



1994

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The Effects of Exposure to Glucocorticoids on the Retention of a Spatial Task in Rats Injected Bilaterally with Beta-Amyloid into the Hippocampus.

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Running Head: EXPOSURE TO STRESS

ABSTRACT

The pathology of Alzheimer's disease is characterized by neuritic plaques and neurofibrillary tangles. The core component of the plaques is an amino acid named Beta-amyloid (A β). A recent study done by Dornan, Kang, McCampbell, and Kang (1993) reported that bilateral injections of A β along with a subthreshold dose of ibotenic acid (IBO) into the hippocampus significantly impaired the acquisition of a spatial learning task in rats. Dornan et al suggest that the results seen in their study maybe due to A β +IBO working synergistically via NMDA receptors to cause calcium dyshomeostasis. Another way that calcium dyshomeostasis occurs in the brain is via glucocorticoids. In a study done by Sapolsky (1985), exposure to stress levels of glucocorticoids exacerbated cholinergic acid damage to hippocampal neurons, suggesting the possibility that glucocorticoids may endanger neurons by making them more vulnerable to outside toxic insults. Therefore, in this study we assessed the effects of glucocorticoids (7mg of corticosterone in 1ml of sesame oil, injected daily for two weeks) on the retention of a spatial task in animals that received bilateral intrahippocampal injections of A β . Animals injected with 7mg of corticosterone along with bilateral injections of Beta-amyloid did not have significant differences in the retention of the spatial task as compared to control animals.

Alzheimer's disease (AD), is a progressive neurodegenerative disease resulting in impairment of memory, visuospatial ability, language skills, and cognitive skills, like decision making and abstract thinking.

AD is the most common form of age related dementia. Epidemiological studies indicate that over 4 million people suffer from late onset AD in the U.S. alone (Yankner, 1991). AD accounts for approximately 70% of all dementia cases, in the U.S.A. It afflicts an estimated 5-11% of the population over 65 and more than 47% over the age of 85 (Yankner, 1991; Katzman, 1991).

The pathological hallmarks of AD, as first described by Alois Alzheimer in 1907, are the accumulation of extracellular neuritic plaques (NP) and intracellular neurofibrillary tangles (NFT) in the hippocampus, neocortex, and parahippocampal structures, including the cholinergic forebrain, entorhinal cortex, olfactory bulb, dorsal tegmental serotonergic nuclei, and the locus coeruleus noradrenergic nuclei (Katzman, 1991; Selkoe, 1993; Rosenberg, 1993). These brain areas, especially the hippocampus are associated with learning and memory.

The neuritic plaques found in AD brains are comprised of a core of extracellular fibrous amyloid protein and degenerating nerve endings, and abnormal mitochondria (Katzman, 1991; Rosenberg, 1993). The amyloid core of NP, has been identified as a 39-43 amino acid long peptide with a beta pleated structure and has been named beta amyloid (A β) (Yankner, 1991). Beta amyloid is derived from

Amyloid precursor protein (APP) (Yankner, 1991; Murphy, 1992; Cai, 1993; Rosenberg, 1993).

APP is a naturally occurring glycoprotein that exists in several forms as a result of differential RNA splicing (Mattson, 1993; Mullan, 1993; Cai, 1993). Two forms of APP contain protease inhibitor domains (Yankner, 1991; Murphy, 1992). APP spans the cell membrane (transmembrane protein) and contains an intracellular carboxyl terminal and an extracellular amino terminal. Within the APP sequence, A β is located in a segment that lies partially in the extracellular space and partially within the cell membrane (Siman, 1992; Rosenberg, 1993; Mattson, 1993).

APP is cleaved via two different pathways (Mattson, Cheng, Culwell, Esch, Lieberburg and Rydel, 1993). Enzymatic cleaving of APP by the α -secretase pathway through the A β sequence results in the release of secreted forms of APP (APPs), and non amyloidogenic peptide fragments (Mattson, 1993; Rosenberg, 1993; Murphy, 1992). The secreted forms of APP are believed to be important in protease regulation (in forms containing the protease inhibitor domain), cell adhesion and proliferation, calcium regulation and neuro protection (Mattson, 1993). For example, Mattson, Barger, Cheng, Lieberbug, Swintosky, and Rydell (1993) reported that APPs reduced the increase in calcium that mediates hypoglycemic damage and protected cultured rat hippocampal and septal neurons, as well as human cortical neurons.

Alternate cleaving of APP at the amino terminal of A β by the

β -secretase pathway results in $A\beta$ release (Siman, 1992; Rosenberg, 1993; Mattson, 1993). In contrast to the APPs, $A\beta$ has been implicated in neuronal death (Yankner, 1993; Kowall, McKee, Yankner and Beal, 1992; Mattson and Rydel, 1993). For example, Malouf (1992) reported that $A\beta$ was neurotoxic to primary hippocampal neurons in culture (Mattson and Rydel, 1993; Malouf, 1992). Recently Cotman, Pike, and Copini suggested that the toxicity of the $A\beta$ peptide may be due to its aggregational state (Pike, Burdick, Walencewicz, Glabe and Cotman, 1993; Mattson and Rydel, 1993; Cotman, 1992). Increased $A\beta$ production leading to increased peptide aggregation may serve as a causal factor in the development of AD (Cai, 1993).

