

Dendritic Reorganization in Pyramidal Neurons in Medial Prefrontal Cortex after Chronic Corticosterone Administration

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ABSTRACT: Chronic stress produces deficits in cognition accompanied by alterations in neural chemistry and morphology. For example, both stress and chronic administration of corticosterone produce dendritic atrophy in hippocampal neurons (Woolley C, Gould E, McEwen BS. 1990. Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. *Brain Res* 531:225–231; Watanabe Y, Gould E, McEwen BS, 1992b. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Res* 588:341–345). Prefrontal cortex is also a target for glucocorticoids involved in the stress response (Meaney MJ, Aitken DH. 1985. [³H]Dexamethasone binding in rat frontal cortex. *Brain Res* 328:176–180); it shows neurochemical changes in response to stress (e.g., Luine VN, Spencer RL, McEwen BS. 1993. Effect of chronic corticosterone ingestion on spatial memory performance and hippocampal serotonergic function. *Brain Res* 616:55–70; Crayton JW, Joshi I, Gulati A, Arora RC, Wolf WA. 1996. Effect of corticosterone on serotonin and catecholamine receptors and uptake sites in rat frontal cortex. *Brain Res* 728:260–262; Takao K, Nagatani T, Kitamura Y, Yamawaki S. 1997. Effects of corticosterone on 5-HT_{1A} and 5-HT₂ receptor binding and on the receptor-mediated behavioral responses of rats. *Eur J Pharmacol* 333:123–128; Sandi C, Loscertales M. 1999. Opposite effects on NCAM expression in the rat frontal cortex induced by acute vs. chronic corticosterone treatments. *Brain Res* 828:127–134), and mediates many of the

behaviors that are altered by chronic corticosterone administration (e.g., Lyons DM, Lopez JM, Yang C, Schatzberg AF. 2000. Stress-level cortisol treatment impairs inhibitory control of behavior in monkeys. *J Neurosci* 20:7816–7821). To determine if glucocorticoid-induced morphological changes also occur in medial prefrontal cortex, the effects of chronic corticosterone administration on dendritic morphology in this corticolimbic structure were assessed. Adult male rats received s.c. injections of either corticosterone (10 mg in 250 μ L sesame oil; $n = 8$) or vehicle (250 μ L; $n = 8$) daily for 3 weeks. A third group of rats served as intact controls ($n = 4$). Brains were stained using a Golgi-Cox procedure and pyramidal neurons in layer II-III of medial prefrontal cortex were drawn; dendritic morphology was quantified in three dimensions. Sholl analyses demonstrated a significant redistribution of apical dendrites in corticosterone-treated animals: the amount of dendritic material proximal to the soma was increased relative to intact rats, while distal dendritic material was decreased relative to intact animals. Thus, chronic glucocorticoid administration dramatically reorganized apical arbors in medial prefrontal cortex. This reorganization likely reflects functional changes and may contribute to stress-induced changes in cognition. © 2001

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Keywords: dendritic morphology; prefrontal cortex; rat; corticosterone; stress

INTRODUCTION

A wealth of data documents the adverse effects of chronic stress on physiology and behavior. Chronic stress is associated with increased risk for illness, the

development of a variety of psychological disorders, and changes in cognition. For instance, chronic exposure to a stressor results in the development of gastric ulcers (Henke, 1990). In addition, individuals experiencing increased numbers of stressful life events are more likely to develop respiratory infections (Stone et al., 1987). Stress has also been hypothesized to play a causal role in several psychological disorders. For instance, depressed individuals are more likely than

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nondepressed individuals to have experienced at least one stressful life event prior to diagnosis (Brown and Harris, 1989), and stressful life events appear to increase the probability of a psychotic episode in schizophrenics (Ventura et al., 1989). Animal studies have also demonstrated detrimental effects of stress on many behaviors. For instance, several studies have demonstrated stress-induced deficits in a variety of cognitive tasks, including shuttle escape (Seligman and Maier, 1967), water maze (Altenor et al., 1977), appetitively motivated operant conditioning (Rosellini, 1978), and radial maze tasks (Luine et al., 1994).

Many of the effects of chronic stress are thought to be mediated by stress-induced increases in circulating levels of glucocorticoids (e.g., Uno et al., 1989), and in fact, chronic elevations of circulating glucocorticoids have been shown to produce a variety of cognitive deficits. For instance, rats exposed to daily corticosterone injections for 8 weeks demonstrated decreased spontaneous alternation on a T maze (Bardgett et al., 1994). Likewise, 21-day corticosterone implants that produced a two- to four-fold increase in serum corticosterone levels in rats impaired acquisition of a passive-avoidance task (Bisagno et al., 2000). In addition, chronic corticosterone treatment has been shown to impair both acquisition of a radial arm maze task (Dachir et al., 1993) and accuracy of recall of spatial information in the Morris water maze (Sousa et al., 2000) in rats. Finally, chronic administration of stress levels of cortisol has been shown to impair response inhibition in squirrel monkeys (Lyons et al., 2000).

