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ORIGINAL ARTICLE

Dexamethasone-Induced Insulin Resistance Impaired Artemin Levels in the Hippocampus and Altered Behavioural Patterns

Hasan Çalışkan[1]

Abstract

Background/Aim: Insulin resistance (IR), a hallmark of metabolic syndrome, contributes to glucose dysregulation, obesity, dyslipidaemia and hypertension. While the systemic effects of IR are well-documented, its impact on neurotrophic factors such as artemin (ARTN) remains unclear. This study investigates the relationship between IR-induced metabolic dysfunction, ARTN expression in specific brain regions and associated behavioural alterations.

Methods: Sixteen male Wistar rats were used (control and an insulin resistance (IR) group, each group n = 8). The IR group received intraperitoneal dexamethasone (1 mg/kg/day) for five days to induce IR. Behaviours were evaluated using the open-field test. Metabolic profiling included blood glucose, serum insulin and HOMA-IR calculations. ARTN levels were analysed in the prefrontal cortex (PFC), striatum, hippocampus and serum.

Results: Dexamethasone-treated animals displayed pronounced anxiety-like behaviours and metabolic deterioration (elevated glucose, insulin resistance). While ARTN levels in the PFC, striatum and serum remained unchanged between groups, hippocampal ARTN was remarkably lower in the IR group compared to controls.

Conclusion: Early-stage IR selectively reduces hippocampal ARTN levels, accompanied by increased anxiety and decreased locomotor activity. These findings suggest a region-specific vulnerability of ARTN to metabolic dysfunction, warranting further investigation into its neuroprotective role in the progression of IR.

Key words: Anxiety; Behaviour; Artemin; Locomotion; Hippocampus; Insulin resistance.

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Introduction

Insulin resistance (IR) is the inability of insulin to effectively take up and use glucose in target organs, such as the liver, skeletal muscle and adipose tissue.[1] Global prevalence indicates that insulin resistance affects 15.5 % to 46.5 % of adults, with significant regional variations.[2] IR serves as a central mechanistic driver in the development and progression of metabolic syndrome. Additionally, IR is linked to several related conditions, including glucose intolerance, obesity, dyslipidaemia and hypertension.[3, 4] Saklayen reported that the prevalence of metabolic syndrome could be predicted to be approximately one-quarter of the global population.[5] The presence of insulin resis-

tance in various age demographics and metabolic disorders has not been fully established; however, these conditions are likely to affect an increasing number of people in the future.[6]

IR also has a detrimental effect on the different organ systems. Insulin resistance impairs blood glucose regulation and can lead to the development of diabetes.[7] IR also damages the cardiovascular system, resulting in an increased risk of atherosclerosis, myocardial fibrosis, ventricular hypertrophy and cardiac diastolic dysfunction.[8] Beyond its established cardiometabolic effects, emerging evidence suggests IR can induce deleterious neurobiological changes, potentially contributing to central nervous system dysfunction. A link between psychiatric disorders and insulin resistance has been shown in clinical studies.[9-11] Similarly, insulin resistance has been associated with significant behavioural changes in rodent models.[12, 13] Diabetes and IR have been shown to significantly downregulate BDNF expression, impairing this vital neurotrophins's role in neuronal maintenance and plasticity.[14, 15]

Neurotrophic factors are groups of distinct molecular entities that promote the growth, survival and function of neurons.[16] Artemin (ARTN) is a neurotrophic factor that belongs to the GDNF family of ligands, which are derived from glial cells.[17] The protective effect of ARTN on the nervous system has been demonstrated, particularly in animal models and cell cultures.[18, 19]

This study aimed to investigate ARTN levels in different brain regions in an insulin-resistant rodent model induced by dexamethasone.