It is interesting to note that individuals afflicted with Down's syndrome also exhibit AD pathology (Mullan, 1993). Down's syndrome is a result of genetic abnormalities on the long arm of chromosome 21. The gene coding for APP has also been localized on chromosome 21 (Cai, 1993; Rosenberg, 1993). Mutations of the APP gene have been linked to a hereditary form of AD. Gene mutations may result in aberrant processing of APP leading to an increased $A\beta$ production (Rosenberg, 1993; Mullan, 1993).

Although there is a plethora of information regarding the physiological consequences of $A\beta$, little is known regarding the effects of $A\beta$ on learning and memory. Recently, Dornan, Kang, McCampbell and Kang (1993) reported that low dose injections of $A\beta$ into the hippocampus with a non toxic dose of ibotenic acid (an excitotoxin that works through calcium channels), disrupted the

acquisition of a spatial task in the rat. In that same study they reported that bilateral intrahippocampal injections of A β alone did not cause significant disruption in the acquisition of the spatial task. These results support the role of A β and ibotenic acid working synergistically by increasing neuronal vulnerability and exerting neurotoxic effects on hippocampal neurons via a calcium dependent mechanism. In that study Dornan et al, suggested that this effect may be mediated via NMDA receptors found in the hippocampus' (Dornan, 1993). NMDA receptor activation has been reported to induce neurotoxicity via calcium dyshomeostasis.

Another way that calcium dyshomeostasis can occur in the hippocampus is through glucocorticoids (Lanfield, Thibault, Mazzanti, Porter and Kerr, 1992). Research indicates that stress hormones may play a role in the pathogenesis of AD (Sapolsky, 1985; McEwen, 1992; Sapolsky, Packan and Vale, 1985). Glucocorticoids (GC) are naturally occurring steroid hormones, that are secreted by the adrenal glands in response to stress. They are important in the adaption of the body to stressors. GC, in response to stress, promote gluconeogenesis. That is the formation of glucose from non-carbohydrate, fat and protein molecules. Basal levels of glucocorticoids are necessary for normal metabolic function of cells, however, prolonged exposure to GC can result in detrimental effects.

The hippocampus, an area especially vulnerable in AD pathology (Rosenberg, 1993; Yankner, 1991; Kowall, McKee, Yankner and Beal,

1992), is also sensitive to the effects of glucocorticoids (Sapolsky, 1985; McEwen, 1992; Sapolsky, 1985; Sapolsky, Packan and Vale, 1985). For example, many studies have reported a significant reduction of GC receptors in the pyramidal region of the hippocampus in aged rats (McEwen, 1992; Landfield, 1989). This loss of GC receptors is accompanied by the loss of hippocampal neurons (Sapolsky, 1985; Landfield, 1989). The age related loss of hippocampal neurons is believed to be mediated by GC action. Since the hippocampus regulates a negative feedback control over glucocorticoids, the loss of hippocampal neurons result in the inhibition of the negative feedback loop regulating GC release (McEwen, 1992). This leads to a "cascade effect" with increasing GC's causing more hippocampal cell death which in turn further decreases the negative feedback mechanism (McEwen, 1992; Sapolsky, 1985; Sapolsky, Packan and Vale, 1985). Not surprisingly, several studies report reducing life long exposure to GC reduces neuronal damage. Removal of adrenal glands (adrenalectomy) was found to make hippocampal neurons less vulnerable to cell death with age (McEwen, 1992; Sapolsky, 1985).

Considerable evidence supports the role of GC as endangering the ability of the hippocampus to withstand a variety of neurological insults such as neurotoxins, antimetabolites, and oxygen radical generators (Sapolsky, Packan and Vale, 1985). In a study done by Sapolsky in 1985, exposure to high circulating levels of corticosterone (A form of GC's that occur in the rat),

1 week prior, and 1 week after microinfusions of kainic acid dramatically increased hippocampal damage in rats. In contrast, adrenalectomized rats had the least amount of damage to the hippocampus after kainic acid treatment. This effect of GC, was seen with levels of hormone, that by itself was not damaging to the hippocampus. Glucocorticoids appear to synergize with kainic acid impairing the ability of neurons to survive. This apparent synergy was most dramatic in the hippocampus. Glucocorticoids exacerbated kainic acid damage to primary hippocampal neurons in vivo. It did not, however, increase kainic acid damage to cell cultures from the cerebellum and the hypothalamus (Sapolsky, 1985).

The mechanism by which GC's increase the susceptibility of neurons to kainic acid is not known. It is possible, however, to conclude from studies done by Sapolsky (1985) that the steroid does not mediate its action by increasing kainic acid toxicity. Increasing the toxicity of kainic acid would include, increasing the diffusion of the acid through the hippocampus or increasing the binding of kainic acid to the hippocampal neurons. GC's do not work through the above mechanisms to increase the vulnerability of the hippocampus. The synergistic effect of GC's and kainic acid in cell culture is blocked by RU 38486, a specific glucocorticoid receptor antagonist (Sapolsky, 1985). This suggests the possibility of GC's increasing neuronal vulnerability via GC receptors in the hippocampus and that the effects of the hormone are primarily on the neuron.

Intriguingly, a recent study by Hortnagl, Berger, Havlec, and Hornykiewicz (1993) also reported that glucocorticoids enhanced the susceptibility of the septohippocampal cholinergic neurons to a cholinergic neurotoxin, ethylcholine aziridinium (AF64A). This effect was attenuated by ADX. This suggests the possibility that the cholinergic degeneration found in AD brains may be due to increased stress enhancing the susceptibility of these neurons towards toxic insults (Hortnagl, 1993).

