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Adrenal Steroid Regulation of Neurotrophic Factor Expression in the Rat Hippocampus

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ABSTRACT

Adrenal steroids and neurotrophic factors are important modulators of neuronal plasticity, function, and survival in the rat hippocampus. Adrenal steroids act through two receptor subtypes, the glucocorticoid receptor (GR) and the mineralocorticoid receptor, and activation of each receptor subtype has distinct biochemical and physiological consequences. Adrenal steroids may exert their effects on neuronal structure and function through the regulation of expression of neurotrophic and growth-associated factors. We have examined adrenal steroid regulation of the neurotrophins brain-derived neurotrophic factor, neurotrophin-3, and basic fibroblast growth factor, as well as the growth associated protein GAP-43, through activation of GR or mineralocorticoid receptor with selective agonists. Our findings indicated that in CA2 pyramidal cells, adrenalectomy resulted in decreases in the levels of basic fibroblast growth factor and neurotrophin-3 messenger RNA, which were prevented by activation of mineralocorticoid but not glucocorticoid receptors. Adrenalectomy-induced increases in GAP-43 and brain-derived neurotrophic factor messenger RNA levels could be blocked by activation of glucocorticoid receptors in CA1, but not in CA3, pyramidal cells. Thus the extent to which adrenal steroids regulate hippocampal neurotrophic and growth-associated factors, appears to be dependent both on the adrenal steroid receptor subtype activated and on the hippocampal subregion examined. (*Endocrinology* **139:** 3112–3118, 1998)

A VARIETY of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and basic fibroblast growth factor (bFGF), have been shown to play important roles in regulating the plasticity and function of hippocampal neurons (1–6). In the hippocampus, the expression of the neurotrophins BDNF, NT-3, and bFGF as well as the receptors to which they bind (trkB, trkC, and FGFR, respectively), suggests that these factors may act locally through autocrine mechanisms to exert their neuromodulatory and protective effects (7–13).

Adrenal steroids have a multitude of effects on the structure, function, and survival of hippocampal neurons (14–16). The hippocampus is particularly sensitive to adrenal steroid action due to the prominence in this brain region of two distinct receptor subtypes, the mineralocorticoid receptor (MR or type I receptor), and the glucocorticoid receptor (GR or type II receptor). The mineralocorticoid receptor has a high affinity for corticosterone and aldosterone (17, 18), and, within the hippocampus, is most abundant in CA2 pyramidal cells with moderate levels expressed in the other hippocampal subfields (19–21). The glucocorticoid receptor has a lower affinity for aldosterone but a higher affinity for synthetic agonists such as dexamethasone and RU28362 than MR (22, 23). In the hippocampus, the level of GR expression is highest in the CA1 subfield, lowest in the CA3 subregion, and intermediate in the dentate gyrus (20, 21, 24).

For many of the electrophysiological, biochemical, and morphological effects of adrenal steroids on hippocampal neurons, there are markedly different consequences to activation of one adrenal steroid receptor subtype or the other (14, 16). These effects of glucocorticoids on neuronal structure and function, may be mediated through their actions as transcriptional regulators of target genes such as the growth-associated protein GAP-43, whose expression is closely correlated with axonal growth and neuronal plasticity (25–27), or the neurotrophic factors BDNF, NT-3, or bFGF. To investigate this putative mechanism of action, we have examined the ability of ligands specific for each adrenal steroid receptor subtype, to regulate the expression of GAP-43 and the neurotrophic factors BDNF, NT-3 and bFGF, in the different subregions of the rat hippocampus.

Materials and Methods

Experimental animals

Adult male Sprague-Dawley rats (CD strain, Harlan, Indianapolis, IN) were maintained on a 12-h dark, 12-h light cycle and had access to both water and 0.5 M NaCl from 7 days before surgery, until animals were euthanized.

