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Review Article

The Emerging Role of Adropin in Neurological Health: A Systematic Review

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Abstract

Background: Adropin, a peptide hormone has role in various various physiological processes, including metabolic regulation and cardiovascular health. This systematic review aimed to synthesize findings from observational studies on the involvement of adropin in neurological disorders and cognitive performance.

Methods: An extensive literature search was conducted across PubMed, Scopus, Web of Science, Embase, CORE, and Google Scholar using terms such as "adropin," "Neurological Disorders," "cognitive function," "Alzheimer's disease," "Parkinson's disease," "cognition," and "brain function." Studies published from 2020 to 2024 were selected and reviewed. The search and selection process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Out of 127 screened articles, 5 met the inclusion criteria for this review.

Results: The combined research findings suggest a consistent link between decreased adropin levels and a range of neurological disorders and cognitive impairments. In particular, reduced adropin levels were seen in individuals with dementia, cognitive impairment, bipolar disorder, Parkinson's disease, and multiple sclerosis. These findings highlight adropin's potential role in modulating neurological health and cognitive function.

Conclusion: This systematic review underscores the importance of adropin in neurological health and its potential as a therapeutic agent. Based on the observed connections, adropin might serve as a new focus for treating neurological disorders, prompting the need for more research and trials.

Keywords: Adropin; Neurological disorders; Cognitive function; Neuroprotection; Systematic review

Introduction

Adropin is mainly found in the liver, brain, and endothelial cells and has an important role in lipid metabolism and energy homeostasis (1-5). It is a peptide hormone produced by the *ENHO* gene. It has a major role in enhancing endothelial function and also in decreasing vascular inflammation (6-12). It helps maintain blood glucose levels and improves insulin sensitivity (13).

Adropin is essential for cardiovascular health due to its vasodilatory effects on blood vessels (14,15).

Adropin may protect against neurodegenerative conditions like Alzheimer's and Parkinson's by mitigating oxidative stress, inflammation, and metabolic dysfunction, which contribute to neuronal damage (16). Adropin has a noted ability to enhance endothelial function and to decrease inflammation. It could potentially help in improving these pathological processes (17).

Adropin influences brain energy homeostasis and neuronal function, making it a potential factor in neurological disorders characterized by metabolic dysregulation (3). Cognitive function includes processes like memory, attention, and executive function. Adropin levels are linked to cognitive performance. Higher levels of adropin are associated with better cognitive outcomes while lower levels are associated with cognitive impairment (18). This link is thought to be mediated by how adropin affects neuroinflammation and endothelial function which is important for blood flow in the brain and against cognitive decline.

While adropin's role in metabolic regulation is well-documented, its specific contributions to neurological disorders and cognitive health remain underexplored. This systematic review aimed to address this gap by synthesizing findings on adropin's associations with neurological health and cognitive function. This review synthesizes evidence from observational studies to evaluate adropin's association with neurological disorders and its influence on cognitive function, providing insights into its potential as a biomarker or therapeutic target.

Adropin Structure and Gene Expression

The *ENHO* gene is found on chromosome 9 (9p13.3) and consists of 1948 bp, encoding for a 76 amino acid peptide. Adropin is composed of two functional parts: adropin1−33 as a secretory signal peptide enabling its excretion, and adropin34−76 as a biologically active part responsible for its physiological effects (1, 2).

The first tissues in which adropin expression was described were the liver and the brain (3,4). Subsequent studies revealed its expression in a greater number of tissue types. In the liver, adropin is expressed in sinusoidal cells. In the central nervous system, however, immunoreactivity to adropin was detected in the vascular area and pia matter, neuroglial cells, Purkinje cells, granular layer, and neurons. Immunohistochemical techniques have revealed the presence of adropin in acinar cells and capillaries of the islets of Langerhans within the pancreas, and in kidney samples, it was found within the renal glomeruli and peritubular capillaries (5-7).

On the other hand, adropin is believed to be a secretory and membrane-bound peptide, and its secretion is observed to be synthesized in human embryonic kidney (HEK293) cells and C57BL/6J mice. It has also been linked to a number of physiological functions, including the regulation of endothelial function where it activates angiogenesis, proliferation, and migration of the endothelium. While a well-described, specific receptor for adropin's biological effects has not been identified, adropin was proposed to act through the orphan G protein-coupled receptor GPR19 in the brain and potentially on VEGFR2 in endothelial cells, thereby promoting vascular health and function (1).