The behavioral deficits induced by chronic corticosterone administration have typically been attributed to corticosterone-induced changes in the hippocampus, which is a primary neural target of glucocorticoids (Gerlach and McEwen, 1972) and is involved in many of the behaviors altered by chronic corticosterone administration. Both chronic corticosterone administration and chronic stress result in extensive atrophy of apical dendrites of pyramidal neurons in hippocampal area CA3 (Woolley et al., 1990; Watanabe et al., 1992; Magarinos et al., 1996), and administration of cyanoketone, which blocks stress-induced increases in corticosterone, prevents the stress-induced atrophy of CA3 apical dendrites (Magarinos and McEwen, 1995). This dendritic atrophy appears to be mediated by both the glutamatergic and serotonergic systems: administration of either the NMDA receptor antagonist CGP 43487 (Magarinos and McEwen, 1995) or the serotonin uptake inhibitor tianeptine (Watanabe et al., 1992a) prevents the stress-induced dendritic atrophy.

However, prefrontal cortex is also a target for glucocorticoids involved in the stress response: [³H]dexamethasone binds to receptors in frontal and

prefrontal cortex at about 75% of the concentration found in hippocampus. In addition, [³H]dexamethasone binding in frontal cortex is altered by both corticosterone treatment and adrenalectomy, indicating the presence of endogenously regulated corticosterone receptors (Meaney and Aitken, 1985). Furthermore, prefrontal cortex is also involved in many of the tasks that are influenced by chronic elevations of circulating glucocorticoids. For instance, lesions of prefrontal cortex in rats impair spontaneous alternation, radial maze performance, and passive avoidance. Likewise, lesions of prefrontal cortex in primates impair inhibition of the line-of-sight response (e.g., Dias et al., 1996). Thus, potential alterations in prefrontal cortex may mediate some corticosterone-induced behavioral changes. Chronic corticosterone administration has been shown to produce a variety of neurochemical changes in prefrontal cortex, including decreased 5-HT_{1A} (Crayton et al., 1996) and 5-HT₂ receptor binding (Takao et al., 1997), as well as decreased serotonin levels (Luine et al., 1993). In addition, chronic elevations of corticosterone result in decreased expression of the neural cell adhesion molecule (NCAM; Sandi and Loscertales, 1999), a cell-surface macromolecule involved in regulating aspects of synapse stabilization, which suggests the possibility of structural changes as a result of chronic stress levels of corticosterone. Therefore, to determine if glucocorticoid-induced morphological changes also occur in medial prefrontal cortex, the effects of chronic corticosterone administration on dendritic morphology of layer II-III pyramidal neurons in this corticolimbic structure were assessed.

METHODS

Animals

Adult male Sprague-Dawley rats (175–200 g, approximately 50 days old at the initiation of the experiment; Harlan Sprague-Dawley, Indianapolis, IN) received s.c. injections of either corticosterone (RBI, Natick, MA; 10 mg in 250 μ L sesame oil; $n = 8$) or vehicle (250 μ L; $n = 8$) daily for 3 weeks. The corticosterone dose is based on that of Woolley et al. (1990) and results in peak plasma corticosterone levels comparable to stress levels, which then fall to nonstress levels within 24 h (Hauger et al., 1987). This dose is sufficient to produce pronounced atrophy of apical dendrites of pyramidal neurons in hippocampal area CA3 (Woolley et al., 1990). A third group of rats served as untreated controls ($n = 4$). Rats were individually housed in a vivarium with a 12:12 h light/dark cycle (lights on at 7 a.m.), ambient temperature of 23–25°C, and free access to food and water. All experimental procedures occurred between 10:00 a.m. and 2:00 p.m., and were approved by the Bloomington Institutional Animal Care and Use Committee.

Histology and Dendritic Analyses

Approximately 24 h after the final injection, tissue was processed using Glaser and Van der Loos' modified Golgi stain (Glaser and Van der Loos, 1981), which allows visualization of whole neurons including processes. Animals were overdosed with urethane and then perfused with 0.9% saline. Brains were removed and immersed in Golgi-Cox solution (a 1:1 solution of 5% potassium dichromate and 5% mercuric chloride diluted 4:10 with 5% potassium chromate). When staining was complete (10–14 days; determined in pilot animals by developing test sections at regular intervals and assessing the presence of dendrites trailing off into a series of dots; see Coleman and Flood, 1987), brains were dehydrated in 1:1 absolute ethanol:acetone (3 h), followed by absolute ethanol and then 1:1 ethanol:ether (30 min each). Brains were then infiltrated with a graded series of celloidins before being embedded in 8% celloidin [8% (v/v) parlodion in 1:1 absolute ethanol:ether]. Coronal sections were cut at 145 μm on a sliding microtome (American Optical 860). Free-floating sections were then alkalized in 18.7% ammonia, developed in Dektol (Kodak), fixed in Kodak Rapid Fix (prepared as per package instructions with Solution B omitted), dehydrated through a graded series of ethanols, cleared in xylene, mounted, and coverslipped (see Glaser and Van der Loos, 1981).

