and characteristic of chronically stressed animals, diabetic rats show an elevated and prolonged ACTH and corticosterone response to stressors such as histamine injection (71).

It is unclear why adrenal cortical function is elevated in diabetes, but it may relate to disruption of corticosterone feedback. Decreased feedback is evidenced by a resistance to dexamethasone suppression and an inability of glucocorticoids to diminish stress-induced ACTH release (71). These changes may be related to a decrease in central corticosterone receptors previously reported in diabetic rats (75).

Diabetic rats exhibit normal adrenal responsiveness to ACTH (71). As previously mentioned, pituitary ACTH secretion is increased in diabetic rats. This is reflected by the increased weight of the adrenals in diabetic animals (71). Diabetic rats exhibit normal pituitary responsiveness to both CRH and AVP (71). Hypothalamic CRH release was reduced in diabetic male rats at 5 and 9 days after STZ treatment despite normal corticosterone levels (76). CRH secretion was restored after insulin replacement. The authors suggested that increased AVP secretion previously seen in diabetic rats (77) may have negated the effects of reduced CRH secretion on plasma ACTH and corticosterone levels.

## Adrenal Medulla Function

Elevated levels of plasma catecholamines are seen in uncontrolled type I diabetes, but there are conflicting data about catecholamine levels in patients with good glycemic control (78, 79). Many of these conflicts can probably be explained by differences in diabetic severity and duration, as these factors correlate with the incidence of autonomic neuropathies and adrenal pathology. Also, many of the earlier studies did not separately report plasma norepinephrine and epinephrine concentrations.

Reports of plasma catecholamine levels in Type II diabetes also vary considerably. In NIDDM, insulin levels are initially high and insulin is known to stimulate the sympathetic nervous system (80). Obesity is also a confounding factor in such studies as it is associated with reduced sympathetic activity either in the presence or absence of diabetes (81).

Diabetic patients often exhibit a diminished epinephrine response to a number of stimuli including hypoglycemia (79, 82) and exercise (83). The deficit in the epinephrine response to exercise may relate to the duration and severity of the disease, since it is not observed in all diabetics (79). In contrast to the decline in epinephrine secretion, patients with poorly controlled diabetes often exhibit exaggerated NE responses to exercise which could explain abnormal increases in systolic pressure, heart rate, and platelet aggregation (84, 85).

There have been relatively few studies of adrenal medullary function in diabetic animals. Bitar and colleagues (86) have reported that adrenal contents of DA, NE, and EPI are elevated in rats with streptozotocin-induced diabetes. Increases in the activity of the rate-limiting enzymes for the synthesis of these catecholamines were also elevated, suggesting that plasma levels were also elevated. Unfortunately, plasma catecholamine levels were not measured. Alterations in basal plasma NE and epinephrine levels in STZ-treated male rats were reported by Fushimi *et al.* (87). In these studies, the magnitude and direction of change varied with the duration of diabetes. Basal catecholamine levels tended to be higher with longer duration of diabetes. However, in long-term diabetic rats the norepinephrine and epinephrine increment due to blood withdrawal is severely diminished. Recent studies from our laboratory demonstrated that immobilization stress caused a significant rise in plasma norepinephrine (NE) levels in control but not in diabetic rats (88). The effects of stress on hypothalamic catecholamine metabolism were also affected. *In vitro* epinephrine secretion from diabetic female BB-Wistar rat adrenals was markedly attenuated as compared with controls despite similar adrenal NE and epinephrine levels (89).

Mechanism accounting for altered adrenal medullary function in diabetes have not been elucidated. Several possibilities are evident. First of all, adrenal medullitis of a possible autoimmune etiology is seen in a number of Type I diabetic patients (90). Furthermore, this medullitis appears to progress to a medullary fibrosis which may be an anatomical correlate of diminished secretory capacity. Adrenal catecholamine metabolism is controlled by several factors that are known to be altered in diabetes. For example, the adrenal medulla is perfused with blood containing high levels of glucocorticoids and these steroids have several effects on medullary activity, including, most notably, an increase in TH and PNMT synthesis (91). As previously discussed, the hypothalamic-pituitary adrenal cortical axis is altered in diabetic patients and animals. Adrenal catecholamine release is stimulated by presynaptic cholinergic neurons, which may in turn be adversely effected by diabetes (89).

