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Review

Neuropeptides as Potential Biomarkers in Vascular Dementia

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Abstract

Neuropeptides are endogenous active substances within the central and peripheral nervous systems that play important roles in a wide range of brain functions, including metabolism, food intake, social behavior, reproduction, learning, sleep, and wakefulness. This article reviews recent advances in the involvement of neuropeptides in vascular dementia. Neuropeptides are present in the brain as chemical signals and last for nearly 50 years. Peptide hormones are chemical signals of the endocrine system. Thus, neuropeptides are the most diverse class of signaling molecules in the brain, involving the genomes of many mammals, encoding neuropeptide precursors and many bioactive neuropeptides. Here the aim is to describe the recent advances in classical neuropeptides, as well as putative neuropeptides from other families, in the control of or as diagnostic tools for vascular dementia. Additionally, its molecular mechanisms are described to explore new avenues of treatment and early diagnosis, as there is increasing evidence that dysregulation of vascular processes is associated with different pathological conditions.

Keywords: neuropeptides; vascular dementia; therapeutics; potential biomarker

1. Introduction

1.1 Vascular Dementia

Vascular dementia (VaD), the second most prevalent form of dementia, results from a variety of factors, including age, hypertension, arteriosclerosis, diabetes, and stroke [1]. VaD subtypes are determined by characteristics such as vascular lesion type and extent, intracranial and extracranial vascular involvement, anatomical location of tissue alterations, and time elapsed since the initial vascular event [2]. Identified subtypes of VaD encompass multiple infarct dementia (cortical VaD), small vessel dementia (subcortical VaD), strategic infarct dementia, hypoperfusion dementia, and hereditary VaD that occurs predominantly in rare familial syndromes [3,4]. Traditional risk factors, such as hypertension, diabetes, and homocysteine concentration, along with inflammatory mediators, significantly contribute to VaD development. VaD is characterized by a syndrome of cognitive decline linked to reduced cerebral blood perfusion in the absence of other disorder [5]. Hypoperfusion, oxidative stress, and inflammation form the pathogenic foundation of vascular alterations, consequently causing endothelial damage, blood-brain barrier disruption, immune activation, and impairment of the nutritive coupling between brain cells and blood vessels. The hemispheric white matter is particularly susceptible to the detrimental effects of vascular risk factors, serving as the primary target for these vascular alterations. The subsequent demyelination and axonal loss contribute to the widespread changes in brain function that underlie cognitive impairment and brain atrophy.

1.2 Neuropeptides

Neuropeptides drive a wide variety of biological actions and mediate multiple regulatory functions involving all organ systems. In the 1970s, De Wied [6] discovered an endogenous peptide in nerve cells and proposed the term neuropeptide. There is a general consensus that there is a widespread distribution of neuropeptides in the both the peripheral and central nervous system that regulate metabolism, memory, sleep, and other social behaviors. Neuropeptides have been classified into classical and putative neuropeptides. All regulatory peptides from adipose tissue and their structural relatives are expressed in the brain. Recent studies suggest that neuropeptides may be involved in the pathophysiology and potential treatment of VaD [7]. This review provides an overview of the current knowledge about the pathogenic mechanisms involved in the regulatory function of neuropeptides in the control of VaD.

2. Classical Neuropeptide Regulation in Vascular Dementia

2.1 Vasopressin, Copeptin

VaD is a form of cognitive impairment that involves damage to the brain's blood vessels. Pathologically, VaD is associated with reduced blood flow to the brain, leading to

neuronal damage, oxidative stress, inflammation, and impaired cognition. Neuropeptides, such as vasopressin, have been implicated in the pathophysiology of VaD.