In view of the above findings, this study attempted to assess the effects of Glucocorticoids and bilateral A β (1-42) injections on the retention of a spatial learning task in the rat.

METHODS AND MATERIALS

Experiment 1: The effects of basal and stress levels of glucocorticoids on the hippocampus, were assessed following ADX on animals during a two week period. Histologies of the animals will be used as baseline controls in comparing hippocampal damage of animals injected with A β (1-42) and daily injections of corticosterone (A form of glucocorticoids that occur in the rat).

Animals and Surgery

21 male Long Evan rats were used in this experiment. Rats were individually housed in wire bottom cages under a reversed 12 hour light/dark cycle, and were given free access to food and water during the experiment.

Nine rats were adrenalectomized(ADX) using the dorsal

approach, and three control rats were sham operated (the animals received surgery without removal of the adrenal glands) under sodium pentobarbital (50mg/ kg, body weight i.p.) ADX were conducted in order to control the variability in GC levels in rats. Sham operations were used as controls, for the effects of surgery. Adrenalectomized rats will be maintained on 0.9% sodium chloride drinking water solution through out the experiment. (The adrenal glands are involved in maintaining sodium /water homeostasis in the body).

Animals received either corticosterone (a form of glucocorticoid found in the rat) or sesame oil (vehicle) treatment. The following groups were used in the experiment:

Group 1 : (N=4) ADX animals maintained on basal corticosterone levels (5ul/1L) dissolved in drinking water.

Group 2 : (N=5) ADX animals injected subcutaneously (s.c.) with 7mg corticosterone dissolved in 1 ml sesame oil, daily (The dose represents chronic stress levels of GC's as suggested by Sapolsky, Personal communication).

Group 3 : (N=6) Intact control animals injected s.c. with 7mg corticosterone dissolved in 1 ml sesame oil, daily.

Group 4 : (N=3) Sham operated controls.

Group 5 : (N=3) Intact controls injected s.c. with 1ml sesame oil daily.

Histology

Following a two week period animals were sacrificed using an

overdose of sodium pentobarbital and perfused in 300ml saline and 600ml of 4% paraformaldahyhe. Brains were removed and post fixed overnight in 4% paraformeldehyhe and stored in a 20% phosphate buffered sucrose solution. Hippocampal brain sections of each animal will be stained, using a cressyl violet stain and examined under microscope.

Experiment 2: The effects of glucocorticoids (7mg corticosterone in 1 ml · sesame oil) on animals that received bilateral intrahippocampal injections of A β (1-42) was assesed on a spatial retention task.

Animals and Surgery

18 male Long Evans rats were used in this study. The animals were maintained at 85% of their normal body weight with free access to water throughout the experiment.

One week prior to and one week following surgery the animals received the following treatment conditions:

Group 1: Daily subcutaneous injections of 7mg of corticosterone in 1 ml sesame oil. (n=6).

Group 2: Daily subcutaneous injections of 1 ml sesame oil. (n=5).

Group 3: Bilateral adrenalectomies using a dorsolateral approach under sodium pentobarbital anesthesia (50mg/Kg body weight, i.p.). Animals were maintained on basal corticosterone (5mg/1L) dissolved in 0.9% sodium chloride drinking water. (n=5).

Stereotaxic surgery was conducted on all animals using sodium

pentobarbital (50mg/Kg body weight, i.p.) using the stereotaxic coordinates AP -3.6, ML +/- 2.3, DV -3.6,. The coordinates were empirically determined using Paxinos and Watson atlas (Dornan et al, 1993). All animals received bilateral injections of A β (1-42) 7nmol per microliter (.5ml per side) in DMSO vehicle. Each injection took place over a period of 5 minutes. The syringe was left in place after injections for an additional 3 minute period in order to minimize tissue damage and backflow. Two animals, one from group 2 and one from group 3 were lost during stereotaxic surgery.

Behavioral Testing

Apparatus:

Animals were tested on a eight arm radial maze which contained 5 baited arms and 3 unbaited arms. At the end of each arm a white painted plastic container will be attached to contain food. Fruit loops will be used as bait. The radial arm maze consists of a center platform 2.5' across with eight 6" wide 2.5' long arms radiating from the center. The arms do not contain sides. The maze was elevated approximately 2' from the floor.

Procedure:

Animals were habituated on the radial arm maze for a period of 4 days. During habituation, animals were placed on the center platform of the maze for a period of 5 minutes/per day, with the reinforcer (fruit loops) liberally scattered on it. Following habituation the animals were pretrained for 14 days. Animals

achieving a criterion, of entering a minimum of two arms for at least 5 days were used in the study. Following surgery animals were assessed on the following behavioral parameters: the number of arms revisited (total errors); correct errors, (repeated entry into baited arms); incorrect errors, (repeated entry into unbaited arms); reference memory errors, (entry into arms that were never baited, and total number of choices, (total number of arms entered).

At the beginning of each test session each animal was placed on the center of the maze and permitted to choose among the arms, until it completes the test; that is till it obtained all food reinforcers or 10 minutes elapsed. If no choice was made during the first 5 minutes of each test session, the test was terminated. For testing purposes each animal was randomly assigned to one of three maze orientations on a random set of 5 arms which will serve as the baited set, for the duration of the experiment. Testing was conducted blind. After each session the radial arm maze was wiped with water to control for odor. Each rat received one trial a day for a period of two weeks over a seven day testing block. Each trial was conducted at the same time every day. All data was summed and averaged over each testing block.

