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Research Article

Acute Intermittent Hypoxia Therapy alters Cognitive Behavioral Parameters in Wistar Albino Rats

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ABSTRACT

Cognitive disorders, including dementia and Alzheimer's disease, pose substantial global health challenges, demanding effective prevention and treatment strategies. Intermittent hypoxia therapy (IHT), involving brief exposures to reduced oxygen levels, is a novel approach with potential cognitive benefits. This study investigates the effects of IHT on cognitive behavior in wistar albino rats through comprehensive behavioral experiments, including the open field test (OFT) and Morris water maze (MWM). The results reveal that IHT promotes locomotor activity, reduces anxiety-related behaviors, and positively impacts cognitive flexibility. In the OFT, the IH group exhibited increased grid crossings and distance traveled, indicating heightened locomotion, which may be associated with cognitive improvement. Furthermore, IH significantly reduced thigmotaxis behavior and the number of fecal boli, indicating reduced anxiety levels compared to the control group. While IHT did not significantly enhance spatial memory acquisition in the MWM, it improved platform recognition during the probe test. The IH group spent more time in the target quadrant, suggesting enhanced memory retrieval and recognition. Additionally, in the reverse MWM, IH demonstrated moderate improvements in cognitive flexibility, with faster latency on trial 1. These findings suggest that IHT holds promise as a non-invasive intervention for cognitive enhancement, particularly in terms of locomotor activity, anxiety reduction, and certain aspects of memory and cognitive flexibility. Further research is warranted to elucidate the underlying mechanisms and explore the potential therapeutic applications of IHT in cognitive disorders. In summary, this study highlights the cognitive benefits of IHT in rats, paving the way for future investigations and potential clinical applications in the realm of cognitive disorders.

INTRODUCTION

Cognition, the complex process of acquiring, processing, and utilizing knowledge, is at the core of human behavior, distinguishing us from other species and driving our progress.[1] However, cognitive disorders like dementia and Alzheimer's disease pose significant global health challenges, affecting millions,[2,3] leading to profound cognitive impairment and diminished quality of life.[4] Understanding the fundamental mechanisms of these disorders is crucial for effective prevention and treatment. Lifestyle factors such as exercise, social engagement, and mental stimulation have been identified as potential ways to reduce cognitive decline.[5]

Intermittent hypoxia therapy (IHT), involving brief exposure to reduced oxygen levels, presents an innovative approach akin to the benefits of physical exercise.[6] Effective IHT protocols depend on factors like the severity and duration of hypoxia exposure, with modest and acute

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exposures showing potential benefits.[7] Severe hypoxia can lead to cellular damage and an increased risk of neurodegenerative disorders.[8] In contrast, IHT triggers adaptive mechanisms, promoting neuroplasticity and potentially enhancing brain function.[9, 10]

To explore IHT's potential in promoting cognition, this study examines cognitive parameters in wistar albino rats using behavioral experiments such as the open field test (OFT) and Morris water maze (MWM).[11,12] These tests provide comprehensive insights into various cognitive facets and are valuable for preclinical research on cognitive function and therapeutic interventions.

IHT offers a non-invasive, non-pharmacological approach to enhancing cognitive function, particularly in conditions like Alzheimer's disease and dementia, without traditional medication side effects. Its translational potential from animal models to clinical settings holds promise for accessible and personalized treatment regimens, reducing healthcare burdens and aligning with patient-centered care principles. Additionally, IHT's affordability and wider accessibility make it a promising pharmaceutical option to address the pressing needs of patients in the current healthcare landscape.

Materials and Methods

Animal Procurement

Wistar albino rats aged 3 to 6 months were procured from the National Institute of Nutrition (NIN), Hyderabad, and maintained in an independent animal housing facility at Bharathidasan University. Animals were housed three per cage and allowed ad-libitum food and water consumption. The room temperature was maintained at 25°C with a 12-hour light-dark cycle. After 2 weeks of habituation, the animals were subjected to experiments. Animals were grouped into control and IHT groups (N = 6). All the experiments carried out adhered to the guidelines and approval of the Institutional Animal Ethics Committee (BDU/IAEC/P02/2018).

Custom-made Hypoxic Chamber

The IHT treatment requires a hypoxia chamber to effectively create an intermittent hypoxic condition. Since no commercial model was available on the Indian market, a custom-designed hypoxic chamber was developed in the lab. A glass chamber with an airtight acrylic top lid was made (Fig. 1). Holes were made on the acrylic top lid to allow piping for the nitrogen gas inlet and outlet. An oxygen sensor is placed inside the chamber to monitor the oxygen level. Through the gas inlet, nitrogen gas is passed to replace the air content inside the chamber. The replacement of air with nitrogen leads to a reduction in oxygen concentration. This procedure is carried out until the final concentration is dropped to 12% oxygen, which is sufficient to induce intermittent hypoxia for over 2 hours.

