BEHAVIORAL AND NEURAL BIOLOGY 60, 103–109 (1993)

Cognitive Deficits Induced in Young Rats by Long-Term Corticosterone Administration

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Corticosterone slow-release pellets, implanted for 9 weeks in young Fischer 344 rats, resulted in continuous high plasma levels of the hormone which are comparable to those of rats under mild stress. One week following termination of the drug treatment, the rats were tested in an eight-arm radial maze. During the initial acquisition stages, corticosterone-treated rats exhibited cognitive impairments in contrast to placebo-treated rats. The deficits were observed in all three parameters which were monitored, the total number of errors, the number of correct entries out of the first eight, and the total time needed to complete the test. This study is the first to report specific behavioral decrements related to the previously observed morphological hippocampal changes induced by long-term corticosterone administration.

It has been suggested that high levels of corticosteroids, as well as stressful conditions, may be correlated with an accelerated age-dependent degeneration of neurons in the hippocampus (Landfield, Waymire, & Lynch, 1978; Sapolsky, Krey, & McEwen, 1985; Kerr, Campbell, Applegate, Brodish, & Landfield, 1991; Landfield & Eldridge, 1991). The influence of stress and the endocrine system on central aging processes, primarily related to the hippocampus, has been one of the intriguing subjects in neuroscience research during the last two decades (Landfield, Sundberg, Smith, Eldridge, & Morris, 1980; Sapolsky, Krey, & McEwen, 1986; Eldridge, Brodish, Kute, & Landfield, 1989a; Eldridge, Fleenor, Kerr, & Landfield, 1989b; van Eekelen, Rots, Sutanto, & de Kloet, 1991). Glucocorticoids, vital hormones whose secretion increases under stress, were found to bind to specific areas of the hippocampus (McEwen, Weiss, & Scharts, 1968; McEwen, De Kloet, & Rostene, 1986; de Kloet, Reul, & Sutanto, 1990; Sutanto & de Kloet, 1991). The role of these brain structures in the regulation of the hypothalamic–pituitary–adrenocortical axis, recently reviewed in detail by Jacobson and Sapolsky (1991), is still not fully understood. Glucocorticoid toxicity in the hippocampus was demonstrated both in vitro, in primary cultures of fetal hippocampal neurons (Sapolsky, Packan, & Vale, 1988), and in vivo (Sapolsky et al., 1985; Uno, Tarara, Else, Suleman, & Sapolsky, 1989).

The hippocampal formation and its substructures have emerged in many studies as important brain regions involved in cognitive processes (e.g., Olton, Walker, & Gage, 1978; Lipp, Schwegler, Heimrich, Cerbone, & Sadile, 1987). Recently, a highly significant correlation between age-related hippocampal changes and behavioral deficits in aging rats was shown in our laboratory (Kadar, Silbermann, Brandeis, & Levy, 1990). In another study, 23- to 27-month-old rats with cognitive impairment showed significantly higher neuron loss in the hippocampus, in contrast to unimpaired age-matched group (Issa, Rowe, Gauthier, & Meaney, 1990). This impaired subgroup of rats was also found to maintain higher levels of corticosterone following termination of a 20-min immobilization stress.

Stress-related hormonal systems have been implicated in learning and memory processes (de Wied, 1977; McGaugh, 1983), and acute corticosteroid administration impaired cognitive performance (Bohus & de Wied, 1980). Acute exposure to cold stress led to deficiency in the retrieval of a spatial task (Rauch, Welch, & Gallego 1989a,b). High-stress-re-

[1] The support of Bayer AG for this study is gratefully acknowledged. The authors thank Dr. Rachel Brandeis for her valuable contribution to the statistical analysis of the results. The research is part of a Ph.D. thesis by Shlomit Dachir. Address correspondence and reprint requests to Dr. Aharon Levy, Israel Institute for Biological Research, Ness-Ziona 70450, Israel, Fax: 972-8-401404,. WXPHAR@WEIZMANN.AC.IL.

0163-1047/93 $5.00

sponder rats were found to be impaired in the learning and retention of a water T-maze, in contrast to low-stress responders (Vogel & Harris, 1991).