Arginine vasopressin (AVP) is a neuropeptide synthesized in the hypothalamus. It plays crucial roles in fluid balance, vasospasms, and stress response regulation [8]. In VaD, AVP secretion diminishes antioxidant capacity in the paraventricular nucleus of the hippocampus, contributing to disease pathogenesis and impairing cognitive function. Furthermore, research has demonstrated that AVP enhances nerve communication in the hippocampus by upregulating N-methyl-D-aspartate receptor subunit 2B and postsynaptic density protein 95. AVP dysregulation has been associated with hippocampal damage and cognitive decline in VaD [9–11]. As a potential biomarker for VaD, AVP volume increases have been observed in the right parahippocampal gyrus of Alzheimer's disease (AD) patients compared to healthy individuals. However, limitations in using AVP as a diagnostic biomarker for VaD include its non-specificity, possible interference from other diseases, and the necessity for standardized testing procedures [12]. Despite these limitations, AVP's potential as a diagnostic biomarker for VaD emphasizes the importance of further investigating neuropeptide regulation in cognitive disorders.

Copeptin, a 39-amino acid glycopeptide, originates from the C-terminal portion of the same precursor molecule as AVP [13]. It responds to osmotic pressure, hemodynamics, and nonspecific pressure-related stimuli as rapidly as AVP, rendering it a reliable surrogate marker for the neurohypophyseal hormone. Copeptin strongly correlates with AVP release in blood vessels and serves as a dependable prognostic marker for patients following myocardial infarction and heart failure. Recent studies have also revealed that copeptin can predict the risk of long-term recurrence of vascular events and death, particularly after myocardial infarction, transient ischemic attack, and stroke. However, elevated plasma copeptin levels are a risk marker for VaD, not AD [14]. These findings imply that the AVP-copeptin hormone system may be implicated in VaD development. Further randomized controlled studies with large multicenter samples are needed to ascertain whether copeptin is a valuable biomarker for predicting VaD after vascular events. In a follow-up random cohort study by Nilsson *et al.* [15], copeptin did not predict the incidence of all-cause dementia.

2.2 Gastrin-Releasing Peptide

Neurogenic gastrin-releasing peptide (GRP) is a multifaceted mammalian peptide functioning as a G-protein-coupled receptor within the Bombesin receptor family. It is secreted by nerves located in the brain, intestine, and pancreas and has been implicated in various neurological disorders, including dementia [16,17]. GRP *in vivo*, contributes to arterial injury and intimal hyperplasia following atherosclerosis by augmenting the proliferation and migration of vascular smooth muscle cells (VSMCs) and initiating their phenotypic transition from a contractile to an active state [18]. Interestingly, GRP also mitigates cognitive deficits associated with VaD by attenuating alterations in neural activity within the hippocampal cornu ammonis 3 (CA3)-CA1 pathway [19]. GRP signaling is crucial for maintaining the survival and development of new neurons. In a mouse model of hippocampal neurogenesis, GRP stimulates neurogenesis by enhancing the phosphorylation of cyclic adenosine monophosphate (cAMP) response element-binding protein. However, GRP also exerts a negative influence on the proliferation of neural stem cells in both *in vivo* and *in vitro* settings [20]. Moreover, putative GRP peptides have been found to disrupt neuronal development in calmodulin dependent protein kinase II alpha (CaMK2α)-h knockout mice. These findings indicate that GRP plays a regulatory role in neuronal development and modulates cognitive impairment linked to the hippocampus. In conclusion, GRP is a versatile peptide that participates in diverse functions across the nervous, vascular, and digestive systems. Its involvement in neurological diseases, particularly dementia, necessitates further exploration [21].

2.3 Glucagon-Like Peptide

Glucagon-like peptide (GLP) is a proglucagon-derived peptide and a product of proglucagon gene expression. GLP-1 amide, a neuroendocrine hormone, functions as a novel neuropeptide in the brain, exhibiting various biological effects [22]. Recently, GLP-1 has become a focus of interest as a potential connection between metabolism and brain injury, with associations to neurodegenerative diseases primarily through the inhibition of oxidative stress, inflammation, and apoptosis. Furthermore, GLP-1 improves cognitive impairment by modulating synaptic plasticity and reducing hippocampal neurodegeneration via glucagon-like peptide 1 receptor agonists (GLP-1Ras) [23]. In diabetic mice, evaluations of cerebrovascular neovascularization indices, Barnes maze, and water maze tests demonstrated that GLP-1 agonists yield protective neurovascular effects on pericyte functions. This occurs through the induction of vascular remodeling and the mitigation of cognitive impairment and dementia [24]. In addition to the GLP family, GLP-2 is also widely present in the cerebral cortex, cerebellum, hypothalamus, and other central nervous system regions [25]. In a VaD mouse model, GLP-2 injections enhanced learning and memory capabilities, suggesting a potential treatment for VaD through the activation of the extracellular signal-regulated kinase signal (ERK) transduction pathway in the central nervous system [26]. Genetic variations in GLP-1 analogs, observed in sulfonylureas for Alzheimer's disease (AD) treatment, are linked to a reduced risk. Future research will necessitate exploring potential mechanistic pathways between GLP-1 and AD [27].

