

Glucocorticoid Effects on Mesotelencephalic Dopamine Neurotransmission

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Multiple neurochemical estimates were used to examine peripheral corticosterone (CORT) effects in dopaminergic terminal regions. Acute CORT administration, which elevated plasma CORT (5 h), slightly decreased dihydroxyphenylacetic acid (DOPAC) to dopamine (DA) ratios in the striatum but not in other regions examined. Two weeks of adrenalectomy (ADX) increased both medial prefrontal cortex DOPAC/DA and homovanillic acid (HVA)/DA and striatal HVA/DA. A reciprocal pattern of changes was observed with CORT replacement in ADX animals. In contrast, CORT replacement in ADX animals did not significantly influence tyrosine hydroxylase content, basal dihydroxyphenylalanine (DOPA) accumulation after NSD 1015 treatment or the decline in

DA after alpha-methyl-para-tyrosine, suggesting that neither DA neuronal activity nor release are altered by CORT. Moreover, neither gamma-hydroxybutyric acid lactone-induced increases in DOPA accumulation or stress-induced increases in DA utilization were influenced by CORT replacement, indicating that neither autoreceptor regulation of DA synthesis nor acute stress regulation of DA utilization are changed by CORT. The findings are most consistent with direct inhibition of basal DA metabolism in the medial prefrontal cortex and striatum. The possible physiological and behavioral significance of this inhibition is being further explored.

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Adverse environmental stimuli evoke a number of physiological responses, including activation of the hypothalamic–pituitary–adrenal (HPA) axis and ascending catecholaminergic neurons. Although these responses are critical to an organism's ability to adapt metabolically and behaviorally to stressful events, it has also been hypothesized that sustained alterations in

these systems may underlie the pathophysiology of some psychiatric disorders (Dinan 1996; Nemeroff 1993; Piazza and Le Moal 1996; Schatzberg et al. 1985). For example, the cognitive disturbances in psychotic depressed patients may be secondary to the effect of HPA axis alterations on central dopaminergic neuronal activity (Schatzberg and Rothschild 1988; Schatzberg et al. 1985; Wolkowitz 1994).

In support of adrenal steroids influencing dopamine (DA) neurotransmission, a number of behaviors believed to be associated with dopaminergic neurons are influenced by corticosterone (CORT). For example, glucocorticoids attenuate D₂ receptor agonist-induced behaviors (Cador et al. 1993; Cools and Peeters 1992; Faunt and Crocker 1988; Faunt and Crocker 1989). In addition, glucocorticoids facilitate stimulant self-administration and stimulant-induced locomotor activity (Marinelli et al. 1994; Ortiz et al. 1995; Patacchioli et al. 1997; Piazza et al. 1993; Rivet et al. 1989) and mediate

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stress-induced sensitization of extracellular DA release by cocaine (Rouge-Pont et al. 1995).

Furthermore, indirect biochemical data support the hypothesis that adrenal steroids modulate these behaviors through an influence on mesotelencephalic DA neurotransmission. In vitro, CORT regulates tyrosine hydroxylase (TH), the rate-limiting enzyme in DA synthesis (reviewed in Meyer 1985). For example, the glucocorticoid receptor agonist dexamethasone increases TH expression in both PC12 cells (Baetge et al. 1981; Lewis et al. 1983) and the adrenal medulla (Stachowiak et al. 1988). In addition, CORT increases the rate of tyrosine phosphorylation in the ventral tegmental area, containing the mesocortical and mesolimbic perikarya (Nestler et al. 1989). Moreover, 50% of mesocortical, mesolimbic, and nigrostriatal perikarya (A8–A10) are immunoreactive for type II glucocorticoid receptors (Harfstrand et al. 1986). However, previous in vivo studies directly investigating the effects of CORT on DA neurochemical estimates of neuronal activity have produced apparently conflicting results. For example, CORT has been observed to increase, decrease, or not alter DA utilization and extracellular DA release (Dunn 1988; Imperato et al. 1992; Inoue and Koyama 1996; Rothschild et al. 1985; Tanganelli et al. 1990; Thomas et al. 1994; Wolkowitz et al. 1986). The present study, therefore, utilized estimates of DA metabolism, synthesis, and turnover and TH expression to systematically examine the effects of both acute and sustained alterations in peripheral corticosterone on mesocortical, mesolimbic, and nigrostriatal DA neurotransmission. In addition, CORT effects on DA autoreceptor regulation of DA synthesis and stress-induced stimulation of DA utilization were investigated.

