Brain region-dependent effects of dexamethasone on counterregulatory responses to hypoglycemia in conscious rats

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Sandoval, Darleen A., Ling Ping, Ray Anthony Neill, Bin Gong, Kristen Walsh, and Stephen N. Davis. Brain region-dependent effects of dexamethasone on counterregulatory responses to hypoglycemia in conscious rats. Am J Physiol Regul Integr Comp Physiol 288: R413–R419, 2005. First published October 14, 2004; doi:10.1152/ajpregu.00674.2003.—The aim of this study was to determine whether activation of central type II glucocorticoid receptors can blunt autonomic nervous system counterregulatory responses to subsequent hypoglycemia. Sixty conscious unrestrained Sprague-Dawley rats were studied during 2-day experiments. Day 1 consisted of either two episodes of clamped 2-h hyperinsulinemic (30 pmol·kg⁻¹·min⁻¹) hypoglycemia (2.8 ± 0.1 mM; n = 12), hyperinsulinemic euglycemia (6.2 ± 0.1 mM; n = 12), hyperinsulinemic euglycemia plus simultaneous lateral cerebroventricular infusion of saline (24 μl/h; n = 8), or hyperinsulinemic euglycemia plus either lateral cerebral ventricular infusion (n = 8; LV-DEX group), fourth cerebral ventricular (n = 10; 4V-DEX group), or peripheral (n = 10; P-DEX group) infusion of dexamethasone (5 μg/h), a specific type II glucocorticoid receptor analog. For all groups, day 2 consisted of a 2-h hyperinsulinemic (30 pmol·kg⁻¹·min⁻¹) or hypoglycemic (2.9 ± 0.2 mM) clamp. The hypoglycemic group had blunted epinephrine, glucagon, and endogenous glucose production in response to subsequent hypoglycemia. Consequently, the glucose infusion rate to maintain the glucose levels was significantly greater in this group vs. all other groups. The LV-DEX group did not have blunted counterregulatory responses to subsequent hypoglycemia, but the P-DEX and 4V-DEX groups had significantly lower epinephrine and norepinephrine responses to hypoglycemia compared with all other groups. In summary, peripheral and fourth cerebral ventricular but not lateral cerebral ventricular infusion of dexamethasone led to significant blunting of autonomic counterregulatory responses to subsequent hypoglycemia. These data suggest that prior activation of type II glucocorticoid receptors within the hindbrain plays a major role in blunting autonomic nervous system counterregulatory responses to subsequent hypoglycemia in the conscious rat.

autonomic failure; corticosteroids

THE SUPPRESSIVE EFFECTS OF corticosteroids on responses to stress have been studied for several decades (34). In the 1980s, it was proposed that one function of an endogenous increase in corticosteroids was to blunt and consequently reduce self-damage incurred by stress-induced defense responses (22). Since then, several studies have demonstrated that chronic administration of exogenous corticosteroids produces blunted physiological responses to a variety of differing stresses. Chronically elevated cortisol levels have been found to reduce basal epinephrine and norepinephrine concentrations (37) and to blunt norepinephrine synthesis and release to a similar extent as repeated immobilization stress (27) in rats. In primates, corticosteroid replacement inhibits norepinephrine responses following surgery in a dose-dependent manner (38). Conversely, adrenalectomy augments norepinephrine responses to repeated immobilization stress in rats (24). In humans, 1 wk of prednisone administration (20 mg/day) was found to reduce basal levels of norepinephrine and muscle sympathetic nerve activity (14). Another study found that a 50-mg bolus injection plus a 3-h infusion of hydrocortisone at 50 mg/h decreased basal and also apnea-induced increases in muscle sympathetic nerve activity in men (11).

Corticosteroids have also been found to have an effect on responses to hypoglycemia. For example, antecedent cortisol has been found to blunt epinephrine and ACTH responses to insulin-induced hypoglycemia in sheep (17) and dogs (16). In healthy humans, antecedent elevations of cortisol by direct infusion of cortisol (6) or indirectly by infusion of ACTH (19) have also been found to blunt neuroendocrine and metabolic counterregulatory responses to next-day hypoglycemia. Antecedent intracerebroventricular (ICV) infusions of cortisol into the rat brain also caused blunting of neuroendocrine and metabolic responses to subsequent hypoglycemia, suggesting a central effect of the steroid (33).

