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Chronic Corticosterone Impairs Inhibitory Avoidance in Rats: Possible Link With Atrophy of Hippocampal CA3 Neurons

VERÓNICA BISAGNO,* MÓNICA FERRINI,‡ HUGO RÍOS,§
LUIS M. ZIEHER* AND SILVIA I. WIKINSKI*†

*Cátedra de Farmacología, Facultad de Medicina, Universidad de Buenos Aires, Paraguay 2155, piso 15 (1113), Capital Federal, Argentina;
†Instituto de Investigaciones Farmacológicas, CONICET, Junín 956, piso 5 (1113), Capital Federal, Argentina;
‡Laboratorio de Bioquímica Neuroendócrina, Instituto de Biología y Medicina Experimental-CONICET, Vuelta de Obligado 2490 (1428), Capital Federal, Argentina; and
§Instituto de Biología Celular y Neurociencias "Profesor E. de Robertis," Facultad de Medicina, UBA, Paraguay 2155, Buenos Aires, Argentina

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V. BISAGNO, M. FERRINI, H. RIOS, L. M. ZIEHER AND S. I. WIKINSKI. *Chronic corticosterone impairs inhibitory avoidance in rats: Possible link with atrophy of hippocampal CA3 neurons.* PHARMACOL BIOCHEM BEHAV **66**(2) 235–240, 2000.—The aim of our work was to evaluate the effect of a chronic (22 days) administration of corticosterone, which induces supraphysiological serum levels of the hormone, on an inhibitory avoidance learning in rats (one-trial step-through learning task, footshock: 0.5 mA, 2 s). We also studied hippocampal markers of neuroanatomical CA3 pyramidal neuron atrophy by using the Golgi staining method. Chronic exposure to high CORT serum levels induced a significant impairment of inhibitory avoidance learning. The CORT group also showed hippocampal glucocorticoid receptor (GR) downregulation and the decrease of hippocampal CA3 branch points and total dendritic length in the apical tree that would be causally related with the learning impairment. © 2000 Elsevier Science Inc.

Corticosterone Chronic treatment Inhibitory avoidance Learning Golgi staining
Hippocampal dendritic atrophy Glucocorticoid receptor Rats

HIGH circulating levels of endogenous or exogenous corticosteroids are frequently associated with cognitive impairment. Numerous reports in the clinical literature link memory impairment with syndromes of sustained hypercortisolism such as those seen in hypercortisolemic depressive patients, Cushing's syndrome, and patients on long-term therapeutic glucocorticoid treatment (16,21,26,28).

It has been demonstrated that the hippocampus plays an important role in the formation of this kind of associative learning: the inhibitory avoidance (13). During acquisition of memory traces, the hippocampus must receive information from the working memory/manager regions of the prefrontal cortex, which are related with the entorhinal cortex and the dentate gyrus. In the postraining period of the inhibitory avoidance, the hippocampus operates concertedly with the amygdala (that act adding emotional or aversive "tignes" to the memory) and medial septum/diagonal band area, and 30 to 60 min later, with the entorhinal and parietal cortex (12).

The hippocampus is one of the principal targets for steroid action in the brain. Two types of corticosteroid receptors are present in this structure: type I or mineralocorticoid receptor (MR), and type II or glucocorticoid receptor (GR), which are able to bind corticosterone (CORT) with different affinities: MR bind CORT, cortisol analogous in rats, with an affinity 10-fold higher than the GR (6). Low basal CORT levels predominantly occupy the MR. The GR can be activated addi-

Requests for reprints should be addressed to Dr. Silvia I. Wikinski, Instituto de Investigaciones Farmacológicas, (ININFA), Junín 956, piso 5 (1113).

tionally to the MR only when the CORT levels are high, i.e., at the circadian peak, during stress or with high doses of corticosteroid exogenous administration.

The activation of both MR and GR is necessary for acquisition and consolidation of memory traces, and a different role has been proposed for MR and GR in memory formation (4,22,23,25).