Histology

Following the completion of the experiment, animals were given an overdose of sodium pentobarbital and then perfused with 300 ml saline, and 600 ml of 4% paraformaldahyhe. Brains were removed and

post fixed overnight in 4% paraformeldehyde and stored in a 20% phosphate buffered sucrose solution. Sections of each brain will be taken and stained using cresyl violet to verify the lesion site. Each brain will also be stained with congo red to visualize amyloid deposits and examined under microscope for necrosis and glial cell proliferation.

RESULTS

Animals that received daily injections of 7mg corticosterone were compared to animals injected with sesame oil, and adrenalectomized animals, as well as with animals injected bilaterally with A β (1-42) alone, DMSO vehicle alone, and with a scrambled sequence of A β (1-42). (Control animals injected with A β (1-42), DMSO, and the scrambled sequence of A β (1-42) were from a study conducted at Illinois Wesleyan University by A. McCampbell, A. Peterson, & G. Tinkler, spring 1994, using the same behavioral paradigm).

Statistical analysis of the data was conducted using Analysis of Variance on the animals running the radial arm maze. A split plot test (mixed design) was performed on correct error, incorrect errors, total errors, reference memory errors, percent correct choice and total number of choices. The treatment condition was used as the between group measure and the testing blocks were used as the repeated measure.

As can be seen from Figure 1 animals injected with

corticosterone had significantly greater numbers of reference memory errors on block 4, ($F=4.4064$, $p<.001$), and an significantly greater number of total choices on block 3, ($F=2.0315$, $p<.05$), (Figure 2).

Insert Figures 1-2 about here.

As can be seen from Figures 3-6 bilateral injections of A β (1-42) along with daily injections of corticosterone failed to significantly alter retention of the radial arm maze task in the experimental animals compared to controls, on measures of total errors, correct errors, incorrect errors and percent correct choice. However, these animals exhibited increased correct errors, incorrect errors, total errors, and decreased percent correct choices from pre-surgery block 2 to post-surgery block 4. Control animals exhibited decreased numbers of correct, incorrect, and total errors and increased percent correct choices from block 2 to 4 in accordance to a normal learning curve.

Insert Figures 3-6 about here.

DISCUSSION

The results of the present study indicate that animals injected with A β (1-42) and subjected to daily injections of 7mg

corticosterone were not significantly impaired in their retention of a spatial task when compared to controls. However, the animals in the experimental group had significantly higher reference memory errors (entry into an arm that was never baited). Intriguingly the results demonstrate the presence of a "saw shaped" learning curve for the animals injected with corticosterone. It is noteworthy that Dornan et al (1993) also observed a "saw shaped" learning curve when animals injected with A β (25-35) and ibotenic acid were tested on the radial arm maze and the morris water maze.

Above threshold levels both glucocorticoids and ibotenic acid exert neurotoxic effects on the hippocampus via calcium dyshomeostasis. It is possible that beta-amyloid interacts synergistically with insults such as stress hormones, to cause hippocampal damage and the resulting behavioral deficits .

In interpreting the results of the study several important factors must be kept in mind. The present study lacked a control group of animals that were only subjected to stress levels of corticosterone. Such a control group is essential in order to understand possible interactions of A β with stress levels of glucocorticoids. Measures of plasma glucocorticoid levels in animals injected with corticosterone were not taken, therefore it is not possible to state definitely that animals had elevated levels of glucocorticoids circulating in their bodies. It is also important to note that the number of animals in each group was small (n=6, or n=5). The small statistical samples in each group,

make meaningful statistical analysis difficult and increases the probability that random effects will be magnified.

At present histological examinations of the animal brains has not been completed. This is required to verify the injection site into the hippocampus as well as to provide information on the effects of the injection on the hippocampus. Without histological verification the results of the study must be acknowledged with caution.

The sensitivity of radial arm maze to measure hippocampal damage with attendant memory dysfunction is at present controversial. Research indicates that hippocampal damage results in an inability to perform tasks requiring the use of declarative memory. Declarative memory is the ability to form mental representations in relation to different contexts. As opposed to declarative memory the expression of procedural memory is often seen in stereotyped learning such as riding a bike or typing. This form of memory is believed to be independent of the hippocampus. The ability of the RAM task to serve as a behavioral measure of hippocampal damage depends on its ability to effectively tap the declarative memory process. In order to navigate the maze with minimum entry into arms the animal must form spatial representations with extraneous cues that would successfully identify baited arms containing the reinforcer. The animals are also required to keep track of arms visited in order to avoid subsequent choices among those arms. Both these abilities are

dependent on declarative memory process. However , it is possible that animals with hippocampal damage may learn the task successfully using procedural memory, by running down all arms systematically in a stereotyped manner. The animals may have learned a strategy for completing the RAM task and therefore not have taxed declarative memory function. Therefore the pattern of results seen may be due to the intrinsic problems associated with measuring declarative memory process using the RAM task.

Due to time constraints we were unable to test the animals on other tasks, such as the Morris water maze, another spatial learning task. Additional testing of the animals would have strengthened the validity of our study. It is also possible that extensive hippocampal damage must occur before any behavioral deficits are observed in animals. Compensatory mechanisms within the brain may also respond to the hippocampal damage with time and animals may relearn the task without much difficulty.

