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Effect of the hypothalamic serotonin on body weight change in the context of brain insulin resistance in Alzheimer's disease

Ebru Afşar[1*]

[1]Department of Biochemistry, Faculty of Dentistry, Kapadokya University, Nevşehir, Türkiye

ABSTRACT

Aims: The present work was designed to evaluate how alterations in serotonin (5-hydroxytryptamine, 5-HT), 5-HT receptor subtype 2B (5-HT2BR), and neuropeptide Y (NPY) are associated with body weight regulation in a rat model of brain insulin resistance (B-IR) that mimics the early pathological features of Alzheimer's disease (AD).

Methods: B-IR was induced in rats through intracerebroventricular (i.c.v.) administration of amyloid-β_{1-42} oligomers at a dose of 2.5 nmol in a total volume of 10 µL. 5-HT concentrations were quantified in brainstem and hypothalamic samples, while hypothalamic levels of 5-HT2BR and NPY were determined using enzyme-linked immunosorbent assay (ELISA) methods. Body weight variation for each animal was defined as the difference between post-experimental and initial measurements. Group comparisons were conducted using the Mann–Whitney U test, and statistical significance was accepted at $p < 0.05$.

Results: Rats in the B-IR group showed a tendency toward increased 5-HT levels in brainstem tissue compared to the control group ($p > 0.05$), whereas hypothalamic 5-HT levels were significantly decreased in the B-IR group compared to controls ($p < 0.01$); body weight was significantly reduced in the B-IR group compared to the control group ($p<0.01$). In addition, rats in the B-IR group showed a downward trend in hypothalamic 5-HT2BR and NPY levels compared with the control group ($p > 0.05$ for both).

Conclusion: These findings suggest that decreased hypothalamic 5-HT levels in the B-IR group may be associated with the observed reduction in body weight. Additionally, the downward trends observed in 5-HT2BR and NPY levels may also be related to this change.

Keywords: Alzheimer's disease, serotonin, serotonin receptor, neuropeptide Y, brain insulin resistance

INTRODUCTION

Alzheimer's disease (AD) is a chronic disorder of the central nervous system in which abnormal protein aggregation disrupts neuronal integrity. The disease is characterized by the extracellular buildup of amyloid-β (Aβ) assemblies and the intracellular formation of tau-based fibrillary structures, processes that progressively impair synaptic communication and ultimately result in neuronal loss [1,2]. Evidence from recent research suggests that Aβ aggregation in the brain commences nearly two decades prior to the appearance of overt clinical manifestations, including impairments in cognition and memory [3]. In addition, emerging data indicate that metabolic disturbances, including central and peripheral insulin resistance, as well as alterations in body weight regulation, arise during the early phases of AD and contribute substantially to its progression and severity [4,5]. Therefore, brain insulin resistance (B-IR) models that reflect the early phase of AD are particularly important, especially for elucidating the molecular basis of body weight changes during this critical period [6,7]. However, many aspects of the mechanisms underlying body weight changes during the early phase of AD remain unresolved.

***Corresponding Author:** Ebru Afşar, ebru.afsar@kapadokya.edu.tr

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Body weight is regulated by a complex interplay of hormones and neural circuits that control calorie intake and appetite. Serotonin (5-hydroxytryptamine, 5-HT) is a critical molecule that functions as both a hormone and a neurotransmitter in the central and peripheral nervous systems. 5-HT is biosynthesized from L-tryptophan (Trp), an essential amino acid, through distinct pathways operating in the central nervous system and in peripheral tissues. Outside the brain, 5-HT synthesis is largely confined to enterochromaffin cells of the intestinal mucosa, whereas within the brain, it is primarily produced by serotonergic neurons of the brainstem raphe complex. Because 5-HT cannot cross the blood–brain barrier (BBB), these central and peripheral sources represent separate, independently regulated 5-HT systems [8].