METHODS

Animals

Male Sprague–Dawley rats (175–200 gm; Simonsen Labs, Gilroy, CA) were maintained under controlled temperature and lighting (12/12 light/dark) with food and water provided ad libitum. Animals were housed two per cage and acclimated for at least 7 days. Adrenalectomy was performed either by the vendor (Simonsen Labs) 2 weeks before experimentation or in house using a dorsolateral approach and confirmed by plasma radioimmunoassay of corticosterone.

Drugs

Corticosterone 21-hemisuccinate (Steraloids Inc., Newport, RI) was dissolved in water. For chronic studies, corticosterone pellets (21-day release; Innovative Research, Sarasota, FL) were implanted SC 1 week before

sacrifice under methoxyflurane anesthesia. Corticosterone replacement was confirmed by radioimmunoassay and by monitoring body weight. Gamma-hydroxybutyric acid lactone (GBL, Sigma, St. Louis, MO) m-hydroxybenzylhydrazine (NSD 1015, Sigma) and alpha-methyl-dl-para-tyrosine (Sigma) were all dissolved in 0.9% saline.

Restraint Stress

Animals were removed from their cages, placed in Plas-Labs rat restraints (Baxter, Hayward, CA) for 30 min. and sacrificed by decapitation. Control animals were removed from their cages and immediately killed by decapitation.

Tissue Preparation

After removal from the adjoining housing area, pair-housed animals were immediately removed from their cages and sacrificed by decapitation. All experiments were conducted during the first 2 hours of the light cycle, unless otherwise noted. Trunk blood was collected on ice, brains were removed, quick frozen on dry ice, and stored at -80°C .

Frozen brains were sliced into 250- μm sections with a cryostat. The mPfx (AP 13.7–12.2 mm) was dissected with a scalpel, and striatum (AP 10.7 to 9.7 mm) was removed with stainless steel cannulae from frozen sections (Paxinos and Watson 1997). Tissue was dissected within 24 to 72 h of slicing. The core and shell of the nucleus accumbens (AP 10.7–9.77 mm) were removed, as previously described (Deutch and Cameron 1992). Tissue was placed in 0.1 M perchloric acid with 0.1 mM EDTA and stored for no more than 2 weeks at -80°C until assay (modification of Palkovits 1973).

Neurochemical Assays

Samples were thawed, homogenized by sonication, and centrifuged for 2 min. Tissue pellets were dissolved in 1.0 N NaOH, and proteins were determined (Bio-Rad, Richmond, CA). Cortical supernatants were filtered through a 45- μm filter, and aliquots of supernatants were injected directly on a C18 reverse phase analytical column (5 μm , 250 \times 4.6 mm; Biophase ODS, BAS, West Lafayette, IN) protected by a precolumn cartridge (5 μm , 30 \times 4.6 mm, BAS), as previously described, with modification (Lindley et al. 1988). For cortical regions, a conditioning electrode set at +0.35 V and a dual analytical electrode cell set at 0.02 V and -0.32 V, respectively (ESA, Bedford, MA) were used. For other regions, a single analytical electrode set at +0.72 V was used (BAS, West Lafayette, IN). Corticosterone was determined by RIA (ICN Biochem, Costa Mesa, CA).

Western Analysis of Tyrosine Hydroxylase

The substantia nigra and ventral tegmental area (AP 3.7–2.7 mm) (Paxinos and Watson 1997) were removed with stainless steel cannulae from frozen sections and homogenized by sonication in Tris buffer (0.125 M Tris, 0.1% SDS, pH 6.8). Samples were adjusted to a protein concentration of 2 µg protein/µl in sample buffer [0.125 M Tris, 0.16% SDS, 5% glycerol (v/v), 0.08 M DTT, 0.0002% bromophenol blue (w/v)]. Aliquots containing 50 µg of protein were immediately subjected to SDS polyacrylamide gel electrophoresis (10% acrylamide/0.4% bisacrylamide). Proteins were electrophoretically transferred to nitrocellulose (Schleicher and Schuell, Keene, NH) and assessed for TH protein. Briefly, membranes were rinsed in TBST (0.05 M Tris, 0.15 M NaCl, 0.1% Tween-20), blocked with TBST containing 10% NSS (normal sheep serum, Sigma) and 1% BSA (bovine serum albumin, Sigma), and incubated with monoclonal mouse anti-TH IgG (1:10,000; Sigma) in TBST + 1% NSS for 1 hour at room temperature with gentle agitation. Membranes were washed with TBST, incubated with an alkaline phosphatase conjugated antimouse IgG (anti mIgG-AP; Promega, Madison, WI) for 1 hour at room temperature and washed with TBST. TH was detected using a chromophoric substrate by incubating the membrane in development solution (100 mM Tris, 100 mM NaCl, 5 mM MgCl₂, pH 9.5) containing 0.66% nitro blue tetrazolium chloride monohydrate (v/v) and 0.33% 5-bromo-4-chloro-3-indolyl phosphate, p-toluidine salt (v/v) for 1 to 15 min. Protein was then quantified using computerized densitometry.

