Short- and Long-Term Treatments with Dexamethasone have Different Effects on Spatial Learning and Memory

Adriana Berenice Silva-Gómez1, Héctor Rafael Eliosa-León1 and Gustavo Rubalcaba-Zenteno2

1Laboratorio de Neurofisiología Experimental, Escuela de Biología, Universidad Autónoma de Puebla, Mexico
2Hospital General de Sub-Zona UMF No. 8 Instituto Mexicano del Seguro Social, Mexico

Corresponding author: D. en C. Adriana Berenice Silva-Gómez, Laboratorio de Neurofisiología Experimental, Escuela de Biología, Universidad Autónoma de Puebla, Ciudad Universitaria S/N, Jardines de San Manuel Puebla, Puebla, México, CP. 72570, Tel: (52-222) 2295500; Ext: 2743; Fax: (52-222) 2295500; Ext: 7087; E-mail: berenice71@yahoo.com

Received: April 18, 2014; Accepted: July 03, 2014; Published: July 10, 2014

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Abstract

Dexamethasone (DEX) to promote an increase in levels of corticosterone, the hormone that initiates stressful responses. We analyzed the effect of DEX on spatial learning and memory (Morris water maze) in young male Sprague-Dawley rats. We administered two different treatment regimens of daily 0.2 mg/kg DEX as independent variable. One treatment consisted of DEX treatment for 5 days, and the second consisted of DEX treatment for 14 days. The short-term treatment promoted improved spatial learning without any effects on memory. The long-term treatment caused deficits in spatial learning and memory. We also observed that a Control group (CON) treated for 14 days with a vehicle (SSI: 0.9% saline solution) was more efficient in the test compared with a control group that was treated for 5 days with SSI. These results show that simply the time of exposure to stressful stimuli as injection, can cause changes in the Morris water maze execution.

Keywords: Dexamethasone; Morris water maze; Spatial learning; Spatial memory; Synthetic glucocorticoid; HPA system

Introduction

Dexamethasone (DEX) is a synthetic glucocorticoid widely prescribed during late gestation to promote maturation of fetal lungs [1]. DEX and other synthetic glucocorticoids are also prescribed for treatment of arthritis, asthma, autoimmune diseases and other inflammatory disorders [2]. However, these drugs can induce a variety of psychiatric symptoms such as depression, mania and affective psychosis [3,4]. In rats, these symptoms reflect damage to hippocampal pyramidal cells, and to neurons of the caudal striatum, globus pallidus, putamen and dentate gyrus [5,6]. DEX is commonly used experimentally to study the effects of stress [7]. In the present study, we evaluate the effect of DEX on spatial learning and memory after short- and a long-term treatment in juvenile rats.

Material and Methods

Animals

We used 34 male Sprague-Dawley rats that were 35 days of age and had an average weight of 128.97 ± 3.33 g. They were housed in the Vivarium Claude Bernard of the Universidad Autónoma de Puebla, Mexico. The animals were maintained under a 12:12 hr light-dark cycle and with ad libitum access to food and water. All animal procedures were performed according to the Technical Guide for the production, care and use of laboratory animals issued by SAGARPA, Mexico (NOM-052-ZOO 1999) and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Dexamethasone treatment

The first group of rats (n=9) received 0.2 mg/kg of DEX (Alin, Chinoin Depot Pharmaceuticals Ltd) dissolved in a 0.9% saline solution (SSI) for five consecutive days. A second group (n=8) received the same dose of DEX for seven days, followed by seven days of no medication, followed by an additional seven days of DEX, for a total of 14 days of DEX medication. The control groups (n=9 and n=8 to the first and second group of DEX, respectively) received only the saline solution. The DEX and SSI were administered intraperitoneally at a relation volume/body weight of 1 ml/1 kg between 0900 and 1000 hours. These treatments are related with short and long dosage time. In toxicity studies is considered acute scheme when dosage time is by one week or less (three doses for example) while when treatment is longer that is considered by chronic treatment [8].

