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Vasopressin, Central Autonomic Control and Blood Pressure Regulation

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Abstract

Purpose of Review We present recent advances in understanding of the role of vasopressin as a neurotransmitter in autonomic nervous system control of the circulation, emphasizing hypothalamic mechanisms in the paraventricular nucleus (PVN) involved in controlling sympathetic outflow toward the cardiovascular system.

Recent Findings Suggest that somato-dendritically released vasopressin modulates the activity of magnocellular neurons in the PVN and SON, their discharge pattern and systemic release. Advances have been made in uncovering autocrine and paracrine mechanisms controlling presympathetic neuron activity, involving intranuclear receptors, co-released neuroactive substances and glia.

Summary It is now obvious that intranuclear release of vasopressin and the co-release of neuroactive substances in the PVN, as well as the level of expression of vasopressin receptors, modulate sympathetic outflow to the cardiovascular system and determine vulnerability to stress. Further research involving patho-physiological models is needed to validate these targets and foster the development of more efficient treatment.

Keywords Vasopressin · Blood pressure · Autonomic control · Paraventricular nucleus · Magnocellular neurons · Somato-dendritic release

Introduction

Cardiovascular diseases are the most frequent cause of morbidity and mortality in the world [1]. Given the complex etiology and pathogenesis, partially effective treatment and disconcerting global epidemiological data, there is still a need for better comprehension of the mechanisms whose failure lead to cardiovascular deregulation. But, is the 'road to Damascus', when it comes to effective treatment of cardiovascular disorders paved with the necessity to firstly understand the basic mechanisms that regulate normal functioning of cardiovascular system? From the standpoint of new drug discovery it is.

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Vasopressin is one of the key mechanisms in cardiovascular control. It was discovered more than a century ago, its physiological roles have been well defined but its contribution to the pathogenesis of cardiovascular diseases is still elusive. Vasopressin is a nonapeptide, mostly synthesized in the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus, wherefrom it acts both as hormone and neurotransmitter. At the periphery it is a key contributor to hydromineral homeostasis and is a most potent vasoconstrictor. Centrally vasopressin mediates many tasks; it is a powerful modulator of the stress response, vital autonomic functions (cardio-respiratory and body temperature regulation), behavior, memory etc. [2]. This paper focuses on recent advances in understanding the role of vasopressin as neurotransmitter in autonomic nervous system control of the circulation. Evidence given over the last 5 years has elucidated central hypothalamic mechanisms in the PVN by which vasopressin, as a neurotransmitter, contributes to increased sympathetic outflow.

Central Autonomic Control of Blood Pressure

Blood pressure is a vital function that supplies blood flow, oxygen and nutrients to organs. It is fine-tuned by changes

in peripheral resistance and cardiac output interconnected by the activity of autonomic nervous system reflexes (baroreflex, chemoreflex etc). The sympathetic nerves innervating the blood vessels and the heart, and the vagus nerve innervating the heart, subserve efferent autonomic pathways. Over the years, it has been shown that the central nervous system (CNS) plays a pivotal role in maintaining sympatho-vagal balance in cardiovascular homeostasis. As stated by Dampney and his collaborators [3, 4], the CNS regulates the cardiovascular system in the short term by two general means—feed-back regulation or reflex control (predominantly by baroreceptor and chemoreceptor reflexes) and feed-forward regulation or central command (changes in the cardiovascular system that arise during physical exercise, acute stress, etc). Long-term regulation of blood pressure depends on interrelations between the sympathetic nervous system and humoral systems.

Brain structures crucially involved in autonomic regulation of blood pressure (Fig. 1) are the paraventricular nucleus of the hypothalamus (PVN), rostral ventrolateral medulla (RVLM), caudal venrolateral medulla (CVLM) and the nucleus tractus solitarius (NTS) [5]. Circumventricular organs (area postrema, organum vasculosum laminae terminalis and subfornical organ), dorsomedial hypothalamus [5], anterior hypothalamus and the arcuate nucleus [6] periaqueductal gray (PAG) [4], have also been implicated. Dysfunction of central control of blood pressure regulation is thought to lead to the chronic hyperactivity of sympathetic nervous system, which substantially participates in the pathogenesis of neurogenic hypertension [7, 8].