Endogenous corticosteroids initiate their actions by binding to mineralocorticoid and/or glucocorticoid receptors or via non-genomic mechanisms. Thus there are a number of putative physiological mechanisms by which corticosteroids can produce their effects. The aim of this study was to test the hypothesis that central activation of type II glucocorticoid receptors is the mechanism responsible for blunting of sympathetic and metabolic responses to subsequent hypoglycemia in conscious unrestrained rats. To test this hypothesis, dexamethasone (DEX), a specific type II glucocorticoid receptor agonist, was infused directly into the lateral cerebral ventricle of the brain or the periphery on day 1 in the presence of systemic hyperinsulinemic euglycemia, and responses to subsequent hypoglycemia were studied during the following day (day 2). Because we found discrepant results between the lateral ventricle and peripheral infusion of DEX, we then studied a separate group of rats that had fourth cerebral ventricle infusion of DEX plus a hyperinsulinemic euglycemic clamp on day 1 and examined their subsequent responses to day 2 hyperinsulinemic hypoglycemia.

METHODS

Animals. Sixty male Sprague-Dawley rats (300–350 g) bred and purchased from Harlan (Indianapolis, IN) were studied. The rats were

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housed and individually caged in the Vanderbilt University Animal Care Facility under controlled conditions (12:12-h light-dark cycle, 50–60% humidity, 25°C) with free access to water. All procedures for animal use were approved by the Institutional Animal Care and Use Committee at Vanderbilt University.

**Animal preparation.** Two weeks before the study, 26 rats had a 6-mm stainless steel cannula placed in the lateral ventricle of the brain under a general anesthesia mixture (5 mg/kg acepromazine, 10 mg/kg xylazine, and 50 mg/kg ketamine). Rats were placed on a stereotaxic frame (KOPF Instruments, Tujunga, CA) for placement of the guide cannula at stereotaxis coordinates of −0.9 mm anteroposterior, +1.4 mm mediolateral, and −4.5 mm dorsoventral from bregma, according to the atlas of Paxinos and Watson (28). Ten additional rats had a 11-mm stainless steel cannula placed in the fourth ventricle of the brain at stereotaxis coordinates of −2.6 mm anteroposterior and −7 mm dorsalventral from lambda. The intracranial cannulas were held in place with cranioplastic cement to three skull screws. Seven days after surgery in the first group of rats and in 24 additional rats, catheters were placed in the carotid artery (for blood sampling) and in the external jugular vein (for infusions) also under a general anesthesia mixture (5 mg/kg acepromazine, 10 mg/kg xylazine, and 50 mg/kg ketamine). Catheter lines were kept patent by flushing with 150 U/ml heparin every 3 days. Rats had free access to rat chow before surgery and experiments. Seven days postsurgery, only rats with >90% of their presurgery body weight were used for the 2-day experiments.

**Experimental design.** Six groups of rats were studied during a 2-day experimental protocol outlined in Fig. 1. On day 1, animals had either two 2-h periods of clamped hyperinsulinemic euglycemia (EUG group, n = 12), hypoglycemia (HYPO group, n = 12), or euglycemia plus lateral cerebral ventricular infusion of saline (24 μl/h; SAL group, n = 8) or euglycemia plus lateral cerebral ventricular (5 μg/h; LV-DEX, n = 8) or peripheral (5 μg/h; P-DEX; n = 10) infusions of DEX. Water-soluble DEX (20 μg; Sigma, St. Louis, MO) was diluted with 96 μl of 0.9% saline and infused at a rate of 5 μg/h (24 μl/h) during the morning and afternoon glycemic clamps. The use of saline avoids any potential confounding side effects of the dissolving medium. Because we saw discrepant results between the LV-DEX and P-DEX rats, we studied a sixth group in which 5 μg/h of DEX was infused into the fourth cerebral ventricle (4V-DEX, n = 10). On day 2, all rat groups were exposed to a 2-h hyperinsulinemic hypoglycemic clamp. Rats were fasted overnight before each day of the 2-day study and remained conscious and unrestrained throughout the experimental protocols. To prevent a fall in hematocrit, after each blood draw, washed red blood cells plus normal saline were reinfused through the jugular cannula of the rat. The morning of the study, extensions were placed on the exteriorized catheters for ease of access and were removed between day 1 and day 2 studies.