Pyramidal neurons in layer II-III of medial prefrontal cortex (Zilles and Wree's Cg1 and Cg3; Zilles and Wree, 1985) were drawn. The Cg1-3 area of medial prefrontal cortex is readily identified by its position on the medial wall of rostral cortex, and its location dorsal to infralimbic cortex, which is markedly thinner than the Cg1-3 area and has fewer, less well-defined layers [Zilles and Wree, 1995; Fig. 1(A)]. Within Cg1-3, layer II-III is readily identifiable in Golgi-stained material based on its characteristic cytoarchitecture. Its position is immediately ventral to the relatively cell-poor layer I (which also contains the distal dendritic tufts of layer II-III pyramids) and immediately dorsal to layer IV; in medial prefrontal cortex, this boundary is pronounced because of the greater cell-packing density and smaller somata of pyramidal cells in layer II-III relative to layer IV (Cajal, 1995; Zilles and Wree, 1995). Pyramidal neurons were defined by the presence of a basilar dendritic tree, a distinct, single apical dendrite, and dendritic spines [Fig. 1(B)]. To control for potential confounds due to shorter apical dendrites in layer II pyramidal neurons relative to those in layer III, the proportions of layer II and layer III neurons included were approximately equal across groups. Neurons with somata in the middle third of sections were chosen to minimize the number of truncated branches. However, when present, truncated branches were reconstructed across sections. For each animal, 10 neurons were drawn; this number yields a within-animal error of approximately 10% (mean within-animal S.E.M. for total branch number and length = $11 \pm 1\%$), and thus was considered to provide a valid and representative sample of layer II-III pyramidal neurons in medial prefrontal cortex. All neurons were drawn at 750X and morphology of apical and basilar arbors was quantified in three dimensions using a computer-

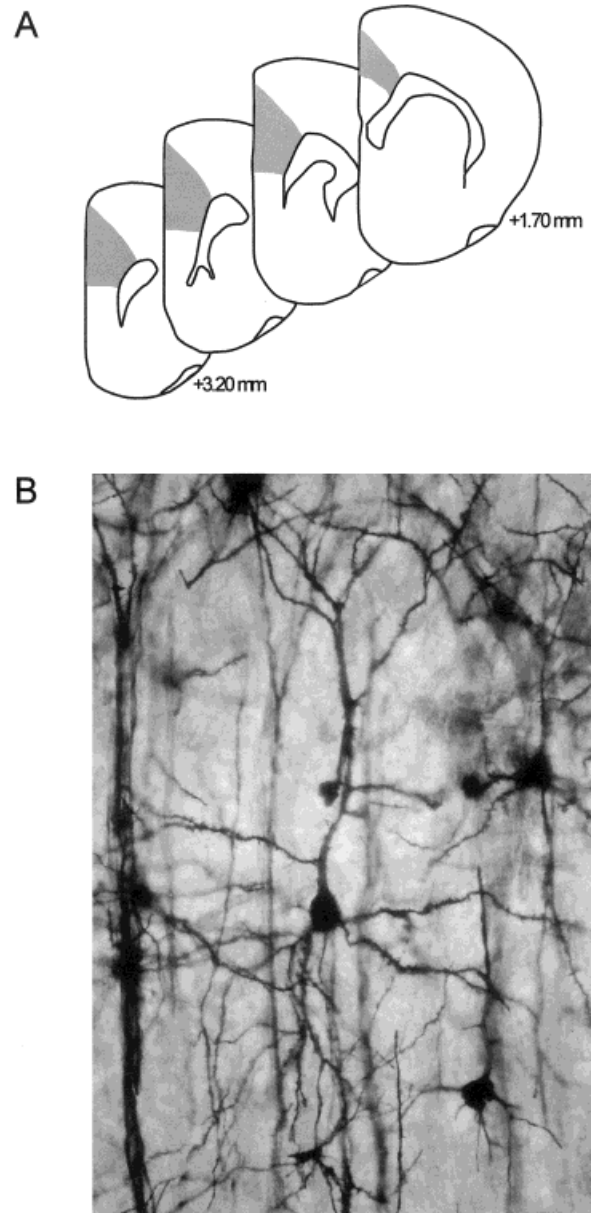


Figure 1 (A) Schematic diagram of coronal sections through rat prefrontal cortex. The portions of area Cg1-3 from which neurons were sampled is shown (shaded areas). Coordinates indicate position relative to bregma (Paxinos and Watson, 1997). (B) Photomicrograph of Golgi-stained neuron in layer II-III of medial prefrontal cortex in an untreated rat.

based neuron tracing system (NeuroLucida, MicroBrightfield) with the experimenter blind to condition.

RESULTS

In all treatment groups, complete impregnation of numerous cortical pyramidal neurons was apparent

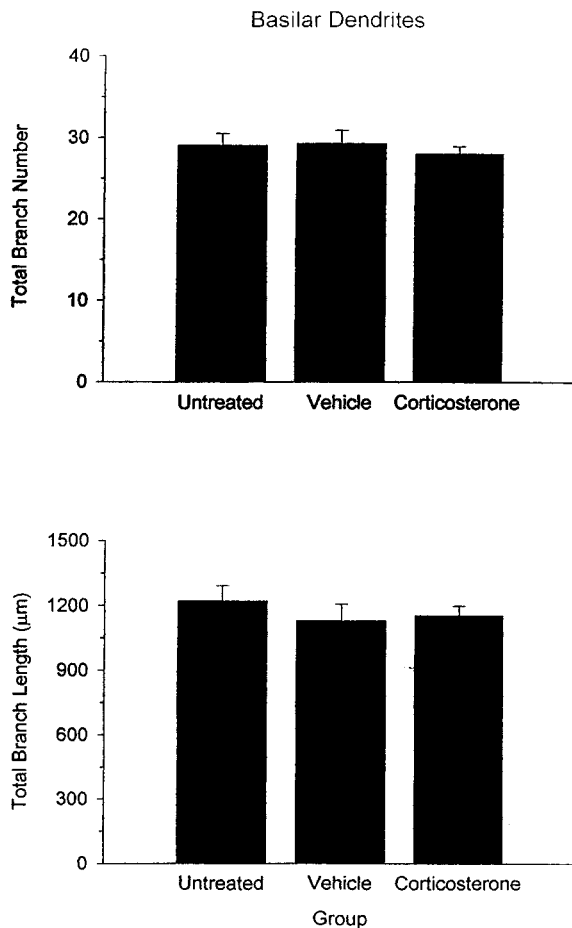


Figure 2 Mean basilar branch number (top) and length (bottom) for untreated ($n = 4$), vehicle- ($n = 8$), and corticosterone-treated rats ($n = 8$). Overall basilar branch length and number did not vary across groups. Vertical bars represent S.E.M. values.