5-HT modulates energy balance and feeding behavior by interacting with specific receptors expressed on orexigenic and anorexigenic neuronal populations in the arcuate nucleus (ARC) of the hypothalamus. Through this receptor-mediated signaling, 5-HT influences the production or suppression of key neuropeptides involved in appetite regulation [9]. To date, at least 14 5-HT receptor subtypes (including 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6, and 5-HT7) have been identified as mediators of the diverse physiological actions of 5-HT. However, research addressing the role of 5-HT in energy homeostasis and glucose metabolism has primarily focused on the 5-HT2 receptor family, which comprises three distinct subtypes: 5-HT2AR, 5-HT2BR, and 5-HT2CR [10]. Studies have shown that 5-HT increases neuropeptide Y (NPY) levels by binding to 5-HT2BR in the hypothalamus, leading to excessive eating (hyperphagia). On the other hand, serotonergic systems are impaired in AD. Studies highlight that Aβ-induced mitochondrial dysfunction suppresses 5-HT release, and decreased extracellular 5-HT levels are closely associated with the pathogenesis of AD [11]. Consequently, while the clinical features of AD continue to be cognitive and memory loss associated with neurodegeneration, evidence is accumulating that changes in metabolism and body weight play a significant role in AD [12]. Taken together, these findings suggest that alterations in the 5-HT/5-HT2BR pathway may represent a potential mechanistic link underlying early body weight changes in the AD. Therefore, in the present study, this hypothesis was investigated in a B-IR rat model reflecting the early stage of AD.

METHODS

All animal-related interventions were performed in accordance with the ethical framework established by the Animal Experiments Ethics Committee of the Akdeniz University Experimental Animals Application and Research Center (approval dated 06.05.2024, decision no. 2024/18).

Experiments were carried out using three-month-old male albino Wistar rats with body weights ranging from 200 to 300 g. The animals were housed in metal cages under standardized laboratory conditions, with ambient temperature maintained at approximately 23± °C, relative humidity around 50%, and a controlled 12-hour light/dark cycle. Throughout the study, rats had unrestricted access to standard pelleted feed and drinking water.

Study Design and Surgical Procedures

The rats were randomly divided into two experimental groups (n = 6 per group): a control group and a brain insulin resistance (B-IR) group. B-IR was induced by intracerebroventricular (i.c.v.) administration of $A\beta_{1-42}$ in

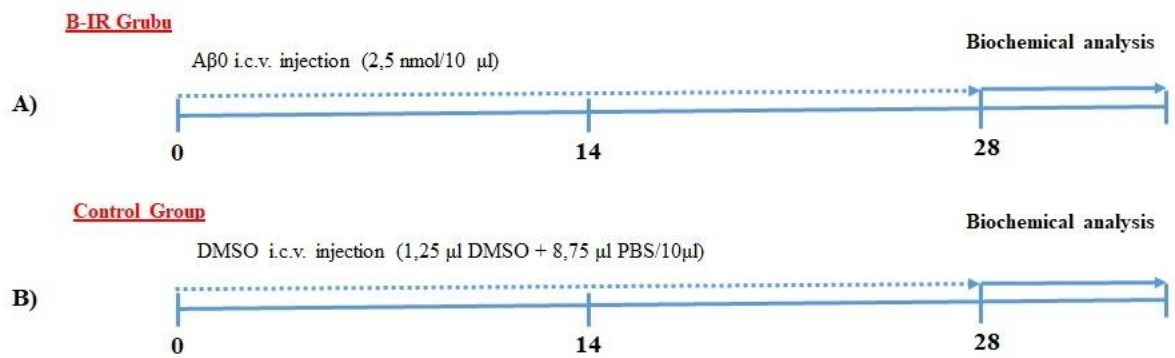

Figure 1. *Study design.* ***A:*** *B-IR group,* ***B:*** *Control group.* ***Abbreviations:*** *B-IR, Brain insulin resistance; I.c.v., intracerebroventricular, DMSO, dimethyl sulfoxide; PBS,* phosphate buffer saline.

the B-IR group.