**Day 1 procedures.** At time 0, rats were moved to an experimental cage and allowed to acclimate to the surroundings. At 120–240 and 360–480 min, the ICV or peripheral infusions of saline or DEX were started in the SAL and DEX groups, respectively. Also, during these time periods, a hyperinsulinemic (30 pmol/kg⁻¹·min⁻¹) euglycemic (for EUG, SAL, LV-DEX, P-DEX, and 4V-DEX groups), or hypoglycemic (for the HYPO group) clamp was performed (clamping procedures described below). Plasma measurements of glucose were taken every 5–15 min and of insulin at times 240 and 480. Between morning and afternoon clamps, plasma glucose was measured every 15–30 min, and glucose infusion was adjusted to maintain euglycemia at 6.1 mM. At the conclusion of day 1 procedures, rats were fed 5–8 g of rat chow.

**Day 2 procedures.** At time 0, rats were moved to an experimental cage and allowed to acclimate to the surroundings. The experiment consisted of a basal period (time 90–120) and an experimental period (time 120–240) during which a hyperinsulinemic hypoglycemic clamp (described below) was performed. To measure glucose kinetics...
during the clamp, a primed (10 μCi) constant (0.2 μCi/min) infusion of HPLC-purified [3-3H]glucose (Perkin Elmer Life Sciences, Boston, MA) was administered via a precalibrated infusion pump (Harvard Apparatus, South Natick, MA) at time 0 and continued through 240 min. During the experimental period, blood was drawn every 5 min for measurements of plasma glucose, every 10 min during the basal period, every 15 min during the experimental periods for [3-3H]glucose, and at time 90, 120, 180, 210, and 240 for counterregulatory hormones. Rats were euthanized after day 2 procedures, and placement of ICV (by infusion of cresyl violet staining), carotid, and jugular cannulas were verified.

Glycemic clamping procedures. From time 120–240 (day 1 and day 2) and from time 360–480 (day 1 only), a primed (60 pmol·kg⁻¹·min⁻¹) continuous (30 pmol·kg⁻¹·min⁻¹) infusion of insulin (Eli Lilly, Indianapolis, IN) containing 9.7% (vol/vol) of rat plasma was administered via a precalibrated infusion pump (Harvard Apparatus). Plasma glucose was measured every 5–15 min. For the euglycemic clamp, a 50% dextrose infusion was adjusted to maintain glucose at ~6.1 mM. For the hypoglycemic clamp, glucose levels were allowed to fall (reaching nadir in ~30 min), and a 20% dextrose infusion was adjusted to maintain glucose at ~2.9 mM for 90 min.

Tracer calculations. Rates of glucose appearance (Ra), endogenous glucose production (EGP), and glucose utilization were calculated according to the methods of Wall et al. (39). EGP was calculated by determining the total Ra (this comprises both EGP and any exogenous glucose infused to maintain the desired hypoglycemia) and subtracting it from the amount of exogenous glucose infused. It is now recognized that this approach is not fully quantitative because underestimates of total Ra and rate of glucose disposal can be obtained. The use of a highly purified tracer and the taking of measurements under steady-state conditions (i.e., constant specific activity) in the presence of low glucose flux eliminate most, if not all, of the problems. In addition, to maintain a constant specific activity, isotope delivery was increased proportionally to increases of exogenous glucose infusion.

Analytical methods. Plasma glucose was measured in duplicate by the glucose oxidase technique on a Beckman glucose analyzer. Catecholamines were determined by HPLC (2) with an interassay coefficient of variation (CV) of 12% for both epinephrine and norepinephrine. We made two modifications to the procedure for catecholamine determination: 1) we used a five-point rather than a one-point standard calibration curve, and 2) we spiked the initial and final samples of plasma with known amounts of epinephrine and norepinephrine so that accurate identification of the relevant catecholamine peaks could be made. Corticosterone (ICN Biomedicals, Irvine, CA; interassay CV of 7%), cortisol (clinical assays gamma coat radioimmunoassay kit; interassay CV of 6%), insulin (40) (interassay CV of 11%), and glucagon (Linco Research, St. Louis, MO; interassay CV of 15%) were all measured using radioimmunoassay techniques.

Statistical analysis. Data are expressed as means ± SE and were analyzed using standard, parametric, two-way ANOVA, with repeated measures where appropriate. A Tukey’s post hoc analysis was used to delineate statistical significance. A P value of ≤0.05 was accepted as statistical significance.

