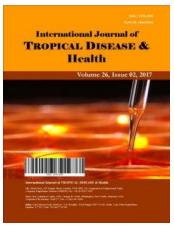

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Starvation-induced Changes in Memory Sensitization, Habituation and Psychosomatic Responses

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Authors' contributions

This study was carried out in collaboration by all authors. All authors read and approved the final manuscript.

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ABSTRACT

Starvation is a global challenge. Nutritional status of an organism may influence its psychosocial behavior and other nervous system processes like motor responses and its ability to learn and memorize. This study determined the impact of starvation-induced stress on memory sensitization, habituation and psychosomatic responses in an experimental animal design. 25 wistar rats were randomly sampled and grouped into 1-control, 2- feed after 6 hours deprivation, 3-feed after12 hours deprivation, 4-feed after 18 hours deprivation and 5-feed after 24 hours deprivation. Behavioral tests carried out included the multiple maze tests and elevated plus maze test. Grip strength test was performed to determine neuromuscular response and endurance in all groups. Biochemical investigation of brain stress markers was done on the last day of the study. There was a significant (P≤0.05) enhancement in memory processes and anxiolytic behavior after 6 hours feed

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deprivation. An increase in antioxidants after 6 hours feed deprivation was suspected to be a compensatory response. A progressive decrease in memory facilitation, anxiolytic behavior and muscular strength was reported after 12, 18 and 24 hours feed deprivation. The increase in habituation and decrease in psychosomatic response was observed and appreciated as the duration of feed deprivation was increased. This study provided evidence about a possible link between memory processes and stress-related alterations in calcium, magnesium and nitric oxide. Starvation may impair learning, memory and motor responses, but this tendency is dependent on the extent of feed deprivation and nutrient depletion.

Keywords: Starvation; behavior; memory; anxiolytic; stress.

1. INTRODUCTION

Humans are constantly exposed to various forms of environmental stressors. These stressors may not necessarily be traced pathologically, but may also be as a result of regular physiologic processes like physical activity, emotional disturbances and hunger [1]. Our daily activities 'burn-out' energy stores [2], therefore, we need continuous supply of energy to sustain life. The nervous system, functionally, occupies a central role in regulation of our daily physical and mental responses. Mental processes include our ability to learn and consolidate memory. The process of facilitation of memory is referred to as memory sensitization. Exposure to a particular stimulus modifies neural connectivity, synaptic transmission and postsynaptic activity which may lead to either increased awareness to such a stimulus or attenuation and subsequent habituation of an organism to the stimulus. Several studies have revealed a positive correlation between stress and memory impairment [2,3]. This impairment becomes evident when rodents are required to use brain regions such as the hippocampus and the surrounding cortex in tasks such as the navigation multiple maze test, in which they use the spatial relationships between the lanes to navigate to an exit. Cognitive deficiencies have also been reported in other behavioral tests, such as T-maze [4], radial maze [5], object recognition test [6], as well astests whose responses are not necessarily linked to thehippocampus and to the cerebral cortex [7].Stress, which is a condition, related to modern world dynamics, is another health issue affecting millions of people [8]. Stress may result from aparticular condition and/or lifestyle and may lead to a wide rangeof behavioral changes. Among these changes, it is worth emphasizing those related to eating habits, which reflect theinteraction between the body physiological status and the environmental conditions [9]. The relationship among chronicstress, brain plasticity and cognition is complex [10]. Thehippocampus and the amygdala are particularly susceptible to corticosteroid-mediated physiologic changes [10,11], since both structures contain a large number of receptors for glucocortoids. Several types of stressors may be categorized according to their psychogenic factors and related to the psychological or neurological disorders which they cause. Before this study, there was no data to determine the effect of psychophysiological stimuli like starvation-induced stress on cognitive, motor and behavioral responses. This study can therefore, be said to be novel on its own path to global scientific innovations.

2. MATERIALS AND METHODS

2.1 Animals and Experimental Groups

The herein presented study used malewistar rats collected from the matrices of the Research Animal Facility in Madonna University, Nigeria, and kept in the PhysiologyResearch Laboratory of same institution subjected to normal light/dark cycle, with food and liquidsoffered according to the study design.All animals used were 48 days old.The animals were kept in five cages containing five animalseach.All efforts were made to minimize restraint and suffering.