While the results of the present study did not highlight significant difference between animals injected with stress level doses of corticosterone and control animals in the retention of a spatial task, they are sufficiently intriguing to merit further investigation for a possible interaction between glucocorticoids and β -amyloid and a causative role in the pathogenesis of Alzheimer's Disease.

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Figure Caption

Figure 1. Group differences in the mean number of reference memory errors made over pre surgery block 2 and post surgery blocks 3 and 4 (1 block = 7 test sessions). Reference memory error is an entry into an arm that was never baited. Vertical lines indicate standard errors.

Reference Memory Errors

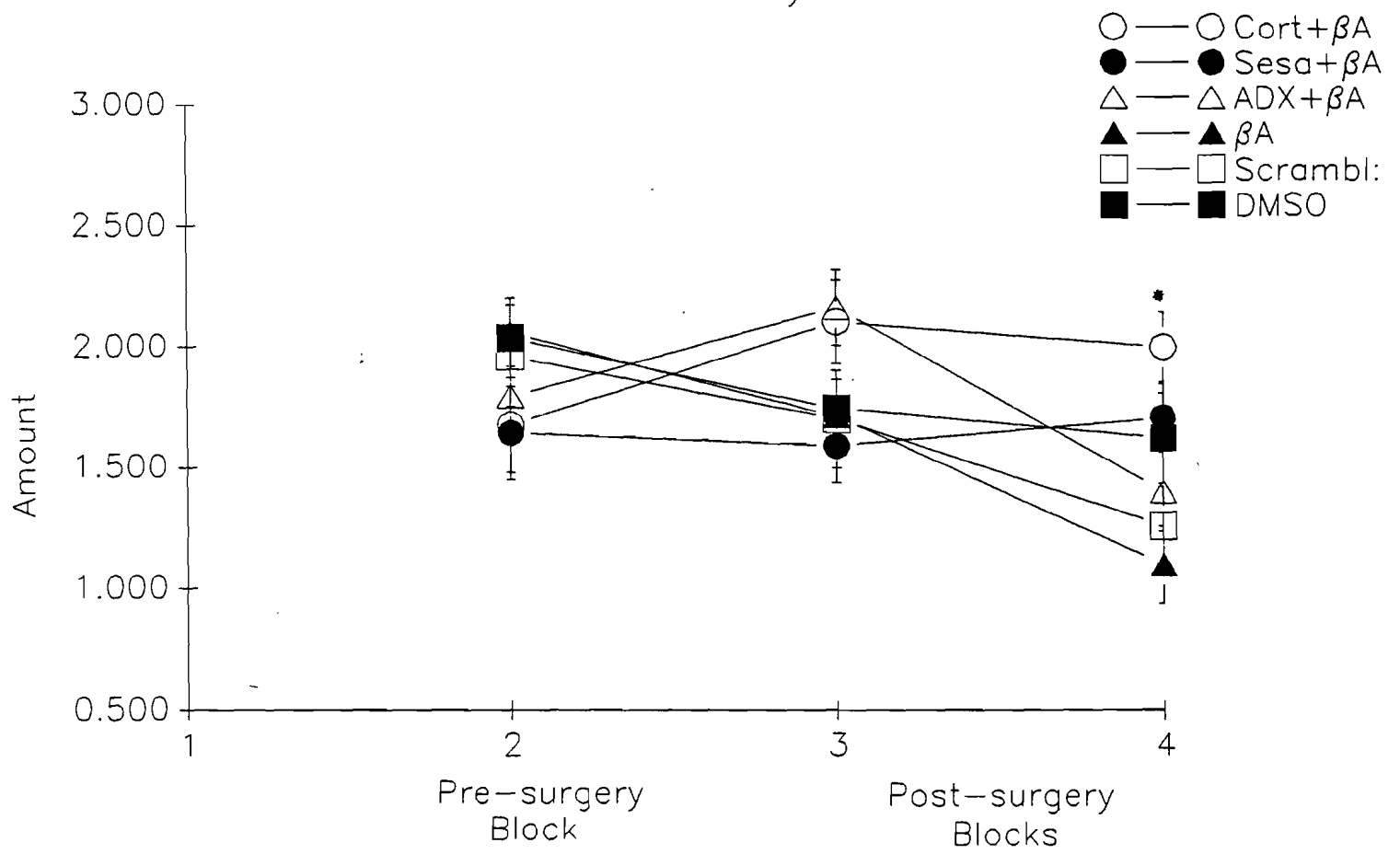


Figure Caption

Figure 2. Group differences in the mean total number of choices (total number of arms entered per session) made over pre surgery block 2 and post surgery blocks 3 and 4 (1 block = 7 test sessions). Vertical lines indicate standard errors.