Understanding the Mechanisms of Adropin in Maintaining Neural Health

Adropin exerts its neuroprotection by a sequence of concerted actions that together enhance the health and resistance of neurons against different forms of injury. One of the major signaling pathways modulated by adropin is the PI3K/Akt and MAPK/ERK1/2 cell survival pathway. These signaling pathways have a significant effect on maintaining cell survival, as they coordinate processes opposing apoptosis, enhancing neuronal stress resistance. Adropin acts through the activation of these pathways to support the survival of individual neurons, as well as the overall structural integrity of neural networks, which is absolutely vital for the preservation of cognitive function and neural plasticity (2, 18-22).

On the other hand, adropin, by acting through the activation of eNOS, contributes significantly

to the health of the cerebrovascular system. An enzyme responsible for NO (nitric oxide) production, eNOS produces this powerful vasodilative molecule. NO, through the relaxation of blood vessels, assures the proper flow of blood within the brain in order to make sure that during conditions like ischemic stroke, neurons have a steady supply of oxygen and nutrients. By increasing the activity of eNOS, adropin will help preserve the function of the blood-brain barrier—another very important structure that is on one hand impermeable to potentially toxic molecules from entering the brain but also allows important molecules to cross (23-26).

In addition to its vascular effects, adropin interacts with a GPR19 receptor regarding metabolic processes in the brain. It participates in the regulation of pyruvate dehydrogenase complex, an enzyme complex playing a key role in the conversion of pyruvate to acetyl-CoA serving for the Krebs cycle and ATP synthesis. In greater detail, adropin controls pyruvate dehydrogenase kinase 4, so that the proper tissue can efficiently switch back and forth from one energy source to another—a property most important during metabolic stress states such as those experienced after a stroke or in neurodegenerative diseases (27,28).

Adropin's participation in the Notch1 signaling pathway offers additional evidence that this peptide plays a role in neural repair and regeneration (29). The Notch1 pathway has been found to be one of the major players in cell fate during development and still relevant in the adult brain by modulating neurogenesis and neuronal plasticity. Through interaction with NB-3 and a Notch1 agonist, adropin supports recovery from injury and improvement in the reparation of impaired neural tissues, which might possibly obstruct neurodegeneration (30-32).

Overall, adropin serves as a multi-faceted protector of neural health in that it modulates the functioning of vasculature, energy metabolism, and cellular repair mechanisms. These properties allow adropin to decrease oxidative stress, improve endothelial function, and maintain BBB integrity, making it an important molecule to be further explored with therapeutic potential for the treatment and/or slowing down of neurodegenerative diseases, ischemic events, and age-related cognitive decline.

Methods

Search Strategy

We conducted a systematic search in six major databases using relevant keywords, following PRISMA guidelines (34). A comprehensive search strategy was designed capture all relevant studies related to adropin and neurological disorders. The search terms included combinations of keywords such as “adropin,” “neurological disorders,” “cognitive function,” “Alzheimer’s disease,” and “Parkinson’s disease” (Table 1). Search filters included observational study designs, human studies, and English language publications.

Table 1: Search Strategy used for extraction of data (article)

Database	Search Terms	Search String	Time Frame	Additional Steps
PubMed, Scopus, Web of Science, Embase, CORE, Google Scholar	"adropin," "Neurological Disorders," "cognitive function," "Alzheimer's disease," "Parkinson's disease," "cognition," "brain function"	"adropin" AND ("Neurological Disorders" OR "cognitive function" OR "Alzheimer's disease" OR "Parkinson's disease" OR "cognition" OR "brain function")	Till - June 2024	Checked reference lists of relevant articles

Inclusion and Exclusion Criteria

This study included only observational studies, such as cross-sectional, case-control, and cohort designs; only human studies involving participants with Neurological Disorders like Alzheimer's disease or Parkinson's disease, or those assessing cognitive function; Studies reporting on Adropin levels about Neurological Disorders or cognitive function; and finally, articles that were published in English.

Interventional studies, animal studies, in vitro studies, case reports, reviews, and editorials; Studies not involving human participants or those without a clear focus on Neurological Disorders or cognitive function; Studies not reporting specific data on adropin levels; and articles published in languages other than English were excluded from this study.