Spatial learning and memory

We evaluated the spatial learning and memory ability of the rats using a Morris water maze on the day after completion of the DEX treatment. The test apparatus was a cylinder that was 135 cm in diameter at the base, 180 cm in diameter internally, and 80 cm deep. The cylinder was filled with water to a depth of 42 cm. The water was tinted with titanium dioxide and was maintained at 22 ± 2°C during testing. The swimming surface was divided into four imaginary quadrants with reference to cardinal compass points. A circular escape platform (15 cm in diameter) was placed in the southeast quadrant at a depth of 40 cm. Noise was minimized in and around the cylinder, and extra-labyrinthine signals were placed as reference points for the location of the platform.

The complete test consisted of a learning phase (20 trials per rat) and a memory phase (4 trials per rat), which together were applied over 6 days (4 trials per day). For both phases, the results were...
measured as escape latency in seconds, defined as the time to reach the escape platform. We began all of the trials by dropping the rat gently onto the surface of water. In the learning phase, during the first four trials, the rats were allowed to swim for 120 seconds or until they found the escape platform. They were then allowed to remain on the platform for an additional 30 seconds to promote learning of the platform’s location. On trials 5 to 20 (2 to 5 days) the rats were allowed to swim for 120 seconds or until they found the platform, and were then removed immediately. After the final tests of the learning phase, the rats were allowed to rest for 16 days. We then began the memory phase, in which half the rats were subjected to 4 trials in the cylinder to measure spatial memory.

The dependent variable in both phases was escape latency, measured as the time in seconds to reach the escape platform.

**Statistical analysis**

The means of the escape latencies of blocks of four daily trials per rat were used for statistical analysis. We used repeated Two-way ANOVA for analysis, with treatment and test phase as independent variables. The significance level was set at P<0.05.

**Results**

All of the animals, regardless of dose or treatment group, showed a decrease in escape latency during the trials. This indicates that they all learned how to escape. Figure 1A and Figure 1B show the results of five days of DEX treatment on learning and on memory. Figure 1C and Figure 1D show the results of 14 days of DEX treatment on learning and on memory.

![Figure 1](image)

**Figure 1**: DEX effect on spatial learning and memory (Morris water maze). A) Complete test over five days of treatment. B) Escape latency in the learning phase was decreased in rats after five days of treatment with DEX (P<0.0001). C) Complete test over 14 days of treatment. D) Escape latency in the learning and memory phase was increased in rats after 14 days of treatment with DEX (P<0.05).

The data are shown as the means ± SE.

Five days of DEX treatment resulted in a decrease in escape latency (DEX:F(1,40)=22.18, P<0.0001) during the learning phase (Figure 1A). However, the memory phase was not affected (Figure 1B; DEX:F(1,42)=8.739, P=0.0058; Phase:F(1,42)=34.97, P<0.0001; interaction DEX x Phase:F(1,42)=1.825, P=0.6160). Fourteen days of DEX treatment resulted in an increase in escape latency (Figure 1C; DEX:F(1,42)=19.48, P=0.0001) in both the learning and memory phases (Figure 1D; DEX:F(1,28)=14.43, P=0.0007; Phase:F(1,28)=27.04, P=0.0001; interaction DEX x Phase:F(1,28)=0.2589, P=0.6149).

Table 1 shows the mean values of escape latency of the control rats (CON Groups) that received either 5 or 14 days of saline solution intraperitoneally. The 14 day control rats showed larger decreases in escape latencies compared with the 5 day control rats. This result was observed in both the learning phase (DEX:F(1,30)=2.992, P=0.5884; Treatment days:F(1,30)=2.219, P=0.1467; Interaction DEX x Treatment days:F(1,30)=12.61, P=0.0013) and the memory phase (DEX:F(1,30)=1.901, P=0.1781; Treatment days:F(1,30)=0.4910, P=0.4889; Interaction DEX x Treatment days:F(1,30)=9.796, P=0.0039).

<table>
<thead>
<tr>
<th>Phase</th>
<th>Treatment days</th>
<th>Mean ± SE</th>
<th>n</th>
<th>P</th>
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</thead>
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<td>44.45 ± 3.95</td>
<td>9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>27.61 ± 2.89</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>5</td>
<td>21.35 ± 3.48</td>
<td>9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>10.19 ± 2.01</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1**: Escape latency (in seconds) of control rats during the learning and memory phases (Morris water maze). Animals received SSI (0.9%) at a dose of 1 ml/1kg body weight, intraperitoneally.