Total Number of Choices

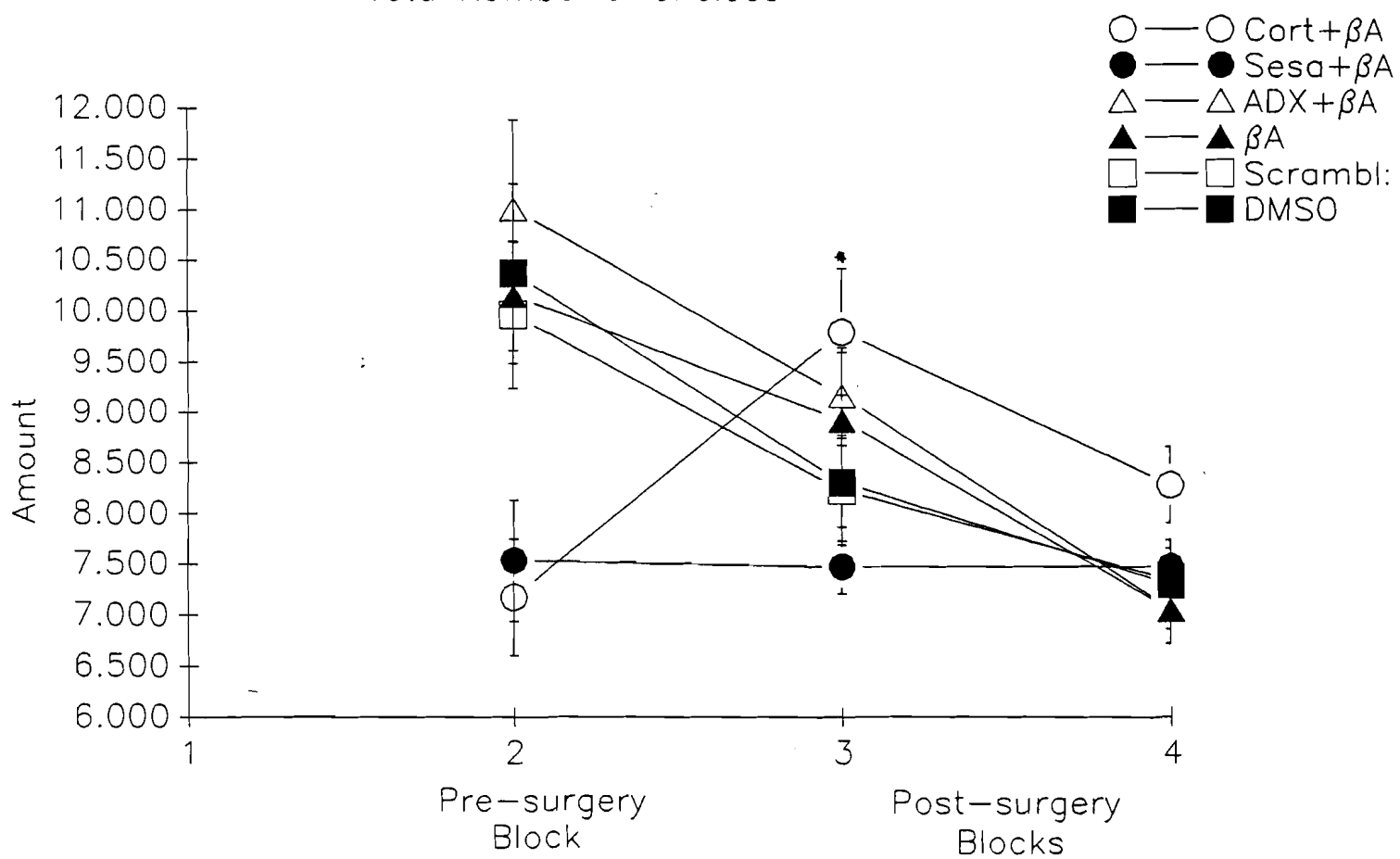


Figure Caption

Figure 3. Group differences in the mean number of total errors committed over pre surgery block 2 and post surgery blocks 3 and 4 (1 block = 7 test sessions). Total errors include correct errors, incorrect errors, and reference memory errors. Vertical lines indicate the standard errors.