Data Extraction and Quality Assessment

Two reviewers (RS & KA) independently extracted data using Covidence, focusing on study design, participant characteristics, and adropin assessment techniques. Discrepancies were resolved through discussion with a third reviewer (VM) to ensure rigor. Study quality was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates selection, comparability, and outcomes (scores: 0–9). Studies were categorized as low, moderate, or high risk of bias (34,35).

Study Selection

The study selection process involved two stages: title/abstract screening and full-text review. Initially, duplicates were removed using Covidence software. Two reviewers (RS and KA) independently screened the remaining titles and abstracts against the inclusion and exclusion criteria. For full-text review, the same reviewers assessed eligibility, resolving disagreements through consensus or consulting a third reviewer (VM). Studies published between 2020 and 2024 were considered to capture recent and relevant data. Overall, 127 records were found in the database searches. After duplicates were removed 74 records remained. Overall, 74 of these were assessed for relevance and eligibility. Sixty-nine were excluded for the following reasons: 58 were not relevant to adropin and Neurological Disorders/cognitive function, 4 intervention studies, animal studies, or in vitro studies, 2 had no data on adropin levels, 1 was not in English, 4 had no full text available. After these exclusions, 5 full-text articles were evaluated for eligibility. All 5 met the criteria for inclusion in the qualitative synthesis. The process and outcomes of the literature search are shown in Fig. 1.

Data synthesis

We found five studies that matched our criteria. Because of the diversity of these studies, a narrative synthesis method was employed. Data were summarized descriptively, focusing on trends in adropin levels across different neurological conditions. No meta-analysis was performed due to the small number of studies and variation in methods.

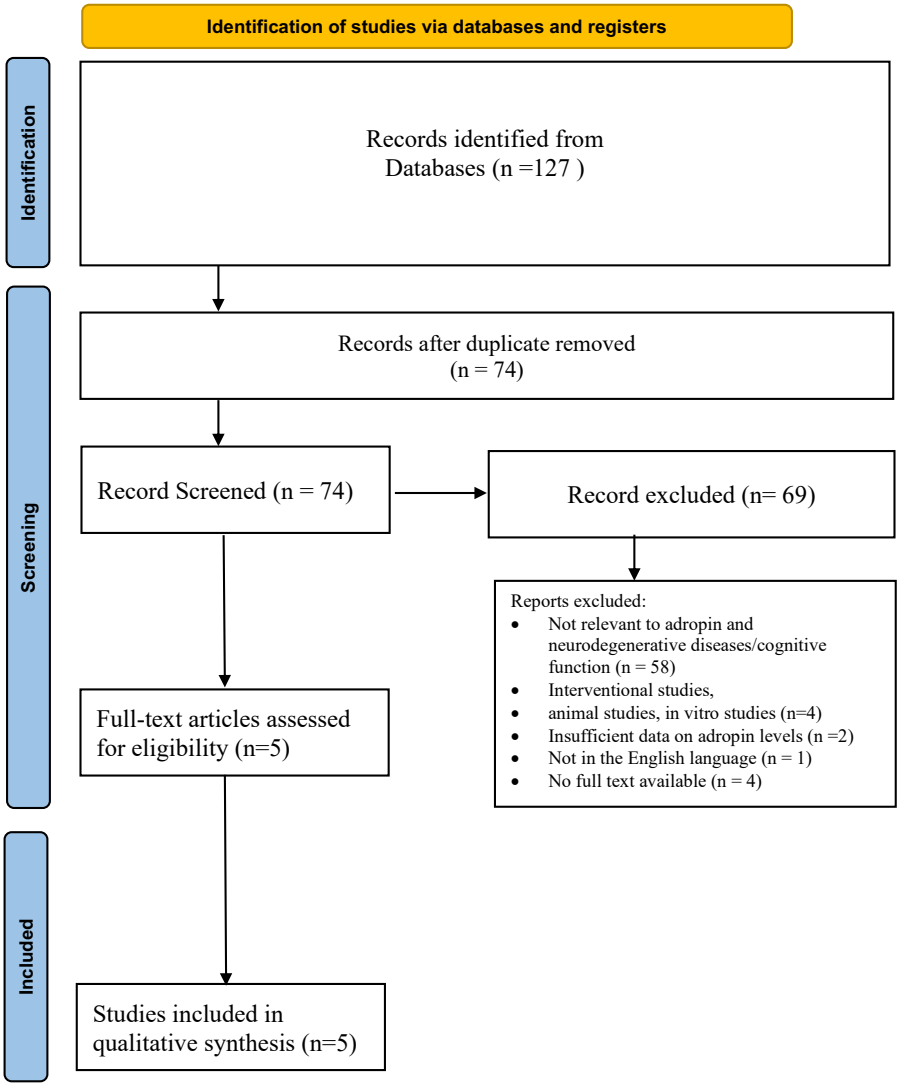

Fig. 1: Flowchart depicting the selection process of studies for the systematic review

