

THE EFFECT OF EARLY ADMINISTRATION OF GLUCOCORTICOIDS ON LEARNING AND SPATIAL MEMORY

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Summary: Synthetic Glucocorticoids are commonly administered to early low-birth weight infants to prevent the onset of chronic lung disease. During this period, the brain is undergoing significant structural and functional changes and is therefore particularly vulnerable to external influences. It has been observed that steroids administered postnatally may have transient retarding effect on learning and memory functions, and that animal age and sex may modify such effects. This study aims to illustrate the effect of early administration of glucocorticoids on learning and spatial memory. Wistar rat pups were grouped into two (control and treatment) of six pups each. 0.5mg/kg of dexamethasone was administered to four day old pups for a period of three days. At 35 days the pups were subjected to spatial memory testing. Spatial memory was assessed using a Y- Maze. It was observed that the animals in the treatment group preferred to return to the start arm or explore the other arm. This is indicative of impaired spatial memory. Steroids administered postnatally may have transient retarding effect on learning and memory functions.

Keywords: *Glucocorticoids, learning, memory, brain, rat*

Introduction

The brain, for long has been studied in terms of its bioelectric properties and anatomical connectivity. It has been recognized as a complex target tissue for the genomic effects of steroid hormones which bring about long lasting alterations in brain structure and neurochemistry as well as changes in behaviour and endocrine functions (McEwen, 1997).

Consolidation of short term memory to long term memory is a function of the medial temporal lobe, an area which includes the hippocampus (Fox, 2002). The hippocampus is a critical component of the memory system. The hippocampus and associated structures of the medial temporal lobe are needed for the acquisition of new information about facts and events and for consolidation of short term memory to long term memory storage. Synaptic long-term memory potentiation is the mechanism for the storage of recent memories by the hippocampus (Kierman, 1998). The hippocampus not only forms an important part of the limbic brain system and its involvement in learning and memory but is also believed to be involved in the control of the hypothalamic-pituitary-adrenal (HPA) axis through the effects of its two corticoid receptors (Jacobson and Sapolsky, 1991).

Increased glucocorticoid exposure in humans, including endogenous glucocorticoids (cortisol) associated with stress, decreases memory and learning function (Heffelfinger and Newcomer, 2001). According to Reus and Walkowitz (1992),

prolonged elevation of glucocorticoid levels result in impairment of memory and hippocampal atrophy.

Glucocorticoids are often administered to preterm infants in an attempt to lessen the progression of chronic lung disease. The timing of this exposure corresponds with the critical periods of neural development and as such can lead to impairment in development and long lasting neurobehavioral effects, including effects on learning and spatial memory.

Materials and methods

The experimental animals used in this research work were 15 adult Wistar Rats (*Rattus norvegicus*). The rats were housed in the Animal House of the Department of Human Anatomy, Ahmadu Bello University, Zaria, Nigeria. The animals were kept at 25°C room temperature in 12 hour light and dark cycles. They were allowed free access to food and water. The animals were fed growers' mash obtained from Nassarawa Feeds, Kaduna and were grouped into five of three rats each using the trio mating system (2 females: 1 male), (Flagel *et al.*, 2002). The female rats were separated from the male rats at approximately gestational day 18 and housed in pairs. The counting of the gestational days started after 12 hourly assessments showed consistent presence of smear characteristic of diestrous stage of the estrous cycle (which is associated with pregnancy). The litter of each dam was considered as one group. The litters were

culled so that each group consisted of six pups. Two groups were used (control and treatment). Day of birth was considered as day 1. The pups in the treatment groups were administered with 0.5mg/kg of dexamethasone for three days, (Flagel *et al*, 2002), starting on day 4 and ending on day 6. The mode of administration was by subcutaneous injection. The control groups were administered with normal saline. The pups were bred until day 35 when they were then subjected to spatial memory testing using a Y- Maze.

Spatial memory was assessed using a Y- Maze which was first described by Dellu *et al* (1992) and subsequently validated as a task requiring hippocampal function (Conrad *et al.*, 1997) and spatial memory. The arms were labelled start arm (where the rat was initially placed), other arm and novel arm (blocked arm).

The Y- Maze training began by placing a rat in one arm of the maze. One arm of the maze was blocked with plywood. The rats were allowed to explore the other 2 arms of the maze. After 15

minutes of exploration, the rats were transported back to their cages. 4 hours later, the rats were returned to the maze and allowed to investigate all 3 arms for a period of 5 minutes. The number of entries made into each arm measured spatial memory and locomotion. An entry was counted when the upper half of the rats' body entered the maze. The number of entries into each arm was calculated as a percentage of the total number of entries into all the arms.

Results

The results from the memory testing in the Y – Maze are presented in Fig.1 and Fig.2. The animals were tested for impairment of spatial memory using a Y- Maze. The animals in the control group (fig. 1) were observed to enter the novel arm more frequently than the other arms of the maze. Most of the animals in the treatment groups (fig. 2) showed a tendency to return more often to the start arm of the maze.