Statistical Analyses

Statistical analyses in studies with single comparisons were conducted using Student's *t*-test. For multiple comparisons, the effect of CORT treatment was analyzed by analysis of variance (ANOVA) followed by Bonferroni's test for individual comparisons. Differences were considered significant if the probability of error was less than 5%.

RESULTS

CORT Effects on DA Utilization

The acute effects of peripheral CORT manipulations on central dopaminergic neural transmission in terminal regions were first examined by determining the ratio of the DA metabolite dihydroxyphenylacetic acid (DOPAC) to DA, an estimate of DA utilization. DA utilization was measured in the mesocortical DA projections to the medial prefrontal cortex (mPfx), the nigrostriatal projections to the striatum (ST), and the mesolimbic projections to the nucleus accumbens shell (NAs) and core (NAc). Administration of corticosterone 21-hemisuccinate (100 µg/ml) in the drinking water for 5 h beginning at the start of the dark cycle produced a 458% increase in plasma corticosterone (5.81 ± 0.86 to 26.63 ± 5.27 µg/dl) but only a small, but statistically significant, decrease (14.6%) in DOPAC/DA in the striatum and no significant changes in the other regions examined (Figure 1). The decrease in the ST was a reflection of a sig-

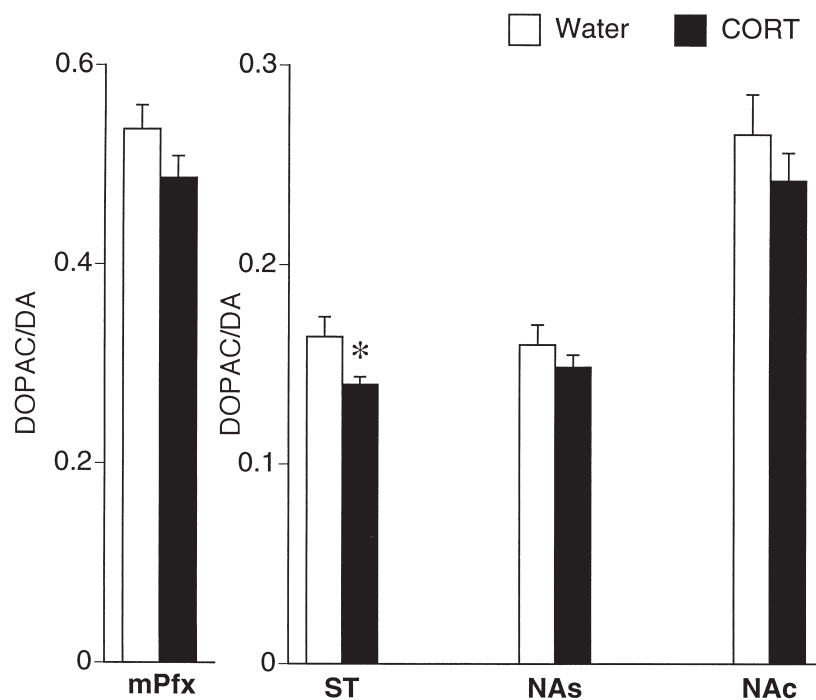


Figure 1. Effects of acute corticosterone administration on DOPAC/DA in selected rat brain regions. Animals were administered either water or corticosterone 21-hemisuccinate (100 µg/ml, po, 6 h) during the dark phase. Data are expressed as the ratio of DOPAC to DA \pm SE ($n = 8-10$). *Values significantly different from control ($p \leq .05$).

nificant decrease in absolute DOPAC concentrations (15.55 ± 0.91 to 13.10 ± 0.49 pg/ μ g protein). In contrast, when glucocorticoids were acutely elevated (≤ 24 h) during the light phase, with single injections of corticosterone, dexamethasone, or corticotropin-releasing factor, no significant alteration in DA utilization in any terminal region was observed (unpublished findings).