Results

Study Characteristics

Five observational studies were included, comprising cohort and case-control designs. Adropin levels were measured via ELISA in diverse populations, including individuals with cognitive impairment, Bipolar Disorder, Parkinson's disease, and multiple sclerosis (Table 2). Study populations ranged from 66 to 400 participants, with most studies controlling for confounders such as age and sex.

Two studies consistently reported lower adropin levels in individuals with cognitive impairment compared to controls. Lower quintiles of adropin were associated with poorer cognitive performance, while another study observed similar trends in a Chinese cohort (36,37).

In Bipolar Disorder, Ersan et al (38) found significantly lower adropin levels in patients than in controls. However, no association was observed between disease stage and adropin levels.

Lower adropin levels were observed in Parkinson's disease and multiple sclerosis patients. Lama et al (39) reported a significant reduction in

adropin levels in Parkinson's patients compared to controls. Similarly, Cinkir et al (40) noted lower levels in multiple sclerosis cases, correlating with disease severity.

Table 2: The main characteristic of included observational studies related to Neurological Disorders and cognitive function

First Author (Year)	Population / Country	Sex / Sample Size	Confounders removed	Study Design	Measurement Method	Adropin levels (Mean ± SD) ng/mL
Aggarwal et al., (2023) (36)	Poor cognitive performance/ USA	B / M: 110, F: 218 T: 328	Late-middle-aged people with dementia.	Cohort study	ELISA	Low quin: 2.87 ± 1.22 High quin: 3.34 ± 1.48
Li (2023) (37)	Cognitive Impairment/ China	B / T: 400	NA	Cohort study	ELISA	Low quin: 1.37 ± 0.40 High quin: 3.35 ±0 .12
Ersan et al., (2021) (38)	Bipolar Disorder/ Turkey	B / M: 36, F: 37, T: 72	NA	Case Control	ELISA	Case: 88.15 ± 31.40 Control: 125.52 ± 19.75
Lama et al., (2022) (39)	Parkinson's Disease/ Iraq	B / M:45 F: 21 T: 66	Patients with Osteoporosis	Case-Control	ELISA	Case: 0.21±0.02 Control: 0.58 ± 0.03
Cinkir et al., (2021) (40)	Multiple sclerosis/ Turkey	B / M:23 F: 61 T: 84	NA	Case Control	ELISA	Case: 504.12 ± 311.17 Control: 747.0 ± 309.42

Quality Assessment

In Fig. 2, we evaluated the quality of the cohort studies using the Newcastle-Ottawa Scale (NOS) (32). The assessment revealed varying levels of methodological rigor among the studies (36, 37). Aggarwal et al (36) achieved a score of 7 out of 9 stars, suggesting higher quality due to robust selection and comparability criteria, although it did not report on outcome assessment. A study by Li (37) also scored 5 out of 9 stars, indicating moderate quality with a reasonable selection and comparability criteria.

One study (38) received a score of 6 out of 9 stars, indicating moderate quality. This study demonstrated adequate selection and comparability of cases and controls; however, weaknesses were identified in the assessment of exposure. Another study (39) scored 4 out of 9 stars, indicating lower quality. Weaknesses across all assessed domains, including selection criteria, comparability of cases and controls, and ascertainment of exposure. Cinkir et al (40) also scored 6 out of 9 stars, reflecting moderate quality. Similar to the study by Serpil et al., this study showed adequate selection and comparability but had weaknesses in exposure assessment.