**Discussion**

We show in the present study that short treatment with DEX promotes improved performance on the Morris water maze but long treatment produces performance deficits on the same test. Also we highlight that, chronic administration of a saline vehicle produces more efficient spatial learning and memory.

Previous studies have demonstrated that high doses of DEX cause hippocampal neuronal death, alterations in glucocorticoid expression and alterations in granular layers of the dentate gyrus [9,10]. In contrast, the low doses used in the present work do not cause neuronal death [11,12] but alterations in spine dendritic density of the dorsal hippocampus have been reported [13]. These effects can be related with deficits in learning and memory.

Stress hormones, principally corticosterone, are released during the learning process and participate in the establishment of long-term memory [14] by increasing spine density in CA1 pyramidal neurons [15]. However, large amounts of these hormones produce deficits in spatial learning and other cognitive activities [16]. In hypoxia-ischemic models, in which a reduced capacity for spatial learning has been shown, treatment with DEX results in improved learning [17]. DEX is therefore not harmful in itself but high doses of this drug are responsible of their side effects. This synthetic glucocorticoid is used as an initial treatment in various diseases because it has anti-inflammatory and immunosuppressive properties [18]. However, the use of high doses of DEX must be considered carefully because of their effects on learning and cognitive capacities [19].
Learning and memory have been evaluated after exposure to such stressors as short and long periods of chronic restraint, social stress or unpredictable stress. Although short periods of stress improved learning, long periods produce important deficits without alterations in memory [20]. The longer period of DEX treatment in this study also had negative effects on memory.

The hippocampus plays an important role in encoding, consolidation and processing information to generate learning and memory in both rodents and humans [21]. The hippocampus also shows balanced Mineralocorticoid (MR) and Glucocorticoid (GR) receptor expression. However, stress can produce alterations in regulatory mechanisms and promote chronic hyperactivity of the HPA [1]. This causes hippocampal atrophy and neuronal death [6,22], decreased neurogenesis in the dentate gyrus, deficits in cognitive activities, suppression of Long-term Potentiation (LTP) and burst stimulation. In contrast, stress causes hypertrophy in CA1 neurons [20] that may be reflected in the decreased escape latencies observed in the present study and then learning and memory capacities improved. When DEX is applied to CA1 neurons in vitro has also been observed to increase dendritic spine density, which leads to the development of LTP [23].

The molecular mechanisms associated with stress and with DEX effects on neuronal activity and improved cognitive functions involve genomic and non-genomic responses to glutamate and NMDA receptor metabolism. Changes in receptor function are necessary for LTP and LTD expression and the consequent changes in cognitive functions [24]. All of the changes are age-dependent as evidenced by young individuals being more susceptible than older individuals to harmful effects [25].

Chronic stress models involve repetitive application of the same stressor. Such stressed individuals do habituate and adapt to the stressor [26], perhaps because of a decrease in GR expression and changes in spine density [27,28]. However, acute or chronic DEX administration after SSI results in negative effects in the hippocampus and striatum [5]. We noted in the present experiment that the control rats that received only the vehicle (SSI) were more efficient in responding to the Morris water maze. We suggest that the single injection of SSI and water immersion promote an increase in glucocorticoid levels [29], which promotes readiness of response to any environmental demand.

In summary, DEX has two operating modes [30] on spatial learning and memory capacity in young rats. Its effects differ after short and long treatments, allowing us to suggest that stress generated by exposure to stressful stimuli becomes harmful only when exposure to the stressor is prolonged.

Acknowledgments

The authors wish to thank Dr. Carlos Escamilla for his help with the animal care and to Dr. Daniel I. Limón for his help with the Morris water maze. ABSG applied water maze test, performance data analysis and wrote the paper, HREL applied dexamethasone treatment to all groups, and GRZ contributed information related with dexamethasone uses and with comments to final manuscript.

Declaration of Interest

This work was supported by F-PROMEP-21/Rev 05 SEP-23-003-A and CA-PIFI 2009. Support was provided AB Silva-Gómez. None of the funding institution had any further role in the study design, the collection of data, analyses and interpretation of data, writing of the report or in the decision to submit the paper for publication. Elsevier Language Editing Services was hired for editing the English-language text. All authors have no conflicts of interest.

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