**Supplemental Methods**

*Animals.* Adult male Wistar rats and adrenalectomized (ADX) and sham-operated Wistar rats were obtained from Harlan Laboratories (Harlan, IN). ADX animals were allowed to recover for 1-wk following surgery at Harlan Laboratories and subsequently allowed to acclimate for 1-wk at the University of Washington prior to study. Animals were housed individually in a temperature-controlled room at 22°C with a 12:12-hr light:dark cycle under specific-pathogen free (SPF) conditions and had ad libitum access to water and chow (PMI Nutrition, MO) unless otherwise stated.

*Experimental protocols.* To determine if HPA axis activation is required for diabetic hyperglycemia we utilized adult male Wistar rats that had undergone either an ADX or a sham operation (Harlan Laboratories, Harlan, IN). Per vendor recommendations and as required by IACUC, ADX rats were offered ad libitum access to both water and a solution containing saline (0.9%) and sucrose (1%). Separate studies showed that variation in the amount of intake of the latter solution did not affect glycemia of diabetic animals. A 3-hr fasted blood sample was also obtained for measurement of plasma corticosterone levels to verify the success of ADX relative to sham-treated controls (data not shown). Animals subsequently received either a subcutaneous injection of STZ (65mg/kg/bw) to induce uDM or vehicle (NaCit, pH 4.5) at 10:00. Body weight, food and water intake and blood glucose in the fed state was monitored daily during the early light cycle (10:00). At study completion, blood samples were collected from 3-hr fasted animals during the mid-light cycle (13:00) from trunk blood in appropriately treated tubes as previously described (4).

To examine whether glucocorticoid receptor blockade is sufficient to ameliorate hyperglycemia in STZ-DM, we followed the protocol outlined by Perry, *et al.*, (15). Following acclimation, adult male rats received a single subcutaneous injection of STZ (65 mg/kg/bw) to induce uDM or vehicle (NaCit, pH 4.5) in the early light cycle (09:00). At dark cycle onset (18:00), 9-hr later, food was withdrawn. The following morning (09:00; 24-hr later), those STZ-injected animals with a tail vein blood glucose level >250 mg/dl were included in the study. These animals subsequently received an intraperitoneal injection of the glucocorticoid receptor antagonist, mifepristone (40mg/kg), or its vehicle. Fasting blood glucose levels were monitored hourly over a 3-hr period and blood was collected at 12:00 for measurement of plasma ACTH levels. Animals then received daily ip injections of mifepristone (40mg/kg) or its vehicle for 3 consecutive days at 09:00 and blood glucose was measured in the fed state at 12:00.

To determine whether normalization of the HPA axis can be achieved using a dose of leptin below that needed to normalize glycemia, we followed the protocol outlined by Perry, *et al.*, (15), similar to that outlined above, in which adult male rats also underwent catheter placement to both the carotid artery and jugular vein. Following a 1-wk recovery period, animals received a single subcutaneous injection of STZ (65 mg/kg/bw) to induce uDM or vehicle (NaCit, pH 4.5) in the early light cycle (09:00) and had food withdrawn at dark cycle onset 9-hr later (18:00). The following morning (09:00; 24-hr later), those STZ-injected animals with a tail vein blood glucose level >250 mg/dl were included in the study and subsequently received either a systemic intravenous infusion of leptin for 6-hr (150μg/kg total) or an equivalent volume of vehicle (PBS, pH 7.9). Overnight-fasted arterial blood samples were obtained for measurement of glucose,

insulin and leptin at 09:00 and 21-hr fasted blood samples were obtained for measures of leptin, corticosterone and ACTH at study completion (15:00).

To determine whether suppression of hypercorticosteronemia is required for leptin's anti-diabetic effects, ADX rats were implanted subcutaneously with a pellet containing corticosterone (35 mg in a 21-day release pellet; Innovative Research of America, FL) designed to maintain plasma corticosterone levels within the physiological range (18). Animals then underwent cannulation of the lateral ventricle (Alzet, DURECT Corporation, CA) under isoflurane anesthesia (stereotaxic co-ordinates 1.5mm lateral, 0.8mm posterior to bregma, and 3.5mm below the skull surface) and were allowed to recover (4). Three days following STZ administration, animals underwent subcutaneous implantation of an osmotic minipump (Alzet, DURECT Corporation, CA) that was connected to the cannula to allow icv delivery of either vehicle or leptin at dose (3μg/d) previously established to normalize glycemia in rats with STZ-DM (4). The tubing connecting the osmotic minipump to the lateral ventricle cannula was filled with vehicle and cut to a pre-determined length to allow leptin delivery to begin 24-hr after surgery; i.e., 4 days following STZ administration. In the same surgical session, animals also received either an additional corticosterone pellet (35mg, 21-day release; Innovative Research of America, FL) (CORT-high) or underwent a sham operation (CORT-low). Fed blood glucose, body weight, food intake and water intake were monitored daily at 09:00. At the completion of the study, trunk blood samples were collected from 3-hr fasted animals during the mid-light cycle (13:00) for plasma hormonal measures in appropriately treated tubes.

*Hormonal assays*

Blood samples were subsequently centrifuged, the plasma removed, aliquoted and stored at -80°C for subsequent hormonal assay. Plasma immunoreactive insulin and leptin levels (Crystal Chem, IL), ACTH (Phoenix Pharmaceuticals, CA) and corticosterone levels (Alpco, NH) were determined by ELISA. Blood glucose was measured using a hand-held glucometer (Accu-Chek, IN).