In addition to changes in catecholamine levels, diabetes-induced changes in the physiological responses to catecholamines must also be considered. Marked decreases in $\alpha$ and $\beta$ adrenergic receptors were demonstrated in myocardial membranes from diabetic rats (86). These changes could represent receptor downregulation secondary to increased catecholamine levels and may partially account for the reduced response of the diabetic heart to pharmacologic challenge by agents such as isoproterenol (92). Of course, numerous other factors associated with diabetes such as neuropathies, altered thyroid function, and metabolic insults to the myocardium must also play a role (93). Enhanced

vascular responses to catecholamines in diabetes have been described in human and animal studies. Numerous studies in vascular preparations have demonstrated enhanced vasoconstriction, but a consensus on the effects of the different components of contraction and the mechanisms accounting for these changes has not been reached (94, 95). It is notable that reactivity changes with duration of diabetes and that changes are seen both in studies of large vessels and in the microvasculature.

## Reproductive Function

**Male.** Sexual and reproductive dysfunction, including impotence, reduced libido, and impaired spermatogenesis, is frequently associated with diabetes in men (96–98) and experimental animals (99–104). Impotence is the most common form of sexual dysfunction in diabetic men. Although peripheral autonomic nervous system and circulatory changes have been described as principal causes of impotence, changes in endocrine function and central nervous system control of sexual arousal undoubtedly have an important contributory role. There exist considerable data in the literature concerning the relationships between sexual dysfunction and the endocrine system in diabetic men (105–109); however, much less is known about central nervous system (CNS) involvement. Though there are contradictory reports on basal hormone levels in diabetics (105–111), attenuation of pulsatile and circadian Prl and testosterone release have been documented in men with insulin-dependent diabetes mellitus (105, 108, 112). These results are of particular interest due to the presumptive role of PRL in the development of male impotence (112, 113).

Adult rats with STZ-induced diabetes provide a relevant model to study reproductive dysfunction since they exhibit a number of deficits in reproductive function that resemble those seen in human diabetics. Furthermore, understanding of the CNS control of sexual behavior and neuroendocrine function and on pertinent *in vivo* and *in vitro* techniques is more complete for the rat than for any other species. Reproductive changes in STZ-treated male rats include decreased accessory organ weights, decreased gonadotropin titers, low plasma testosterone levels, and a reduced gonadotropin response to castration (103, 114–116). In addition, we have demonstrated that severe deficits in copulatory behavior are associated with STZ-induced diabetes (103, 104, 117). These effects are most likely due to an altered metabolic state due to the absence of insulin or the resistance to insulin rather than to a direct effect of STZ since the Zucker rat (even after caloric restriction to prevent weight gain) and certain strains of diabetic mice also show reduced sexual behavior and abnormal reproductive function (99, 100, 118, 119). Testosterone replacement does not restore normal sexual behavior in the diabetic rat (104). Furthermore, we have also shown that insulin replacement reverses many of the effects of diabetes on sexual function (120).

Pituitary gonadotropin responses to exogenous LHRH in the male rat appear to be unaffected by diabetes (121) although studies need to be repeated using lower doses of LHRH to fully address the question. The diabetic male rat is more sensitive to testosterone negative feedback (115), which taken together with low gonadotropin levels and unchanged pituitary function suggests that the locus of diabetes action is at the hypothalamus and involves reductions in LHRH release. In this regard, basal or phenylephrine-induced LHRH release from hypothalamic explants are not different between diabetic (4 weeks after STZ treatment) and control rats (122), suggesting that stimulatory input to LHRH neurons may be the locus of diabetes's adverse effect on pituitary-gonadal function. However, the function of LHRH neurons may eventually become impaired since *in vitro* LHRH release from hypothalamic slices in response to 60 m*M* KCl, norepinephrine or the protein kinase C agonist, phorbol 12,13-dibutyrate was reduced when tested 8 months after the induction of diabetes with STZ (123). Basal LHRH release was unaffected.