(Fig. 1), and layer II-III was readily identifiable. Because relatively thick sections were taken through prefrontal cortex, the apical and basilar arbors of almost all neurons selected were completely contained within a single section.

To assess overall changes in dendritic morphology, total length and number of basilar and apical dendrites were compared across groups. One-way ANOVAs revealed no significant difference across groups in either length or number for both basilar and apical dendrites [all F 's(2, 17) < 0.36, ns; Figs. 2 and 3].

To assess differences in the amount and location of dendritic material, a three-dimensional version of a Sholl analysis (Sholl, 1956) was performed. A Sholl analysis estimates the amount and distribution of dendritic material by counting the number of intersections of dendrites with an overlay of concentric rings centered on the soma. In the present study, the number of intersections of dendrites with concentric spheres at

10- μ m intervals were assessed. To simplify analyses, the basilar and apical arbors were divided into thirds based on the average maximal extent of the arbor in intact animals; the Sholl data were then summed over the 10- μ m intervals to assess amount of dendritic material in the proximal, middle, and distal thirds of the basilar and apical arbors. These data were compared using two-way ANOVAs (treatment \times distance from soma).

The distribution of basilar dendritic material did not vary across groups at any distance from the soma [for main effect of treatment, $F(2, 17) = 0.17$, ns; for interaction of treatment and distance from soma, $F(4, 17) = 0.37$, ns; Fig. 4]. On the other hand, although no overall effect of treatment was present [for main effect of treatment, $F(2, 17) = 0.79$, ns], Sholl analyses demonstrated a significant redistribution of apical dendrites in corticosterone-treated animals [for interaction of treatment and distance from soma, $F(4, 17) = 4.66$; $p < .01$; Fig. 5]. Posthoc analyses (Fish-

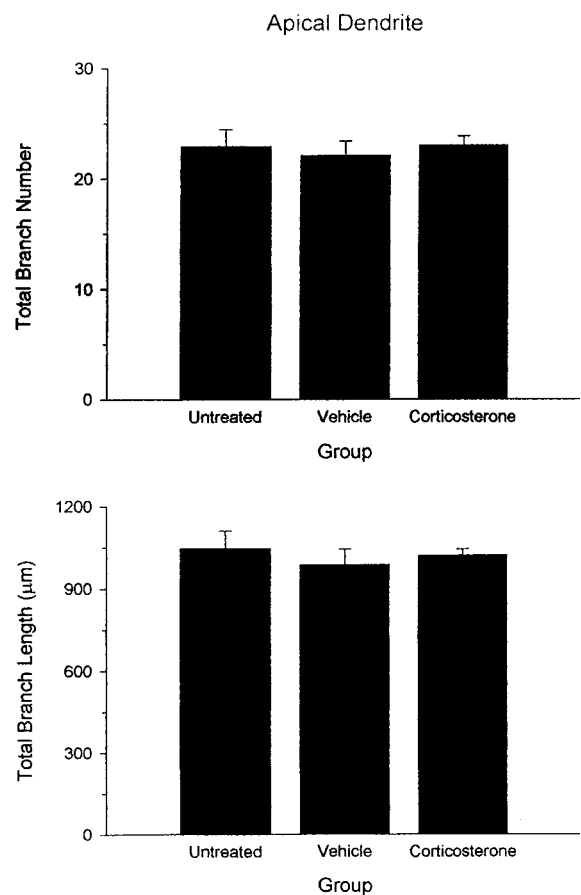


Figure 3 Mean apical branch number (top) and length (bottom) for untreated ($n = 4$), vehicle- ($n = 8$), and corticosterone-treated rats ($n = 8$). Overall apical branch length and number did not vary across groups. Vertical bars represent S.E.M. values.