Methods

Animals

Sixteen adult male Wistar albino rats were sheltered under standard laboratory conditions with *ad libitum* access to food and tap water. Sample size was determined using the equation method for two-group comparisons, with eight animals per group providing sufficient statistical power.[20] All conditions of the experiment complied with the NIH Guide for the Care and Use of Laboratory Animals.[21]

Insulin resistance protocol

The study followed the protocol of Inácio et al,[22] in which the drug dexamethasone (*Dexacort*, Deva Holding) was administered at a dosage of 1 mg/kg/day via intraperitoneal injection (ip) for five consecutive days to induce IR.[22] To validate the model, glucose, insulin and HOMA-IR values were analysed. The index can be calculated via the following formula: HOMA-IR = (fasting insulin [Mu/L] × fasting glucose [mg/dL]) /405.[23] Control group subjects received 1 mL/kg of physiological saline (ip) for 5 days.

Open field test

Anxiety-like behaviours and locomotor activity parameters were examined via the open-field test.[20] Subjects escape from the open field and seek refuge in the walls, which serve as a safe zone. As anxiety increases, the time spent in the central area decreases. In the present study, subjects were examined via a camera to record their behaviour during a 5-minute open-field test. The subjects' total distance travelled, the time spent in the central zone, the number of entries into the central zone and the rearing behaviours were analysed.

Artemin analyses

Fifty mg/kg ketamine and 10 mg/kg xylazine were administered ip. Under deep anaesthesia, the rats were then exsanguinated by cardiac puncture and serum was obtained from blood taken from the left ventricle. The rat brain atlas was used to guide the removal of the prefrontal cortex (PFC), striatum and hippocampus from an ice block.[24] For enzyme-linked immunosorbent assay (ELISA) analysis, the tissue and serum were stored at a temperature of 80 °C. Artemin was performed according to the procedure described in the ELISA kit provided by the commercial company (Catalogue No: BT Lab, no: E3432Ra).

Statistical analysis

Statistical analyses were performed using the *GraphPad Prism* 10.5 software (Boston, MA, USA). Data normality was evaluated by the Shapiro-Wilk test. Normally distributed parametric data were analysed with Student's t-test and expressed as mean ± standard deviation (SD). Non-parametric data were assessed using the Mann-Whitney U test, with results reported as median, interquartile range and mean ± SD. Statistical significance was set at $p < 0.05$ for all analyses.

Results

Behavioural results

The data from the open-field test were presented in Figure 1. In the IR group (16.50 ± 8.41), the time spent in the central area was significantly reduced compared to the control group (30.38 ± 10.74), ($p < 0.05$). Similarly, the number of entries into the central area was significantly reduced in the IR group (2.75 ± 1.16, median: 2, interquartile range: 1.75) compared to the control group (1.5 ± 0.53, median: 1.5, interquartile range: 1). The total distance travelled, a locomotor activity parameter, also significantly reduced in the IR group (control: 1178 ± 166.5; IR: 405 ± 158.1), ($p < 0.05$). The number of rearing episodes, a measure of exploratory behaviour and vertical movement, was significantly reduced in the IR group (5.5 ± 1.85) compared to the control group (9.12 ± 2.69), ($p < 0.01$).

Biochemical results

Biochemical data were presented in Figure 2. In the IR group, blood glucose (C: 84.63 ± 10.89; IR: 242.1 ± 3.01), insulin (C: 2.14 ± 0.48; IR: 6.43 ± 0.53) and HOMA-IR (C: 0.43 ± 0.1; IR: 3.61 ± 0.69) values were significantly higher than those of the control group ($p < 0.0001$).

Artemin results

Artemin brain and serum data are presented in Figure 3. No significant change was observed in artemin levels in the PFC (C: 89.75 ± 11.95; IR: 96.38 ± 13.57) and serum (C: 107.6 ± 9.21; IR: 119.1 ± 22.84) ($p > 0.05$). Similarly, no significant difference was observed in artemin levels in the striatum between the control group (93 ± 12.78, median: 94, interquartile range: 24) and the IR group (105.1 ± 13.57, median: 117.5, interquartile range: 37.75) ($p > 0.05$).