2.2 Ethical Consideration

All experimental procedures were in correspondence to the guidelines by the Ethics Committeeon Animal Use (CEUA) IF Goiano, GO, Brazil (protocol n.003/2012).

2.3 Test for Cognition and Anxiety Related Behaviors

These tests were performed using navigational multiple maze test (MMT) and elevated plus maze test (EPM). Protocols observed have been described previously [2].

2.4 Test for Motor Activity

This test was performed using hand grip test previously described [12].

2.5 Experimental Design

This study was conducted between November 2018 to January 2019; with strict observation of behavioral changes. It lasted for 42 days.

Table 1. Study design

Groups	Treatment protocols
1	Pelleted feed ad libitum
2	Feed after 6 hours deprivation
3	Feed after 12 hours deprivation
4	Feed after 18 hours deprivation
5	Feed after 24 hours deprivation

N=5

2.6 Tissue Preparation

All animals were anaesthetized with pentobarbital sodium salt (0.5 ml i.p.) and transcardially perfusedwith saline (0.9% NaCl) followed by 4% paraformaldehyde (PFA) in phosphate buffer (PB; 0.1 M; pH 7.4). All extracranial tissue was removed and the brains were left in the skullsto minimize the potential risk of deformation. After overnight post-fixation at 4^{o}C, the skulls containing the brains were stored in the refrigerator (4^{o}C) in phosphate buffer with 0.01% sodium azideuntil use for biochemical analysis.

2.7 Biochemical Analysis

Biomarkers assayed are brain stress markers-superoxide dismutase (SOD), catalase (CAT), nitric oxide (NO), reduced glutathione (GSH); electrolytes-calcium (Ca^{+}) and magnesium (Mg^{+}). The assay protocols used havealready been described previously [2].

2.8 Statistical Analysis

Data was expressed asmean ± SEM. All statistical analyses were performed using SPSS version 20.0 (IBM, UnitedStates).All values werestatistically significant at a confidence interval less than or equal to 95%.By adopting an appropriate method by Chuemere, et al., 2018, percentage change (%c) was also calculated using the formula V_2-V_1/V_1 X 100 [2,13].

3. RESULTS

3.1 Effect of Feed Deprivation on Anxiety-related Responses

All groups showed similar behavior in first trial. In second trial, after 6 hours feed deprivation, there was a significant decrease in duration of time spent in open arm with a percentage change of 9.22 compared to control and in third trial there was a significant increase in duration with a percentage change of 5.92 compared to first trial. In closed arm, the same group showed a significant progressive increase in duration from first trial to second trial with a percentage change 6.60 and from second trial to third trial with a percentage change of 4.0. After 12 hours feed deprivation, there was a significant decrease in duration of time in open arm with a percentage change of -38.3 and -8.1 from trial one to two and trial two to three respectively. 18 hours feed deprivation showed similar trend to 12 hours deprivation but with a greater progressive decrease and increase in duration of time in open closed arm respectively. After 24 hours feed deprivation, the test spent almost the entire period in the closed arm, as a progressive increase was noticed from trail one through three with an overall percentage change of 120.3.

Table 2. Effect of feed deprivation on anxiety-related responses

Groups	Open arm			Closed arm		
	Trials					
	1	2	3	1	2	3
Control	31.3±0.2	32.0±1.3	32.1±0.4	40.2±0.3	41.3±1.4	41.4±0.4
Feed deprivation						
6 hours	30.4±1.2	29.3±1.0^{a}	32.2±0.3^{b}	44.2±2.2	47.1±0.1^{ab}	49.0±1.1^{ab}
12 hours	34.2±1.3	21.1±0.4^{ab}	19.4±0.2^{ab}	44.3±2.4	57.3±0.4^{ab}	61.4±0.2^{ab}
18 hours	33.1±0.2	17.4±0.2^{ab}	12.3±0.3^{ab}	41.2±1.3	60.2±1.1^{ab}	72.4±0.1^{ab}
24 hours	32.3±0.3	12.2±0.2^{ab}	9.2±0.4^{ab}	42.3±0.2	83.4±1.2^{ab}	93.2±1.3^{ab}