Exp 1. Animals were (1) sham-operated and implanted with mock minipumps (Sham); (2) adrenalectomized and implanted with mock minipumps (adrenalectomy, ADX); (3) ADX and implanted with Alzet no. 2001 minipumps delivering aldosterone at 1 μg/h (ADX + Aldo); (4) ADX and implanted with minipumps delivering corticosterone at 10 μg/h (ADX + CORT); n = 5–6 per treatment group. Daily fluid intakes were monitored following surgery. Animals were euthanized 7 days after surgery, and brains and trunk blood were collected. Plasma corticosterone levels were assessed by RIA. Daily fluid intakes and plasma corticosterone levels were previously reported (28).

Exp 2. Animals were (1) sham-operated and implanted with mock minipumps (Sham); (2) adrenalectomized and implanted with mock minipumps (ADX); (3) ADX and implanted with Alzet no. 2001 minipumps delivering aldosterone at 1 μg/h (ADX + Aldo); (4) ADX and implanted with minipumps delivering RU28362 at 10 μg/h (ADX + RU);and (5) ADX and implanted with minipumps delivering aldosterone at 1 μg/h and RU28362 at 10 μg/h (ADX + Aldo + RU); n =

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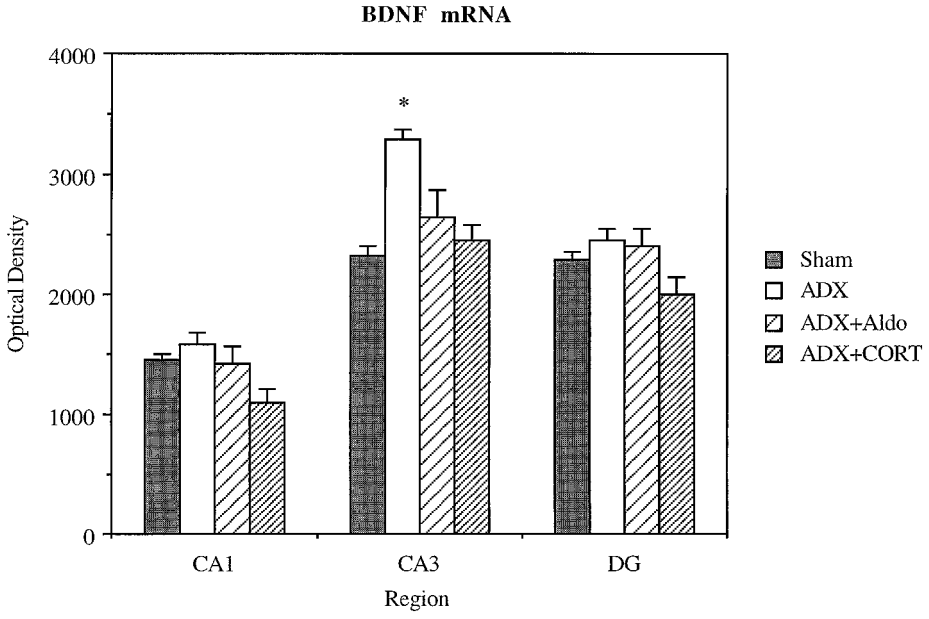

FIG. 1. Hippocampal BDNF mRNA expression in Exp 1. Levels of BDNF mRNA expression were assessed in the CA1 pyramidal cell layer (CA1), CA3 pyramidal cell layer (CA3), and granule cell layer of the dentate gyrus (DG). Statistical analysis indicated that the ADX animals were significantly different from the Sham animals in the CA3 subregion (*, $P < 0.05$).