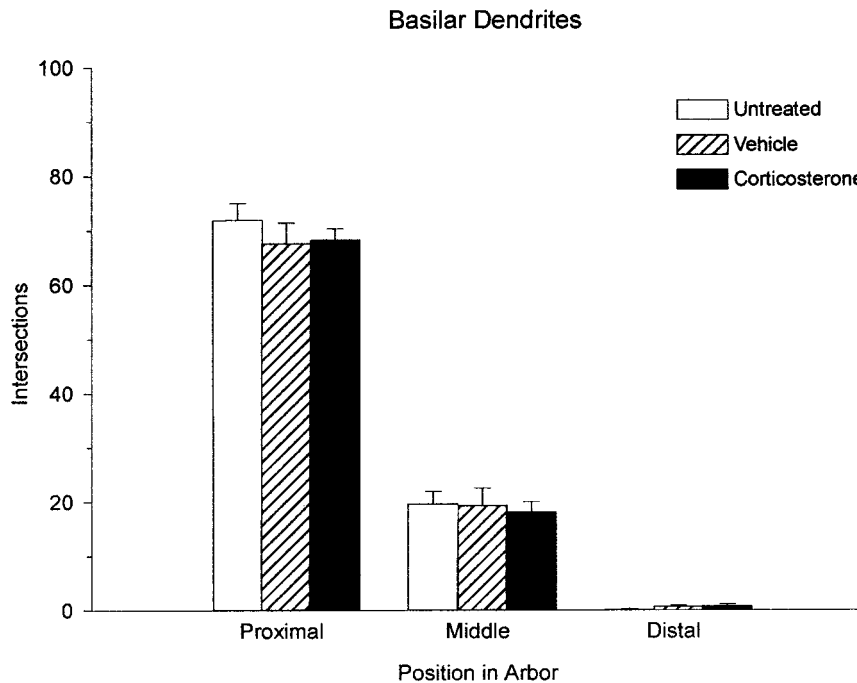


Figure 4 Mean intersections of basilar dendrites with 10- μ m concentric spheres summed across the proximal, middle, and distal third of the arbor for untreated ($n = 4$), vehicle- ($n = 8$), and corticosterone-treated rats ($n = 8$). The distribution of basilar dendritic arbor did not differ across groups. Vertical bars represent S.E.M. values.

er's PLSD) revealed that the amount of dendritic material proximal to the soma was increased by 21% in corticosterone-treated rats relative to untreated rats [$t(19) = 7.78$; $p < .01$], while dendritic material in the middle and distal portions of the arbor was decreased 22 and 58%, respectively, relative to untreated controls [$t(19) = -8.60$ and -3.25 ; $p < .01$].

Interestingly, the distribution of apical dendritic material in vehicle-treated rats was intermediate to that seen in untreated and corticosterone-treated animals. The number of intersections proximal to the soma in vehicle-treated rats did not differ significantly from that of either untreated or corticosterone-treated rats [$t(19) = 3.59$ and -4.19 , ns]; intersections in the middle portion of the apical arbor were significantly decreased by 22% in vehicle-treated rats relative to untreated rats [$t(19) = -8.56$; $p < .05$]; and the 51% decrease in intersections in the distal portion of the arbor in vehicle-treated rats relative to untreated controls approached significance [$t(19) = -2.81$; $p < .08$; Fig. 5].

DISCUSSION

Chronic corticosterone administration dramatically reorganized apical arbors of layer II-III neurons in

medial prefrontal cortex, with an increase of 21% in dendritic material proximal to the soma, along with a decrease of up to 58% in dendritic material distal to the soma. Interestingly, vehicle-treated animals showed similar but less pronounced changes in apical arbors. Thus, the stress of daily s.c. injections alone may have altered apical dendritic arbors of layer II-III pyramidal neurons in medial prefrontal cortex.

Our findings contrast with the morphological changes seen in hippocampal area CA3 after chronic corticosterone administration. Chronic elevation of corticosterone results strictly in regressive changes in area CA3 pyramidal neurons (Woolley et al., 1990); in prefrontal cortex, the same dose and length of administration results in a reorganization of dendrites rather than simple atrophy. Thus, while dendritic morphology in medial prefrontal cortex is altered by chronic corticosterone administration, the nature of the dendritic response here differs markedly from that seen in the hippocampus.

Furthermore, whereas chronic injection of vehicle has no effect on the morphology of hippocampal neurons (Woolley et al., 1990), these same vehicle injections resulted in changes in layer II-III neurons in medial prefrontal cortex that were parallel to, but less pronounced than, the corticosterone-induced changes. Thus, the relatively mild stress of daily injections