$A\beta_{1-42}$ oligomers ($A\beta_{1-42}$) (Sigma-Aldrich, USA; catalog no. A9810) were initially solubilized in dimethyl sulfoxide (DMSO) to obtain a 2 mM stock solution. This solution was subsequently diluted eight times with sterile phosphate-buffered saline (PBS). The mixture was agitated at room temperature using a vortex mixer for 30 minutes and then subjected to centrifugation at 15,000 × g for 60 minutes at 4 °C. Following centrifugation, the supernatant (250 µL) was collected, divided into 25 µL portions, and stored at −20 °C. Prior to experimental use, the aliquots were equilibrated at 4 °C and utilized within 24 hours to ensure oligomer integrity [13]. General anesthesia was achieved via intraperitoneal injection of ketamine (80 mg/kg) combined with xylazine (5 mg/kg), both dissolved in sterile saline. Throughout the surgical intervention, body temperature was continuously stabilized at 36–37 °C using an electrically heated pad. A midline incision was made on the scalp to expose the skull, after which the bregma and lambda points were identified as anatomical landmarks. Based on stereotaxic coordinates referenced to the bregma (AP: −0.8 mm; ML: +1.4 mm; DV: −3.6 mm), two burr holes were carefully drilled into the skull to permit the placement of the injection needle [13,14].

The administration of either $A\beta_{1-42}$ or vehicle solution was performed using a 26G Hamilton microsyringe at a controlled infusion speed of 1 µL/min. Following the injection, the needle was kept in place for an additional 2 minutes to prevent reflux. Animals assigned to the B-IR group were intravenously treated with $A\beta_{1-42}$ preparation at a dose of 2.5 nmol in a total volume of 10 µL (**Figure 1A**). Control rats received an equivalent volume of the vehicle solution consisting of DMSO diluted in PBS (1.25 µL DMSO + 8.75 µL PBS per 10 µL), following the same injection protocol (**Figure 1B**). After completion of the injections, the scalp incision was closed using sutures to finalize the surgical procedure. To reduce the risk of postoperative infection, a topical antibiotic ointment was applied to the sutured area for three consecutive days. Postoperative care included oral administration of penicillin (100,000 U/day) and paracetamol (200 mg/kg) for analgesic support over a three-day period. The injected $A\beta_{1-42}$ was allowed to exert its pathological effects over a 28-day period [13]. Body weight measurements were obtained at two time points: prior to surgery and on day 28, immediately before sacrifice. In addition, fasting blood glucose levels were assessed at the same time points, in line with our previously published protocol, to verify impairment of glucose regulation [15]. Fasting glucose concentrations were determined using a handheld glucometer with blood samples collected from the tail vein (plusMED Blood Glucose Meter, Accuro pM1-300, Bionime Corporation, Taiwan) [15].

Tissue Collection and Biochemical Analyses

After the end of the experimental period, rats were anesthetized with ketamine (80 mg/kg, i.p.) and xylazine (5 mg/kg, i.p.). Following euthanasia by decapitation, brain tissues were collected for biochemical analysis. After removing all brain tissue, one hemisphere was preserved as the total brain. The brainstem and hypothalamus regions of the other hemisphere were dissected according to anatomical boundaries using the rat brain atlas as a reference. During dissection, the hypothalamus was isolated from the region between the optic chiasm and the mammillary bodies; the brainstem was isolated from the pons and medulla oblongata levels according to atlas coordinates [14]. All tissues were stored at -80°C until the day of measurement. When measurements were to be performed, the tissue samples were weighed and homogenized in PBS on ice.

