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Impact of B-Carotene on Cognitive and Behavioral Changes in Mice Subjected To Intermittent Fasting and Binge Eating

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Abstract

Eating Disorder (ED) treatment research continues to strive for a deeper comprehension of the mechanisms that drive the development and recovery of these challenging conditions. Intermittent Fasting (IF) and Binge Eating (BE) are increasingly popular, yet their neurobehavioral impacts are worrisome. The study examined whether β-Carotene (BC), renowned for its various health benefits, can alleviate anxiety-related behaviors linked to IF and BE in *Swiss Albino* mice. The study aims to assess the impact of β-carotene on neurobehavioral patterns, including stress, anxiety, and depression, in mice subjected to IF and BE sessions on alternative days. The experimental subjects were divided into Negative Control, Control, Standard, BC-I and BC-II. For study, stress was induced with IF and BE for 6 weeks of duration & on 6th week of study, treatment was scheduled and then neurobehavioral assessment were performed using the Open Field Test, Mirror Chamber Test and Elevated Plus Maze Test. β-Carotene was administered at doses of 10 mg/kg and 25 mg/kg, while Diazepam was given at 5 mg/kg of single dose on last day to respective groups intraperitoneally. Statistical analysis involved ANOVA followed by the Tukey-Kramer test. Mice exposed to IF and BE exhibited anxiety-like behaviors and decreased locomotor activity. The study indicated that β-Carotene had potential anxiolytic effects, reducing anxiety-related behaviors induced by IF and BE. Future studies should explore the molecular mechanisms by which β-Carotene modulates neurobehavioral changes in IF and BE models, focusing on neurotransmitter systems and oxidative stress pathways.

Keywords: Intermittent Fasting, Binge Eating, β-Carotene, Neurobehavioral Effects, Anxiety-like Behaviors, Swiss Albino Mice.

Introduction

In recent years, the role of dietary components and their impact on cognitive function and behavior has gained substantial interest in the field of neuroscience. Research on Eating Disorder (ED) treatment aims to better understand the mechanisms behind their development and recovery. EDs impact millions globally, resulting in substantial physical and psychological distress. Individuals suffering from EDs frequently experience symptoms of depression and anxiety.[1] Intermittent Fasting (IF) improves detoxification, energy levels, inner peace, addressing unnoticed metabolic issues in modern sedentary lifestyles.[2] IF surged in popularity due to its effectiveness in promoting weight loss, increasing energy, enhancing mental clarity, and potentially extending lifespan.[3] The strong link between the brain and the gut underscored how diet significantly affected mental health. Remarkably, about 95% of serotonin, a crucial neurotransmitter for mood regulation, was produced in the gut.[4] IF methods like time-restricted eating, modified-calorie fasting, and alternate-day eating offer adaptable options for different lifestyles.[5] Some studies found that IF caused anxiety, depression-like behaviors, memory impairment, and increased cortical spreading depression in rodents.[6] Binge Eating Disorder (BED) prompted new cognitive-behavioral frameworks; studies showed calorie limits and diet affect mental health management.[7] Recent studies suggested that BE could trigger anxiety-like behaviors in mice. Research that utilized a High-Fat diet (HFD) to induce BE observed notable behavioral changes, including heightened anxiety levels.[8] β-Carotene (BC), abundant in fruits and vegetables like carrots, sweet potatoes, spinach, offers significant health benefits, including antioxidant, CNS support, lipid-lowering, anti-inflammatory, anti-diabetic, reduced risks of CVD, cancer, and age-related disorders. It aids stress adaptation, neuroprotection, and overall mental health by reducing oxidative stress, brain edema, and reactive oxygen species from brain injuries.[9] This study aims to assess the impact of β-carotene on neurobehavioral patterns, including stress, anxiety, and depression, in mice subjected to IF and BE.[10]

Materials and Methods

Animals

Six to eight-week-old *Swiss Albino* mice housed with free access to food and water at room temperature (22°C ± 2°C) with a relative humidity of 45-55%, on a 12-hour light/dark cycle in a pathogen-free environment. All experimental/ research procedures and protocols employed in the research were approved by the Institutional Animal Ethics Committee (IAEC) at IPS Academy College of Pharmacy, Indore, adhering to the guidelines set forth by the CCSEA, Ministry of Environment and Forest, Government of India. Ethical standards were strictly upheld throughout the experiment.