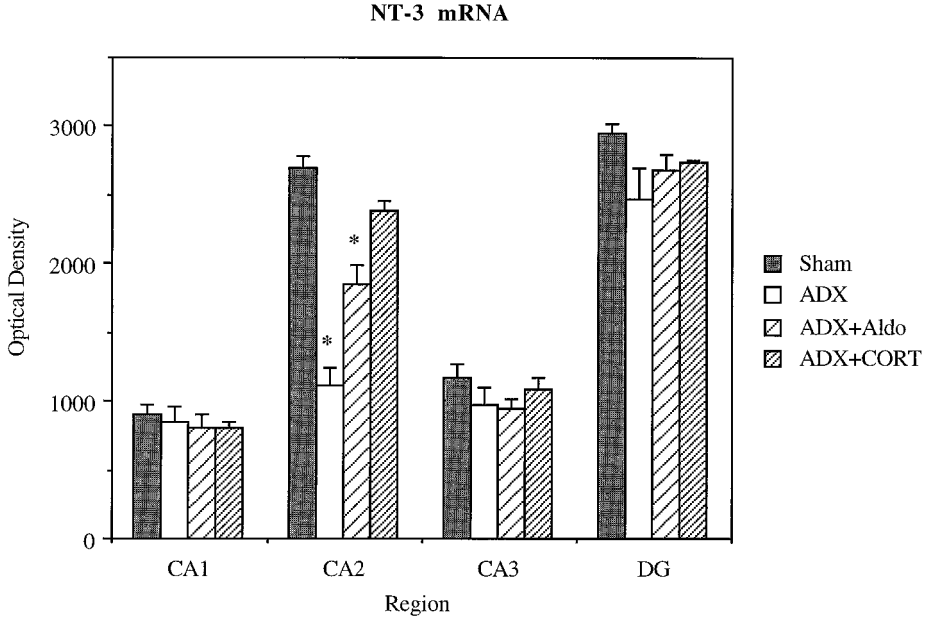

FIG. 2. Hippocampal NT-3 mRNA expression in Exp 1. Levels of NT-3 mRNA expression were assessed in the CA1 pyramidal cell layer (CA1), CA2 pyramidal cell layer (CA2), CA3 pyramidal cell layer (CA3), and granule cell layer of the dentate gyrus (DG). Statistical analysis indicated that the ADX and the ADX + Aldo animals were significantly different from the Sham animals in the CA2 subregion (*, $P < 0.05$).

5–6 per treatment group. Daily fluid intakes were monitored and animals exhibiting aberrant intake levels were eliminated from the study. Seven days after surgery, body weights were recorded, animals were euthanized, and brains and trunk blood were collected. Plasma corticosterone and aldosterone levels were assessed by RIA. Daily fluid intakes, body weights, and plasma steroid levels were previously reported (28).

In situ hybridization

Brains were removed, immediately frozen, and stored at −70 C. Sixteen-micron sections were prepared on a cryostat microtome, collected on gelatin-coated slides, and stored frozen until hybridization. Before hybridization, sections were fixed in 4% formaldehyde in PBS, acetylated in a solution of 0.25% acetic anhydride in 0.1 M triethanolamine-HCl, pH 8.0, rinsed in 2 × SSC, and allowed to air-dry. Antisense riboprobes radioactively labeled with ^{35}S were transcribed from complementary DNA clones corresponding to BDNF (29), NT-3 (30), bFGF (31), and GAP-43 (32). The hybridization mix (50% formamide; 10% dextran sulfate; 600 mM NaCl; 1 × Denhardt's solution; 10 mM Tris-HCl, pH 7.5; 1 mM EDTA, pH 8; 100 μg/ml denatured salmon testis DNA; 10 mM dithiothreitol; radiolabeled probe) was added at 0.2 ml per slide, the slides were coverslipped, and the sections were incubated overnight at 55 C. Following hybridization, the coverslips were removed, and the sections were rinsed in 2 × SSC. The sections were treated with 10 μg/ml RNase A, washed in RNase A buffer and in 2 × SSC at room temperature, followed by 0.5 × SSC at 55 C. The sections were allowed to air dry and then were apposed to x-ray film for autoradiography.

The optical densities of the autoradiographic images were determined on the Imaging Research image analysis system. The value of the low hybridization signal in the medial aspect of cortical layer 1 was taken (by definition) as background and subtracted from the optical density values for the hippocampal cell layers. The data were expressed as optical density (means ± SEM). Statistical analysis was by one-way