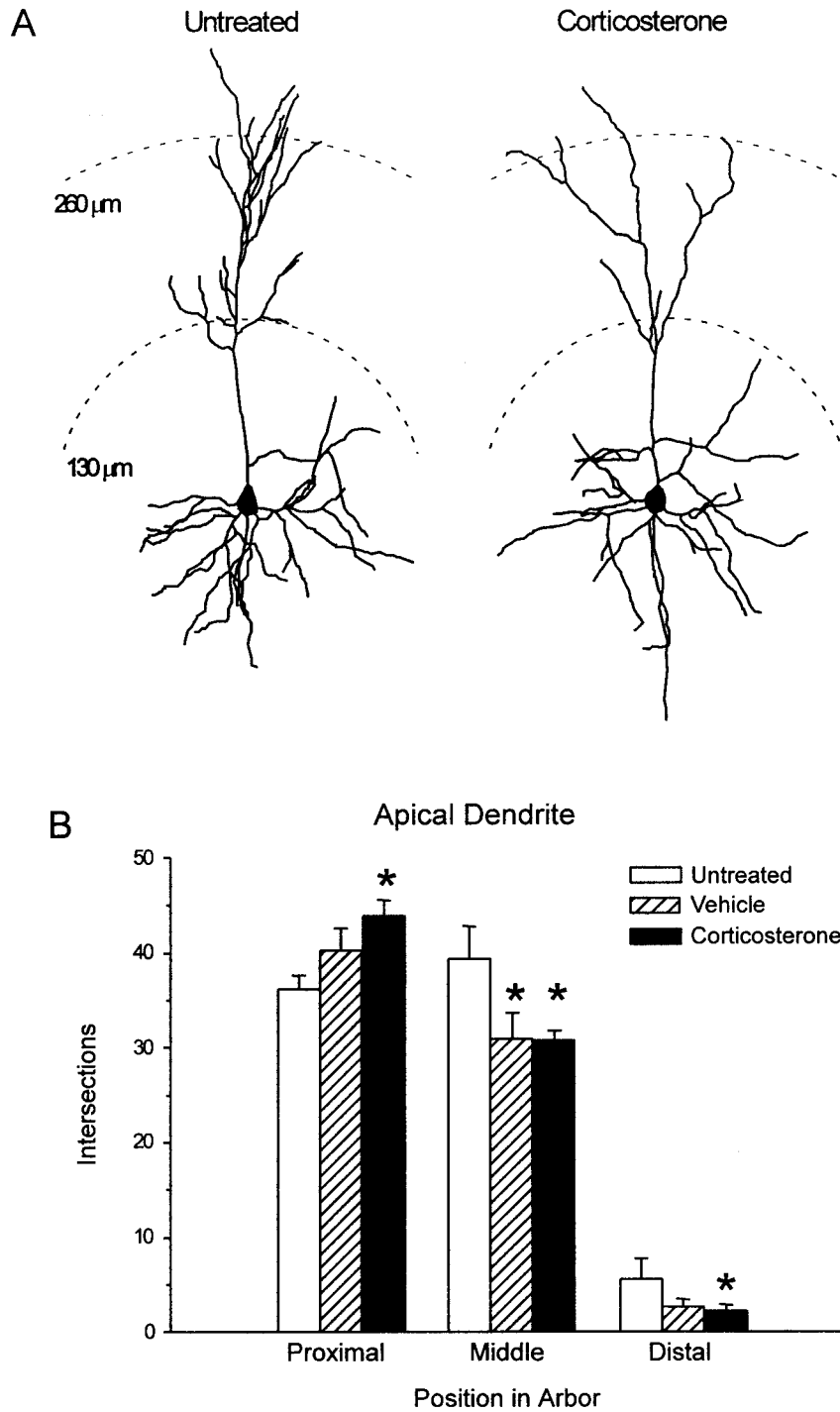


Figure 5 (A) Computer-assisted reconstructions of Golgi-stained pyramidal neurons in layer II-III of medial prefrontal cortex in an untreated and corticosterone-treated rat. Apical dendritic material is increased proximal to the soma and decreased distal to the soma. (B) Mean intersections of apical dendrites with 10- μ m concentric spheres summed across the proximal, middle, and distal third of the arbor for untreated ($n = 4$), vehicle- ($n = 8$), and corticosterone-treated rats ($n = 8$). Vertical bars represent S.E.M. values; asterisks (*) indicate significant difference relative to untreated rats.

alone appears to alter the morphology of medial prefrontal cortex, suggesting an exquisite sensitivity to chronic stress—perhaps even greater than that seen in

the hippocampus. Given that both stress (e.g., Brown and Birley, 1968; Brown and Harris, 1989; Ventura et al., 1989) and dysfunction of prefrontal cortex (e.g.,

Baxter et al., 1989; Mayberg, 1997; Berman and Weinberger, 1999) are hypothesized to play important roles in disorders such as depression and schizophrenia, the morphological sensitivity of prefrontal cortex to chronic elevations of corticosterone, and perhaps to chronic stress, has important implications for the etiology of these disorders.

Given that glucocorticoid receptors are plentiful in medial prefrontal cortex (Meaney and Aitken, 1985), the reorganization of apical dendrites here could be a direct effect of corticosterone in prefrontal cortex. Alternatively, it is also possible that the atrophy of distal dendrites of layer II-III pyramidal neurons is a result of loss of input from CA3 pyramidal neurons. In addition to producing regressive dendritic changes in CA3 pyramidal neurons (Woolley et al., 1990), both administration of corticosterone and chronic stress alter hippocampal excitability (e.g., Foy et al., 1987, 1990; Joëls and de Kloet, 1989). Hippocampal areas CA1 and CA3 both project directly to medial prefrontal cortex. In rats, injections of retrograde tracers centered in infralimbic cortex but extending into the Cg1 and 3 areas label CA1 pyramidal cells (Swanson, 1981), and injections of tritiated amino acids into CA3 label cingulate cortex (Swanson and Cowan, 1977). In fact, the projection from CA3 to cingulate cortex terminates exclusively in layer I (Swanson and Cowan, 1977). Given that electrophysiological data suggest that excitatory synapses on proximal apical dendrites of prefrontal neurons serve to amplify EPSPs generated in distal apical dendrites (Seamans et al., 1997), the increase in proximal dendritic material seen in the present study could be a compensatory response to distal atrophy—an attempt to maintain the excitation provided by now-reduced distal inputs. The systemic administration of corticosterone used in the present study prevents discrimination between these two possible sites of action; however, future studies will address this question by assessing dendritic morphology in prefrontal cortex after chronic administration of corticosterone directly into either hippocampus or medial prefrontal cortex.

Several studies have documented changes in hippocampal neurochemistry in response to chronic corticosterone administration (e.g., Luine et al., 1993; Orchinik et al., 1995; Nair et al., 1998), and studies have demonstrated that the atrophy of CA3 pyramidal neurons is mediated by NMDA receptors (Magarinos and McEwen, 1995) and can be prevented via manipulations of the serotonergic system (Watanabe et al., 1992a). On the other hand, relatively few studies have examined the neurochemical changes in prefrontal cortex induced by chronic administration of high levels of corticosterone. However, chronic corticosterone administration

produces serotonergic alterations in prefrontal cortex (Luine et al., 1993; Crayton et al., 1996; Inoue and Koyama, 1996; Takao et al., 1997), while stress alters glutamate release in prefrontal cortex (Moghaddam, 1993; Jedema and Moghaddam, 1994; Bagley and Moghaddam, 1997). These findings suggest that similar neurochemical mechanisms could mediate the dendritic alterations seen in hippocampus and prefrontal cortex as a result of chronic elevations of corticosterone.

