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Review

# Evaluation of spatial memory and locomotor activity during hypercortisolism induced by the administration of dexamethasone in adult male rats

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ABSTRACT

In neurosurgery practice glucocorticoids are commonly used. Steroids may have central nervous system side effects affecting whole body, including steroid-induced mental agitation and psychosis. In experimental and clinical studies conducted by using dexamethasone (DEX), it has been reported that DEX adversely affects learning and memory skills. Unfortunately, there are yet no clinically accepted clinical approaches to prevent DEX-induced cognitive dysfunction. In this experimental study it was aimed to investigate the effect of chronic DEX administration on learning-memory and locomotor behaviors in adult male Sprague Dawley rats. In addition, it was also aimed to explore the potential favorable contribution of melatonin (MEL) and vitamin C (Vit C) having antioxidant and neuroprotective properties to the effects of DEX on learning-memory and locomotor behaviors. For this purpose, rats were injected 10 mg/kg DEX intraperitoneally, both alone and in combination with MEL (40 mg/kg) and Vit C (100 mg/kg), for 9 days, and the animals were tested using the radial arm maze and open field apparatus. The test results revealed that DEX caused a significant decrease in spatial memory and locomotor activities and MEL and Vit C failed to reverse losses in these activities. Furthermore, DEX led to a gradual weight loss that reached 30% of the initial weight at 9th day of the injection. DEX administration causes a generalized loss of behavioral activity of rats. Experimental studies devised to investigate effects of DEX should take into account this DEX-induced generalized behavioral loss when assessing the effects of DEX on learning and memory skills.

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## Contents



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## 1. Introduction

Glucocorticoids (GCs) are widely used for treatment of many diseases owing to their anti-inflammatory, anti-allergic, immunosuppressive, and antirheumatic effects. Dexamethasone (DEX) is a synthetic adrenocortical steroid with high GC potency. In neurosurgery practice it is commonly used in treatment of peritumoral edema and associated neurological deficits due to primary or metastatic brain tumors and in spinal cord injuries (Galicich et al., 1961; Hurlbert, 2000; Ryken et al., 2010). It is also utilized for management of carcinomatous meningitis and central nervous system lymphoma (Todd et al., 1986). Steroids may have central nervous system side effects affecting whole body, including steroid-induced mental agitation and psychosis (Braughler and Hall, 1985).

It has been reported that GCs and acute stress affect long-term memory (Rashidy-Pour et al., 2004). Other studies have reported that acute stress and GCs alter memory capabilities in both animals and humans (Lupien and McEwen, 1997; Roozendaal, 2000). In subsequent years the mechanisms of these effects have been scrutinized (Pakdel and Rashidy-Pour, 2006). It has also been reported that DEX alters neuronal activity in specific areas of brain, leading to alterations in memory-related brain activities and long-term memory problems, especially those with verbal memory in children (Edelmann et al., 2013). It has been reported that long-term exposure to GCs may hinder glucose utilization and lead to excitotoxic neuronal death via an increased glutamate concentration (Sapolsky et al., 1990). Some studies have reported that long-term GC use is associated with reduced synaptic plasticity in hippocampal neurons and central nervous system development (Hajek et al., 2006).

Historically, various drugs including melatonin (MEL), schisandrin, astragalus, and urtica dioica have been used to prevent cognitive side effects of DEX (Li et al., 2011; Patel and Udayabanu, 2014; Tongjaroenbuangam et al., 2013; Xu et al., 2012). Vitamin C (Vit C), an antioxidant, prevents memory problems resulting from a variety of causes (Delwing et al., 2006; Pettenuzzo et al., 2002; Tagliari et al., 2011). MEL is produced by pineal gland and acts to protect nuclear and mitochondrial DNA from being injured (Reiter et al., 2001). It is a powerful antioxidant and free radical scavenger (Maldonado et al., 2007). It has been shown that MEL mitigates side effects of GCs by preventing GC-induced apoptosis and reducing GC's receptor activity (Quiros et al., 2008). Recent studies have shown that MEL improved DEX-induced cognitive functions (Tongjaroenbuangam et al., 2013). GC-induced apoptosis has been reported to result from intracellular calcium overload and oxidative stress (Squier and Cohen, 1997). It has been suggested that MEL may have a protective effect against calpain- and caspase-induced death mediated by DEX (Suwanjang et al., 2013). Vit C, in addition to an antioxidant activity in brain and neurons, plays a role in electron biosynthesis for catecholamine production or genesis of neuropeptides (Harrison and May, 2009). In a study of rats it has been reported that Vit C, by virtue of its antioxidant properties, prevents memory deficits associated with depression and other stress disorders (Tagliari et al., 2011). Studies on rats have demonstrated that it prevents memory disturbances induced by chronic hyperprolinemia and propionic acid administration (Delwing et al., 2006; Pettenuzzo et al., 2002). There are no studies yet investigating the effects of Vit C, which has been reported to prevent memory disturbances owing to its antioxidant property, on DEX-induced memory impairment.

Experimental and clinical studies with DEX have shown that it adversely affects learning and memory skills (Danilczuk et al., 2006; Edelmann et al., 2013; Keenan et al., 1996; Luine et al., 1994; Newcomer et al., 1994; Starkman et al., 1992). Unfortunately, there are yet no clinically accepted clinical approaches to prevent DEX-induced cognitive dysfunction. In this experimental study we aimed to investigate the effect of chronic DEX administration on learning-memory and locomotor behaviors in Sprague Dawley rats. In addition, it was also aimed to explore the potential favorable contribution of MEL and Vit C having antioxidant and neuroprotective properties on the effects of DEX on learning-memory and locomotor behaviors.

## 2. Results

This study was devised to evaluate the effects of chronic high-dose DEX (10 mg/kg i.p. for 9 days) on memory and locomotor behaviors of rats. In addition, this study also aimed to assess the effects of Vit C (100 mg/kg i.p. for 9 days) and MEL (40 mg/kg i.p. for 9 days) injected in separate combinations with DEX. The chronological order of injections as well as tests and applications is shown in a flow diagram (Fig. 1).

This study was conducted to test the spatial memory of rats with use of the radial arm maze test. The eight-armed radial labyrinth performance of the rats was assessed by 2 parameters. The first one was the latency of finding the arm on which food was previously placed (finding the right arm). The prolonged latency of finding the right arm is considered a sign of impaired spatial memory. The latencies with scopolamine, DEX, DEX+MEL, and DEX+Vit C were found $64\pm19$, $128\pm22$, $155\pm25$, $156\pm23$, and $180\pm0$ s. All groups had an increased latency of finding the right arm compared to the control group, although only the DEX+Vit C group had a significant difference ($p=0.002$; Fig. 2). These results suggest that, in addition to scopolamine group, all groups in which DEX and its different combinations were used exhibited signs