Key; Trials (in seconds±SEM); ^{a}- value statistically significant at P≤0.05 compared to control; ^{b}- value statistically significant compared to previous trial within same treatment group

Table 3. Effect of feed deprivation on neuromuscular strength

Groups	Trials		
	1	2	3
Control	4.3±0.2	5.1±0.4	5.4±0.2
Feed deprivation			
6 hours	4.4±1.3	7.4±0.3[ab]	8.0±1.3[a]
12 hours	4.1±0.4	7.3±1.2[ab]	8.2±1.1[ab]
18 hours	4.1±0.3	4.0±1.2[a]	3.3±1.0[a]
24 hours	4.0±0.1	3.1±0.1[a]	2.4±0.2[ab]

Key; Trials (in seconds±SEM); [a]- value statistically significant at P≤0.05 compared to control; [b]- value statistically significant compared to previous trial within same treatment group

Table 4. Effect of feed deprivation on memory facilitation

	Trials		
	1	2	3
Control	40.1±0.1	39.4±1.4	37.1±0.4
Feed deprivation			
6 hours	41.2±1.3	37.3±0.3[b]	34.2±2.2[ab]
12 hours	40.3±0.2	38.2±1.4[b]	37.3±0.4
18 hours	40.2±1.1	44.5±0.1[ab]	57.3±1.3[ab]
24 hours	42.4±1.4	64.1±14[ab]	77.1±0.3[ab]

Key; Trials (in seconds±SEM); [a]- value statistically significant at P≤0.05 compared to control; [b]- value statistically significant compared to previous trial within same treatment group

3.2 Effect of Feed Deprivation on Neuromuscular Strength

After 6 hours feed deprivation, the muscle strength and response was similar to control. As the interval between feeding was prolonged to 18 hours, the strength of the muscles decreased significantly with a percentage change of -38.9 in third trial compared to control. There was a greater progressive decrease as the test was repeated after 24 hours feed deprivation with a percentage change of -22.5 from trial one to two and -22.6 from trial two to three.

3.3 Effect of feed Deprivation on Memory Facilitation

After 6 hours feed deprivation, memory facilitation was similar to control in first and second trial but a significant change was noticed in third trial with a percentage change of -7.82 compared to control.There was no significant change in all trial after 12 hours feed deprivation compared to control. After 18 and 24 hours feed deprivation, there was a progressive significant increase in duration of time spent by the tests to run the course of the multiple maze. The highest significant increase in time was noticed in third trial after 24 hours feed deprivation with a percentage change of 107.8 compared to control.

3.4 Effect of Feed Deprivation on Brain Stress Markers and Electrolyte Concentration

The level of oxidative stress enzyme markers SOD and CAT decreased progressively as the duration of feed deprivation was increased. There was a compensatory increase in SOD after 6 hours of feed deprivation with a percentage change of 7.82. Same initial increase was noticed in CAT after 6, 12 and 18 hours feed deprivation with a percentage change of 18.7, 16.9 and 12.3 respectively. A compensatory increase in GSH was noticed after 6 hours feed deprivation with a percentage change of 9.94.Thenitrosative agent NO was progressively decreased after 12, 18 and 24 hours feed deprivation.The level of NO was increased after 6 hours feed deprivation with a percentage change of 23.4.Ca^{+} and Mg^{+} level in brain tissue reduced progressively with the greatest reduction seen after 24 hours feed deprivation.

4. DISCUSSION

Starvation is a global challenge [2]. The biochemical manifestation of starvation and its

Table 5. Effect of feed deprivation on brain stress markers and electrolyte concentration

Groups	$SOD_{(u/ml)}$	$CAT_{(u/g)}$	$NO_{(u/ml)}$	$GSH_{(ug/m)}$	$Ca^{+}_{(mmol/L)}$	$Mg^{+}_{(mmol/L)}$
Control	231.3±0.3	214.0±1.2	44.1±0.1	34.2±1.6	6.2±0.02	4.3±0.3
Feed deprivation						
6 hours	249.4±0.1[a]	254.0±1.4[a]	54.4±0.2[a]	37.6±0.3[a]	6.1±0.4	4.7±0.1[a]
12 hours	221.2±0.2[a]	250.2±0.2[a]	43.1±0.3	27.3±1.2[a]	5.2±0.3[a]	3.2±0.4[a]
18 hours	200.2±1.4[a]	244.1±1.6[a]	41.2±0.1[a]	27.1±0.4[a]	4.2±1.0[a]	3.1±1.3[a]
24 hours	182.1±1.2[a]	209.3±1.1[a]	38.1±0.3[a]	20.2±1.0[a]	3.4±1.2[a]	2.1±0.3[a]