Morphological changes in the hippocampus, which were reported following chronic stress (Uno et al., 1989), or following long-term exposure to high levels of corticosterone (Sapolsky et al., 1985), have not been associated yet with a defined behavioral deficit. The purpose of the present study was to monitor possible cognitive impairments, related to these hippocampal morphological changes, following long-term exposure to high levels of corticosterone. To mimic the state of elevated corticosteroids under prolonged stress, we chose to implant corticosterone slow-release (SR) pellets. This method provided better control over corticosterone plasma levels, in contrast to either administration by daily injections (Sapolsky et al., 1985) or maintenance of mild stress for a few hours each day (Kerr et al., 1991). We aimed at corticosterone concentrations with physiological significance, comparable to those found under mild stress. Whereas stress involves various neuronal systems, we assumed that the use of sustained high corticosterone might lead to a more defined physiologic state. Cognitive testing was carried out only following a washout period, when the drug itself was not present, in order to reflect only the residual effects of the prolonged drug treatment. This study was performed using young rats, in order to isolate the effect of high corticosterone only, before investigating the combined effect of high corticosterone and aging in future studies.

MATERIALS AND METHODS

Subjects. Twenty-four young (3 months old upon arrival) male Fischer 344 rats (from Charles River, UK) weighing between 196 and 216 g (206.79 ± 1.12, mean ± SEM) were assigned to 2 groups of 12 rats each, treated with either SR corticosterone or placebo. They were housed in individual cages in a temperature-controlled environment (22 ± 1°C) with lights on from 5:00 AM to 6:00 PM, and had ad libitum access to food (Altromin, Lage, Germany) and water.

Implantation of SR pellets. General anesthesia was induced using a mixture of 5% halothane (Trofield Surgicals A.G., Switzerland) and 95% oxygen and was further maintained with a mixture of 1.5–2% halothane using Fluotec-3 (Cyprane, UK). SR pellets were implanted subcutaneously approximately 4 cm lateral off the median line, on the right and left sides alternately. The hair at the implantation site was closely clipped and a small incision was made through which the pellet was inserted. Pellets used were either 200 mg corticosterone 3-week release or placebo pellets for corticosterone produced by Innovative Research of America (Toledo, OH). The incision was sutured using a Tevasilon thread by making two stitches. Following implantation the rats were returned to their individual cages for recovery.

Experiment protocol. Successive implantation of SR pellets was carried out 3 weeks apart, twice for placebo pellets and three times for corticosterone pellets. Blood samples were collected at the end of the first and third week following each implantation. Each group was subdivided into two subgroups: six rats were bled at 9:00 AM (normally low corticosterone concentrations in plasma) and six other rats were bled at 5:00 PM (1 h before darkness, at the normal peak corticosterone levels).

One week following termination of the last pellet (4 weeks following last implantation) the rats participated in a behavioral study using the radial arm maze (RAM).

In order to follow changes in the circadian rhythm of corticosterone, which might be induced by the drug treatment, two other groups of rats (corticosterone-implanted and control rats; $n = 12$) were used. Blood samples were collected during the first and second week following the first implantation at 7:00 AM and 9:00 AM, 1:00, 5:00, and 7:00 PM, and 1:00 AM from six rats each time. Successive bleeding of the same rat was made only following an interval of 72 h.

Blood collections. Blood was collected from the tail vein into heparinized glass capillaries (Clinitubes, Radiometer, Copenhagen). Each rat was removed from its home cage to the next room and a small cut, a few millimeters long, was quickly made in its tail. Most of the blood samples were collected between 20 and 90 s after touching the rat's cage, never exceeding 120 s. Using this timetable, corticosterone levels of control rats were indeed maintained at normal levels, without any effect of stress related to the procedure. The blood was then centrifuged and plasma was transferred into glass tubes. Samples were stored at −20°C until analyzed for corticosterone concentrations by radioimmunoassay (RIA).

Corticosterone determination. ^{125}I-labeled corticosterone double antibody RIA kit for rats and mice was used (ICN Biomedicals Inc., Costa Mesa, CA). The assay was carried out at room temperature, using rabbit anticorticosterone as the first antibody

and goat anti-rabbit as the second. According to the manufacturer, the cross-reactivity of the first antibody was tested against various steroids and found to be very low. The highest cross-reactivity was found with desoxycorticosterone (0.34 in contrast to 100% for corticosterone). Typical intra-assay variation was around CV of 4–7%, and typical inter-assay variation around 7%. Plasma samples were diluted 1:200 and 0.1 ml duplicates were taken for assay.

Behavioral testing. Behavioral tests were conducted in an elevated (70 cm) eight-arm radial maze, made of white-painted wood (Olton, 1987; Levy, Kluge, & Elsmore, 1983). The arms (75 cm long and 9 cm wide) extended from an octagonal central arena (30 cm wide). Small weighing cups were glued at the end of each arm, in which food pellets were placed.