Concerning the mnesic effects of chronic high corticosteroid levels, there are several reports, somewhat contradictory: both impairment and improvement of spatial memory were reported (9,15). Moreover, there is a study that reported, in young rats, no effect at all (2).

As far as we know, only spatial memory was explored in chronically CORT-treated animals, and no reports on avoidance tasks are available.

It is well known that chronically elevated glucocorticoids produce suppression of the hypothalamic–pituitary–adrenal (HPA) axis and corticosteroid receptor downregulation, among other neuroendocrine effects (6). Prolonged glucocorticoid exposure can also induce neuroanatomical changes in the hippocampus, ranging from reversible atrophy of pyramidal CA3 apical dendrites to neuronal loss (19,24,27).

However, the correlation of cognitive decline with possible neuronal damage associated with high and chronic corticosteroid serum levels in adult animals is still a matter of debate (7). Therefore, the aim of our work was to evaluate the effect of the administration of supraphysiological levels of CORT on an inhibitory avoidance learning. Given the pivotal role of hippocampus on this type of learning, and the evidences suggesting that chronic treatment with CORT may induce neuronal damage in this structure, we were also interested in studing the hippocampal markers of neuroanatomical damage such as CA3 pyramidal neuron atrophy.

METHOD

Animals and Drug Administration

Adult male Sprague–Dawley rats were housed under standard conditions, with lights on from 0700–1900 h, controlled room temperature at 22°C, and food and water ad lib. Twelve-week-old rats were randomly assigned to the corticosterone (CORT) or cholesterol (control) treatment group and treated for 22 days. The animals were anesthetized (ketamine hydrochloride, 50 mg/kg and xilacine 2.5 mg/kg, IP), and two pellets containing 100 mg of CORT or cholesterol were implanted subcutaneously around the area of the nape of the neck. As previously described (2), CORT plasma levels decline over time due to an inflammatory reaction surrounding the pellets, with formation of scar tissue. As this impairs the absorption of the drug, new pellets were implanted near the first implant site on day 11 after the onset of the treatment. Serum CORT levels were determined, both in CORT and control groups (not used for behavioral tests) using a competitive protein binding radioassay employing [^{3}H]corticosterone as a tracer and 2% horse serum in water containing 0.5% gelatin as the source of the Corticosterone Binding Globulin (20).

Behavioral Test

On day 21 of the chronic treatment, an inhibitory avoidance one trial step-through test was performed. This behavioral test is based in the innate preference of rodents for dark instead of lighted environments. The inhibitory avoidance box consists of a bright and a dark (20 × 30 × 26-cm width, length, height) compartment. The training and test trials were performed between 1000 and 1200 h in a sound-attenuated room. During the training trial (on day 21), rats were placed into the bright compartment. The door separating the two compartments was opened 30 s later, and the latency to enter the dark compartment was measured. After the rats had entered the dark compartment a foot shock was delivered (0.5 mA, 2 s). During the testing trial, 24 h later (on day 22), the rats were again placed into the bright compartment; 30 s later the door was opened, and the latency (seconds) to reenter the dark compartment was measured. The testing trial was finished after 180 s if the animal remained in the bright compartment. No foot shock was given during the tests sessions. Training and test session latencies among each group and between groups were compared by a Mann–Whitney *U*-test.

CA3 Hippocampal Dendritic Morphology

This parameter was assessed by the Golgi staining procedure. Animals were sacrificed by decapitation. The brains were processed using the mixed Golgi argentic impregnation method (3). Brains were cut in 1-cm sections containing the hippocampal region and were incubated for 4 days in a 3% potassium dichromate solution in distilled water at 24–25°C. Then the sections were immersed in 3% potassium dichromate + 1% osmium (20:6) at 24–25°C for at least 5 days. Afterwards, the sections were washed three times in a silver nitrate solution (0.75%) and incubated in the same solution for 5 days. Then the tissues were rinsed in distilled water, dehydrated, and placed in a toluene:alcohol mix (1:1) for 24 h. They were clarified in toluene and embedded in Paraplast. Sections were cut at 40 μm and mounted on glass slides previously dipped in 1% gelatin, air dried, and coverslipped with Permount.