2.4 Adrenomedullin

Since 1993, human adrenomedullin (AM) has been identified as a multifaceted neuropeptide involved in various processes such as vasodilation, hormone secretion, antimicrobial defense, cell growth, angiogenesis, and exhibiting anti-apoptotic and anti-inflammatory effects [28,29]. The impact of AM on vascular structures is well documented, including its role in the development, remodeling, and regeneration in a mouse model of cerebral ischemia [30]. Interestingly, the adrenomedullin gene is highly expressed in endothelial cells and along with nitric oxide (NO) and endothelin, it is considered a secreted product of the vascular endothelium, synthesized in all vascular endothelial cells [31]. AM expression significantly increases following vascular events, potentially restoring and repairing vascular function by upregulating both vascular endothelial and fibroblast growth factors [32]. A deficiency in AM may be associated with the exacerbation of VaD, leading to the evaluation of AM as a potential biomarker for VaD [33,34]. Furthermore, polyethylene glycol-conjugated human adrenomedullin has been proposed as a potential therapeutic agent for treating ischemic brain injury or VaD in a rat model [35]. However, the precise mechanism of AM in VaD remains unclear. Additionally, the utilization of increased vasodilator peptides and decreased vasoconstrictors could potentially worsen VaD [30]. In VaD models, astrocytes might modify the blood-brain barrier through an immune response. In the case of AD, mid-regional proadrenomedullin (MR-ProADM) is considered a novel predictor of VaD, as the elevation in MR-ProADm levels is directly related to the white matter lesion process and inversely associated with cognitive function [31].

2.5 Brain Natriuretic Factor

Brain natriuretic peptide (BNP) plays a role in the central nervous system's control of blood volume, pressure, and electrolyte composition, exhibiting similarities to atrial peptide in diuretic, natriuretic, and smooth muscle relaxant bioassays [36]. Gunstad J *et al*. [37] have demonstrated that elevated BNP levels may predict cognitive performance in patients with heart failure. Plasma BNP levels have been associated with moderate subcortical VaD but not Alzheimer's disease [38], suggesting BNP as a potential independent predictor. N-terminal pro–B-type natriuretic peptide (NT-proBNP), an inactive N-terminal fragment of pre-BNP, is released from ventricular myocytes as a prohormone in response to ischemic injury and is identified as an inactive amino-terminal of proBNP [39]. Intriguingly, higher serum NT-proBNP levels have been linked to cognitive impairment or brain microstructural changes in some cross-sectional studies [40]. A population-based prospective study on Caucasians revealed a significant association between serum NT-proBNP levels and cognitive decline and dementia, particularly in subclinical VaD. However, only one study has investigated the association between the NT-proBNP group and VaD. Thus, the exact functioning of BNP and its regulation of vascular mechanisms remain unclear.