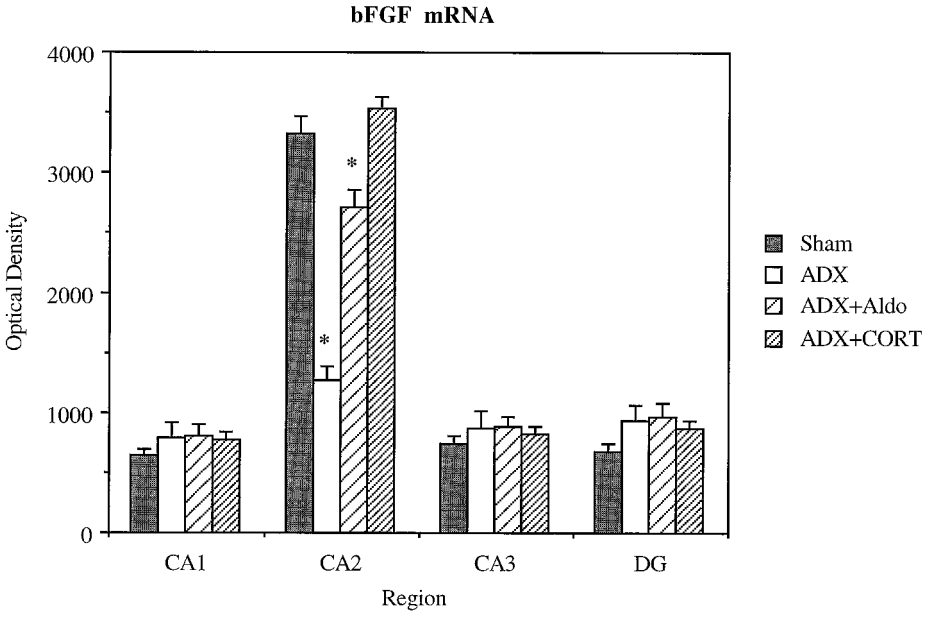

FIG. 3. Hippocampal bFGF mRNA expression in Exp 1. Levels of bFGF mRNA expression were assessed in the CA1 pyramidal cell layer (CA1), CA2 pyramidal cell layer (CA2), CA3 pyramidal cell layer (CA3), and granule cell layer of the dentate gyrus (DG). Statistical analysis indicated that the ADX and the ADX + Aldo animals were significantly different from the Sham animals in the CA2 subregion (*, $P < 0.05$).

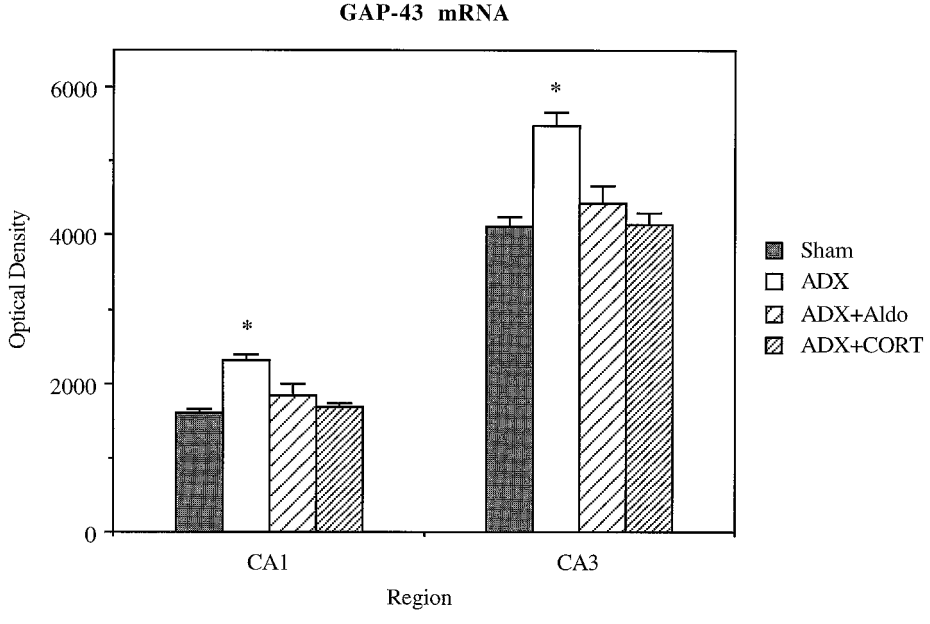

FIG. 4. Hippocampal GAP-43 mRNA expression in Exp 1. Levels of GAP-43 mRNA expression were assessed in the CA1 pyramidal cell layer (CA1) and CA3 pyramidal cell layer (CA3). Statistical analysis indicated that the ADX animals were significantly different from the Sham animals in the CA1 and CA3 subregions (*, $P < 0.05$).