We selected Golgi impregnated neurons to be analyzed using parameters previously described (17) Analyzed neurons fitted the following characteristics: location within the CA3 region of the dorsal hippocampus, dark impregnation throughout the extent of all the dendrites, relative isolation form neighboring impregnated cells. For each brain, four to six pyramidal cells from CA3 were selected. Each neuron was traced at a 400× drawing tube attachement. From these drawings the number of dendritic branch points within a 40 μm-thick section of each dendritic tree was determined for each selected neuron. The length of the dendrites was determined for each dendritic tree using a digital analysis system.

Spine quantification was performed as previously described (11). Briefly, for each cell, spine density was determined from the most lateral tertiary dendrite on the apical tree, and the most lateral secondary dendrite on the basal tree. Camera lucida drawings (1000×) were obtained from selected dendritic segments, the spines were counted, the length of the segment was determined with an image analysis system, and spine density values were expressed as the number of spines/50 μm of the dendrite. For each animal a total of 12 dendritic branches were analyzed.

For each variable and for each brain, means ± SEM were determined, and the resulting values were analyzed by a Student's *t*-test.

Binding to Cytosolic Hippocampal Glucocorticoid Receptors

Two separated (not subjected to behavior) groups of animals (control and CORT) were used for the GR assay. At day 22 of the treatment, animals were adrenalectomized, CORT and cholesterol pellets were removed, and 72 h later were killed by decapitation and the hippocampi were dissected out.

Tissues were homogenized in 10 mM Tris-HCl, 2 mM mercaptoethanol, 1.5 mM EDTA, 10% glycerol, 20 mM sodium molybdate, and centrifuged at 105,000 × *g* for 45 min to obtain cytosolic fraction. For a single point assay aliquots of cytosol were incubated with tritiated ligands to determine GR, as previously described (10). GR sites were determined after substracting the values of incubations containing 20 nM [^{3}H]-dexamethasone (sp. act. 35.8 Ci/mmol) in the presence of 250× RU 26988, from total binding. Incubations were carried out for 20 h at 0–4°C, at the end of which time, bound and free hormones were separated in minicolumns of Sephadex LH-20. The results of specific binding were expressed as fmol/mg protein. Differences between groups were determined by a Student's *t*-test.

Drugs

All the tritiated ligands were purchased from New England Nuclear, Boston, MA. Other reagents were purchased from Sigma Chemical Company, St. Louis, MO except cholesterol (Merck, Argentina), ketamine hydrochloride (Parke-Davis, Argentina), and xilacine (Bayer, Argentina).

RESULTS

Serum Corticosterone Levels, Adrenal, and Body Weights

During the period of treatment (Table 1), the CORT group showed higher serum levels than the control group. Indeed, chronic treatment with CORT for 22 days had also a significant effect on body weight (CORT 259.4 ± 8.7 g, control 315 ± 12.7 g, $p < 0.01$) and on relative adrenal weight (CORT 9.2 ± 0.8, control 19.3 ± 1.7, mg/100 g of body weight, $p < 0.001$). Results were compared by a Student's *t*-test.

Behavioral Test

After 22 days of CORT treatment a memory impairment in an inhibitory avoidance test was observed (Fig. 1). CORT group training latencies were not different from ones of the control group. When test latencies of the control group were compared with values obtained from the training session, we found an increment of 320% ($p < 0.006$). On the other hand, when the same comparison was performed in the cort group, no differences were observed between test and training sessions latencies ($p = 0.2$). Moreover, the CORT group showed a significatively lower test latency than the control group ($p < 0.05$).

CA3 Hippocampal Dendritic Morphology

Quantitative analysis of Golgi-impregnated cells (Table 2 and Fig. 2), revealed that 22 days of CORT administration significatively reduced the number of dendritic branch points by 49% ($p< 0.001$) and total dendritic length by 59% ($p < 0.004$) in the apical tree of hippocampal CA3 pyramidal neurons without affecting spine density. Values of the same parameters in the basal tree were not different between groups.