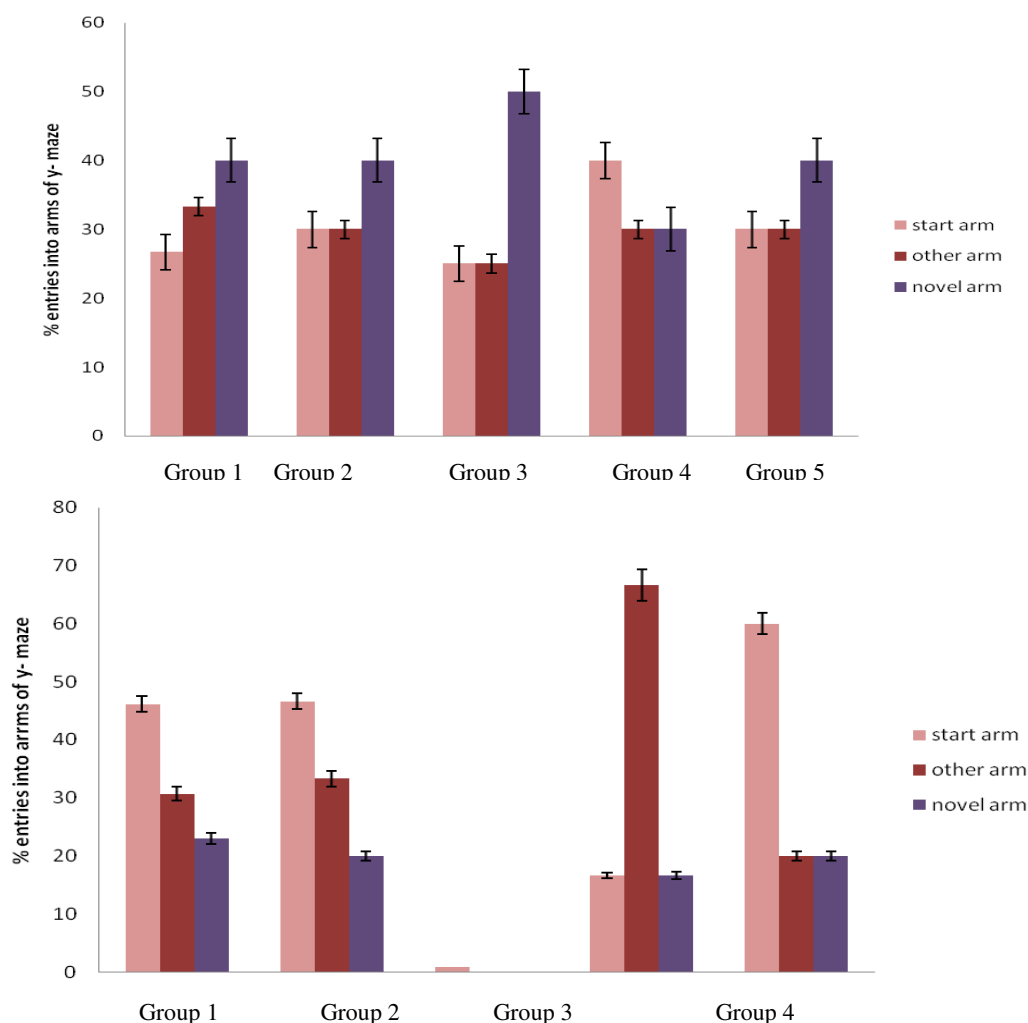


Fig.2: Memory Testing Treatment Group

Discussion

Animals with impaired spatial memory would be likely to explore all the other arms equally. Four of the animals in the control group were observed to enter the novel arm more frequently, while one of the groups showed a tendency to return to the start arm. The animals in the treatment group preferred to return to the start arm or explore the other arm. This is indicative of impaired spatial memory. Studies with animals have shown that an intact hippocampus is required for simple spatial memory tasks (for instance, finding the way back to a hidden goal) (Ekstrom *et al*, 2003). An impaired hippocampus could lead to problems in retaining spatial memory. Researchers believe that the hippocampus plays a particularly important role in finding shortcuts and new routes between familiar places.

Steroids administered postnatally may have transient, retarding effect on learning and memory functions. According to Janowsky *et al* (2000) steroids have effects on hippocampal synaptogenesis and modify cortical function. Due to the high density of glucocorticoid receptors in the hippocampus, and the critical role of this brain area in learning and memory, considerable interest has been focused on possible effects on the immature hippocampus (Coe and Lubach, 2005). Machhor *et al*. (2004) observed that steroids administered postnatally may have transient, retarding effect on learning and memory functions, and that animal age and sex may modify such effects. It has been indicated that age-related decline in spatial memory is due to functional and morphological changes in the hippocampal function (Wyss *et al* 2000; Miller and Callaghan 2003).

In light of the results it can be concluded that, glucocorticoids may lead to adverse effects on the development of the hippocampus and on spatial memory.

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