Total Errors

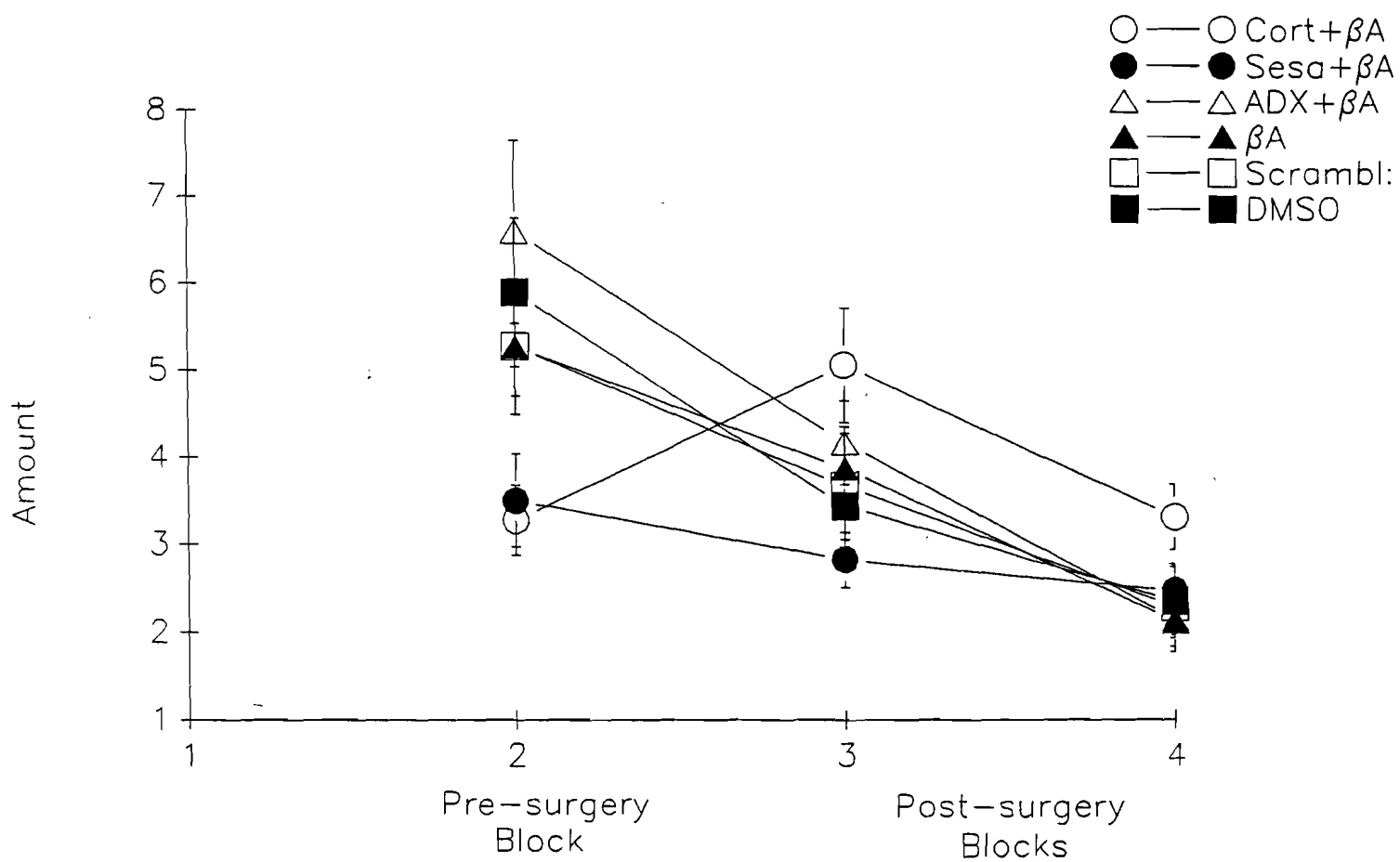


Figure Caption

Figure 4. Group differences in the mean number of correct errors committed over pre surgery block 2 and post surgery blocks 3 and 4 (1 block = 7 test sessions). Correct errors are reentry into baited arms. vertical lines indicate standard errors.