ANOVA followed by Tukey's posthoc test, with $P < 0.05$ as the criterion for statistical significance.

Results

Exp 1: steroid replacement of adrenalectomized animals with aldosterone or corticosterone

In the adrenalectomized animals there was a significant induction in BDNF messenger RNA (mRNA) expression in the CA3 subfield, relative to the Sham animals. This increase was prevented by treatment of the ADX animals with either aldosterone or corticosterone (Fig. 1).

Adrenalectomy resulted in a significant decrease in the level of NT-3 mRNA in CA2 pyramidal cells, relative to Sham animals. The expression of NT-3 mRNA in the CA2 subregion was markedly increased in ADX animals receiving aldosterone or corticosterone treatment, compared with the untreated ADX group (Fig. 2). Expression of bFGF mRNA in the CA2 subregion showed this same pattern of adrenal steroid regulation (Fig. 3).

The expression of GAP-43 mRNA was increased by adrenalectomy in the CA1 and CA3 hippocampal subregions, relative to the Sham animals. This induction was prevented by treatment of the ADX animals with either aldosterone or corticosterone (Fig. 4).

Exp 2: steroid replacement of adrenalectomized animals with aldosterone and/or RU28362

Adrenalectomy caused a significant increase in the expression of BDNF mRNA in pyramidal cells, relative to Sham animals, with no change observed in the granule cells of the

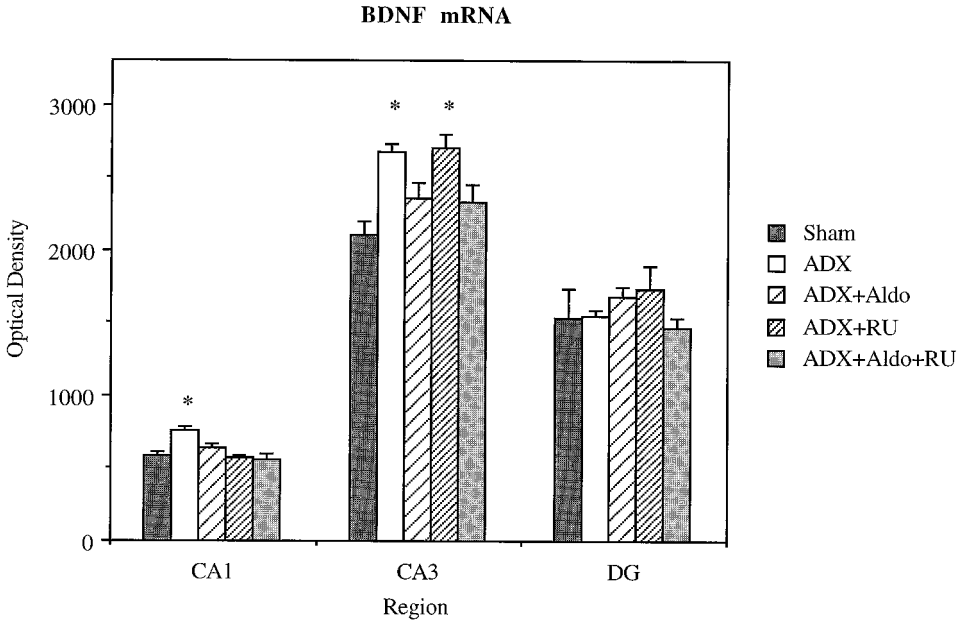

FIG. 5. Hippocampal BDNF mRNA expression in Exp 2. Levels of BDNF mRNA expression were assessed in the CA1 pyramidal cell layer (CA1), CA3 pyramidal cell layer (CA3), and granule cell layer of the dentate gyrus (DG). Statistical analysis indicated that the ADX animals were significantly different from the Sham animals in the CA1 subregion, and that the ADX and the ADX + RU animals were significantly different from the Sham animals in the CA3 subregion (*, $P < 0.05$).