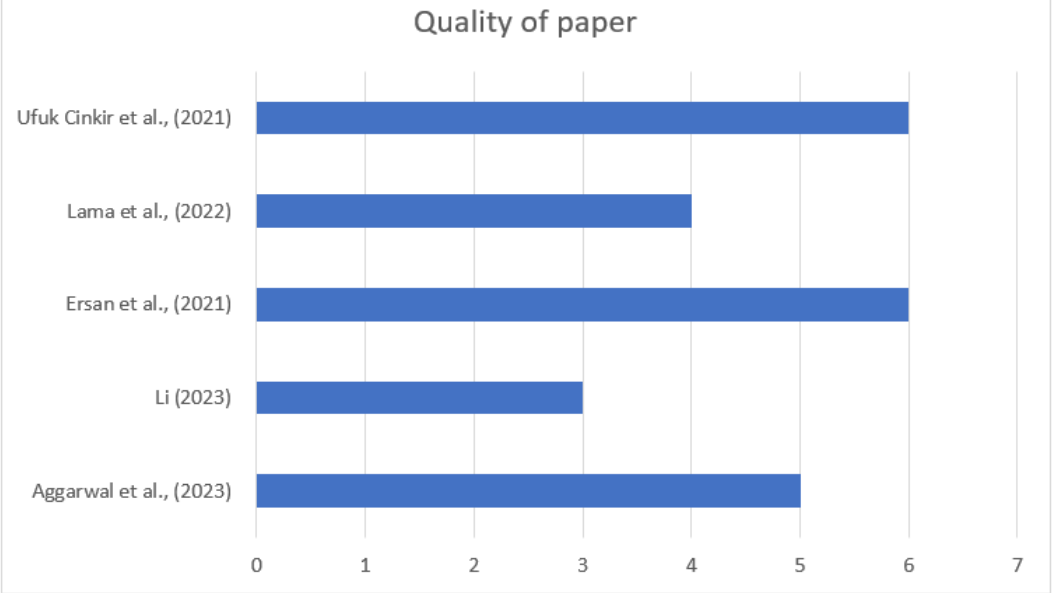

Fig. 2: Quality assessment of studies included by New-Castle Ottawa scale

In Fig. 3, the risk of bias assessment using the Newcastle-Ottawa Scale (NOS) revealed varying levels of methodological quality among the studies evaluated. This highlights the varying methodological quality among the studies, with one study showing a low risk of bias and the majority demonstrating moderate risk.

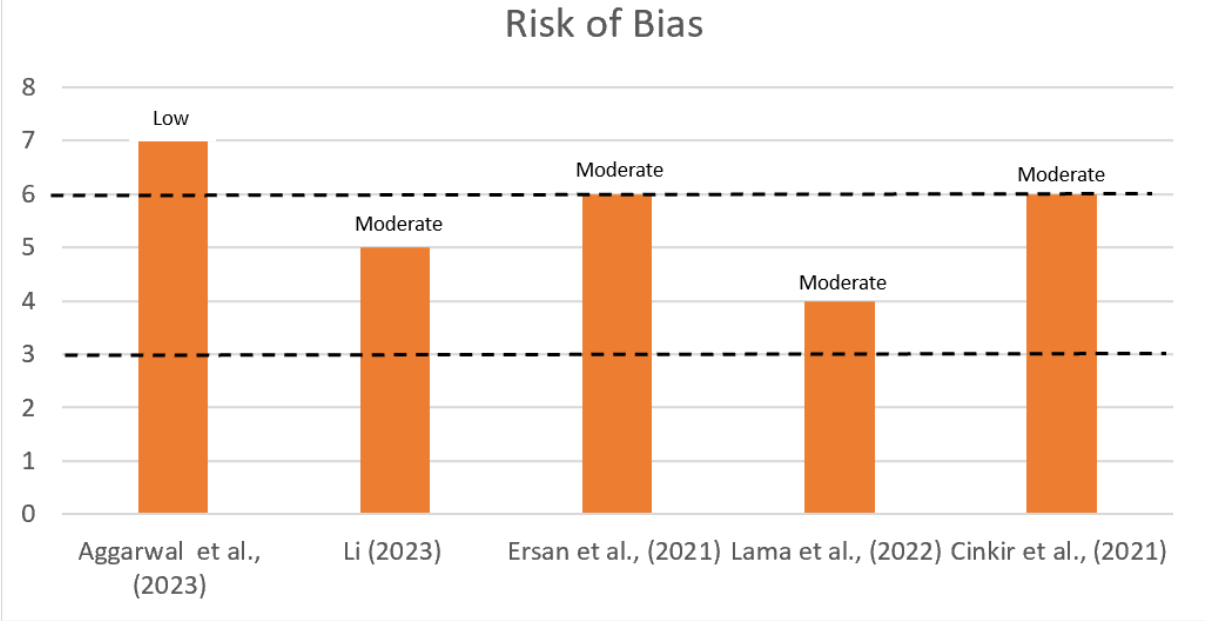

Fig. 3: Risk-of-Bias Graph: Judgments Across Included Studies

The dashed lines at scores 3 and 6 indicate the thresholds for high and moderate risk of bias, respectively.