The effects of sustained plasma CORT alterations were also examined. Depletion of endogenous CORT by adrenalectomy (ADX) produced a 25.4% increase in DOPAC/DA in the mPfx but not in the ST, NAs, or NAc (Figure 2A). Sustained replacement of CORT (200 mg but not 10 mg CORT pellet) produced a decrease in mPfx DOPAC/DA (29.7%) (Figure 2B). The ratio of the DA metabolite homovanillic acid (HVA) to DA was also significantly increased with ADX and decreased with CORT replacement in both the mPfx and ST (data not shown). Overall, the effects of sustained CORT on DA utilization were a reflection of mostly nonsignificant increases in metabolite concentrations and decreases in DA concentrations.

CORT Effects on DA Turnover, Synthesis, and Tyrosine Hydroxylase Expression

The effects of sustained CORT alterations on the rates of DA turnover, synthesis, and expression of TH were also investigated. DA turnover, estimated by the percentage decline in DA 60 min after inhibition of tyrosine hydroxylase by α -methyl-dl-para-tyrosine, was not significantly different between ADX and CORT-replaced animals (Figure 3). DA declined to a greater extent in the mPfx than in other regions, consistent with a higher rate of DA turnover in the mPfx (Deutch et al. 1990; Roth et al. 1988). Sustained CORT replacement in ADX animals also did not alter tyrosine hydroxylase content in the substantia nigra, containing nigrostriatal perikarya, or the ventral tegmental area, containing mesolimbic and mesocortical perikarya (Figure 4). Consistent with these findings, DA synthesis, estimated by the accumulation of the DA precursor dihydroxyphenylalanine (DOPA) 30 min after decarboxylase inhibition by NSD 1015, was also not significantly different between ADX and CORT-replaced animals (Figure 5).