Drugs and Chemicals

β-carotene was procured from Neelhans Herbs & Bioscience, Indore, Madhya Pradesh (India).

Marketed Preparation of Diazepam Tablets I.P. were used and other chemicals was procured from IPS Academy College of Pharmacy Indore.

Experimental Design

The animals were divided into Nine groups (n=6 animal in each group) which were Negative Control group, Control group, Standard group, BC-I and BC-II. Each group were further divided into IF and BE subgroups. The Negative Control group animals were not subjected

to stress or treatment. For the study, stress was induced with IF and BE for the duration of 6 weeks & on 6th week of study there was treatment schedule as followed given below.

Negative Control: No stress or treatment, normal feed.

Control IF & Control BE: Received vehicle (0.1% Sodium CMC, i.p.).

Standard IF & Standard BE: Received single dose of Diazepam (5 mg/kg, i.p.) on last day of 6th week 30 mins prior to evaluation of neurobehavioral parameters.

BC-I (IF) & BC-I (BE): Received β-Carotene (10 mg/kg, i.p.).

BC-II (IF) & BC-II (BE): Received β-Carotene (25 mg/kg, i.p.).

Intermittent Fasting and Binge Eating in Swiss Albino Mice

In the IF study, mice followed Every Other Day Fasting (EOD) schedule, involving alternating 24-hour periods of food access and deprivation, while maintaining free access to water for six weeks. Food was given at 9 a.m. and removed at the same time the next day.[11] In the period of BE, mice were provided with a regular diet in their cages, and they were exposed to BE provide standard diet every other day for a period of six weeks.[12] The BE diet comprised a High Fat Diet (HFD) containing 20 grams of fat per 100 grams of diet, consisting of 19 grams of coconut oil and 1 gram of soybean oil, along with 10% sucrose dissolved in tap water.[13]

Physical and Biochemical Estimation

Body Weight and Blood Sugar level

Body weight was monitored three times: at Baseline, Before dosing and After dosing.[14] Blood sugar levels were measured using a glucometer. Glucose levels were examined three times: Baseline, Before and After dosing on the particular feeding schedules.[15]

Evaluation of Neurobehavioral Parameter

Open Field Test

The open field test took place in a white wooden chamber measuring 50 cm in length, 50 cm in width, and 38 cm in height. The floor was divided into a 10x10 square grid with 4x4 grid lines, and an additional 20x20 cm square zone was designated at the center. Each mouse was placed individually at the center of the chamber, and its activity was monitored for 10 minutes. Different parameters, such as time spent in the central zone and corners, path length traveled, and instances of rearing up, were recorded for each mouse. These observations were recorded manually in a double-blind manner, with each recording being observed three times to reduce errors.[16]

Mirror Chamber Test

The mirror chamber, made of wood and measuring 40 x 40 x 30.5 cm, contained a 30 x 30 x 30 cm mirror at its center. Placing the mirrored cube in the middle of the enclosure created a 5 cm corridor surrounding it. Animals were individually placed into the mirrored chambers, starting from a designated corner. Throughout the Five-minute experiment, the following parameters were monitored: (a) the time taken for the animals to enter the mirror chamber, (b) the frequency of entries into the mirror chamber, and (c) the total duration spent inside the mirror chamber.[17]

Elevated Plus Maze Test

The setup featured two open arms and two closed arms, the latter covered with wooden board to block light, all extending from a central platform. Elevated on a base, the arms sat 38.5 cm above the floor. Testing began by placing the mouse on the central platform, facing an open arm, and observing it for 5 minutes. The mouse

was deemed to be on the central platform when two paws were on it and inside an arm when all four paws were within it. Behavioral variables, including the number and duration of entries into open and closed arms, time spent in open and closed arms.[18]

Statistical Analysis

The results were expressed as Mean ± Standard Error of Mean (S.E.M.), and statistical evaluation was carried out using Ordinary One-Way Analysis of Variance (ANOVA), followed by the "Tukey-Kramer" multiple comparison test, with a significance level set at $p<0.05$. Statistical analysis was conducted using "Graph Pad Prism" version 10.0.3 for Windows, software developed by Graph Pad Software based in San Diego, California, USA (www.graphpad.com).