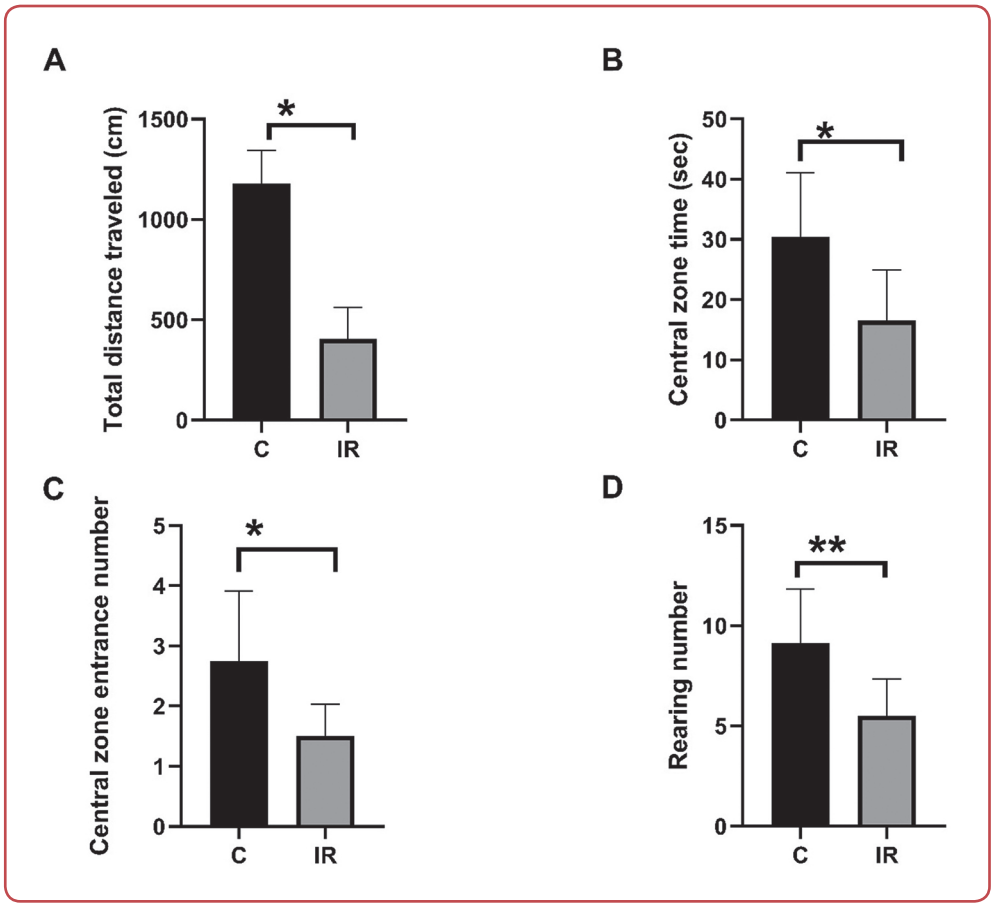

Figure 1: *Behavioural findings of the open field*

C: control; IR: insulin resistance; *: $p < 0.05$; **: $p < 0.01$;

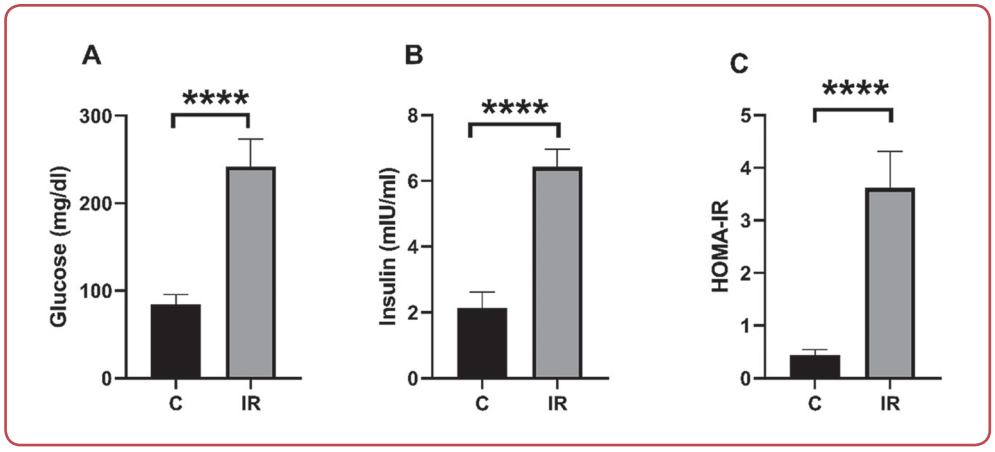

Figure 2: *Biochemical findings*

C: control; IR: insulin resistance; ****: $p < 0.0001$;