The following table summarizes the major findings and limitations of the selected studies on adropin. These studies investigate serum adropin levels and their associations with cognitive performance, disease severity, and metabolic parameters across various neurological conditions (Table 3).

Table 3: Major findings and limitations of the observational studies that are included related to Neurological Disorders and cognitive function

Study/Year	Major Findings	Limitation
Aggarwal et al., (2023) (36)	The research indicated that patients with impaired cognition had reduced serum adropin levels. Elevated adropin levels correlated with a reduced incidence of cognitive impairment. Weak associations were identified with other indicators; nevertheless, years of education also proved to be a significant predictor of cognitive decline.	The research just included participants from a single geographic region and concentrated entirely on African Americans from two distinct socioeconomic strata. Inclusion criteria for the research mandated a minimum MMSE score of 16, so excluding late middle-aged adults with dementia.
Li (2023) (37)	The research indicated that those with the lowest circulating adropin levels had diminished cognitive ability, as both genders demonstrated reduced MMSE and ANT scores relative to those with elevated levels. Cognitive deterioration was seen in the cohort with the lowest MMSE+ANT scores, but not in the total ANT scores when contrasted with those possessing elevated adropin levels. Reduced adropin levels correlated with a heightened risk of cognitive impairment, especially in the lowest group relative to those with elevated levels.	The study's limitations include a sample size of 400 individuals, potentially limiting the generalizability of the results to larger groups. Consent-based recruitment presents possible selection bias, compromising the validity of results. The cross-sectional approach obstructs the establishment of causal correlations between adropin and cognitive performance.
Ersan et al., (2021) (38)	Adropin levels were significantly lower in the patient group compared to the control group. However, no significant relationship was found between the disease stages and adropin levels.	The cohort included patients diagnosed with Bipolar Disorder who were undergoing pharmacological treatment. While the individual prescriptions were recorded, no comparisons were conducted regarding the categories of medication. A further weakness of the research was the limited sample size in both the patient and control cohorts. Moreover, participant attributes like dietary habits, lifestyle choices, and smoking status were not evaluated.
Lama et al., (2022) (39)	The primary result indicated that the mean serum adropin level in the control group was markedly elevated compared to the case group. To present, only human research have examined the correlation between adropin and Parkinson's disease.	A limitation of this case-control research is the inability to evaluate possible confounding variables such as nutrition, lifestyle, and smoking status. Furthermore, although the research specified the drugs given to the patients, it failed to compare the various kinds of medication, which may have influenced the outcomes.
Cinkir et al., (2021) (40)	The major finding was that the mean adropin levels were increased in the patient group and decreased in the control group.	Firstly, it did not include any cases of primary progressive MS in the patient population. Secondly, the sample size was quite limited, with only 84 participants. Lastly, the study did not evaluate patients and biochemical parameters according to disease subgroups.

Discussion

This systematic review synthesized findings from multiple studies exploring the association between adropin levels and neurological conditions. The included studies consistently reported lower adropin levels in individuals with cognitive impairment, neurodegenerative disorders, and bipolar disorder compared to controls. Adropin may play a role in neurological health, particularly through mechanisms involving metabolic regulation, neuroprotection, and inflammation reduction.

Adropin and Neurological Health

Adropin may influence neurological health through its modulation of the PI3K/Akt signaling pathway, which is essential for neuronal survival, synaptic plasticity, and regeneration (41). By supporting Akt phosphorylation at Ser-473, adropin activates downstream cascades, including the mTOR pathway, which promotes angiogenesis, synaptic plasticity, and reduces inflammation and apoptosis (22, 42-44). Impaired Akt signaling is a hallmark of neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases, as well as neuropsychiatric disorders like schizophrenia and bipolar disorder, highlighting the importance of this pathway in disease progression (45-49). The ability of adropin to enhance Akt signaling suggests its potential to mitigate neurodegeneration and improve neuronal function in these conditions. However, further studies are needed to validate its therapeutic potential.

Role of Adropin in Metabolic Regulation, Neuroprotection, and Cognitive Function

Energy metabolism is an important aspect of adropin's involvement in cognitive health. Interestingly, it enhances insulin sensitivity for glucose metabolism and energy production in the brain (50-58). Insulin resistance is associated with metabolic disorders and, importantly, stimulates cognitive decline or neurodegenerative diseases such as AD (59). Adropin might enhance insulin sensitivity in order to improve cognitive defects in metabolic disorders.