Binding to Cytosolic Hippocampal Glucocorticoid Receptors

Figure 3 shows that 22 days of CORT administration by implant induced GR downregulation expressed by a significant decrease (by 53%) in the binding of [$_3$H]-dexamethasone to cytosolic GR in hippocampus ($p < 0.01$, control vs. CORT).

DISCUSSION

We studied the effect of a chronic treatment with CORT administered by subcutaneously implanted pellets. This type of administration avoids daily injections, which may be associated with chronic stress. We found supraphysiologic levels in CORT-treated animals in comparison with control ones, together with atrophy of adrenal glands and a decrease of body weight. All these data are compatible with HPA axis suppression.

When we explored the learning of an inhibitory avoidance behavior in our CORT-treated rats we found chronically elevated levels of the hormone-induced memory impairment, with lower test latencies to reenter the dark compartment when compared with the control animals. Specifically, as latencies for stepping through in the control and CORT groups are the same at the time of training acquisition, we may suppose that chronic CORT appears to impair only consolidation and/or retrieval of the inhibitory avoidance. However, other possible pharmacological effects of chronic CORT treatment (i.e., elevation of pain threshold) cannot be excluded as a potential explanation for lack of response in this type of inhibitory avoidance test.

As far as we know, there are no previous studies on the effect of chronic corticosteroid-treated animals in this kind of associative learning. In spatial learning paradigms, using adults (not aged) animals, the results seem to be contradictory. It was shown that 8 weeks of a daily CORT injection significatively impaired spontaneous alternation behavior in a T-maze test (1). It has also been demonstrated that 3-month CORT-implanted rats show an impairment in a radial eight-arm maze performance task (9). In contrast, other reports did not find spatial memory impairments in a Morris water maze following 3 months of CORT administration (2). Moreover, it has been shown that chronic restraint stress, which induces CORT secretion pulses, could enhance spatial memory (15).

Hippocampus plays an important role in the acquisition, consolidation, and retrieval of inhibitory avoidance (12). As recently reviewed (14), CA3 hippocampal region receives a main input from the enthorhinal cortex through the perforant pathway, which plays a key role in allowing memory secquences to be stored in context. Learning in our inhibitory

TABLE 1

SERUM CORTICOSTERONE LEVELS (μg/dl)

Days	1	3	10	22
Control	2.8 ± 0.5	5.3 ± 1.9	1.9 ± 0.9	4.8 ± 0.9
CORT	32.9 ± 9.6*	83.8 ± 18.1*	29 ± 15.6*	10.8 ± 1.6*

Effect of 22 days of CORT treatment with subcutaneous pellets on serum corticosterone levels. Values are expressed as mean ± SEM of 6–9 animals per group.

*$p < 0.01$ vs. control values (Student's *t*-test)

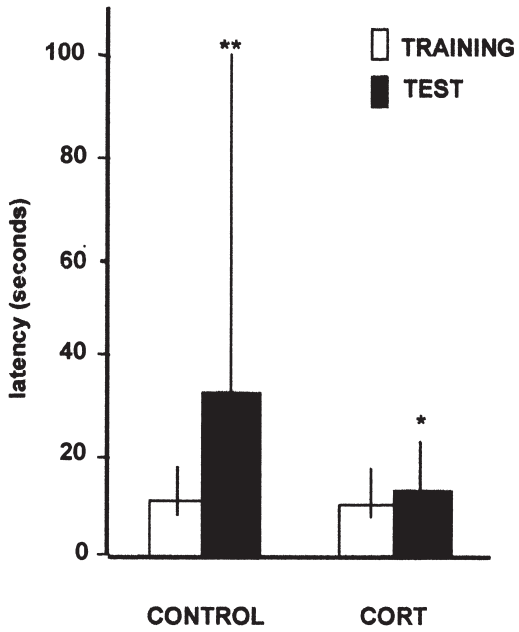

FIG. 1. Effect of chronic treatment with CORT on an inhibitory avoidance test. Values are expressed as median and interquartile range of training and test sessions ($n = 24$ animals per group). $^{**}p < 0.006$ test latencies vs. training latencies in the control group; no differences were found between test and training sessions in the CORT group; $^{*}p < 0.05$ test latencies of CORT vs. test latencies of the control group (Mann–Whitney *U*-test).