Key; Trials (in seconds±SEM); [a]- value statistically significant at P≤0.05 compared to control

relation to memory facilitation and habituation is poorly established. Previous studies have revealed a possible link between stress and memory consolidation [10]. Early studies also suggest that spatial memory can be improved given a moderate level of stress exposure, in non-obese rodents with an"inverted U" relationship between stress and cognitive function, such that a moderate level of glucocorticoids haspro-cognitive effects, whereas too low or too highglucocorticoid levels are detrimental to cognitive processing [9,14].From this study, it can be said that starvation-induced stress causes not only physical changes, but it can as well affect behavioral, neurochemical and morphological processes. Rodents exposed to starvation-induced stress protocol show negative effects, such as memory deficits and adverse responses on central nervous system functions. Starvation depletes important biomolecules necessary for normal nervous system functions. At initial stage of feed deprivation, slight enhancement of cognitive function may be due to a compensatory response maintained by nutrients from an organism's energy reservoir. This compensatory response may be effective, but its effectiveness is only transient and may be quickly altered if feed deprivation continues. The underlying mechanism by which memory is progressively habituated after approximately 12 hours after feed ingestion may be due to the depletion of energy currency; adenosine triphosphate (ATP) [15], as a result of prolonged physical activity in search of feed which requires muscular contraction and burn-out of energy stores. The uptake and recycling of the excitatory neurotransmitter, acetylcholine, is an active process which requires energy. Acetylcholine is the predominant neurotransmitter at the region of the forebrain [15,16]. It mediates sensory information and involved in memory facilitation. This neurotransmitter is believed to be deficient in diseases like Alzheimer's and is also implicated in senile dementia or age-related forgetfulness. Neuromuscular strength showed a decline directly proportional to the extent of feed deprivation. The strength and endurance of muscles depends on the nutritional status of an organism. The level of electrolytes like calcium and magnesium, as reported in this study, may have influenced the cognitive function of the rodents. Calcium and magnesium are essential electrolytes needed by the brain especially at the telencephalic region called the hippocampus [16] [17]. The N-methyl-D-aspartate (NMDA) receptor is present within the hippocampus and is involved in long term potentiation (LTP) of memory [17]. Magnesium iron is dislodged by depolarization caused by sodium to allow for influx of calcium and subsequent activation of an intracellular enzyme cascade that ultimately leads to the formation of nitric oxide (NO) [18]. With low level of calcium, memory formation will be impaired or severely defective. This may affect the activation of nitric oxide synthase enzyme and synthesis of nitric oxide [18]. Nitric oxide, within the hippocampus, is a retrograde neurotransmitter. In some studies, the level of nitric oxide is used to reflect nitrosative stress, but this may not always be the case especially in the central nervous system where the level of this neurotransmitter is inversely related to habituation and subsequent long term depression (LTD) of memory.The progressive decrease in brain stress enzyme markers superoxide dismutase (SOD) and catalase (CAT) is clinical evidence that the generation of reactive oxygen species (ROS) increases in the brain during starvation. These antioxidant enzymes may have been overwhelmed by the free radicals as feed deprivation was prolonged. The initial increase in SOD after 6 hours feed deprivation may be a compensatory response because as the duration of feed deprivation was increased, there was a progressive decrease in this enzyme as seen after 12 hours to 24 hours.

5. CONCLUSION

The outcome of this study revealed that starvation-induced stress may negatively affect memory facilitation and psychosomatic

responses but may increase the tendency for habituation of sensory stimuli. The negative impact of this stress is dependent on the duration of exposure. In addition, alterations in brain stress markers may provide scientific explanations.

CONSENT

It is not applicable.

ETHICAL CONSIDERATION

All experimental procedures were in correspondence to the guidelines by the Ethics Committeeon Animal Use (CEUA) IF Goiano, GO, Brazil (protocol n.003/2012).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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