Five days before starting the behavioral testing in the RAM, food was restricted to about 15 g per day, which were given at 5:00 PM in order to maintain the normal diurnal variation of corticosterone (Kato, Saito, & Suda, 1980). During this period the rats in both groups lost about 10% of their body weight. Two days before training, the rats were fed with precision pellets (Bioserv Inc.) which were later used in the maze as bait for reinforcement.

Training was carried out daily for 10 consecutive days during the morning hours when corticosterone concentrations were low. All eight arms were baited with one 45-mg precision pellet each. Rats were placed in the central arena, one at a time, facing the same direction and were then permitted to run from arm to arm until eight pellets were collected or until 15 min had elapsed (whichever came first). All movements within the maze were recorded, elapsed time as well as correct and incorrect responses.

RESULTS

Weight changes. Since corticosterone treatment may cause changes in body weight (Silbermann, Kadar, & Kovat, 1977; Landfield, 1987), rats were weighed daily. In addition, the daily weighing throughout the experiment was useful in accommodating the rats to human handling.

Figure 1 presents changes in the rats' weight following each implantation, as a percentage of their weight on the day of the surgical procedure. Since young rats are gaining weight continuously, this presentation was chosen in order to compare the situation following successive implantations. According to absolute weights, placebo rats were somewhat heavier in contrast to corticosterone-treated rats on the day the experiment started (280.3 ± 2.9 and 272.2 ± 1.7, respectively; $p < .05$ using t test statistics). The rats implanted with placebo pellets lost very little weight following both implantations, especially following the second one, and within 6 days their weight kept increasing normally.

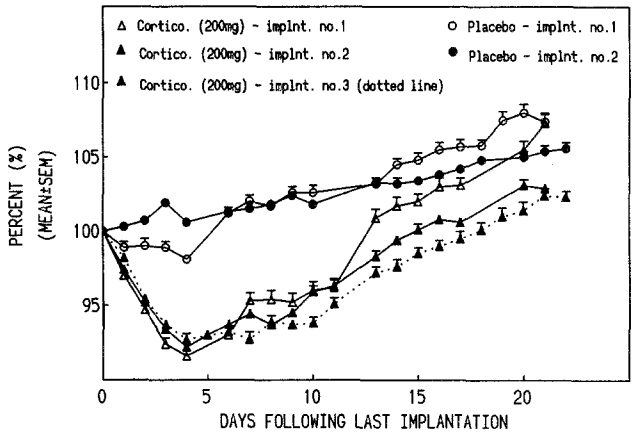

FIG. 1. Rats' weight changes as percentage of weight on day of pellet implantation.

Rats implanted with corticosterone pellets lost about 10% of their body weight following the surgical procedure and it took them at least 20 days to regain this loss. However, following the first implantation rats regained weight faster than following the second one. Following the third implantation they took the longest time to return to their original weight. Thus, on the day on which behavioral testing started, the weight of corticosterone-treated rats was even lower than that of the placebo group (293.2 ± 3.5 in contrast to 317.8 ± 4.0; $p < .001$ according to t test).

Plasma corticosterone. Normally, corticosterone levels of rats are highest around 1 h before dark, and from then on levels decrease and stay low until the increase of the next day (Kato et al., 1980). Plasma levels of corticosterone-implanted rats were significantly elevated and stayed almost steady during the whole day (Fig. 2). Around 5:00 PM, only a small additional increase was observed, at the same time when large increase in the control group had occurred.

Mean (±SEM) plasma concentrations of the two experimental groups (corticosterone and placebo implanted), at various time points throughout the experiment, are presented in Fig. 3 for the morning (9:00 AM) and evening (5:00 PM) (A and B, respectively).

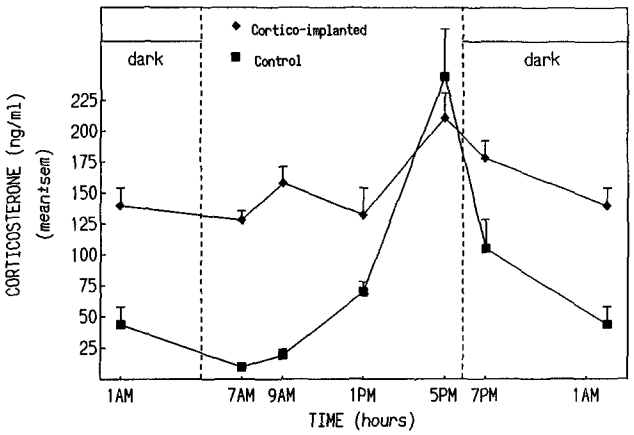

FIG. 2. Corticosterone levels in plasma of corticosterone-implanted vs control rats at various times during the day.