Correct Error

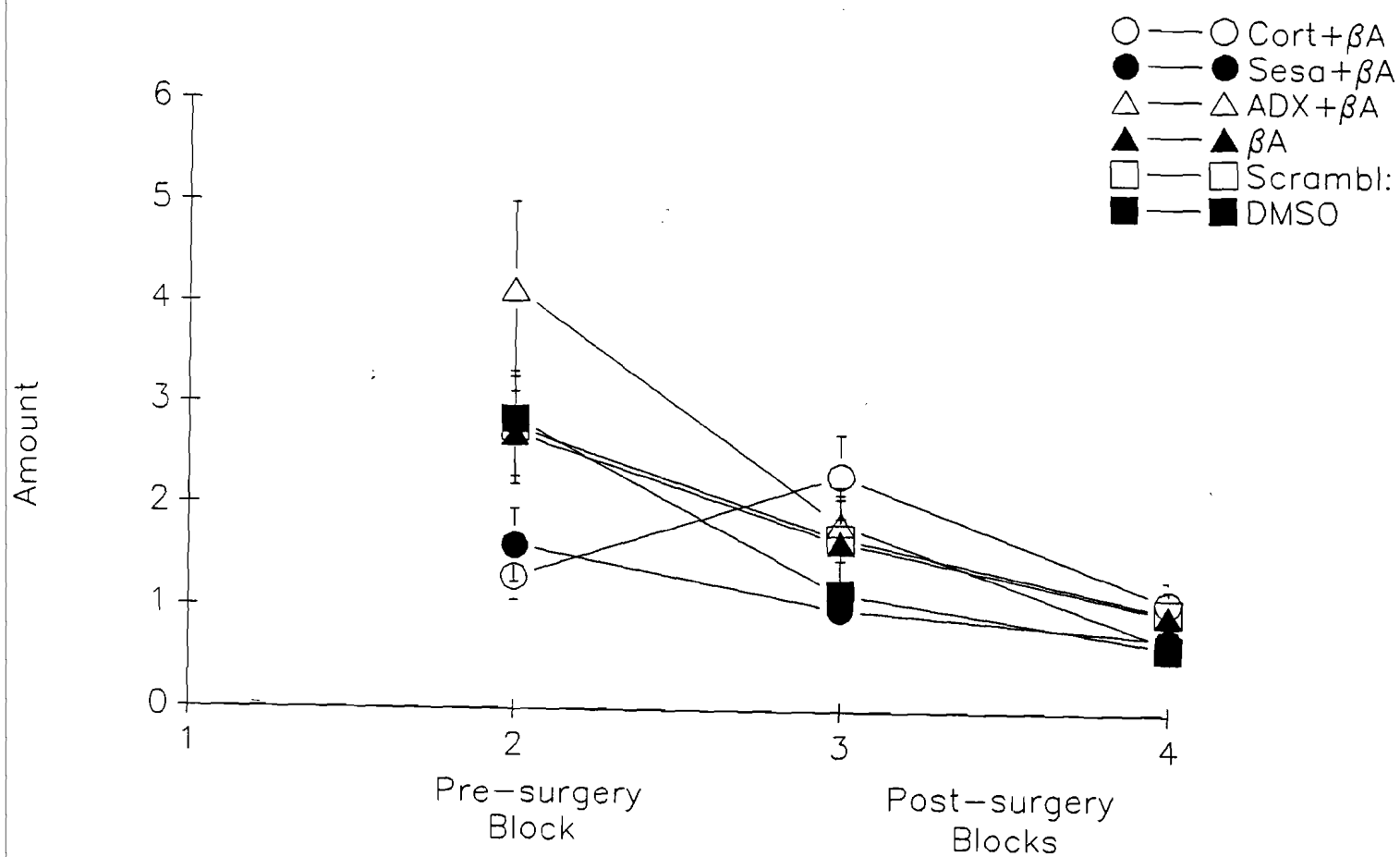


Figure Caption

Figure 5. Group differences in the mean number of incorrect errors committed over pre surgery block 2 and post surgery block 3 and 4 (1 block = 7 test sessions). Incorrect errors are reentry into unbaited arms. Vertical lines indicate standard errors.

Incorrect Error

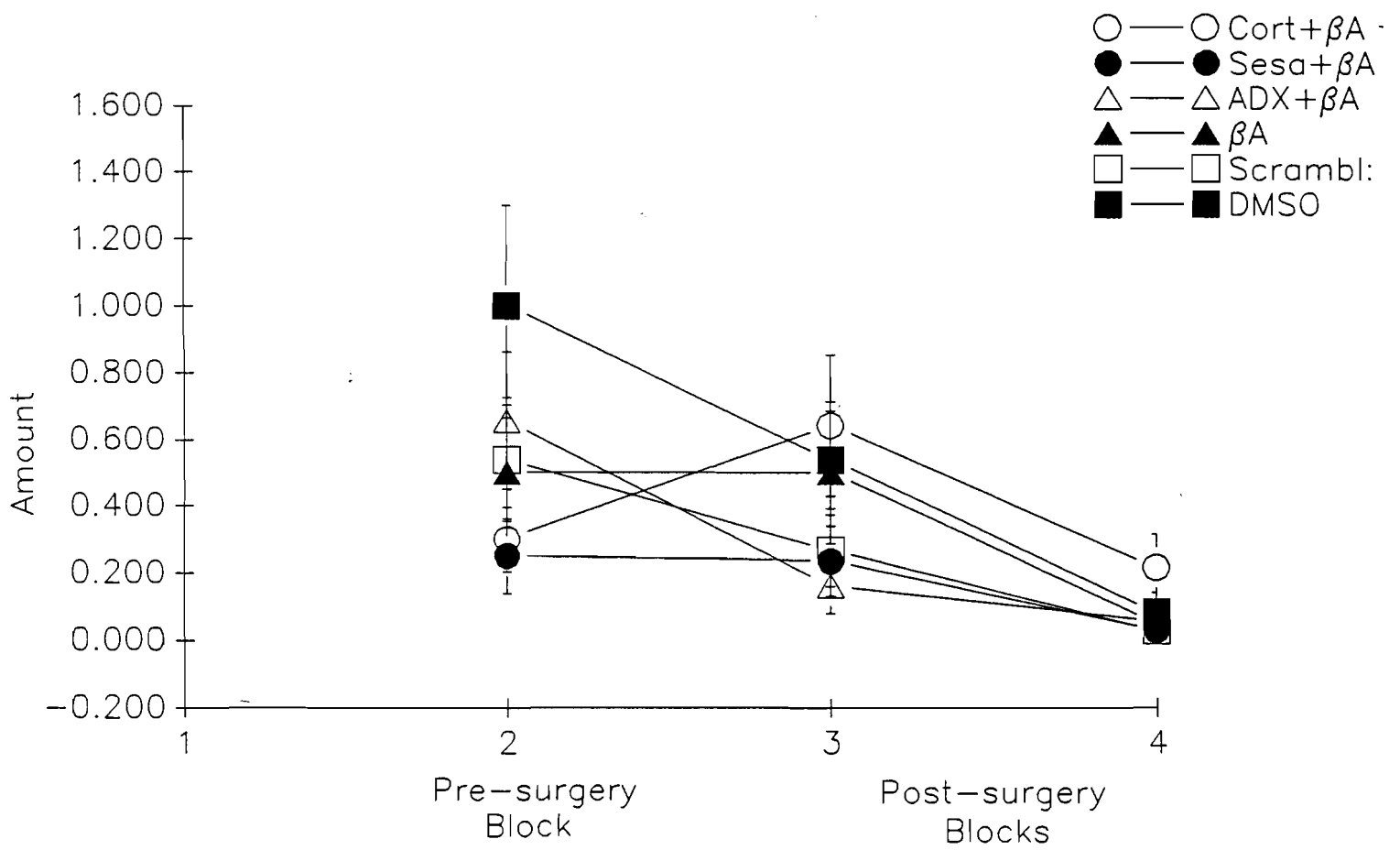


Figure Caption

Figure 6. Group differences in the mean percent of correct choices over pre surgery block 2 and post surgery blocks 3 and 4 (1 block = 7 test sessions). Correct choices are entry into baited arms. Vertical lines indicate standard errors.

Percent Correct Choice