avoidance paradigm is context related, as it is expected that animals associate darkness with electric shock and the illuminated area with safety. Chronic treatment with CORT produced two markers of hippocampal CA3 dendritic atrophy in the apical tree: both a decrease in the number of dendritic branches and in the total dendritic length, and accordingly, our CORT-treated animals with atrophy of CA3 apical dendrites show no increase in the latencies to reenter the dark compartment.

TABLE 2

EFFECT OF 22 DAYS OF CORTICOSTERONE TREATMENT ON THE DENDRITIC MORPHOLOGY OF HIPPOCAMPAL CA3 PYRAMIDAL NEURONS

	Control	CORT
CA3 Apical tree		
Number of branch points	12.91 ± 0.44	6.33 ± 0.72†
Total dendritic length (μm)	1075.7 ± 48.7	636.57 ± 59.3*
Spines/50μm	11.63 ± 1.6	11.92 ± 0.08
CA3 Basal tree		
Number of branch points	7.81 ± 1.8	8.83 ± 0.88
Total dendritic length (μm)	685.16 ± 89.77	748.92 ± 55.21
Spines/50μm	10.32 ± 0.8	10.11 ± 1.16

Effect of 22 days of CORT treatment on apical and basal dendritic morphology of hippocampal CA3 pyramidal neurons. Values are expressed as mean ± SEM of three animals per group.

$^{*}p < 0.004$, $^{\dagger}p < 0.001$ vs. control values (Student's *t*-test).

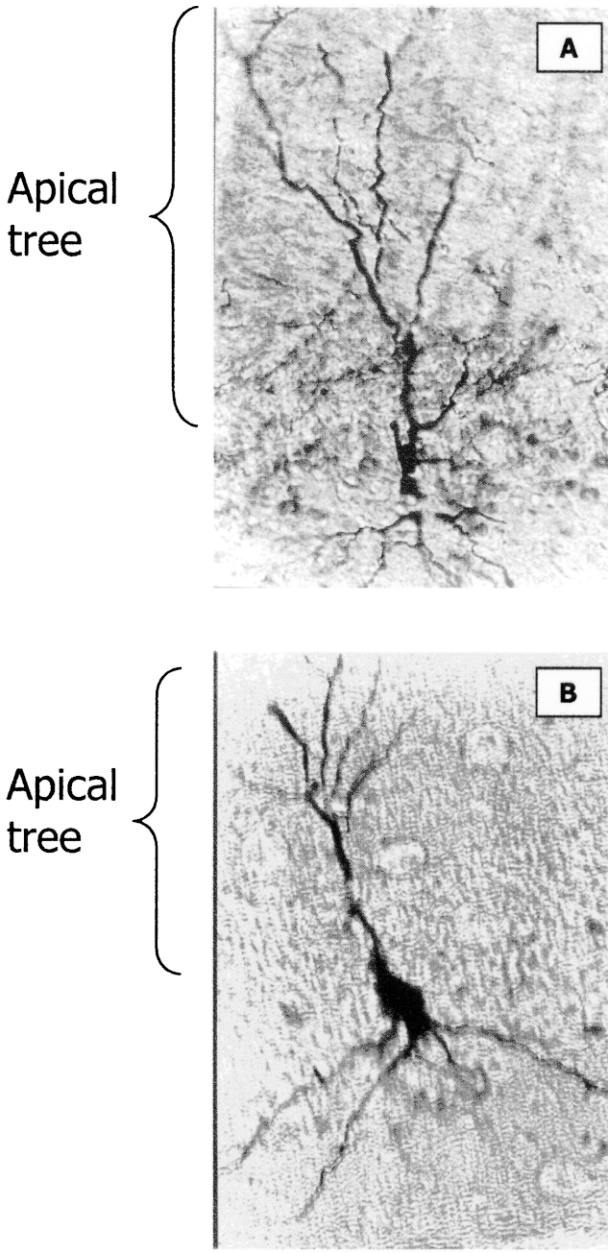

FIG. 2. Examples of representative Golgi-impregnated hippocampal CA3 pyramidal neurons. (A) Control group; (B) CORT group. Magnification, ×400.