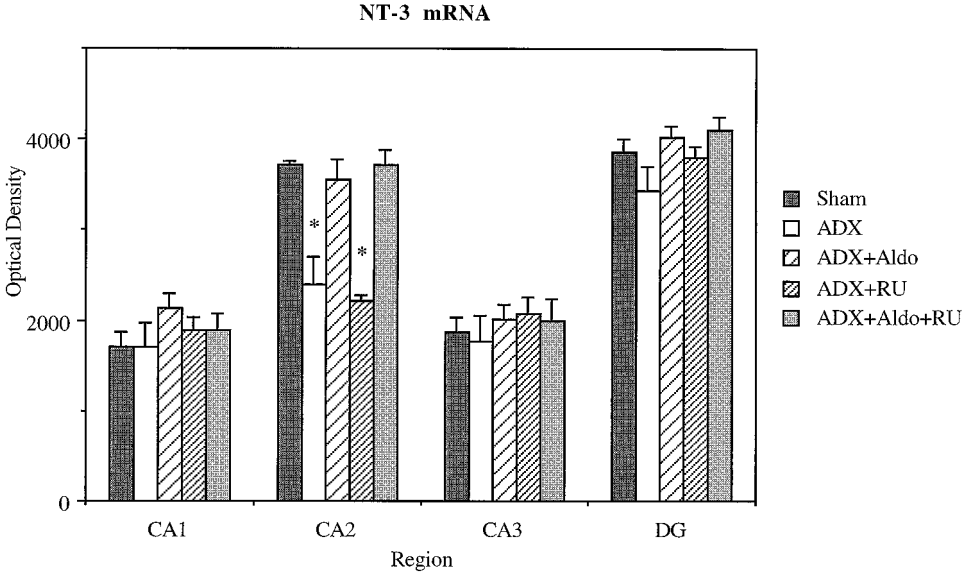

FIG. 6. Hippocampal NT-3 mRNA expression in Exp 2. Levels of NT-3 mRNA expression were assessed in the CA1 pyramidal cell layer (CA1), CA2 pyramidal cell layer (CA2), CA3 pyramidal cell layer (CA3), and granule cell layer of the dentate gyrus (DG). Statistical analysis indicated that the ADX and the ADX + RU animals were significantly different from the Sham animals in the CA2 subregion (*, $P < 0.05$).

dentate gyrus. In the CA1 subregion, but not in CA3 pyramidal cells, this induction was prevented by treatment of the ADX animals with the GR-specific agonist RU28362, in the presence or absence of aldosterone (Fig. 5).

In the adrenalectomized animals there was a significant decrease in NT-3 mRNA expression in the CA2 subfield, relative to the Sham animals. This decrease was prevented by treatment of the ADX animals with the MR-specific agonist aldosterone, in the presence or absence of RU28362, but not by RU28362 alone (Fig. 6). Expression of bFGF mRNA in the CA2 subregion showed this same pattern of adrenal steroid regulation (Fig. 7).

GAP-43 mRNA levels were elevated in ADX animals, in CA1 and CA3 pyramidal cells, relative to the Sham animals. In CA1, but not in CA3, pyramidal cells this induction was prevented by treatment of the ADX animals with RU28362. In both CA1 and CA3 pyramidal cells, the combined treatment of ADX animals with aldosterone and RU28362 resulted in decreased expression of GAP-43 mRNA, compared with the untreated ADX group (Fig. 8).