Result

Body Weight and Blood Sugar Level

The IF group led to a reduction in blood glucose levels which triggerred sensations of anxiety, restlessness and heightened stress responses. Therefore, anxiety-like behaviors in the IF group might have been influenced by decrease in body weight and blood glucose levels. There was no prominent effect of β-Carotene on body weight and blood sugar levels at after dosing. Values remained consistent at before dosing and after dosing, with minimal variations in body weight and blood sugar level in IF groups (Table 1&2).

Conversely, in the BE group, there was an increase in body weight, a common consequence of BE. Excessive calorie intake during binge eating episodes led to obesity, which is associated with anxiety and depression. Furthermore, BE resulted in elevated blood glucose levels, which also had contributed to anxiety-like responses. The values remained stable, with only minor variations in body weight and blood sugar levels observed in the BE groups throughout the study (Table 1&2).

Table 1: Comparison of Body Weight before and after treatment with β-Carotene (10, 25 mg/kg)

Group	Drug Treatment	Dose	Baseline	Before Dosing (6^{th} Week)	After Dosing(7^{th} Week)
Negative Control	-	-	27 ± 0.9	26 ± 0.8	26.7 ± 0.3
Control IF	Sodium CMC	0.5 ml of 0.1% w/v /i.p.	26.4 ± 0.3	25 ± 0.4	24.34 ± 0.3
Control BE			27 ± 0.4	27.7 ± 0.4	27.33 ± 0.5
BC-I (IF)	β-Carotene	10 mg/kg/i.p.	27 ± 0.4	25.6 ± 0.5	24.7 ± 0.6
BC-I (BE)			27 ± 0.4	28 ± 0.4	27.36 ± 0.5
BC-II (IF)	β-Carotene	25 mg/kg/i.p.	26.7 ± 0.5	25.7 ± 0.4	24.7 ± 0.4
BC-II (BE)			26 ± 0.3	27 ± 0.4	27.84 ± 0.4
Standard IF	Diazepam	5 mg/kg/i.p.	26.7 ± 0.4	25.4 ± 0.5	24.4 ± 0.5
Standard BE			25.4 ± 0.4	26.7 ± 0.5	27 ± 0.4

Intermittent Fasting (IF), Binge Eating (BE), β-Carotene (BC) Values were expressed in Mean ± SEM, (n=6); Data were analyzed using one-way ANOVA followed by Tukey-Kramer Multiple Comparison Test, where values were found non-significant.

Table 2: Comparison of Blood Glucose level before and after treatment with β-Carotene (10, 25 mg/kg)

Group	Drug Treatment	Dose	Baseline	Before Dosing (6th Week)	After Dosing (7th Week)
Negative Control	-	-	109.4 ± 0.4	110 ± 1	112.7 ± 1.5
Control IF	Sodium CMC	0.5 ml of 0.1% w/v /i.p.	110.7 ± 0.4	107.7 ± 1.5	106.7 ± 0.5
Control BE			112.7 ± 1.1	128.3 ± 1.9	130.3 ± 0.5
BC-I (IF)	β-Carotene	10 mg/kg/i.p.	112 ± 0.7	114 ± 0.7	112.3 ± 0.9
BC-I (BE)			113.3 ± 1.8	128 ± 3.4	126 ± 2.9
BC-II (IF)	β-Carotene	25 mg/kg/i.p.	116.7 ± 1.5	116.7 ± 0.4	114.3 ± 0.8
BC-II (BE)			110 ± 1.9	129 ± 3.5	125.7 ± 2.9
Standard IF	Diazepam	5 mg/kg/i.p.	113.3 ± 1.5	111.7 ± 1.4	110.3 ± 1.6
Standard BE			114.7 ± 1.1	132.3 ± 1	134.3 ± 1.5

Intermittent Fasting (IF), Binge Eating (BE), β-Carotene (BC) Values were expressed in Mean ± SEM, (n=6); Data were analyzed using one-way ANOVA followed by Tukey-Kramer Multiple Comparison Test, where values were found non-significant.