Fig. 1: Hypoxia chamber model

The image on the left shows the full setup of the hypoxic chamber with the glass chamber and the nitrogen gas cylinder. The image on the right shows the oxygen sensor showing the concentration of oxygen within the chamber.

Intermittent Hypoxia Treatment

Animals assigned to the IH group were exposed to intermittent hypoxia conditions (10–12% oxygen) as per the previously mentioned experimental procedure [13] for 4 hours per day for 14 consecutive days. Animals were monitored for their behavior during the course of this treatment procedure. Post-exposure, both groups were assessed using a set of behavioral experiments.

Open Field Test

To assess locomotion and exploratory behaviors in the experimental rats, OFT was employed. The OFT platform, measuring 140 x 140 cm, was divided into sixteen grids consisting of 35 x 35 cm squares (Fig. 2 A).[14] At the start of each session, the rat was introduced to the central square. The rats were then given 5 minutes to explore the open field before being returned to their home cage. Over 3 days, behavioral parameters such as the total number of grid crossings, total distance traveled, and the display of thigmotaxis by the rats were measured during 3–5 trials per day. These parameters served as indicators of locomotor activity, exploratory behavior, and anxiety levels. The open field sessions were recorded using the computerized video-assisted tracking software SMART 3.0 module (Pan Lab, Harvard Apparatus, Spain) to accurately capture the uninterrupted movement of the animals within the arena.

Morris Water Maze

MWM is a behavioral task utilized in animal studies to evaluate spatial learning, memory formation, and memory retention. In this experiment, the experimental rat was released into a water pool measuring 150 cm in diameter and 50 cm in depth from four different directions. The pool was equipped with spatial cues and appropriate lighting conditions in the room (Fig. 3 A).[14] The rat was trained to navigate and locate an escape platform within the water maze. During the learning phase, the rat underwent four trials per day, each lasting 60 seconds with 30 minutes intervals between trials. The time taken to find the hidden platform (latency) was measured for each trial. The learning phase spanned 14 days. Following the completion of the 14-day learning phase, a probe trial was conducted wherein the escape platform was removed from the pool. The time spent by the rat in the zone previously occupied by the platform was measured using computer-assisted standard tracking software to assess memory function capacity. Additionally, a reverse maze test was performed to evaluate the memory retention function. In this test, the platform was reintroduced into a different quadrant, and a similar protocol of four trials per day was conducted for an additional three days.

Statistical Analysis

The data is presented as mean ± standard deviation (SD). Single comparisons were assessed using the Student t-test, while multiple comparisons were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test.[15] A significance level of $p < 0.05$ was considered statistically significant unless stated otherwise.

Results

IH Promotes Locomotory Behavior in OFT

During OFT, the IH group exhibited an increased number of grids crossed in comparison with the control group (Fig. 2 D). This also correlated with the data that the IH group compared to the control group exhibited the most distance traveled (Fig. 2 E). This significant improvement in grids crossed and distance traveled projects an improvement in locomotory behavior, which has always accentuated cognitive outcomes.

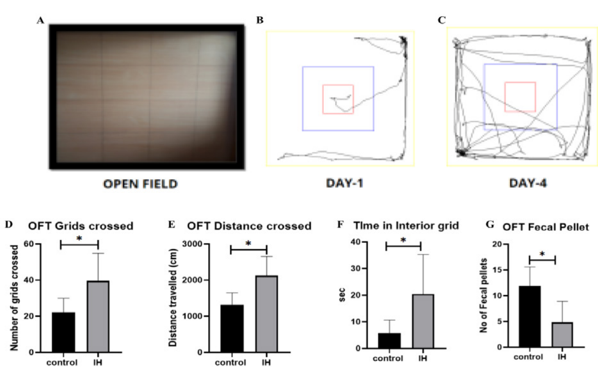

Fig. 2: Open field test experiment arena

(A) Left side image shows the aerial view of the open field. B)The images in the middle and C) on the right show the tracking pattern exhibiting the animal movement. Compared to day-1 during day-4 the animal exhibited more exploratory behavior because of their frequent visit to the grids at the center of the open field. The yellow square represents the outer zone of the test arena, while the blue square represents the inside zone. Results of an open field test lasting five minutes with three trials each day for three additional days, D) shows the number grid crossed and E) shows how far the field has been traversed in centimeters. F) shows time spent on the interior, while G) shows no of fecal pellets produced.