Discussion

The results of our studies have demonstrated that the profile for steroid-regulated neurotrophin expression is dependent upon the neurotrophic factor in question, the adrenal steroid receptor subtype activated, and the hippocampal subregion examined. A comparison of the results from the different hippocampal subfields demonstrates that despite the colocalization of GR and MR in hippocampal neurons (33, 34), there are distinct regulatory mechanisms mediated by either GR or MR activation. The changes we

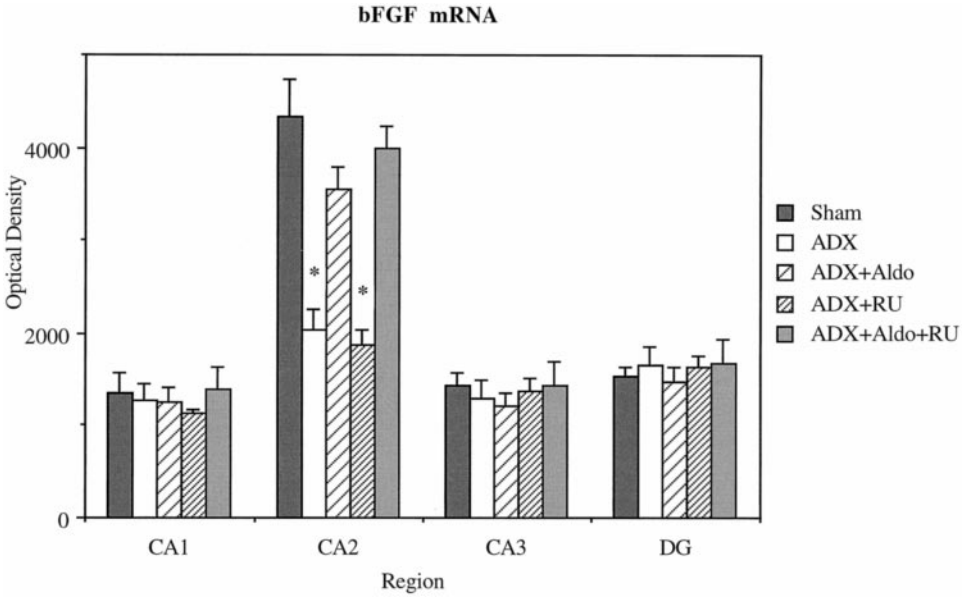

FIG. 7. Hippocampal bFGF mRNA expression in Exp 2. Levels of bFGF mRNA expression were assessed in the CA1 pyramidal cell layer (CA1), CA2 pyramidal cell layer (CA2), CA3 pyramidal cell layer (CA3), and granule cell layer of the dentate gyrus (DG). Statistical analysis indicated that the ADX and the ADX + RU animals were significantly different from the Sham animals in the CA2 subregion (*, $P < 0.05$).