Open Field Test

In the IF group, mice given β-Carotene spent more time in the central zone of open field, which indicated reduced anxiety and increased confidence in exploring exposed areas. This behavior suggested that β-Carotene enhanced exploratory behavior and reduced anxiety-like responses during IF (Fig.1.a). Similarly, in the BE group, β-Carotene positively influenced exploratory behavior. The mice showed increased path length, spent less time in corner squares, and spent more time in central zone. These consistent results suggested that β-Carotene had anxiolytic properties, promoting and reducing anxiety-like behaviors across different eating patterns (Fig.1.b).

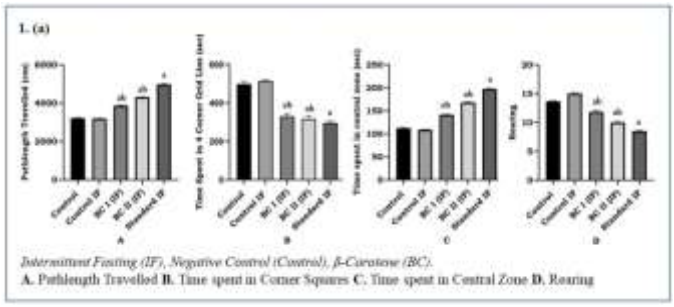

Fig. 1(a): Exploratory behavior of mice on Intermittent Fasting using Open Field Test

Values are expressed in Mean ± SEM, (n=6); Data were analyzed using one-way ANOVA followed by Tukey-Kramer Multiple Comparison Test, where $p^a<0.05$ when compared with Control IF, $p^b<0.05$ when compared with Standard IF.

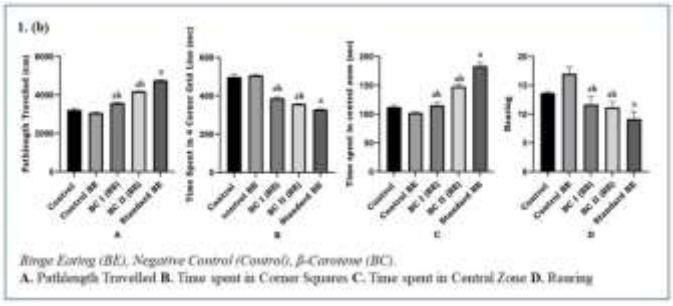

Fig. 1(b): Exploratory behavior of mice on Binge Eating using Open Field Test

Values are expressed in Mean ± SEM, (n=6); Data were analyzed using one-way ANOVA followed by Tukey-Kramer Multiple Comparison Test, where $p^a<0.05$ when compared with Control BE, $p^b<0.05$ when compared with Standard BE.

Mirror Chamber Test

The parameters across the different groups demonstrated significant impacts of Diazepam and β-Carotene on metrics such as Latency to Enter the Mirror Chamber, Number of Entries in the Mirror Chamber, and Time Spent in the Mirror Chamber.

In the IF group, mice received β-Carotene showed increased Latency to Enter the Mirror Chamber, Number of Entries in the Mirror Chamber, and the Total Duration spent inside the Mirror Chamber reduced anxiety-like responses during IF which was notable compared to the Control and Standard groups (Table 3.a).

Similarly, in the BE group β-Carotene significantly enhanced the latency to enter the mirror chamber, the number of entries, and the total time spent inside the mirror chamber which showed reduced anxiety like behavior in mice (Table 3.b).