2.6 Human Urotensin-II

Human urotensin-II (UII) is a cyclic neuropeptide with potent vasoconstrictive activity and is highly expressed in the central nervous system [41]. Human prepro-UII mRNA is most concentrated in the spinal cord but is also present in the brain, blood vessels, and heart cells. Plasma UII levels are considered biomarkers of increased endothelial dysfunction, such as hypertension, ischemic heart disease, and severity of arteriosclerosis [42]. Besides its vascular effects, UII also acts on the brain, stimulating the release of prolactin and thyroid-stimulating hormone [43]. UII is the most potent endogenous vasoconstrictor peptide known to date. It is consistently expressed in VSMCs, endothelial cells, macrophages, macrophage foam cells, and medial VSMCs, functioning in an autocrine-paracrine manner within the vascular wall. UII promotes atherosclerosis development by inducing macrophage foam cell formation, endothelial cell (EC) and VSMC proliferation, and extracellular matrix production [44]. Endothelial cells, the first-line vessel wall cells damaged during vascular events, are influenced by UII, which stimulates EC and VSMC proliferation and fibroblast-mediated collagen deposition progression and development. UII enhances endothelial cell proliferation, inhibits apoptosis through the ERK pathway, upregulates collagen-1 expression, and decreases matrix metalloproteinase-1 expression and activity [45,46]. UII also induces VSMC proliferation via the urotensin (UT) receptor and subsequently activates nicotinamide adenine dinucleotide phosphate oxidase through various intracellular signaling mechanisms [47]. Moreover, plasma immunoreactive UII (IR-UII) levels exhibit a significant independent association with VaD. IR-UII levels serve as a candidate biomarker for atherosclerosis, suggesting that elevated IR-UII levels may be a risk factor for vascular disease and a potential therapeutic target for vascular disease management [48].

2.7 Bradykinin, Kallikrein-Kinin

Bradykinin serves as a neurotransmitter in the central nervous system and peripheral tissues, functioning as a mediator of pain and inflammation [49]. Vasoactive bradykinin (BK) is released and regulated by the plasma kallikrein-kinin system (KKS). Due to the short half-life of BK, peptide KKS is a feasible direct measurement that can be performed in postmortem tissues. KKS is localized to pyramidal neurons in the neocortex and hippocampus. *In vitro* and *in vivo* experiments suggest that KKS expression may be a physiological consequence of brain or neuronal damage, potentially as a means to cope with increased blood flow from inflammation or ischemia, or to counteract the reduced reactivity of amyloid-filled or arteriosclerotic vessels

to vasoactive peptides in VaD. Neuronal KKS may exert a tissue-specific effect in the brain, increasing KKS mRNA in VaD to release BK. Interestingly, KKS mRNA levels in the frontal and temporal neocortex were approximately two-fold higher in both AD and VaD patients. Similarly, KKS protein levels were found exclusively in the temporal cortex of VaD [50]. Alternatively, BK activity influences abnormal VaD by affecting cerebrovascular tone and blood-brain barrier permeability. The relationship between VaD and KKS activation, and even BK release from the plasma kallikrein-kinin system, warrants further exploration. Elevated KKS activity in VaD could have therapeutic relevance and merits additional investigation [51].

2.8 Cerebrolysin

Cerebrolysin, a porcine brain-derived preparation, is purported to exhibit neurotrophic and neuroprotective properties [52]. This compound has been employed in the treatment of VaD [53], demonstrating improvements in memory and mitigation of neuronal atrophy in aged, spontaneously hypertensive rats [54]. Additionally, cerebroprotein hydrolysate-I (CH-I) has been shown to attenuate learning and memory deficits in a VaD mouse model, reduce apoptosis in the hippocampal CA1 region, and inhibit the activation of caspase-3 and caspase-9. CH-I treatment also appears to upregulate Bcl-2 protein levels and stimulate the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway [55]. In the context of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) accompanied by cognitive impairment, Cerebrolysin may confer protection against oxidative stress-induced apoptosis, albeit with limited efficacy [56].

2.9 Serum Somatostatin and Neuron-Specific Enolase

Somatostatin is a 14-amino acid peptide widely distributed throughout the nervous system. As a neurotransmitter or modulator, it participates in the physiological regulation of cognitive functions, motor skills, and sensations [57]. Previous studies have shown that FK962 (N-(1-acetylpiperidin-4-yl)-4-fluorobenzamide), a novel enhancer of somatostatin release, could be a potent cognitive enhancer and might have therapeutic value for cognitive disorders [58]. A study by Shen and Gao [57] has demonstrated that serum neuron-specific enolase and serum somatostatin may be biochemical markers for early VaD. It found that neuron-specific enolase levels increased and serum somatostatin levels decreased, with lower content in the frontal cortex, hippocampus, and temporal lobe, which are closely related to learning and memory.