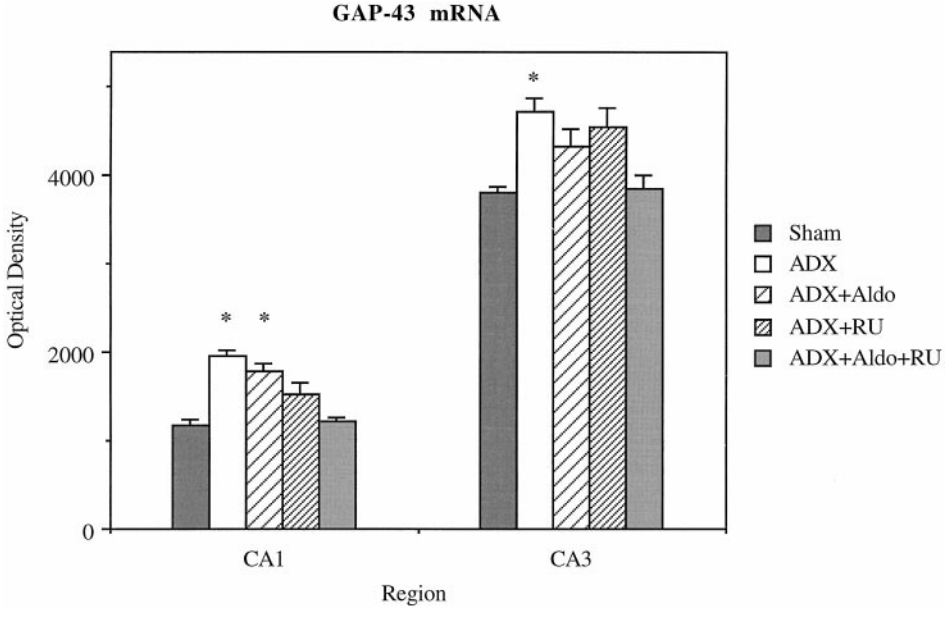

FIG. 8. Hippocampal GAP-43 mRNA expression in Exp 2. Levels of GAP-43 mRNA expression were assessed in the CA1 pyramidal cell layer (CA1) and CA3 pyramidal cell layer (CA3). Statistical analysis indicated that the ADX and the ADX + Aldo animals were significantly different from the Sham animals in the CA1 subregion and that the ADX animals were significantly different from the Sham animals in the CA3 subregion (*, $P < 0.05$).

observed following adrenal steroid treatment were restricted to hippocampal pyramidal cells, and we found no evidence for regulation of neurotrophin expression in the granule cells of the dentate gyrus. Because adrenalectomy has been shown to result in granule cell death (35) the possibility remains that in measurements of the entire granule cell layer, neuronal loss could be obscuring increases in neurotrophin expression in the cells that survive, a question that might be resolved by single-cell analysis of neurotrophin expression.

In the CA3 pyramidal cells of the hippocampus, corticosterone treatment has been shown to cause dendritic atrophy and neuronal damage (36, 37). The increase in BDNF and GAP-43 mRNA expression observed following adrenalectomy suggests that these genes may be under tonic glucocorticoid inhibition and raises the possibility that prolonged glucocorticoid excess could, through repression of such gene products, precipitate a neurodegenerative cascade. Different patterns of steroid-regulated gene expression are apparent when these results are compared with those of studies employing other regimens for sodium replacement following adrenalectomy and investigating different timepoints after surgery (38–40), suggesting that the changes in neurotrophin expression may be sensitive to salt and water homeostasis in addition to adrenal steroid levels, or that they may be transient.

The mRNAs for bFGF and NT-3 showed similar patterns of regulation by adrenal steroids. Adrenalectomy inhibited the expression of bFGF and NT-3 mRNAs in CA2 pyramidal neurons, in agreement with previous results (39–42). Activation by aldosterone of the mineralocorticoid receptor,

which is most highly expressed in the CA2 subregion, was effective in preventing this ADX-induced decrease in neurotrophin expression. While there is scant information on the function of the neurons in the CA2 subregion, the steroid regulation of bFGF and NT-3 in these cells may be of importance because the markedly high levels of expression of these neurotrophic factors could contribute to the resistance of CA2 pyramidal cells to damage in epilepsy (43, 44).

In CA1 pyramidal cells, we have found evidence that adrenalectomy results in an increase in the mRNAs for BDNF and GAP-43. Activation by RU28362 of the glucocorticoid receptor, which is most abundant in the CA1 subregion, can prevent this ADX-induced increase in expression. The finding that adrenalectomy induces growth factor expression is consistent with reports showing that CA1 pyramidal cells are protected from neurodegenerative, neurotoxic, and ischemic damage by adrenalectomy (45, 46). In addition, because there is a well documented reciprocal regulation of neurotrophins and neuronal signaling (3, 4), it is of interest to note that long-term potentiation (LTP), which is impaired in BDNF-deficient animals, can be restored by targeted reexpression of BDNF, and that activation of GR acts to inhibit both BDNF expression and LTP in CA1 neurons (14, 47–49).

In conclusion, adrenal steroids and neurotrophic factors have profound influences on the structure and activity of hippocampal neurons, and our results support the model that adrenal steroids exert their effects, at least in part, through regulation of neurotrophic factor expression. Our findings suggest that adrenal steroids, acting differentially through GR or MR, can elicit distinct patterns of neurotrophic factor expression in the various hippocampal subfields, with diverse consequences for neuronal morphology, function and survival.

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Erratum

In the article, "RORα gene expression in the perinantal rat cerebellum: ontogeny and thyroid hormone regulation," by Noriyuki Koibuchi and William W. Chin (*Endocrinology* **139:** 2335–2341, 1998), parts of Fig. 6 were incorrectly labeled (page 2340): Fig. 6F should be 6E, and 6E should be 6F.