**Female.** Less is known about the effects of diabetes on female reproductive function, but many diabetic women exhibit amenorrhea or oligomenorrhea and have anovulation with disorders in basal and stimulated prolactin and gonadotropin release (124–126). Even less is known about the diagnosis and treatment of sexual problems in diabetic women, since few controlled studies have been reported, despite widespread patient concerns about the problem (127, 128).

STZ-treated female rats are anovulatory and show a greatly attenuated LH response to ovariectomy (129–131). As in the male rat, indirect observations suggest that diabetic-induced changes in LH release appear to be due to reductions in hypothalami LHRH release, although it is possible that diabetes may also reduce LH release by blocking the self-priming effect of LHRH on pituitary LH release (132). This loss of a self-priming action of LHRH could, however, be secondary to altered LHRH secretion and merits further investigation since LHRH regulates its own receptors (133). Hypothalamic LHRH levels are unchanged in diabetic female rats and it has been shown that *in vitro* LHRH release after depolarization with veratrine tends to be elevated, although not significantly so (132). STZ-induced diabetes also inhibits the positive feedback action of gonadal steroids on LH release (129, 132, 134), and this effect is only partially reversed by insulin replacement (135).

The genetically diabetic (db) female mouse is also infertile but the ovary responds to exogenous gonadotropin stimulation (99). Gonadotropin levels are depressed and elevated hypothalamic LHRH content suggests that LHRH release is suppressed since pituitary LHRH responses appear normal.

**Mechanism(s) Accounting for Altered Reproductive Function in Diabetes.** From the studies cited above it appears that many of the actions of diabetes on reproduction are due to the lack of stimulation of LHRH release rather than to an inability of the hypothalamus to

release LHRH or to a decreased pituitary response to LHRH. A change in LHRH release may also be responsible for changes in copulatory behavior, since there is considerable evidence that LHRH can directly stimulate male and female sexual behavior independent of its effect to stimulate gonadotropin release (136–138). The concept that LHRH can affect sexual behavior directly, and thus independent of its action on the pituitary gonadal axis, is strongly supported by its ability to potentiate sexual behavior in hypophysectomized and gonadectomized animals. We, therefore, hypothesize that suppression of LHRH secreting neurons by diabetes provides a common pathway for the effects of this disorder on both male copulatory behavior and pituitary gonadotropin release. This suppression of LHRH release is most likely the result of diabetes-induced changes in central neurotransmitter metabolism.

The brain is not exempt from changes associated with diabetes as evidenced by localized metabolic alterations (139) and functional changes (reviewed by Mooradian [140]). It has been known for some time that dopamine (DA) and norepinephrine (NE) levels in the brain are altered in diabetic rats (141, 142). Several years ago, we demonstrate that the reduction in LH release seen in diabetic male rats is secondary to reductions in NE metabolism in hypothalamic areas known to control LHRH release (103). Insulin replacement restored both LH levels and NE turnover to levels seen in nondiabetic controls (120). Diabetic rats also exhibit reduced LH responses to castration or exposure to receptive female rats and these changes can also be correlated with reductions in hypothalamic NE metabolism (115, 117). Diabetes associated changes in hypothalamic neuropeptide Y (NPY) secretion may also be involved in altered gonadotropin secretion since this peptide potentiates both NE and LHRH actions (143).

The effects of diabetes on NE metabolism in the female rat hypothalamus differ from those seen in the male. STZ-induced diabetes interferes with the postovariectomy rise in LH, although this change is not accompanied by a decrease in hypothalamic NE metabolism (130). However, the diabetic female rat demonstrates an increased sensitivity to the negative feedback effects of estrogen on LH secretion and NE metabolism. The positive feedback release of LH is also markedly depressed in the diabetic female rat, whereas the increase in median eminence NE that has been previously shown to precede the LH surge is not affected (134). In the same study, NE turnover in the anterior hypothalamus and DA turnover throughout the hypothalamus were depressed, but it is unclear how these changes might relate to changes in LH release.