Tissues were homogenized in PBS at a ratio of 1:9 (w/v). The homogenates were then clarified by centrifugation at 5,000 × g for 5 min at 4 °C, after which the resulting supernatants were collected for subsequent biochemical determinations. 5-HT concentrations were quantified in brainstem extracts, whereas hypothalamic samples were analyzed for 5-HT, 5-HT2BR, and NPY using commercially available ELISA kits (Sunred; Rat 5-HT ELISA Kit, Cat. No. 201-11-1683; Rat 5-HT2BR ELISA Kit, Cat. No. SRB-T-84698; Rat NPY ELISA Kit, Cat. No. SRB-T-85360). In addition, total $A\beta_{1-42}$ content in whole-brain tissue was determined with a Sunred ELISA kit (Cat. No. 201-11-0094). Quantification was performed by generating standard calibration curves based on absorbance readings obtained from known concentrations of standards. Data were normalized to tissue protein content and reported as ng/mg protein for 5-HT and NPY, and as ng/g protein for 5-HT2BR. Body weight variation for each animal was calculated as the difference between final and baseline measurements.

Protein Determination

Protein concentrations in brain tissues were determined by the Bradford test using the Coomassie Plus reagent (Pierce Chemical Company, Rockford, IL) [16].

Statistical Analysis

All statistical evaluations were performed with the SPSS software package (version 23.0; IBM, Chicago, IL, USA). Results are presented as mean values accompanied by the

standard deviation (SD). Prior to analysis, the distribution characteristics of each dataset were examined. Data normality was tested using the Kolmogorov–Smirnov method. Because the variables did not satisfy the criteria required for parametric testing, differences between experimental groups were analyzed using the nonparametric Mann–Whitney U test. Statistical significance was defined as a p-value below 0.05

RESULTS

Table 1 presents the total brain $A\beta_{1-42}$ levels and fasting blood glucose levels. Total brain $A\beta_{1-42}$ levels and fasting plasma glucose concentrations were significantly higher in the B-IR group compared to the control group (U = 0.00, $p < 0.01$; U = 0.00, $p < 0.01$).

Table 1 presents the 5-HT levels. 5-HT levels in the brainstem of the B-IR group were higher than in the control group; however, this increase did not reach statistical significance (U=14.00, p>0.05). 5-HT levels in the hypothalamus of the B-IR group were significantly lower than in the control group (U:2.00, p<0.01).

Table 1 presents the hypothalamic changes of 5-HT2BR and NPY levels. Hypothalamic 5-HT2BR levels were lower in the B-IR group than in the control group; hypothalamic NPY levels were lower in the B-IR group than in the control group. However, the decreasing trends did not reach significant levels (U: 8.00, $p > 0.05$; U: 8.00, $p > 0.05$).

Table 1 presents the changes in body weight. In the B-IR group, a statistically significant body weight loss was observed compared to the control group (U:0.00, p<0.001).

DISCUSSION

The present study examined how alterations in B-IR, 5-HT, and the 5-HT2BR influence hypothalamic NPY levels and body weight regulation in an experimental AD model established through i.c.v. administration of $A\beta_{1-42}$ oligomers. The dosage of $A\beta_{1-42}$ employed was selected on the basis of previously published protocols [13]. I.c.v. delivery of $A\beta_{1-42}$ oligomers has been shown to trigger insulin signaling impairment within the brain and to reproduce several hallmark pathological features associated with AD [13]. Consequently, this experimental approach provides a robust platform for exploring AD-related metabolic disturbances and for identifying potential therapeutic targets. Our findings demonstrated elevated fasting blood glucose levels in the B-IR group, accompanied by increased accumulation of $A\beta_{1-42}$ in total brain tissue compared with the control group. These findings are consistent with studies showing a link between insulin resistance and Alzheimer's disease [13,17,18], as well as studies showing its association with various