The PVN is a key nucleus in coordinating behavioral, endocrine and autonomic response to stress. It is a complex nucleus that consists of distinct magnocellular and parvocellular parts [9]. Neurons from the magnocellular part project to neurohypophysis and secrete vasopressin in response to minor changes in natremia/volemia. Neurons in the parvocellular subdivision project to the lower brainstem and spinal cord where sympathetic outflow is set [10, 11] and also to the limbic structures and emminentia mediana [9]. As discovered by Pyner and Coote [12, 13], there are two separate descending sympathetic pathways from the PVN, those that directly project to the IML of the spinal cord and those that project to the RVLM. The third pathway innervates neurons in both IML and RVLM. To emphasize the importance of vasopressin in these projections, it should be noted that over 40% of the PVN neurons projecting to brainstem express vasopressin mRNA [14].

Vasopressin in Central Autonomic Control of Blood Pressure

It is now well acknowledged that effects of vasopressin are mediated by three distinct subtypes of receptors, V1a, V1b and V2 receptors which belong to the large family of G-protein coupled receptors (GPCRs). In the periphery, the activation of V1a receptors (V1aRs) in blood vessels, adrenal gland and kidneys induces vasoconstriction,

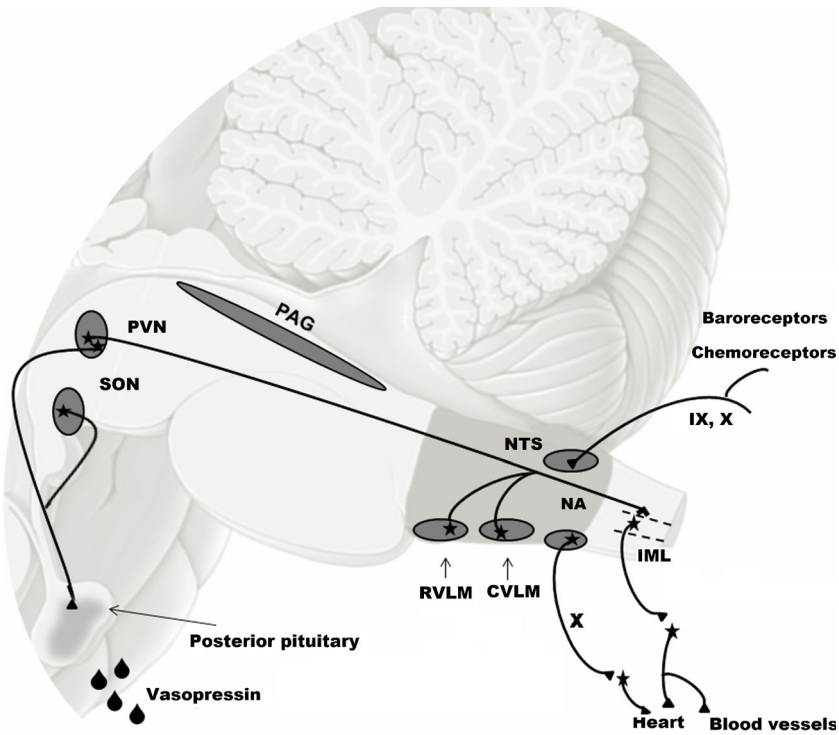

Fig. 1 Brain nuclei in the autonomic control of the circulation. The main sources of vasopressin are the PVN and the SON. Axons of magnocellular neurons in the PVN and SON project to the posterior pituitary and release vasopressin in the circulation. Axons of the parvocellular neurons of the PVN project to brainstem and spinal cord nuclei to modulate sympathetic ouflow to the cardiovascular system. PVN: paraventricular nucleus; SON: supraoptic nucleus; PAG: periaquductal gray; NTS: nucleus of the solitary tract; NA: nucleus ambiguous; RVLM: rostral ventrolateral medulla; IML: intermediolateral column of the spinal cord; CVLM: Central ventrolateral medulla

secretion of aldosterone and glucocorticoids and renin production, whilst central V1aRs contribute to the setting of sympathetic outflow and baroreflex function. V1b receptors and corticotrophin releasing factor (CRF) mediate secretion of adrenocorticotrophic hormone (ACTH) from the pituitary, and catecholamines from the adrenal gland. V2 receptors are most densely expressed in the kidneys where they act to cause water retention [15]. In adult brains, V2 receptors are not found [16], although in some parts of the brain associated with cardiovascular regulation, there are pharmacological indices of V2-like activity [17].