Three-way analysis of variance of the plasma corticosterone concentrations revealed significant differences between the treatment groups ($F(1, 20) = 23.66$, $p < .001$), and between corticosterone levels at 9:00 AM and at 5:00 PM ($F(1, 20) = 251.02$, $p < .001$). The interaction between these two parameters was highly significant ($F(1, 20) = 119.50$, $p < .001$), and the interaction between treatment groups, time of bleeding (9:00 AM and 5:00 PM), and the number of weeks following implantation was also significant ($F(3, 60) = 3.44$, $p < .025$).

Simple main effect contrasts showed that 1 week following first and second implantation, corticosterone-implanted rats had significantly higher ($p < .001$) corticosterone concentration than placebo-implanted rats during the morning. In the drug-treated group, plasma corticosterone levels were not significantly different when comparing concentrations measured at 9:00 AM to those measured at 5:00 PM. In contrast, the same comparison for the placebo group revealed a significant difference ($p < .001$), as plasma corticosterone concentrations at 9:00 AM were significantly lower than those at 5:00 PM.

Three weeks following each implantation, corticosterone concentrations were higher during the evening than during the morning in both groups ($p < .01$ and $p < .001$ for corticosterone- and placebo-implanted rats, respectively). However, corticosterone levels during the morning in the drug-treated group were not different from those found in the placebo group. Accordingly, when rats were tested 1 week later in the maze, they were not under the effect of the drug.

Radial arm maze. Parameters measured in the RAM were total number of errors, correct entries out of the first eight, and total time. The total number of entries, divided by the total time, gave a good estimate of the average speed in which the rats performed in the maze. These parameters are certainly not independent, but they seemed to describe adequately the performance of the rats in the maze.

Using a two-way ANOVA with repeated measures on the total number of errors pooled into 5-day blocks (Fig. 4A) revealed a significant difference ($F(1, 20) = 5.59$; $p < .05$) between the groups.

Scheffe' test showed that the corticosterone-treated group made significantly ($p < .025$) more errors than placebo during the first 5 days of the test (4.0 ± 0.5 vs 2.6 ± 0.3, respectively). However, during the second block of 5 days, corticosterone-treated rats improved their performance, and no difference was detected.

Further comparisons between the two groups revealed that drug-treated rats made significantly (p

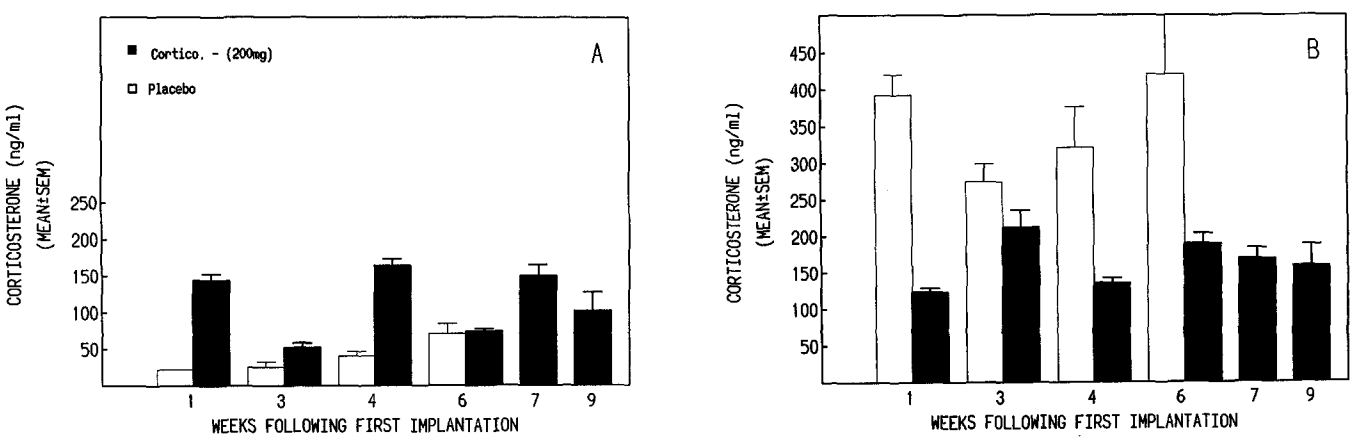

FIG. 3. Plasma corticosterone levels in corticosterone-implanted vs placebo-implanted rats, at various time points throughout the experiment, at 9:00 AM (A) and at 5:00 PM (B).