Table 1. *Biochemical and Metabolic Parameters in Control and B-IR Groups*

	Control group	B-IR group	Percentiles		
	Mean	Mean	25th	50th (Median)	75th
Brainstem 5-HT Levels (ng/mg protein)	22.487±6.117	30.241±13.844	18.910	24.289	28.233
Hypothalamus 5-HT Levels (ng/mg protein)	31.763±22.024	14.411±3.163**	14.443	17.729	23.216
Hypothalamus 5-HT2BR Levels (ng/g protein	146.326±30.485	109.612±39.633	98.884	133.212	156.206
Hypothalamus NPY Levels (ng/mg protein)	2.851±1.991	1.428±0.276	1.396	1.523	2.197
Body Weight Change (g)	22.83±15.690	-18.00±12.066**	-15.00	0.50	24.50
Total brain $A\beta_{1-42}$ Levels (pg/mg protein)	10.312±1.170	16.748±1.394**	10.122	13.386	16.756
Fasting blood glucose levels (mg/dL)	95.33±3.327	114±858**	96.00	103.50	115.25

*Statistical analysis was performed using the Mann-Whitney U test. All values are mean ± SD. n = 6 for each group. *, p<0,05 vs control; **, p<0,01 vs control.* ***Abbreviations:*** *B-IR, Brain insulin resistance; Aβ1-42, amyloid beta 1-42; 5-HT, 5-hydroxytryptamine; 5HT2BR, 5-HT2B receptor 2B; NPY, Neuropeptide Y.*

metabolic diseases [19,20].

Clinical studies and studies using animal models of AD have frequently shown that glucose-insulin homeostasis is disrupted and body weight loss occurs before the onset of AD symptoms [13]. Consistent with this information, our study also showed a significantly reduced body weight in the B-IR group compared to the control group. This information suggests that metabolic pathways involved in the regulation of food intake and/or appetite may be affected in the early stages of AD.

5-HT is known to regulate food intake (calorie consumption) and appetite via serotonergic fibers in the cerebral cortex, thalamus, and hypothalamus [9]. In our study, 5-HT levels decreased slightly in brainstem tissue in the B-IR group compared with the control group. In contrast, 5-HT levels decreased significantly in hypothalamic tissue in the B-IR group compared with the control group. Thus, our findings suggest that a decrease in hypothalamic 5-HT levels may be associated with impaired serotonergic input from the brainstem. Moreover, the significant reduction in hypothalamic 5-HT levels observed in the B-IR group compared to the control group, together with the concomitant significant decrease in body weight, suggests that early weight loss observed in AD may be associated with reduced hypothalamic 5-HT levels.

In AD patients, degeneration of the raphe nucleus and loss of 5-HT-producing neurons occur in the early stages of AD pathogenesis [21,22]. Furthermore, in AD mouse models, activity of dorsal raphe nucleus 5-HT neurons and serotonergic projections (including to the hippocampus) is reduced, leading to depressed serotonergic signaling and associated depressive and cognitive symptoms [23]. However, it has been shown that serotonergic signaling is impaired in multiple brain regions of Alzheimer's patients, including the prefrontal cortex, hippocampus, and temporal cortex, and these deficits have been linked with behavioral and psychological symptoms such as depression, agitation, and other neuropsychiatric manifestations [24]. In this sense, the data we obtained are consistent with studies showing changes in the serotonergic system in the pathophysiology of AD [21-24]. To the best of our knowledge, our study is the first to suggest that early body weight loss in AD may be associated with reduced hypothalamic 5-HT levels. However, this proposed relationship requires further investigation and validation in larger and functionally designed studies.

The hypothalamus is a brain region that plays important roles in maintaining energy homeostasis. 5-HT regulates energy balance and food intake by binding to receptors on orexigenic (feeding-inducing) and anorexigenic (feeding-suppressing) neurons in the arcuate nucleus (ARC) of the hypothalamus, thereby inducing or inhibiting the synthesis of various neuropeptides [25]. In the ARC, anorexigenic pro-opiomelanocortin (POMC) neurons synthesize the anorexic peptide α-melanocyte-stimulating hormone (α-MSH). α-MSH is an agonist of the melanocortin-4 receptor (MC4R) and reduces food intake when activated. NPY and agouti-associated peptide (AGRP), synthesized by orexigenic neurons in the same region, increase food intake [26].