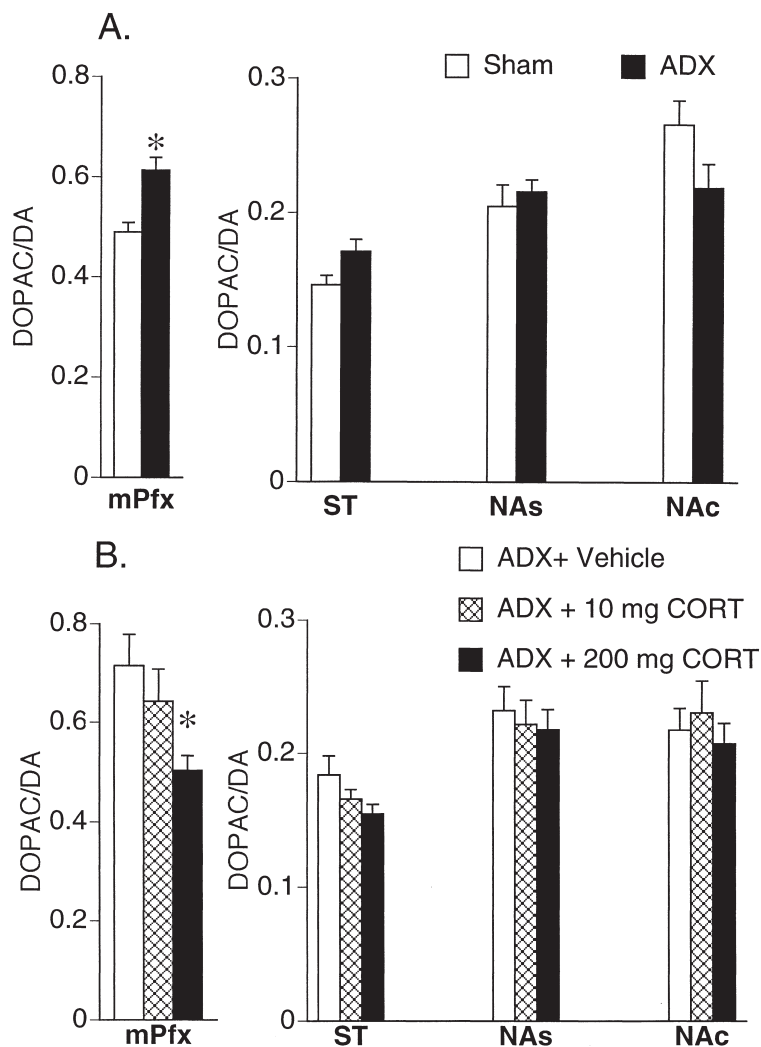


Figure 2. (A) Two weeks of adrenalectomy on DOPAC/DA in selected regions of the rat brain. Animals were either sham or adrenalectomized 2 weeks before decapitation. Data are expressed as the ratio of DOPAC to DA \pm SE ($n = 9-14$). *Values significantly different from vehicle treated control ($p \leq .05$). (B) Effect of replacement of corticosterone after adrenalectomy on DOPAC/DA in selected regions of the rat brain. Animals were adrenalectomized for 2 weeks and implanted with vehicle or 10 or 200 mg corticosterone pellet (21 day release, SC) 1 week prior to decapitation. Data are expressed as the ratio of DOPAC to DA \pm SE ($n = 6-8$). *Values significantly different from vehicle treated control ($p \leq .05$).

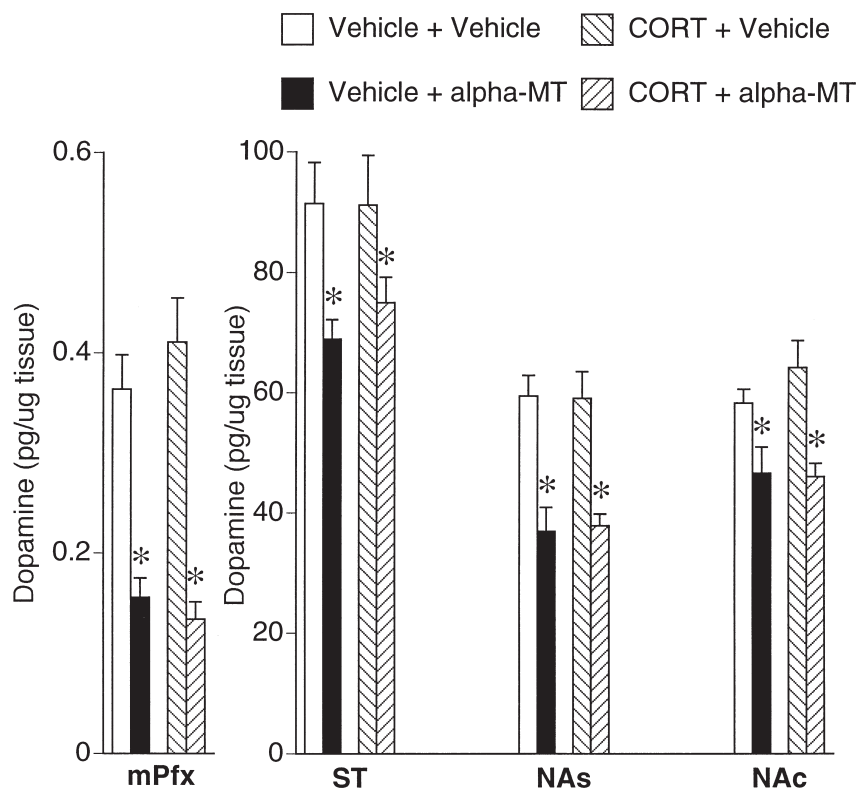


Figure 3. Effect of corticosterone replacement after adrenalectomy on alpha-methyl-para-tyrosine (alpha-MT)-induced decline in DA concentrations. Animals were adrenalectomized and implanted with either vehicle or 200 mg corticosterone pellet (21 day release, SC) for 1 week and administered either vehicle or alpha-methyl-dl-para-tyrosine (100 mg/kg, IP) 60 min before decapitation. Data are expressed as DA \pm SE ($n = 7-8$) *Values significantly different from vehicle treated controls ($p \leq .05$).