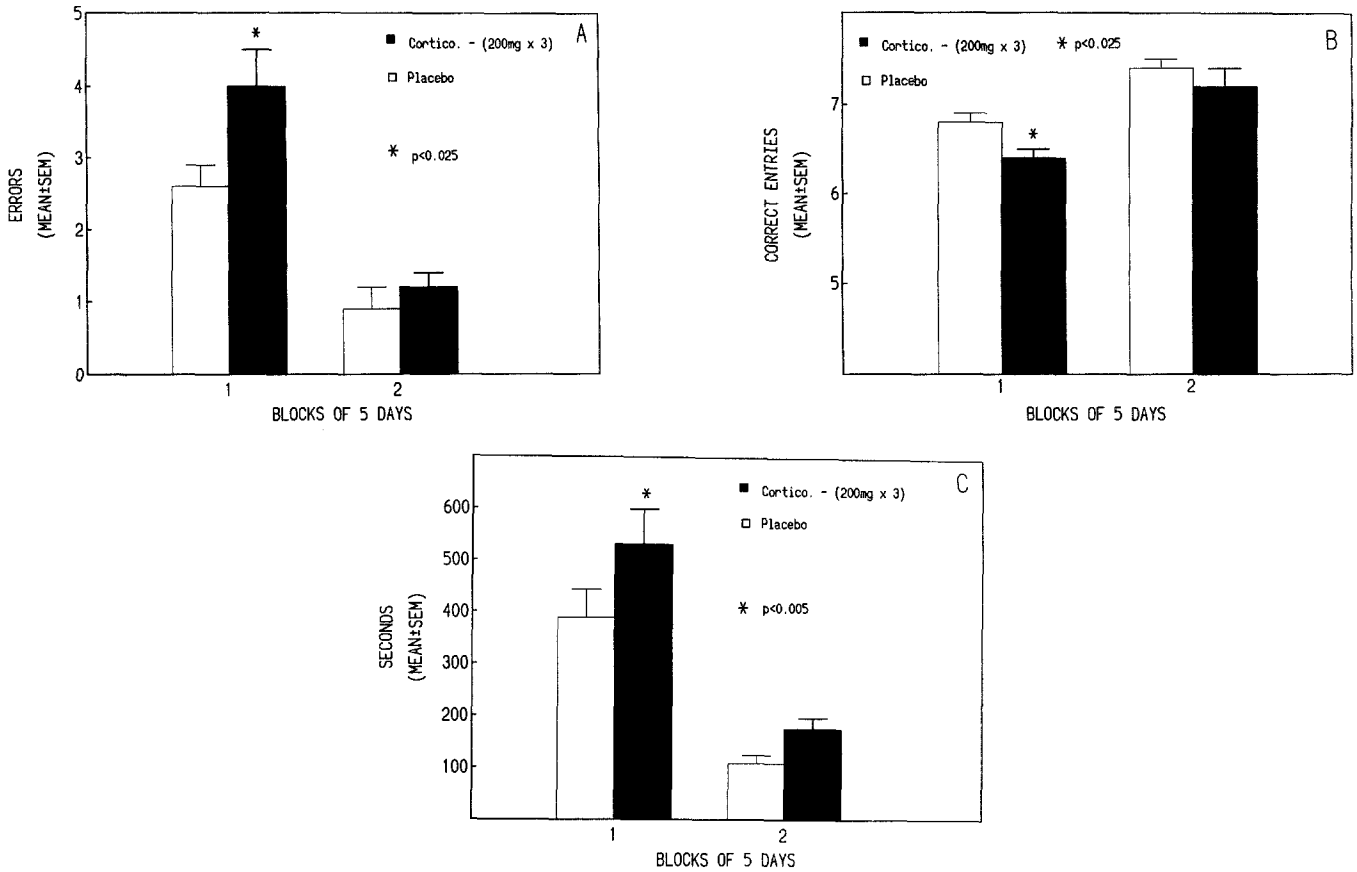

FIG. 4. (A) Total number of errors, (B) number of correct entries out of the first eight, and (C) total time needed to complete the test, in the learning phase of the RAM 1 week following 9-week treatment with corticosterone vs placebo (n = 12 in each group; Mean values ±SEM).