3. Putative Neuropeptides Regulate Vascular Dementia

3.1 Leptin

Leptin, commonly referred to as the body's master hormone, is predominantly an adipocyte-derived hormone, with additional production occurring in granulosa, theca, and cumulus cells of ovarian follicles [59,60]. This hormone has been shown to exhibit neuroprotective properties and promote neurogenesis in the hippocampus of animal models [61]. A population-based study conducted in Chile revealed an increased risk of VaD is associated with low leptin levels. Moreover, reduced leptin availability was observed in elderly individuals with dementia compared to those without dementia [62]. In an earlier 10-year follow-up randomized controlled trial on aging, higher leptin levels were found to be correlated with a decreased risk of cognitive impairment [63].

3.2 Adiponectin

Adiponectin, an adipokine predominantly secreted by adipose tissue, is well-established as a regulatory factor implicated in cardiovascular diseases and diabetes. As one of the most abundant adipocytokines, adiponectin plays a crucial role in promoting vasodilation, counteracting inflammation, and inhibiting atherosclerosis [59]. It is implicated in cognitive dysfunction through the modulation of insulin signaling in the brain and is also involved in maintaining insulin sensitivity. Adiponectin contributes to the development of VaD, itself characterized by adipose tissue accumulation, by activating adenosine monophosphate-activated protein kinase (AMPK) and impairing insulin signaling, ultimately leading to improved cognition. Furthermore, adiponectin stimulates nitric oxide production via the AMPK signaling pathway, influencing cerebrovascular function and ameliorating vascular factors in VaD [64].

3.3 Enkephalins

Met-enkephalin and leu-enkephalin are peptides belonging to the opioid polypeptide family, participating in various physiological processes such as analgesia, angiogenesis, blood pressure regulation, and neuroprotection. These peptides interact with specific opioid receptors, which are extensively distributed throughout various tissues. Adrenocorticotropic hormone, a member of the melanocortin polypeptide family, serves diverse functions, including immune system regulation, stress response, and steroid hormone production in the adrenal cortex. Adrenocorticotropic hormone interacts with specific melanocortin receptors, which are also widely dispersed in the body [65]. Enkephalin involves analgesia, angiogenesis, blood pressure, and neuroprotective mechanisms. Elevated plasma levels of neuropeptide proendephalin A predict mortality and functional outcomes in ischemic stroke, which also decreased in the cerebrospinal fluid of patients with VaD [66]. In a recent study, Holm *et al*. [67] discovered that increased

Table 1. Vascular dementia-related potential neuropeptides.

Types	Related Peptides	Mechanism of regulation of vascular dementia (VaD)	Specific of identification	Reference
Classical neuropeptide	Vasopressin, Copeptin	Vascular spasm; Reduced antioxidant capacity	Plasma	[9,12,14]
	Gastrin-releasing peptide (GRP)	Stimulation of vascular smooth muscle contraction; Reduction of neurons in the hippocampal cornu ammonis 3 (CA3)-CA1 pathway	Tissue	[19,20,22]
	Glucagon-like peptide (GLP)	Inhibits oxidative stress, inflammation, and apoptosis; Stimulates vascular renewal	Tissue	[26,28,31]
	Adrenomedullin (AM)	Upregulation of vascular endothelial growth factor (VEGF) and fibroblast growth factor	Tissue	[34,35]
	Brain natriuretic factor (B-type natriuretic peptide, BNF, BNP)	———	Plasma	[43]
	Human urotensin-II (UNC II)	Contributes to the development of atherosclerosis by inducing macrophage foam cell formation, endothelial cell (EC) and vascular smooth muscle cell (VSMC) proliferation, and extracellular matrix production	Plasma	[48]
	Bradykinin, Kallikrein-kinin	Regulation of cerebrovascular tone and blood-brain barrier permeability	Tissue	[54]
	Cerebrolysin	Inhibits caspase-3 and caspase-9 activation and upregulate Bcl-2 protein levels and activate phosphatidylinositol 3-kinase (PI3K) and Akt	Serum	[59]
	Serum somatostatin and neuron-specific enolase	———	Serum	[62]
Putative neuropeptide	Leptin	Regulates vasodilation, anti-inflammatory, and antiatherosclerosis	Plasma/Tissue	[64]
	Adiponectin	Stimulate nitric oxide (NO) production through an adenosine monophosphate-activated protein kinase (AMPK) signaling pathway to affect cerebral blood vessels	Plasma/Tissue	[66]
	Enkephalins	Appear to be released both from nerve endings and from the adrenomedullary vascular cells	Plasma	[69]
	Tachykinins	Stimulate plasma extravasation, particularly acting through neurokinin-1 receptors in an endothelium-dependent manner	Plasma	[69]