Table 3 (a): Anxiolytic effect of β-Carotene on Intermittent Fasted mice using mirror chamber apparatus

Groups	Drug Treatment	Dose	Latency to enter in mirror chamber (sec)	No. of entries in mirror chamber	Time spent in mirror chamber (sec)
Control	-	-	48.4 ± 2.9	4.6 ± 0.1	24.7 ± 0.6
Control IF	Sodium CMC	0.5 ml of 0.1% w/v/i.p.	52.7 ± 0.7	3.8 ± 0.1	22.8 ± 0.6
BC-I (IF)	β-Carotene	10 mg/kg/i.p.	41.0 ± 1.4^{ab}	5.8 ± 0.2^{ab}	33 ± 0.5^{ab}
BC-II (IF)	β-Carotene	25 mg/kg/i.p.	38.7 ± 1.4^{ab}	6.6 ± 0.3^{ab}	39 ± 0.2^{ab}
Standard IF	Diazepam	5 mg/kg/i.p.	31.5 ±0.7^{a}	8.1 ± 0.1^{a}	50.2 ± 0.3^{a}

Intermittent Fasting (IF), Negative Control (Control), β-Carotene (BC)

Values are expressed in Mean ± SEM, (n=6); Data were analyzed using one-way ANOVA followed by Tukey-Kramer Multiple Comparison Test, where $p^a<0.05$ when compared with Control IF, $p^b<0.05$ when compared with Standard IF.

Table 3 (b): Anxiolytic effect of β-Carotene on Binge Eating mice using mirror chamber apparatus

Groups	Drug Treatment	Dose	Latency to enter in mirror chamber (sec)	No. of entries in mirror chamber	Time spent in mirror chamber (sec)
Control	-	-	48.4 ± 2.9	4.6 ± 0.1	24.7 ± 0.6
Control BE	Sodium CMC	0.5 ml of 0.1% w/v /i.p.	52.8 ± 0.7	3.4 ± 0.1	23.8 ± 0.4
BC-I (BE)	β-Carotene	10 mg/kg/i.p.	41.9 ± 1.5^{ab}	5.8 ± 0.1^{ab}	33.8 ± 0.1^{ab}
BC-II (BE)	β-Carotene	25 mg/kg/i.p.	41.7 ± 1.0^{ab}	7.0 ± 0.3^{ab}	39.5 ± 0.3^{ab}
Standard BE	Diazepam	5 mg/kg/i.p.	34.0 ± 1.2^{a}	9.5 ± 0.4^{a}	48.7 ± 0.6^{a}

Binge Eating (BE), Negative Control (Control), β-Carotene (BC) Values are expressed in Mean ± SEM, (n=6); Data were analyzed using one-way ANOVA

followed by Tukey-Kramer Multiple Comparison Test, where $p^a<0.05$ when compared with Control BE, $p^b<0.05$ when compared with Standard BE.

Elevated Plus Maze Test

In the elevated plus maze test, the introduction of β-Carotene to mice undergoing IF led to significant behavioral changes. Specifically, β-Carotene decreased the number of entries into the closed arm and increased entries into the open arm, indicating reduced anxiety-like behavior. Additionally, mice in the β-Carotene group spent more time in the open arm. In contrast, the control IF group exhibited heightened anxiety-like behaviors, characterized by more time spent in the closed arm and fewer entries into the open arm. The standard group, which received Diazepam, showed the least anxiety-like behaviors, preferring the open arm and spending less time in the closed arm (Fig.2.a). Similar trends were observed in the BE group. β-Carotene reduced anxiety-like behaviors by decreasing the number of entries into the closed arm and increasing entries into the open arm. These mice also spent more time in the open arm. Conversely, the control BE group showed increased anxiety-like behaviors, with more time spent in the closed arm and fewer entries into the open arm. The standard group treated with Diazepam exhibited the least anxiety-like behaviors (Fig.2.b).