< .025) less correct entries out of the first eight than the placebo-treated rats (Fig. 4B) during the first 5-day block. In addition, it took the corticosterone-treated rats significantly longer time ($p <$ .005) to complete the task during the first 5-day block (Fig. 4C). However, they made many more entries; therefore, the speed of the two groups was similar (47.8 ± 8.1 s/entry for corticosterone-implanted rats in contrast to 33.8 ± 6.2 s/entry for placebo rats; $F(1, 20) = 2.2$, $p < .1$).

During the second block of 5 days the performance of both groups was not significantly different although the general trend of better performance for the placebo group remained.

DISCUSSION

Three consecutive implantations of 200-mg 3-week SR pellets of corticosterone resulted in continuous high plasma levels of the hormone which are comparable to those of rats under mild stress (Sapolsky et al., 1985; Kerr et al., 1991). During the time of day when corticosterone plasma concentrations of naive rats are relatively low (20–40 ng/ml), implanted rats exhibited levels around 150 ng/ml. At the end of the 3-week period, these levels were lower (around 70 ng/ml), almost back to the normal morning values, at which time rats were implanted with new pellets again.

Just before dark, when plasma levels of corticosterone normally peaked in control and placebo-implanted rats, plasma concentrations in corticosterone-implanted rats were lower than those of controls. This effect was probably caused by a negative feedback inhibition of ACTH secretion (Hauger, Millan, Catt, & Aguilera, 1987) and resulted in relatively stable high levels of corticosterone in implanted rats throughout the day.

At the end of the third treatment period, corticosterone levels were almost back to normal values and then another week was allowed for a complete washout of the drug before starting behavioral testing. No measurements of corticosterone levels were carried out in this study after the treatment was completed. However, in a later study, in which corticosterone pellets were also used, normal levels

were found 1 week following termination of the corticosterone treatment (Levy, Kadar & Dachir, 1992).

Except for the weight loss during the first 5 days following implantation, no other adverse effects were observed in the corticosterone-treated rats. No physiological deterioration was noted, such as reported in previous high corticosterone-treated rats (Landfield, 1987). The weight loss was regained steadily throughout the 3-week treatment. Although there were some differences in the weight of the groups when behavioral testing started, no effect on motivation was observed, and the rats traversed the maze at the same speed.

Learning impairments were found in rats which were exposed to high corticosterone for 9 weeks (3 $\times$ 200 mg) during the initial stage of acquisition in the radial arm maze. The deficits were exhibited in all the three parameters monitored in contrast to placebo-implanted rats, but not in the speed of the rats in the maze. This seemed to imply that cognitive or at least centrally mediated rather than physical impairment caused the deficits in the maze. In a previous study, in which the radial arm maze was also used, we have shown that the peripheral cholinergic blocker, methyl atropine nitrate, affected only performance speed, while the centrally active atropine also affected accuracy of performance (Levy et al., 1983). Another group of rats, implanted with corticosterone pellets twice only (6-weeks exposure), revealed no behavioral decrements (results not presented).

This study is the first to report behavioral impairments caused by the continuous corticosterone administration. The reason we succeeded might be because we followed changes in the sensitive function of acquisition and noted the transient deficits during the first stage of learning the spatial task. Spatial orientation was shown in many studies to be sensitive to hippocampal lesions (e.g., Olton et al., 1978; Jarrard, Kant, Meyerhoff, & Levy, 1984). The difference in acquisition scores between corticosterone- and placebo-treated groups became insignificant during the second week of training. It is possible that corticosterone-implanted rats adopted at this stage a different nonspatial strategy which enabled them to solve the maze. There was some evidence that the behavior of corticosterone-treated rats was less random than that of placebo-treated rats. However, this change in strategy was not statistically significant, possibly because of the relatively small number of rats in the study. The behavioral impairment measured in this animal model might be a reflection of an accelerated aging of the hippocampus, as measured following prolonged stress by electrophysiologic changes (Kerr et al., 1991).

Preliminary histological examination of the brains of these rats revealed specific damage to pyramidal hippocampal cells in corticosterone-treated rats, mainly at the CA1 and CA4 regions, with only minor damage in some rats at the CA3 subfield. More detailed morphological evaluation will be carried out in future studies. Other studies in older rats will examine the combined effect of high corticosterone and aging.

In conclusion, continuous slow-release administration of corticosterone for 63 days resulted in impaired acquisition of the eight-arm radial maze, which probably reflected the damage to the hippocampus induced by this corticosterone treatment.

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