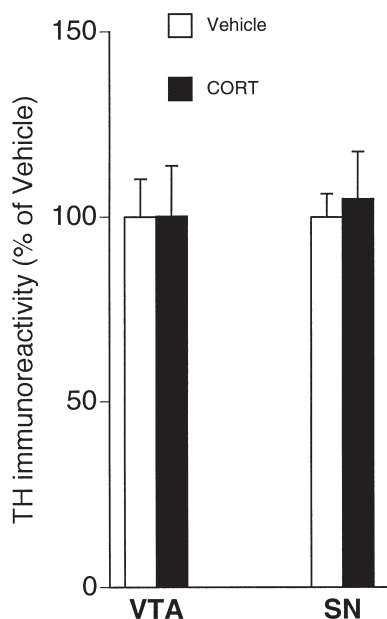


Figure 4. Effect of replacement of corticosterone after adrenalectomy on tyrosine hydroxylase immunoreactivity in the ventral tegmental area (VTA) and substantia nigra (SN). Animals were adrenalectomized and implanted with either 200 mg vehicle or corticosterone pellet (21 day release, SC) 1 week before decapitation. TH immunoreactivity is expressed as percentage of placebo control \pm SE ($n = 7-8$).

CORT Effects on Autoreceptor Regulation of DA Synthesis and Stress Regulation of DA Utilization

CORT effects on stimulated DA synthesis and utilization were also determined. DA autoreceptor regulation of DA synthesis was investigated by determining the effect of inhibition of impulse flow with gamma-hydroxybutyric acid lactone (GBL) on DOPA accumulation after NSD 1015 (100 mg/kg, IP; 30 min). GBL administration (1000 mg/ml, IP; 35 min.) in ADX animals produced a large increase in DOPA accumulation in the ST, NAs, and NAc. This increase in synthesis was not significantly altered by CORT replacement (Figure 5). GBL had no effect on DOPA accumulation in the mPfx in either group, consistent with a relative lack of synthesis-regulating autoreceptors in mesocortical neurons (Galloway et al. 1986).

Finally, the effects of sustained CORT administration on restraint stress-induced increases in DA utilization were determined. Thirty minutes of physical restraint produced an increase in plasma CORT and in DOPAC/DA in the mPfx, NAs, and NAc (Figure 6). This increase in utilization was also reflected in a significant increase in DOPAC concentrations (DOPAC data not shown). In addition, there was also a small, but significant, decrease (17.1%) in DA utilization in the ST, which was not attributable to a significant change in DOPAC concentrations. One week of CORT replacement in intact