Finally, the corticosterone-induced reorganization of apical dendrites documented here likely reflects important functional changes in medial prefrontal cortex. Pyramidal neurons segregate their inputs. For instance, in piriform cortex, the distal part of the apical dendrites of layer III pyramidal neurons receives extrinsic inputs, while more proximal portions of the apical dendrite, as well as the basilar dendrites, receive intrinsic inputs (Price, 1973). While the segregation of inputs to pyramidal neurons in neocortex is not as straightforward, pyramidal neurons in medial prefrontal cortex nonetheless tend to segregate inputs, with extracortical afferents (for instance, from the mediodorsal nucleus of the thalamus and hippocampal area CA3) tending to cluster on distal dendrites (i.e., in layer I; Swanson and Cowan, 1977; Groenewegen, 1988) and synapses of local cortical circuits tending to cluster on proximal portions of the apical and basilar arbor (Scheibel and Scheibel, 1970). Thus, the corticosterone-induced reorganization of the apical dendrites of layer II-III pyramidal neurons in medial prefrontal cortex likely results in a shift in emphasis from subcortical to intracortical information. This functional reorganization of individual neurons likely has important implications for the functioning of medial prefrontal cortex and behaviors mediated by it. Thus, the corticosterone-induced changes in dendritic morphology of medial prefrontal cortex may contribute to stress-induced cognitive changes.

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REFERENCES

- Altener A, Kay E, Richter M. 1977. The generality of learned helplessness in the rat. *Learn Motiv* 8:54–61.
- Bagley J, Moghaddam B. 1997. Temporal dynamics of glutamate efflux in the prefrontal cortex and in the hippocampus following repeated stress: effects of pretreatment with saline or diazepam. *Neurosci* 77:65–73.
- Bardgett ME, Taylor GT, Csernansky JG, Newcomer JW, Nock B. 1994. Chronic corticosterone treatment impairs

- spontaneous alternation behavior in rats. *Behav Neural Bio* 61:186–190.
- Baxter LR, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sumida RM. 1989. Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry* 46:243–250.
- Berman KF, Weinberger DR. 1999. Neuroimaging studies of schizophrenia. In: Charney DS, Nestler EJ, Bunney BS, editors. *Neurobiology of Mental Illness*. New York: Oxford University Press, p 246–257.
- Bisagno V, Ferrini M, Rios H, Zieher LM, Wikinski SI. 2000. Chronic corticosterone impairs inhibitory avoidance in rats: possible link with atrophy of hippocampal CA3 neurons. *Pharmacol Biochem Behav* 66:235–240.
- Brown GW, Birley JLT. 1968. Crises and life changes and the onset of schizophrenia. *J Health Social Behav* 9:203–214.
- Brown GW, Harris TO. 1989. Depression. In: Brown GW, Harris TO, editors. *Life Events and Illness*. New York: Guilford. p 49–93.
- Cajal SRy. 1995. *Histology of the nervous system*. New York: Oxford University Press. 806 p.
- Coleman PD, Flood DG. 1987. Neuron numbers and dendritic extent in normal aging and Alzheimer's disease. *Neurobiol Aging* 8:521–545.
- Crayton JW, Joshi I, Gulati A, Arora RC, Wolf WA. 1996. Effect of corticosterone on serotonin and catecholamine receptors and uptake sites in rat frontal cortex. *Brain Res* 728:260–262.
- Dachir S, Kadar T, Robinzon B, Levy A. 1993. Cognitive deficits induced in young rats by long-term corticosterone administration. *Behav Neural Bio* 60:103–109.
- Dias R, Robbins TW, Roberts AC. 1996. Primate analogue of the Wisconsin Card Sorting Test: effects of excitotoxic lesions of the prefrontal cortex in the marmoset. *Behav Neurosci* 110:872–886.
- Foy MR, Foy JG, Levine S, Thompson RF. 1990. Manipulation of pituitary-adrenal activity affects neural plasticity in rodent hippocampus. *Psych Sci* 1:201–204.
- Foy MR, Stanton ME, Levine S, Thompson RF. 1987. Behavioral stress impairs long-term potentiation in rodent hippocampus. *Behav Neural Bio* 48:138–149.
- Gerlach J, McEwen B. 1972. Rat brain binds adrenal steroid hormone: radioautography of hippocampus with corticosterone. *Science* 175:1133–1136.
- Glaser EM, Van der Loos H. 1981. Analysis of thick brain sections by obverse-reverse computer microscopy: application of a new, high-quality Golgi-Nissl stain. *J Neurosci Meth* 4:117–125.
- Groenewegen HJ. 1988. Organization of the afferent connections of the mediodorsal thalamic nucleus in the rat, related to the mediodorsal-prefrontal topography. *Neurosci* 24:379–431.
- Hauger RL, Millam MA, Catt KJ, Aguilera G. 1987. Differential regulation of brain and pituitary corticotropin-releasing factor receptors by corticosterone. *Endocrinol* 120:1527–1533.
- Henke PG. 1990. Granule cell potentials in the dentate gyrus of the hippocampus: coping behavior and stress ulcers in rats. *Behav Brain Res* 36:97–103.
- Inoue T, Koyama T. 1996. Effects of acute and chronic administration of high-dose corticosterone and dexamethasone on regional brain dopamine and serotonin metabolism in rats. *Prog Neuropsychopharmacol Biol Psychiatry* 20:147–156.
- Jedema HP, Moghaddam B. 1994. Glutamatergic control of dopamine release during stress in the rat prefrontal cortex. *J Neurochem* 63:785–788.
- Joëls M, de Kloet R. 1989. Effects of glucocorticoids and norepinephrine on the excitability in the hippocampus. *Science* 245:1502–1505.
- Luine V, Villegas M, Martinez C, McEwen BS. 1994. Stress-dependent impairments of spatial memory: role of 5-HT. *Ann NY Acad Sci* 746:403–404.
- Luine VN, Spencer RL, McEwen BS. 1993. Effect of chronic corticosterone ingestion on spatial memory performance and hippocampal serotonergic function. *Brain Res* 616:55–70.
- Lyons DM, Lopez JM, Yang C, Schatzberg AF. 2000. Stress-level cortisol treatment impairs inhibitory control of behavior in monkeys. *J Neurosci* 20:7816–7821.
- Magarinos AM, McEwen BS. 1995. Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. *Neurosci* 69:89–98.
- Magarinos AM, McEwen BS, Flugge G, Fuchs E. 1996. Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. *J Neurosci* 16:3534–3540.
- Mayberg HS. 1997. Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsychiat* 9:471–481.
- Meaney MJ, Aitken DH. 1985. [³H]Dexamethasone binding in rat frontal cortex. *Brain Res* 328:176–180.
- Moghaddam B. 1993. Stress preferentially increases extra-neuronal levels of excitatory amino acids in the prefrontal cortex: comparison to hippocampus and basal ganglia. *J Neurochem* 60:1650–1657.
- Nair SM, Werkman TR, Craig J, Finnell R, Joels M, Eberwine JH. 1998. Corticosteroid regulation of ion channel conductances and mRNA levels in individual hippocampal CA1 neurons. *J Neurosci* 18:2685–2696.
- Orchinik M, Weiland NG, McEwen BS. 1995. Chronic exposure to stress levels of corticosterone alters GABA_A receptor subunit mRNA levels in rat hippocampus. *Mol Brain Res* 34:29–37.
- Paxinos G, Watson C. 1997. *The rat brain in stereotaxic coordinates*. New York: Academic Press. 249 p.
- Price JL. 1973. An autoradiographic study of complementary laminar patterns of termination of afferent fibers to the olfactory cortex. *J Comp Neurol* 150:87–108.
- Rosellini RA. 1978. Inescapable shock interferes with the acquisition of a free appetitive operant. *Anim Learn Behav* 6:155–159.
- Sandi C, Loscertales M. 1999. Opposite effects on NCAM expression in the rat frontal cortex induced by acute vs. chronic corticosterone treatments. *Brain Res* 828:127–134.
- Scheibel ME, Scheibel AB. 1970. Of pattern and place in dendrites. *Int Rev Neurobiol* 13:1–26.
- Seamans JK, Gorelova NA, Yang CR. 1997. Contributions