plasma levels of midregional proenkephalin A were associated with a higher risk of VaD, but not with all-cause dementia or Alzheimer's disease.

3.4 Tachykinins

The tachykinin family consists of neuropeptides that govern essential physiological processes such as pain perception, cardiovascular regulation, and immune response. Substance P, the founding member of the tachykinin family, serves as a precursor for various other neural peptides [68]. In a recent study, Tian *et al*. [69]. sought to identify potential biomarkers and therapeutic targets for AD and VaD. By examining differentially expressed genes in AD and VaD and constructing a disease-specific protein-protein interaction network, unique hub genes were revealed as potential biomarkers and therapeutic targets. These findings provide significant insights into personalized treatment approaches for AD and VaD.

4. Conclusions and Future Perspectives

Although VaD was identified over a century ago; its definition and diagnostic criteria remain ambiguous. Numerous factors contribute to its development, including advanced age, diabetes, hypertension, arteriosclerosis, and stroke. Standard diagnostic methods often detect the disease at a late stage. Early diagnosis and therapeutic monitoring would substantially benefit from the identification of biomarkers, particularly blood biomarkers [70,71]. This review reports the association between neuropeptides and VaD based on existing research encompassing vasopressin,

coenzyme, GRP, GLP, and putative neuropeptides (Table 1, Ref. [9,12,14,19,20,22,26,28,31,34,35,43,48,54,59,62,64,66,69]). Neuropeptides have been shown to modulate various aspects of vascular function, such as the activation of cell proliferation and the up- or down-regulation of related signaling pathways. Collectively, such findings support the involvement of neuropeptides in the pathophysiology and analysis of VaD, extending to cognitive impairments beyond dementia, and emphasize outcomes rather than causes. Cerebral small vessel disease is the most frequent silent cerebrovascular disease. Likewise, a clinical study [72] reported that half of the patients with a first-ever lacunar infarct present mild cognitive impairment of subcortical vascular features. Nitric oxide serves as the principal neuropeptide responsible for inducing vasodilation and exerts its effects on vascular smooth muscle cells, which play a pivotal role in regulating blood vessel movement, which its presence may be a predictor of subcortical vascular dementia in the medium-long term [73]. A critical area for future investigation will be the accurate assessment of neuropeptides as potential biomarkers to differentiate between subcortical and non-subcortical VaD, considering the distinct pathophysiology, prognosis, and clinical features observed in subcortical lacunar stroke compared to other acute cerebrovascular diseases [74]. Establishing a factual foundation for treatment and prevention will enable the effective management of VaD. To date, apart from neuropeptide Y, sensitivity and specificity data for other neuropeptides related to VaD are incomplete, with the majority of experiments confined to animal or cellular models and limited data from clinical trials. The limitation of this study lies in the lack of specificity regarding neuropeptides that can serve as reliable biomarkers for dementia diagnosis in clinical settings. Further follow-up data is eagerly anticipated. Nonetheless, the temporal relationship between changes in neuropeptides and behavioral alterations, as well as their involvement in VaD progression, remains uncertain.

Author Contributions

Conception and design: XY, YM, and LY were responsible for the conception and design of the study. Drafting of the manuscript: XY, YM, and SL contributed to drafting the manuscript. Drawing of Table: YM and LY were involved in creating the table. Conceiving and critical revision of the manuscript for important intellectual content: YM, YX and SL provided valuable input during conceptualization and critically revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Yuzhen Xu is serving as one of the Guest editors of this journal. We declare that Yuzhen Xu had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel.

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