Studies support the view that 5-HT positively or negatively regulates food intake, depending on the receptor it binds to [8,27]. A study by Sugimoto et al. showed that in rats treated with clomipramine (a tricyclic antidepressant that inhibits 5-HT reuptake), inhibition of 5-HT2CR led to hyperglycemia [28]. However, 5-HT2BR shares 50% homology with 5-HT2CR and has a less well-known effect on energy homeostasis[8]. Unlike 5-HT2CR, central 5-HT2BR has been found to suppress the MC4R pathway, increase NPY levels, and cause hyperphagia [29]. Previous studies have demonstrated that exposure to Aβ (1–40 or 1–42) oligomers reduces 5-HT2BR-mediated NPY levels in bone marrow–derived mesenchymal stem cells (BM-MSCs) [30].

In our study, consistent with this information, a downward trend in 5-HT2BR and NPY levels was observed in the hypothalamic tissue of rats in the B-IR group compared with the control group. These findings suggest that the 5-HT2BR/NPY pathway may be suppressed early in AD. Furthermore, this potential suppression of the 5-HT2BR/NPY pathway may be associated with the weight loss observed in the early stage of AD, as body weight reduction was also detected in the B-IR group compared to the control group. However, this interpretation should be considered hypothesis-generating.

Study Limitations

This study is limited by the relatively small sample size and the absence of direct functional assays to confirm alterations in 5-HT2BR/NPY signaling. In addition, some molecular findings did not reach statistical significance; therefore, mechanistic interpretations based on these results should be considered cautiously. Larger-scale studies incorporating functional analyses are warranted to validate and further clarify the proposed mechanisms.

In conclusion, our findings suggest that early body weight loss in AD may be associated with reduced

hypothalamic 5-HT levels, potentially reflecting decreased serotonergic input from the brainstem. The observed downward trends in 5-HT2BR and NPY levels may also be related to this alteration; however, these associations should be interpreted cautiously and require further functional validation (**Figure 2**).

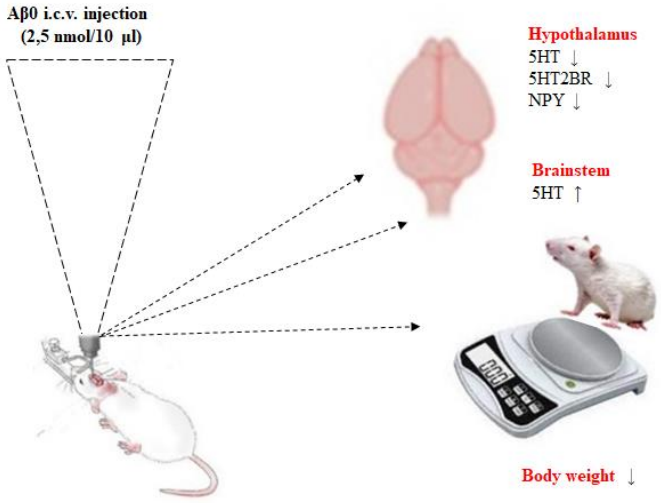

Figure 2. *The role of the 5-HT2BR/NPY pathway on body weight control in the brain insulin resistance rat model.* ***Abbreviations:*** *B-IR, Brain insulin resistance; I.c.v., intracerebroventricular; AβO, Aβ1-42 oligomer; 5-HT, 5-hydroxytryptamine; 5-HT2BR, 5-HT receptor 2B; NPY, Neuropeptide Y.*

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was conducted in accordance with the Declaration of Helsinki and approved by Akdeniz University Ethics Committee on 06.05.2024 with decision number; 2024/18.

Acknowledgements

Not applicable.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Financial Disclosure

The authors declared that this study has received no financial support.

Referee Evaluation Process

Externally peer-reviewed.

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