RESULTS

Glucose and insulin. Plasma glucose levels were similar during day 1 morning and afternoon euglycemic clamps (6.2 ± 0.1 and 6.2 ± 0.1 mmol/l, respectively) in EUG, SAL, LV-DEX, P-DEX, and 4V-DEX groups. Plasma glucose levels were also equivalent during day 1 morning and afternoon hypoglycemic clamps (2.8 ± 0.1 and 2.9 ± 0.1 mmol/l, respectively) in the HYPO group. Glucose levels were also similar among all groups during day 2 hypoglycemic clamps (2.8 ± 0.1 mmol/l; Fig. 2). In addition, day 1 and day 2 insulin levels were similar between all six groups of rats (Table 1 and Fig. 2).

Counterregulatory hormones. Norepinephrine responses during day 2 hypoglycemia were significantly lower in P-DEX and 4V-DEX groups vs. EUG, SAL, HYPO, and LV-DEX groups (0.5 ± 0.1 and 0.6 ± 0.1 vs. 2.6 ± 0.4, 2.1 ± 0.5, 2.1 ± 0.2, and 3.0 ± 0.5 mmol/l, respectively; P < 0.05). Norepinephrine responses were also significantly lower at baseline in the P-DEX and 4V-DEX groups compared with EUG, HYPO, and LV-DEX groups and during the final 30 min in the HYPO compared with the LV-DEX group (P < 0.05). Day 2 plasma glucagon levels were also lower in EUG and HYPO compared with LV-DEX and P-DEX groups (0.1 and 2.1 nmol/l, respectively; P < 0.05). Norepinephrine responses were also significantly lower at baseline in the P-DEX and 4V-DEX groups compared with EUG, HYPO, and LV-DEX groups and during the final 30 min in the HYPO compared with the LV-DEX group (P < 0.05). Day 2 plasma ADH, aldosterone, and ADH were measured in duplicate by radioimmunoassay techniques.
epinephrine responses to hypoglycemia were significantly lower in HYPO, P-DEX, and 4V-DEX groups vs. EUG, SAL, and LV-DEX groups (8 ± 1, 4 ± 1, and 4 ± 1 vs. 15 ± 3, 17 ± 2, and 25 ± 5 nmol/l; P < 0.05; Fig. 3). Plasma glucagon responses to day 2 hypoglycemia were also significantly lower in HYPO vs. EUG, SAL, LV-DEX, P-DEX, and 4V-DEX groups (91 ± 8 vs. 282 ± 47, 258 ± 39, 389 ± 79, 441 ± 79, and 449 ± 162 ng/l; P < 0.05; Fig. 4). Plasma corticosterone responses to hypoglycemia were significantly greater in the 4V-DEX group compared with HYPO, LV-DEX, EUG, SAL, and P-DEX groups (30 ± 5 vs. 13 ± 1, 15 ± 2, 19 ± 2, 14 ± 2, 19 ± 1 nmol/l; P < 0.05; Fig. 4). Plasma corticosterone levels during day 2 hypoglycemia were significantly lower in HYPO and LV-DEX groups vs. P-DEX group (13 ± 1 vs. 19 ± 2, 19 ± 1, nmol/l; P < 0.05; Fig. 4).

Glucose kinetics. Specific activity, listed in Table 2, was stable during the basal and final 30 min of the hyperinsulinemic hypoglycemic clamps in all groups with an average CV of 6 ± 2% for both periods. During the final 30 min of day 2 hypoglycemia, EGP in the HYPO group was significantly less than that shown in the EUG, SAL, LV-DEX, P-DEX, and 4V-DEX groups (10 ± 5 vs. 30 ± 3, 38 ± 4, 46 ± 8, 36 ± 4, and 45 ± 6 μmol·kg⁻¹·min⁻¹; P < 0.05; Fig. 5). Glucose rate of disappearance during the final 30 min of hypoglycemia was similar between all groups (Fig. 5). As a consequence of the lower EGP, glucose infusion rates were significantly greater in HYPO group compared with that shown in the EUG, SAL, LV-DEX, P-DEX, and 4V-DEX groups (57 ± 8 vs. 18 ± 3, 17 ± 5, 19 ± 4, 15 ± 4, and 13 ± 4 μmol·kg⁻¹·min⁻¹; P < 0.05; Fig. 5).