Serotonin metabolism is also affected by diabetes and may play a role in reproductive dysfunction, since central serotonergic systems have been shown to have both stimulatory and inhibitory effects on sex behavior and pituitary hormone release (144–147). Rats made diabetic by alloxan or STZ injection exhibit decreased plasma tryptophan levels and require a higher dose of tryptophan to induce the same changes in brain tryptophan usually produced by a much smaller dose in normal rats (148–150). Insulin increases brain tryptophan uptake indirectly by lowering levels of amino acids that compete with tryptophan for brain uptake. Diabetes-associated changes in brain tryptophan levels are not associated with changes in whole brain concentrations of 5-HT and 5-HIAA (150, 151) but studies of neurotransmitter concentrations can give misleading information about changes in synthesis and release rates. In this regard, Crandall and co-worker (152) showed that whole brain serotonin synthesis was decreased in STZ-treated rats. In another study, brain 5-HT levels increased during the early development of diabetes, probably due to decreased metabolism based on concurrent decreases in 5-HIAA levels (141). Decreases in 5-HT metabolism could in part by due to a decrease in MAO activity that has been observed in alloxan-diabetic rats (153). Recently, STZ-induced reductions in 5-HT synthesis have been demonstrated in specific brain regions controlling sex behavior and gonadotropin in male rats (154).

The catecholamines and indoleamines also play important roles in controlling sex behavior (145). Several studies including those from our laboratory indicate that NE and DA neurons in the medial preoptic area (MPOA) are inhibitory to sex behavior (146, 155, 156). For example, testosterone administration stimulates male sexual behavior and reduces MPOA catecholamine metabolism, while drugs that increase catecholamine metabolism decrease male sexual responses (157–159). We have demonstrated that male rats exposed to a receptive female rat show large increases in LH levels that are associated with increased NE metabolism in several regions of the hypothalamus and reduced NE metabolism in the preoptic area and olfactory bulbs (117, 156). As previously mentioned, STZ-induced diabetes blocks female-induced changes in NE metabolism and attenuated the increase in LH release. These results suggest that endocrine and behavioral responses of male rats to the presence of a female are mediated by changes in catecholamine metabolism in several brain regions and STZ-induced deficits in male behavior may be due to the blockade of these CNS responses to exteroceptive stimuli originating from the female.

## Prolactin Secretion

Patients with insulin-dependent diabetes mellitus (IDDM) of relatively short duration (mean: 5.7 ± 0.9 years) showed no change in basal or TRH stimulated Prl levels but diabetes of greater duration (mean: 14.6 ± 1.0 years) is associated with diminished responses to TRH or blockade of pituitary DA receptors with domperidone (110). These changes were seen despite very strict control of plasma glucose levels and suggest that diabetes associated changes in Prl secretion are due to pituitary factors. However, other investigators suggested that hypothalamic factors were involved since arginine-induced Prl secretion was inhibited in

diabetic subjects while TRH stimulated Prl secretion was not inhibited (160).

We consistently observe reduced plasma prolactin levels in rats with STZ-induced diabetes of a duration from 1 week to several months (103, 120; Steger *et al.*, unpublished data). Other laboratories have reported either decreased (161) or unchanged (162, 163) Prl levels. The response of Prl to stress or TRH stimulation is attenuated in diabetic male rats (162, 163) and the suckling-induced rise in Prl secretion is impaired in diabetic female rats (164). It is still unclear why Prl secretion is reduced but pituitary prolactin content, *in vitro* prolactin secretion and the inhibitory response of prolactin to DA are not changed in diabetic animals (103, 120).

## Summary and Conclusions

In summary, the literature concerning the neuroendocrine and reproductive consequences of diabetes mellitus is largely descriptive, and there has been little attempt to determine mechanisms accounting for changes in sex behavior and pituitary and gonadal function. Apart from our own studies, there have been few attempts to relate diabetes-induced changes in CNS neurotransmitter metabolism to changes in sex behavior and gonadotropin secretion. Furthermore, we are unaware of any attempts to relate the degree of hyperglycemic control to maintenance of sexual and reproductive function. Finally, the neural and endocrine consequences of non–insulin-dependent diabetes have not been addressed, despite the fact that this is the predominant type of diabetes in the human population.

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