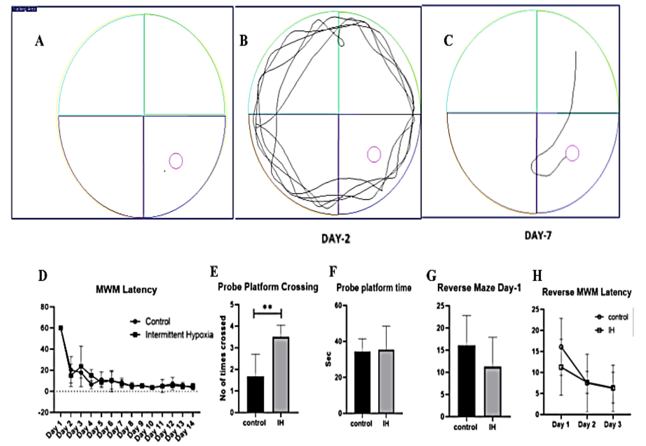

Fig. 3: Morris water maze experiment arena

A) shows the mapping of the watermaze tank in the software. The image on the right shows the path taken by the animal to reach the platform during day 2 (B) and day 7 (C). (D) The mean escape latency on the average of the four trials of each session was taken as a measure of Spatial memory. E) Number of times the animal crossed the platform zone during the MWM probe test. F) Time spent in the target quadrant zone during the MWM Probe test. (G) The mean escape latency on day 1 of rMWM. (H) The mean escape latency on the average of the four trials of each session was taken as a measure of working memory.

IH Reduces Anxiety and its Associated Behaviors in OFT

Rodents typically display thigmotaxis behavior when introduced to a new environment, which is often associated with anxiety. The absence of thigmotaxic behavior allows rodents to explore the central areas of an unfamiliar setting. In the OFT, the IH group demonstrated a higher duration spent in the central grids compared to the control group (Fig. 2 F). An increase in the number of fecal boli can serve as an indicator of heightened anxiety and emotional response in the subject animal. In this study, IH animals exhibited a lower number of fecal boli compared to the control group (Fig. 2 G). Consequently, it can be inferred that IH animals displayed reduced anxiety levels in comparison to the control group.

IH did not Improve the Learning Curve in the MWM

MWM was used to evaluate how IH affected spatial memory. Over 12 days, both groups exhibited learning curves in the water maze experiment. The IH group outperformed the control group on day 2, but over the following days, performance varied, so there was no discernible difference between the groups in latency to find the platform (Fig. 3 D). Similarly, no major difference in distance traveled or speed was observed between the groups.

IH Improved Platform Recognition in the MWM probe test

The IH group spent more time in the target quadrant and made a significant number of crosses in the platform region during the probe test that was conducted on the 13th day (Fig. 3, E, F).

IH Moderately Improved Learning and Memory Parameters in Reverse MWM

In the reverse maze experiment conducted on days 14 through 16, the IH group showed trends of improved cognition, with faster latency on trial 1, but failed to outpace the control groups on consecutive trials (Figs. 3G, H). Thus, the results of experiments in MWM infer that IH has great potential for improving spatial memory.

Discussion

This study aimed to investigate the impact of IHT on various cognitive and behavioral parameters in Wistar albino rats. We employed the OFT and MWM experiments to evaluate these effects. The findings offer a nuanced perspective on how IHT influences cognitive behavior, locomotion, anxiety levels, and spatial memory in these rats.

Enhancement of Locomotory Behavior and Cognitive Function

A notable discovery in this study is the significant enhancement of locomotor activity observed in the IH group during the OFT. Rats subjected to IHT displayed increased grid crossings and covered greater distances when compared to the control group. This heightened locomotion is intriguing, as it may have implications for cognitive outcomes. It is well-documented that heightened locomotor activity is associated with improved neural and motor functions, potentially contributing to enhanced cognitive performance.[16] The correlation between increased locomotion and cognitive improvement implies a complex mechanistic relationship. It is plausible that heightened activity in the IH group triggered the release of neurotrophic factors, potentially influencing cognitive function positively, as demonstrated in prior research. Tsai *et al*.,[13] for example, showcased that post-ischemia intermittent hypoxia (IH) intervention promotes the growth of hippocampal neurons. Increased synaptogenesis, primarily regulated by brain-derived neurotrophic factor (BDNF)/PI3K/AKT, emerged as a mediator of the effects of IH intervention in cultured neurons. This connection underscores the intricate interplay between locomotion, neural activation, neurotrophic factor release, and cognitive function.