DISCUSSION

The present study has examined the effects of antecedent central nervous system and peripheral infusions of DEX, a specific type II glucocorticoid receptor agonist on next-day neuroendocrine and metabolic responses to clamped hypoglycemia. Day 1 antecedent hypoglycemia resulted in significantly blunted neuroendocrine and metabolic responses to subsequent hypoglycemia compared with that shown in the EUG, SAL, and LV-DEX groups. Equivalent amounts of day 1 DEX blunted catecholamine responses to subsequent hypoglycemia when infused peripherally and when infused into the fourth cerebral ventricle but not when infused into the lateral cerebral ventricle. The divergent effects arising from the routes of administration implicate type 2 glucocorticoid receptors located in the hindbrain as a potential mechanism responsible for hypoglycemia-associated autonomic failure.

In rats, one other study has investigated the effect of DEX on responses to inadequate glucose. This study found that subcutaneous injection of DEX (250 μg/rat) or prior glucoprivation induced by 2-deoxyglucose produced similarly blunted food intake during subsequent glucoprivation (32). Supporting this finding, adrenalectomized rats exposed to repeated glucoprivation did increase their food intake during subsequent glucoprivation (32). These data are consistent with our present results,
suggesting that DEX can impair autonomic counterregulatory responses to repeated neuroglycopenia.

Several other studies have reported the potential role played by corticosteroids in inhibiting sympathetic nervous system responses to a variety of stressors (5, 6, 11, 14, 18, 25–27, 36, 38). Conversely, the role of cortisol, per se, in the blunting of autonomic and metabolic responses to repeated stress remains controversial, with some work supportive of (5, 6, 16, 17, 19, 33) and some contradictory to this theory (12, 13, 35). Most of the controversy lies within hypoglycemia stress in the rodent model (see Refs. 12, 13, 35 vs. Ref. 33). Several important experimental differences confound comparison of these studies with our previous (33) and present studies. However, given our present results, route of corticosteroid administration may be an important determinant of the role of glucocorticoids in blunting of subsequent counterregulatory responses. For example, lateral ventricle infusion of cortisol (33) blunted catecholamine responses to subsequent hypoglycemia, whereas corticosterone administered either subcutaneously (13), intravenously (35), or into the third cerebral ventricle (12) did not blunt counterregulatory responses to subsequent hypoglycemia. A lateral ventricle infusion would lead to a large accumulation of corticosteroids in the hippocampus and areas of the insular cortex that lay adjacent to the ventricle, and it would be expected that accumulation in these areas would be greater than peripheral or third ventricle administrations. Although a link between the hippocampus and sympathetic nervous system drive is unknown, areas of the insular cortex have been linked to the nucleus of the solitary tract and could influence autonomic drive (23).

On the other hand, in the present study, on day 1 the P-DEX and 4V-DEX groups, but not the LV-DEX group, showed blunted autonomic but not glucagon or pituitary adrenal counterregulatory responses to day 2 hypoglycemia. Structures within the hindbrain (e.g., the area postrema) that play a role in autonomic regulation may have been affected by peripherally infused DEX to lead to inhibited sympathetic drive. The degree of similarity shown in the 4V-DEX and P-DEX groups regarding blunting of catecholamines support this and suggest that DEX can influence hindbrain regions, leading to blunting of catecholamines with repeated exposure to hypoglycemia. Previous data have demonstrated that regulation of counterregulatory responses to hypoglycemia can be controlled by both the hypothalamus (1, 31) and the hindbrain (29). Considering our previous results with cortisol (33), the present data raise the suggestion that cortisol and dexamethasone may be acting on different regions of the brain to blunt autonomic nervous system responses to hypoglycemia.

### Table 2. Glucose-specific activity at baseline and final 30 min during day 2 hyperinsulinemic hypoglycemia (2.8 ± 0.1 mmol) in conscious rats

<table>
<thead>
<tr>
<th>Group</th>
<th>100</th>
<th>110</th>
<th>120</th>
<th>210</th>
<th>225</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUG</td>
<td>334±61</td>
<td>319±53</td>
<td>325±50</td>
<td>424±77</td>
<td>410±62</td>
<td>438±84</td>
</tr>
<tr>
<td>SAL</td>
<td>380±46</td>
<td>388±46</td>
<td>423±36</td>
<td>720±118</td>
<td>738±127</td>
<td>781±142</td>
</tr>
<tr>
<td>HYPO</td>
<td>503±40</td>
<td>508±38</td>
<td>538±53</td>
<td>862±103</td>
<td>932±142</td>
<td>938±138</td>
</tr>
<tr>
<td>LV-DEX</td>
<td>461±63</td>
<td>461±67</td>
<td>453±56</td>
<td>707±52</td>
<td>778±71</td>
<td>781±73</td>
</tr>
<tr>
<td>P-DEX</td>
<td>480±83</td>
<td>491±78</td>
<td>491±61</td>
<td>660±57</td>
<td>613±31</td>
<td>604±48</td>
</tr>
<tr>
<td>4V-DEX</td>
<td>691±75</td>
<td>675±71</td>
<td>674±71</td>
<td>701±71</td>
<td>740±72</td>
<td>730±75</td>
</tr>
</tbody>
</table>

Values are means ± SE in dpm/mmol.