- of voltage-gated Ca^{2+} channels in the proximal versus distal dendrites to synaptic integration in prefrontal cortical neurons. *J Neurosci* 17:5936–5948.
- Seligman MEP, Maier SF. 1967. Failure to escape traumatic shock. *J Exp Psychol* 74:1–9.
- Sholl DA. 1956. *The Organization of the Cerebral Cortex*. London: Methuen. 125 p.
- Sousa N, Lukoyanov NV, Madeira MD, Almeida OFX, Paula-Barbosa MM. 2000. Reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement. *Neurosci* 97:253–266.
- Stone AA, Reed BR, Neale JM. 1987. Changes in daily event frequency precede episodes of physical symptoms. *J Human Stress* 13:70–74.
- Swanson LW. 1981. A direct projection from Ammon's horn to prefrontal cortex in the rat. *Brain Res* 217:150–154.
- Swanson LW, Cowan WM. 1977. An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. *J Comp Neurol* 172:49–84.
- Takao K, Nagatani T, Kitamura Y, Yamawaki S. 1997. Effects of corticosterone on 5-HT_{1A} and 5-HT₂ receptor binding and on the receptor-mediated behavioral responses of rats. *Eur J Pharmacol* 333:123–128.
- Uno H, Tarara R, Else JG, Suleman MA, Sapolsky RM. 1989. Hippocampal damage associated with prolonged and fatal stress in primates. *J Neurosci* 9:1705–1711.
- Ventura J, Neuchterlein KH, Lukoff D, Hardesty JD. 1989. A prospective study of stressful life events and schizophrenic relapse. *J Abnormal Psychol* 98:407–411.
- Watanabe Y, Gould E, Daniels DC, Cameron H, McEwen BS. 1992a. Taneptine attenuates stress-induced morphological changes in the hippocampus. *Eur J Pharmacol* 222:157–162.
- Watanabe Y, Gould E, McEwen BS. 1992b. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Res* 588:341–345.
- Woolley C, Gould E, McEwen BS. 1990. Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. *Brain Res* 531:225–231.
- Zilles K, Wree A. 1985. Cortex: Areal and laminar structure. In: Paxinos G, editor. *The rat nervous system*. Sydney: Academic Press, p 375–415.
- Zilles K, Wree A. 1995. Cortex: areal and laminar structure. In: Paxinos G, editor. *The rat nervous system*. San Diego: Academic Press, p 649–685.