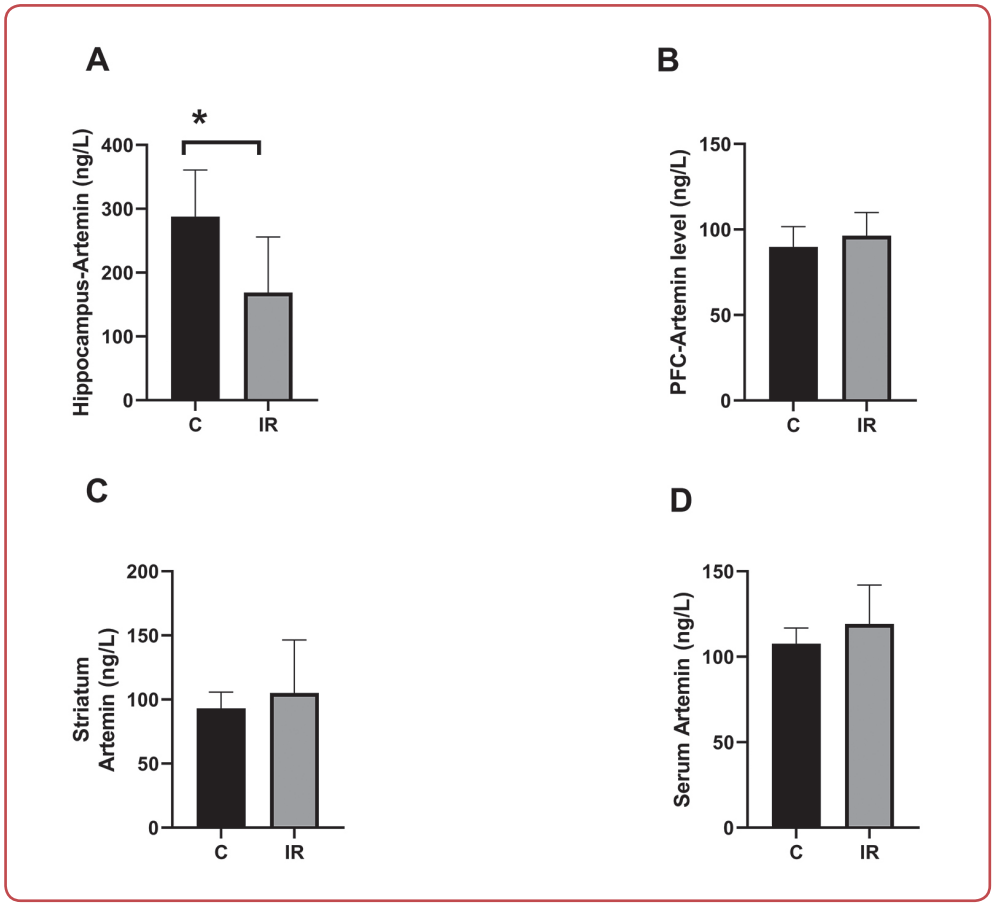

Figure 3: *Artemin findings*

C: control; IR: insulin resistance; *: $p < 0.05$;

HPC was significantly reduced in the IR group (168.9 ± 86.98) compared to the control group (287.8 ± 73.14), ($p < 0.05$).

Discussion

To the author's best knowledge his study investigated artemin levels in various brain regions of an insulin-resistant rodent model for the first time in the literature. Measurements performed

to validate the insulin resistance model revealed significant increases in blood glucose, insulin and HOMA-IR levels. These data are concordant with published reports of dexamethasone-induced insulin resistance in rodents, where comparable metabolic disturbances.[25, 26] In various studies, it has been observed that the dexamethasone dose was either higher or lower and the treatment regimen was similarly applied for either longer or shorter durations.[27, 28]

Anxiety-like behaviours have increased in subjects with insulin resistance. Subjects have tended to move toward areas closer to the walls of the open space, which is perceived as safer. This phenomenon, known as thigmotaxis, has increased in the IR group.