In addition to its metabolic function, adropin exerts powerful neuroprotective properties, including the reduction of oxidative stress, inflammation, and apoptosis within the brain, all of which are important to maintain neuronal integrity and function (60). Such neuroprotective actions underpin neurodegenerative disorders, such as Parkinson's disease (PD) and bipolar disorder (BD), characterized by neuronal damage and a decline in cognitive abilities. The neuroprotective mechanisms of adropin may lessen the neurodegenerative disease course and preserve cognitive functions through the protection of neurons against oxidative insults and neuroinflammatory responses.

Clinical Observations and Potential Therapeutic Implications:

The exact mechanisms through which adropin influences cognitive function and neurological disorders are not fully elucidated. However, potential pathways include modulation of synaptic plasticity, neurogenesis, and neurotransmitter regulation. Adropin's ability to activate signaling pathways like Akt/mTOR, crucial for neuronal survival and synaptic function, underscores its therapeutic potential in mitigating cognitive impairments associated with neurological disorders (60,61).

Studies consistently demonstrate an association between circulating adropin levels and cognitive performance across diverse populations. Research in late middle-aged African Americans and a Chinese cohort revealed that lower adropin levels are linked to cognitive impairment, suggesting a potential protective role for higher adropin levels against cognitive decline (36,37). These findings highlight adropin's potential as a biomarker for cognitive impairment and underscore its relevance in developing therapeutic strategies to preserve cognitive function (37).

The observed decrease in adropin levels in individuals with bipolar disorder suggests a potential link between adropin and the pathophysiology of psychiatric conditions (38). Bipolar disorder is associated with dysregulated signaling in pathways like Akt/mTOR, which are crucial for neuronal plasticity and mood regulation (47,48). Adropin's ability to activate these pathways may contribute to its neuroprotective effects, but further studies are needed to establish causality and elucidate underlying mechanisms.

In Parkinson's disease, studies from Iraq reported significantly lower adropin levels in patients compared to healthy controls (39). Cognitive decline and dopaminergic neuronal degeneration, key features of Parkinson's, are associated with impaired Akt signaling (33). Adropin's ability to enhance Akt activation could support neuronal survival, suggesting its potential as a neuroprotective agent in managing Parkinson's disease. Increasing adropin levels or activity may provide a therapeutic approach to decelerate neurodegeneration and preserve cognitive function in these patients.

Similarly, a Turkish study found reduced adropin levels in multiple sclerosis (MS) patients compared to controls (40). Neuroinflammation, a hallmark of MS, contributes to cognitive impairment. Adropin's anti-inflammatory properties may help alleviate these effects and support cognitive function. Exploring adropin's role in MS could have broader implications for nervous system protection and maintaining cognitive health under inflammatory conditions.

Future Directions and Limitations

This systematic review offers valuable insights into the role of adropin in neurological disorders and cognitive function, but several limitations must be acknowledged. The heterogeneity of the included studies, encompassing differences in design, sample size, population characteristics, and methods of adropin measurement, limits the comparability of findings and introduces variability. Additionally, the reliance on published studies may result in potential publication bias, as positive findings are often overrepresented. The lack of randomized controlled trials and the predominance of cross-sectional designs restrict the ability to establish causal relationships between adropin levels and neurological outcomes, emphasizing the need for longitudinal and interventional studies. Geographic and demographic diversity in the studies was also limited, raising concerns about the generalizability of the findings to broader populations. Despite these limitations, this review has notable strengths, including a comprehensive synthesis of the literature and adherence to PRISMA guidelines, ensuring methodological rigor and transparency. The review highlights critical knowledge gaps, such as the need for standardized adropin measurement techniques and mechanistic studies, offering a novel focus on adropin as a biomarker and therapeutic target for neurological disorders. By bridging basic research and clinical applications, this study lays the groundwork for future research to explore adropin's full potential in improving neurological health.

Conclusion

This systematic review emphasizes the important part played by adropin in neurological health. This peptide hormone might further hold a place as a potential therapeutic target in neurological and neuropsychiatric disorders. Further studies are necessary, with emphasized efforts on the elucidation of the precise mechanisms of action of adropin and exploration of its possibilities as a biomarker and therapeutic agent in clinical contexts.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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