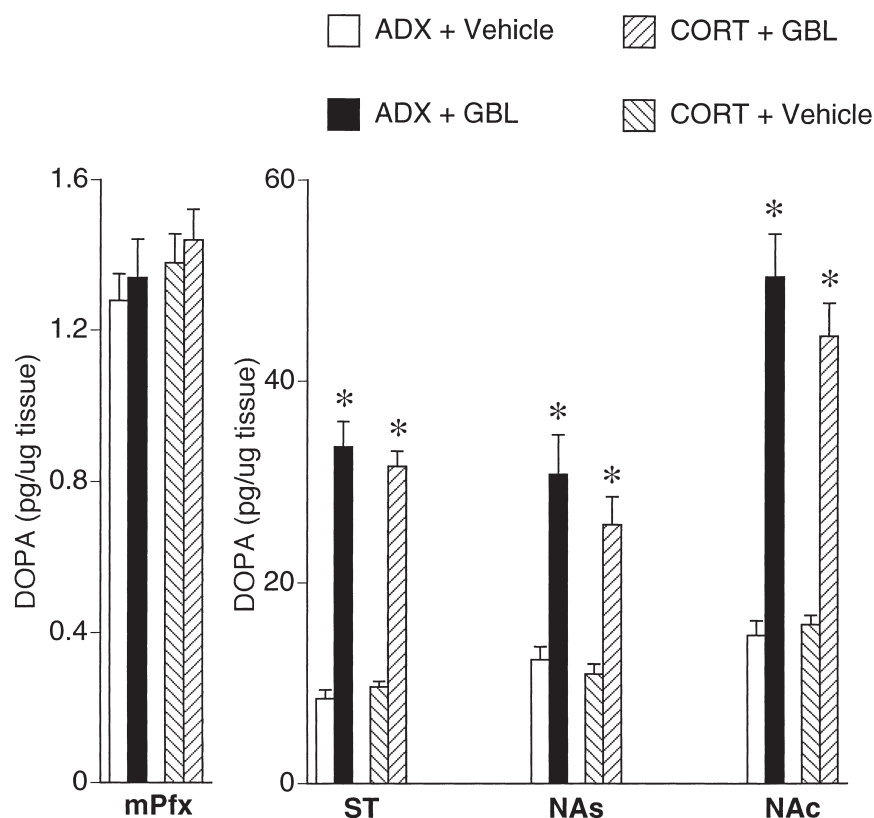


Figure 5. Effect of corticosterone replacement after adrenalectomy on gamma-hydroxybutyric lactone (GBL)-induced increases in DOPA accumulation. Animals were adrenalectomized and implanted SC with either vehicle or 100 mg corticosterone pellet (21 day release) 1 week and administered either 0.9% saline vehicle (1 mg/kg, IP) or GBL (1000 mg/ml, IP) 35 min before decapitation. All animals were administered m-hydroxybenzylhydrazine (NSD 1015, 100 mg/kg, IP) 30 min before decapitation. DOPA concentrations are expressed in pg/ μ g tissue \pm SE ($n = 8-11$). *Values significantly different from respective vehicle treated controls ($p \leq .05$).

animals did not significantly decrease mPfx DA utilization and had no significant effect on the stress-induced changes in DA utilization (Figure 6) or DOPAC concentrations (data not shown) in any region examined.

DISCUSSION

Glucocorticoids have been hypothesized to stimulate DA neurotransmission (Piazza et al. 1996a; Piazza et al. 1996b; Schatzberg et al. 1985; Wolkowitz et al. 1986). However, the present study, utilizing multiple neurochemical estimates to examine mesocortical, mesolimbic, and nigrostriatal DA neurons, under both basal and stimulated conditions, indicates that this is not the case. For example, stimulated DA neuronal activity induces increases in DA synthesis, turnover, utilization, and occasionally, TH expression (Cooper et al. 1991; Roth et al. 1976). The present study did not observe this pattern of CORT-mediated changes in these indices. Instead, only a small, regionally specific, glucocorticoid inhibition of DA utilization was seen. These findings are inconsistent with a significant glucocorticoid-induced increase or decrease in net mesotelencephalic DA neuronal firing or release of DA.

CORT reportedly produces a slight decrease in brain monoamine oxidase (MAO) activity (Caesar et al. 1970; Veals et al. 1977) and MAO-B inhibition increases DA

concentrations, while simultaneously decreasing DA metabolite concentrations (Rodriguez-Gomez et al. 1997). Therefore, the present results are consistent with a limited inhibition of DA metabolism. However, if CORT is inhibiting DA metabolism, this inhibition is not sufficient to provide enough regulatory feedback to produce corresponding changes in DA synthesis or turnover. In support of this possibility, basal extracellular DA concentrations remain stable with selective inhibition of MAO-B (Brannan et al. 1995). CORT also inhibits peripheral catecholamine metabolite concentrations, similar to the decrease in central DA utilization observed here. However, in the case of plasma DA metabolites, this decrease has been strongly associated with glucocorticoid inhibition of sympathetic activity (Kvetnansky et al. 1993; Kvetnansky et al. 1995), and is unlikely to be causally related to changes in central DA metabolism.

Although the results do support the possibility that CORT affects basal DA metabolism, CORT did not affect changes in DA utilization evoked by acute stress or in synthesis evoked by GBL administration. The inability of CORT to influence acute stress-induced increases in DA utilization is consistent with previous findings indicating that mesolimbic and mesocortical DA metabolite and extracellular DA responses to acute stress are not influenced by the presence of the adrenal gland (Claustre et al. 1986; Dunn 1988; Imperato et al. 1991). Although the specific mechanisms by which DOPA ac-