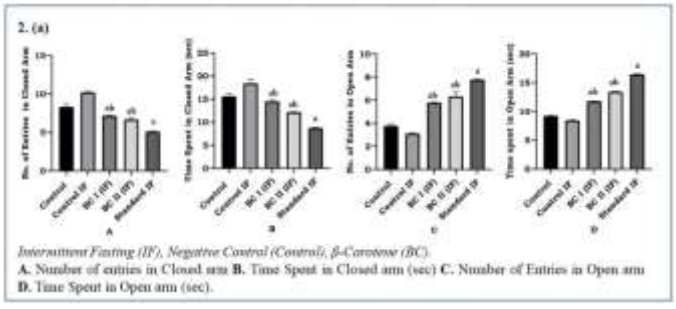

Fig. 2(a): Anti- anxiety effect of β-Carotene on Intermittent Fasted mice using Elevated Plus Maze Test

Values are expressed in Mean ± SEM, (n=6); Data were analyzed using one-way ANOVA followed by Tukey-Kramer Multiple Comparison Test, where $p^a<0.05$ when compared with Control IF, $p^b<0.05$ when compared with Standard IF.

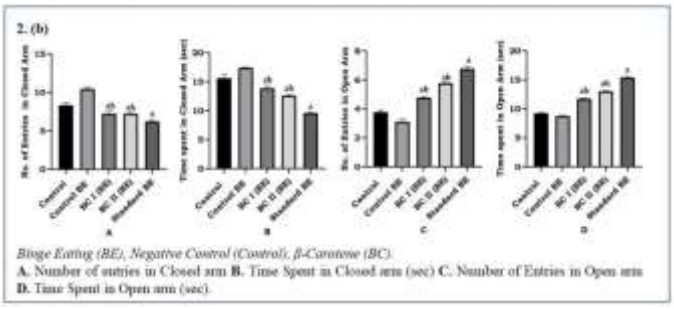

Fig. 2(b): Anti- anxiety effect of β-Carotene on Binge Eating mice using Elevated Plus Maze Test

Values are expressed in Mean ± SEM, (n=6); Data were analyzed using one-way ANOVA followed by Tukey-Kramer Multiple Comparison Test, where $p^a<0.05$ when compared with Control BE, $p^b<0.05$ when compared with Standard BE.

Discussion

The research focused on understanding the neurobehavioral impacts of IF and BE in *Swiss Albino* mice, with a particular emphasis on anxiety and depression-like behaviors.[19] To assess these effects, β-Carotene, a natural compound known for its antioxidant, antidepressant, anti-diabetic, and anticancer properties, was compared to diazepam, a well-established anxiolytic drug. This comparison aimed to evaluate the efficacy of β-Carotene as an alternative treatment.[10,20,21] Behavioral assessments were conducted using several established tests, including the Open Field Test, Mirror Chamber Test, and Elevated Plus Maze. These tests were chosen to measure various aspects of anxiety behavior in mice. The results demonstrated that β-Carotene effectively mitigated anxiety-like behaviors in mice. Mice subjected to IF and BE conditions showed enhanced exploratory

behavior when treated with β-Carotene, indicating its potential as an anxiolytic agent. In addition to behavioral analysis, the study also explored the physiological effects associated with IF and BE dietary patterns. It was observed that IF led to a significant reduction in body weight and blood glucose levels. These physiological changes were potentially linked to a decrease in anxiety, suggesting that IF could have beneficial effects on both physical and mental health. Conversely, BE resulted in increased body weight and elevated blood glucose levels, highlighting the negative impact of this dietary pattern on the mice.[22] The study proposed β-carotene as a natural alternative to diazepam for anxiety management and enhancement of exploratory behaviors, particularly in the context of IF and BE. Unlike diazepam, β-carotene exhibited fewer side effects and no dependency risk, offering a safer, more sustainable option. The research underscored the impact of dietary patterns on neurobehavioral health, showing that β-carotene reduced anxiety behavior. Additionally, IF was linked to health benefits such as decreased body weight and blood glucose levels. These findings advocate for dietary interventions and natural compounds as comprehensive strategies for improving mental health.[23]

Conclusion

β-Carotene exhibited anxiety-reducing effects in mice undergoing IF and BE, improving exploration and diminishing anxiety-like behaviors. Fluctuations in body weight and blood glucose levels were associated with anxiety responses, suggesting a connection between metabolic changes and behavioral outcomes in dietary stress scenarios.

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