Our results are similar to previous reports that indicate that daily injections of CORT during 21 days and chronic restraint stress also produce CA3 apical dendritic atrophy (28). In addition in CA3c, a hippocampal subregion, the administration of CORT dissolved in drinking water only produced a decrease in the number of dendritic branches without affecting total dendritic length (18).

Chronic stress and chronic CORT administration-induced atrophy was prevented by phenytoin and NMDA receptor blockers. From these and other evidences, this type of hippocampal plasticity has been linked to excitotoxicity induced by the activation of NMDA receptors (17).

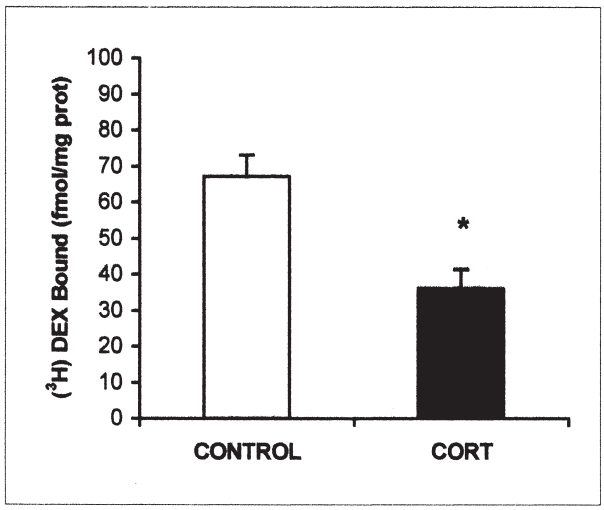

FIG. 3. Effect of 22 days of CORT treatment on (^{3}H)-dexamethasone binding to hippocampal glucocorticoid receptors. Values are expressed as mean ± SEM of four to six animals per group.*$p < 0.01$ vs. control rats (Student's *t*-test).

Although hippocampal dendritic atrophy may account for memory deficits, some other factors can contribute to this alteration. The multiple interactions between several cellular agents and both MR and GR could, in turn, influence learning and memory. Corticosteroid-mediated actions occur through activation or repression of gene transcription. These actions depend on the cellular context, which is determined in part by other agents (i.e., neurotransmitters, hormones, citokines, etc.) [for review, see (7)].

In addition, a direct role of MR and GR activation on learning and memory has been proposed. Hippocampal MR mediates sensory integration, and GR promotes processes underlying acquisition/consolidation (4,23). It has been reported that a detrimental effect of GR activation on spatial recognition memory occurs only when the MR were occupied. The authors suggested that the MR must be occupied and functioning for high GR occupancy to produce a suppression of spatial memory (4). The same group provided evidence that during high stress any beneficial effects on spatial memory of MR activation would be overridden by the high occupation of hippocampal GR (5). Moreover, when the effect of stress was studied at the moment of retrieval, it has been demonstrated that high levels of CORT impair retrieval of a spatial learning task (8).

As can be deduced from our animal's CORTserum levels, both MR and GR has been chronically activated. In fact, hippocampal GR downregulation found in the CORT group further supports this hypothesis, and it is likely that the MR were downregulated as well. This autologous regulation indicates a genomic response due to a long-term receptor–ligand interaction (24).

Finally, it would be also speculated that with continous high levels of CORT there is no "context-related" MR and GR activation. This would be another possible explanation for memory impairment.

In conclusion, high and sustained levels of CORT impaired inhibitory avoidance learning. This phenomenon seems to be causally related with two other findings in our experimental group: sustained high occupancy of hippocampal GR, and CA3 hippocampal dendritic atrophy.

Our results could partially explain the adverse effects on memory function observed in patients receiving high doses of corticosteroids to treat a variety of pathological conditions.

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