Similar increases in anxiety have been observed in other insulin resistance models and diabetes models created in different ways.[13, 29, 30] Subjects exhibit rearing behaviour, which involves standing on two legs to explore their environment.[20] Insulin resistance suppressed rearing behaviour. Horizontal locomotor activity has also decreased significantly in the IR group. According to other preclinical studies, locomotor activity was generally inclined to decrease or remain unchanged.[13, 14, 31] Factors such as the type of model, the short or long-term effects of pharmacological agents and age may influence the outcome.[14]

The glial-derived growth factor family comprises four members, one of which is artemin.[32] The present study examined key brain areas associated with behaviour. The PFC and striatum showed no significant differences. Anterograde transport of a crucial neurotrophic factor, such as BDNF, was demonstrated in both brain regions.[33] The BDNF level of the prefrontal cortex may influence BDNF levels in the striatum.[14, 34] In the insulin resistance model developed by Çalışkan and Karabulut, BDNF levels were found to be reduced in both the PFC and the striatum.[14] BDNF was more affected in the prefrontal cortex, while the effect was moderate in the striatum.[14] In the present study, artemin levels were found to be similar in both brain regions. Similar transport may occur between the two brain regions, as observed with BDNF. Previous studies have demonstrated the protective effects and association of artemin with striatal neurons.[35, 36] However, in the present study, the striatum was not affected in early-stage insulin resistance.

The hippocampus has numerous functions, including learning, memory and pain modulation.[37, 38] Artemin levels were significantly reduced in the early stages of insulin resistance. The hippocampus has a three-layered structure.[39] Its three-layered structure, the ratio of white to grey matter and the possible lateralisation of artemin may have made the hippocampus more sensitive. Studies in prediabetes and diabetes also suggest that other neurotrophic factors are affected in the hippocampus.[12, 40, 41]

According to the currently available data, no significant changes have been observed in the serum. Patients with generalised anxiety disorder were found to have elevated artemin levels, while patients with major depression were found to have decreased artemin levels.[42] Although the sample size of this study is small, it is essential in terms of translational medicine.[42] Examining artemin levels in postmortem brain tissue of depressed patients could be beneficial. Cerebrospinal fluid, urine and saliva are biological samples that can be examined.

The present study investigated the relationship between insulin resistance and anxiety. In addition to anxiety, insulin resistance has been shown to increase depression-like behaviour in experimental models.[43, 44] In addition, there is a bidirectional relationship between insulin resistance and depression.[45-47] Inflammation, abnormalities in insulin signalling and hypothalamic-pituitary-adrenal axis dysfunction contribute to this bidirectional relationship.[46, 47] Due to this bidirectional relationship, each disease may worsen the course of the other.[47] Therefore, multidisciplinary approaches may be beneficial for treatment.

The presented study has certain limitations. Only male rats were used in the experiment. This limitation was due to budget and time constraints. It is also important to conduct experiments with female subjects from the perspective of public health and translational medicine. In this way, the experimental design will better reflect society. Conducting experiments on female rats in future studies would be extremely useful. The second limitation is the examination of the early effects of insulin resistance.

Conclusion

The early effects of dexamethasone-induced insulin resistance were investigated. Early effects of insulin resistance included increased anxiety-like behaviours and decreased locomotor activity. The hippocampus was found to be more sensitive than other brain regions and artemin levels were reduced. Further investigation of the long-term effects in both genders would be beneficial.

Ethics

This study was approved by the Balıkesir University Animal Experiments Local Ethics Committee (Approval No: 2024/11-4), dated 28 November 2024.

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None.

Conflicts of interest

The author declares that there is no conflict of interest.

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Data access

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

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Methodology: HÇ
Formal analysis: HÇ
Investigation: HÇ
Data curation: HÇ
Writing - original draft: HÇ
Writing - review and editing: HÇ

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