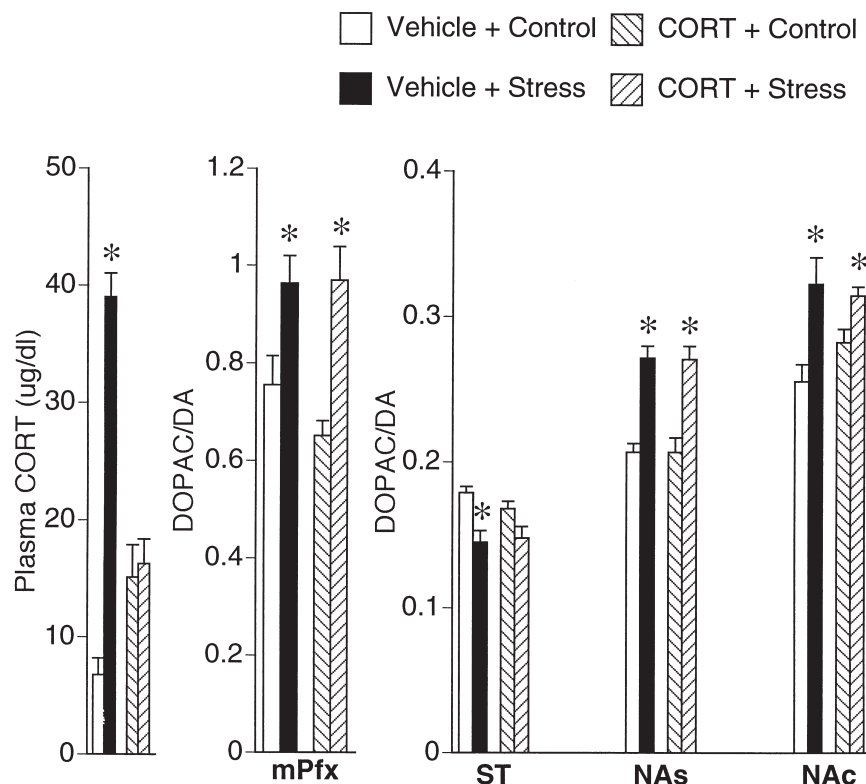


Figure 6. Effect of corticosterone on restraint stress-induced increases in DA utilization. Animals were implanted with either vehicle or 200 mg corticosterone pellet (21 day release, SC) 1 week before decapitation. Animals were either placed in restraining tubes for 30 min or removed from cages and decapitated immediately. DOPAC/DA data is expressed as the ratio DOPAC to DA \pm SE, and plasma CORT is expressed in μ g/dl \pm SE ($n = 7-8$). *Values significantly different from respective nonstressed control ($p \leq .05$).

cumulation increases after inhibition of impulse flow is uncertain, it seems to depend upon the presence of synthesis-modulating autoreceptors (Cooper et al. 1991). Because CORT did not alter this autoregulatory process modulating DA synthesis, it apparently does not influence DA autoreceptor function.

Glucocorticoids stimulate tyrosine hydroxylase biosynthesis in vitro (reviewed in Meyer 1985) and in vivo in the adrenal gland (Stachowiak et al. 1988). The present results demonstrated that CORT did not increase TH protein content in the substantia nigra or ventral tegmentum, where the nigrostriatal and mesolimbic and mesocortical perikarya are respectively located. Hence, our results are consistent with the majority of reports that do not observe CORT-induced stimulation of TH in vivo (Markey and Sze 1984; Smith et al. 1991; Van Loon et al. 1977). However, it is possible that the CORT can influence TH expression in vivo in a regional and strain-specific manner (Ortiz et al. 1995).

Finally, trait and state may alter the magnitude of CORT influences on DA behavior and neurochemistry (Ortiz et al. 1995; Piazza et al. 1993; Piazza et al. 1996b). For example, CORT has been reported to significantly increase extracellular DA concentrations if administered during the dark, but not the light phase, of the cycle (Piazza et al. 1996b). Although the present study accounted for this by administering CORT during the dark phase of the cycle, only a small decrease in DA utilization was observed in the striatum, consistent with the other findings.

In conclusion, the present findings that sustained, but not acute, changes in peripheral CORT concentrations have a small inhibitory effect on mesocortical and nigrostriatal DA utilization without significantly influencing turnover, tyrosine hydroxylase content, or synthesis (basal or stimulated) is most consistent with direct inhibition of DA metabolism or, less likely, reuptake. They are not, however, consistent with a net change in DA neuronal activity or release. Significant behavioral changes can occur with inhibition of basal DA metabolism or reuptake. In addition, it is possible CORT directly alters postsynaptic DA receptor expression or function (Cador et al. 1993; Cools and Peeters 1992; Faunt and Crocker 1988, 1989), or indirectly influences DA neurotransmission, for example, through glutamate neurons (Watanabe et al. 1995; Overton et al. 1996). Despite possible indirect effects, stress-evoked regulation of utilization did not seem to be significantly influenced by CORT. The extent to which CORT influences the physiological function of mesotelencephalic DA neurons remains to be determined.

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