Dexamethasone binds specifically to type 2 (glucocorticoid) receptors, which are ubiquitously expressed in the brain (9), whereas cortisol and corticosterone bind to both type 1 (mineralocorticoid) and type 2 (glucocorticoid) receptors. Although our methodology cannot delineate the extent of the brain regions activated by LV, 4V, or peripheral infusion of DEX, cresyl violet staining verified cannula placement and verified that LV infusion of DEX reached the lateral ventricle of the brain. It has been suggested that DEX may have a greater effect
on the pituitary relative to the hypothalamus (7, 8, 10, 20, 21). Our present data demonstrate that day 2 basal corticosterone levels were 0.5-to 4-fold lower in the peripherally infused compared with both centrally infused DEX groups, but corticosterone responses during hypoglycemia were not influenced by prior DEX and were even greater with prior 4V-DEX. However, both corticosterone and DEX can readily cross the blood-brain barrier, whereas DEX is transported out of the brain via a P-glycoprotein (20). Thus an alternative explanation for the lack of effect of LV-DEX infusion may be due to its transport out of the brain by this transport protein.

In the P-DEX and 4V-DEX (stimulation of type II glucocorticoid receptors) groups, the full spectrum of blunted counterregulatory responses that occurred after antecedent hypoglycemia was not reproduced. The fact that only catecholamines were blunted with DEX vs. catecholamines, glucagon, and EGP with cortisol and hypoglycemia indicates that other mechanisms also play a role in hypoglycemia-associated autonomic failure. Additionally, we cannot exclude the role of mineralcorticoid receptors or nongenomic actions of corticosteroids in the pathogenesis of hypoglycemic-associated autonomic failure. Mineralcorticoid receptors have been found to increase in streptozotocin-diabetic rats (3), suggesting greater sensitivity of these receptors with diabetes. In addition, corticosteroids (corticosterone, cortisol, dexamethasone) blunted corticotropin-releasing hormone-induced ACTH release within 5–15 min of drug administration, suggesting a rapid nongenomic effect (15). This effect was not prevented by prior administration of a type 2 corticosteroid receptor antagonist. Thus further work is needed to elucidate the areas of the brain involved as well as the role of genomic (via mineralcorticoid receptors) or nongenomic mechanisms in the pathogenesis of blunted autonomic nervous system counterregulatory responses following recurrent hypoglycemia.

The rate and volume of infusion of antecedent saline and peripheral and central DEX were identical so that any potential central effect of DEX would be isolated to the drug itself. The dosage of DEX used in this study (5 μg/h for 4 h) was greater than previous studies that used doses of ~2–3 μg/day (or 5–14 μg total over the course of 2–6 days) and reported that ICV-DEX increased food intake and body weight (4, 30). This dose is also approximately five times greater than the usual replacement dosage (relative to kg body weight) prescribed in humans. Despite this increased dose, compared with our previous study (33) where ICV cortisol blunted norepinephrine, epinephrine, glucagon, and EGP responses to hypoglycemia, P-DEX and 4V-DEX groups showed no effects on glucose kinetics. We believe this occurred for two reasons. First, in addition to epinephrine, glucagon also plays a major role in regulating hepatic glucose output during hypoglycemia by increasing both glycogenolysis and gluconeogenesis. Thus the intact glucagon response would have preserved EGP even in the face of the blunted catecholamine responses during hypoglycemia in the P-DEX and 4V-DEX groups. Second, the elevated day 1 levels of DEX would have resulted in day 2 insulin resistance at the liver and muscle, which would have contributed to the relatively preserved glucose kinetics occurring during day 2 hypoglycemia.

In conclusion, our results demonstrate that peripheral and fourth cerebral ventricular, but not lateral cerebral ventricular, administration of the glucocorticoid DEX blunts autonomic responses to subsequent hypoglycemia in conscious unrestrained rats. These results suggest that binding of type 2 glucocorticoid receptors within the hindbrain may play a role in hypoglycemia-associated autonomic failure.

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GRANTS

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