Anxiety Reduction

Another significant observation pertains to the reduction in anxiety-related behaviors within the IH group during the OFT. Thigmotaxis behavior, typically associated with anxiety, diminished in the IH group, suggesting reduced anxiety levels and a greater propensity to explore the central, open areas of the testing environment. Moreover, the IH group exhibited fewer instances of fecal boli, a common stress response in rodents. Collectively, these findings suggest that IHT exerts an anxiolytic effect, reducing anxiety and emotional responses.

The mechanisms underlying the anxiolytic effects of IHT are multifaceted. First, IHT is known to modulate the activity of the hypothalamic-pituitary-adrenal (HPA) axis, a central component of the stress response. Exposure to IH may downregulate the HPA axis, leading to reduced cortisol release in response to stress. Previous research in rats has shown that IH sensitizes acute HPA and noradrenergic stress responses.[17] Lower cortisol levels are linked to decreased anxiety and a more relaxed emotional state.[18] Furthermore, IH-induced alterations in neurotransmitter systems, such as increased serotonin release, can contribute to a reduction in anxiety-like behaviors. Serotonin plays a pivotal role in mood regulation and emotional stability.[19] Therefore, the observed decrease in thigmotaxis behavior and fecal boli in the IH group may be mechanistically linked to changes in the HPA axis, heightened neurotrophic factor expression, and modulation of neurotransmitter systems. Collectively, these mechanisms result in reduced anxiety and emotionality compared to the control group.

Spatial Memory Acquisition and Recognition

Our investigation also extended to the effects of IHT on spatial memory using the MWM. While the IH group did not demonstrate significant improvements in the learning curve of spatial memory acquisition, a notable advantage emerged on day 2, although it was not sustained in subsequent days. This initial advantage may be attributed to IHT's capacity to enhance cerebral blood flow and oxygen delivery to the brain, temporarily bolstering cognitive function and facilitating quicker learning during the early phase of the task.

However, IHT exhibited positive effects on platform recognition during the MWM probe test. On the 13th day, the IH group spent more time in the target quadrant and made more crosses in the platform region when compared to the control group. This implies that IHT improved the ability to recognize and remember the platform's location. These effects might be attributed to the potential neuroplasticity-promoting effects of IHT, including enhanced blood flow, neurogenesis, and synaptic plasticity. These factors could have contributed to the animals' enhanced platform recognition ability.[20, 21]

In the reverse MWM, designed to assess cognitive flexibility, the IH group showed moderate improvements in learning and memory parameters. The IH group displayed faster latency on trial 1, indicating superior initial learning and adaptability to the altered platform location. This suggests that IHT has the potential to enhance cognitive flexibility, enabling animals to adjust to new information and tasks more efficiently.

Implications and Future Directions

In conclusion, the findings of this study offer valuable insights into the potential of IHT to enhance cognitive and behavioral parameters. The observed effects on locomotion, anxiety reduction, and certain aspects of spatial memory suggest that IHT could be a valuable treatment option for cognitive disorders. However, the study has some limitations, including the necessity for long-term follow-up studies to assess sustained effects on cognition and exploration of the effects in neurodegenerative models to make cognitive improvements more distinctive and observable.

Future research should prioritize the assessment of how IHT improves cognition in conditions such as dementia, Alzheimer's disease, Parkinson's disease, and vascular dementia, bridging the gap from animal models to clinical settings. Investigating the potential therapeutic applications of IHT in human cognitive disorders, such as Alzheimer's disease, dementia, or age-related cognitive decline, is also paramount. Furthermore, future studies should delve into the underlying molecular and cellular mechanisms through which IHT affects cognitive behavior. This may involve studying changes in neurotrophic factors, neurotransmitter systems, synaptic plasticity, and neurogenesis in response to IHT.

In summary, this study on IHT and its effects on cognitive behavior in rats opens up new avenues for non-invasive interventions to improve cognition. The non-invasive nature of IHT makes it more accessible for clinical applications, potentially leading to innovative treatments for cognitive disorders. Further research in this area is warranted to uncover the full therapeutic potential of IHT and its precise mechanisms of action, ultimately benefiting individuals affected by cognitive disorders and advancing our understanding of cognitive enhancement strategies.

Author contributions

Conceptualization: SAR, AM; data acquisition: SAR, DG, SB, NP; analysis and interpretation of data: SAR, DG, SKJ, MK, AM; writing–original draft preparation: SAR; writing–review and editing: SAR, SKJ, MK, AM; critical revision of the manuscript for intellectual content: SKJ, MK, AM; supervision: AM

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