Central Vasopressin V1a Receptors

V1aRs are the most abundantly present vasopressin receptor subtype in the brain [18]. They have been detected in the prefrontal cortex, throughout the hypothalamus, including PVN, SON and suprachiasmatic nucleus, hippocampus, amygdala, lateral septum, RVLM, ventral tegmental area, substantia nigra, superior colliculus, dorsal raphe, NTS and the inferior olive [19–22]. V1aRs have also been found in all lamina of the gray matter in the spinal cord, including the intermediolateral column (IML) [23, 24], part of the spinal cord where bodies of sympathetic preganglionic neurons are located. The localization of V1aR in these structures supports the role for central V1aR in the modulation of autonomic control of blood pressure.

It is generally acknowledged that peripheral vasopressin does not contribute to the maintenance of blood pressure under baseline physiological conditions. However, Martin et al. [25] applied the vasopressin centrally (into the lateral ventricle) of rabbits and showed that it increases blood pressure and heart rate. Evidence that vasopressin released from the PVN is involved in sympathetic over-activity and blood pressure increase was recently provided by Han and collaborators [26•]. They observed that centrally injected angiotensin II increases the firing rate of magnocellular neurons, and that this increase was not related to the changes in plasma osmolality, but rather to a decrease in baroreflex inhibition of vasopressin neurons. The authors concluded that changes in the activity of vasopressin neurons contribute to central activation of the sympathetic nervous system and blood pressure increase by angiotensin II. Various studies have shown that the application of vasopressin into the PVN of euhydrated and normotensive rats significantly elevated blood pressure and induced increase in sympathetic nervous activity [27, 28•, 29•, 30], effects that could be antagonized with selective V1a receptor antagonists.

Although the application of a highly selective V1aR blocker into the PVN did not induce any changes on blood pressure [28•, 29•], nor did it modify cardiovascular short-term variability and baroreceptor reflex sensitivity (BRS) under baseline conditions in freely moving normotensive rats [29•], it appeared to be effective in rats after acute hyperosmotic challenge, following chronic salt loading [28•] and during exposure to stress [29•]. Experiments in anesthetized rats bilaterally microinjected by V1aR antagonist into the PVN attenuated the elevation of renal sympathetic nervous activity induced by an infusion of hypertonic saline [28•]. This finding, which demonstrates a significant contribution of vasopressin to sympatho-excitation after acute salt loading, was additionally supported in the study by Ribeiro and authors [28•]. They have shown that V1aR antagonist injected bilaterally into the PVN decreased sympathetic nervous activity and blood pressure, which were considerably elevated after 4 days of high salt intake. Taken together, results from these studies provided novel insights into the involvement of vasopressin and its receptor(s) in the pathogenesis of salt-induced hypertension. One of the noticeable changes during exposure of rats to acute stress is the increase in low frequency oscillations in the blood pressure spectra (LF-BP) that reflects the influence of the sympathetic nervous system on blood vessels [29•, 30]. Lozić et al. [29•] have shown that treatment with selective peptide V1aR antagonist prior to exposure to acute air-jet stress prevented LF-BP increase, suggesting that V1aRs located within the PVN play an important part in stress-induced sympatho-excitation, a major factor triggering sudden death [31].

Experiments on V1aR knockout mice support these findings. Mice lacking V1aRs had significantly lower values of resting blood pressure than their wild-type controls. Even though the vasopressin plasma levels of V1aR knockout mice were higher than wild-type controls, knockout mice had decreased plasma volume, followed by lower RAAS activity and decrease in plasma aldosterone levels. Moreover, it was noticed that V1aR knockout mice had decreased sympathetic nerve activity and baroreceptor reflex functioning. In salt-induced hypertension, V1aR knockout mice exhibited smaller increase in sympathetic nerve activity in response to dietary salt loading than wild-type control animals [32–34]. Altogether, results from V1aR knockout mice revealed very intricate role of V1aRs in cardiovascular homeostasis, especially V1aRs located in the CNS.

In a series of elegant experiments, Gouzène and colleagues [35] have shown that vasopressin is released from somata and dendrites of magnocellular neurons in SON and PVN. Vasopressin acts intranuclearly by the stimulation of V1aR, to foster the population of vasopressinergic neurons to discharge with a phasic pattern known to be most efficient for its systemic release. In 2006, Ludwig and Leng [36] elucidated the mechanism and gave the physiological rationale of somato-dendritic release of neurohypophyseal peptides. They showed that somatodendritic release can be modulated

by changes in intracellular calcium concentration by release of calcium from intracellular stores, regardless the process of depolarization, resulting in priming of dendritic pools for activity-dependent release [37]. In 2013, Son et al. [27] gave further evidence that intranuclearly released vasopressin subserves coordination between otherwise segregated magnocellular and parvocellular part of the PVN by the stimulation of V1aR. They used hyperosmotic challenge to induce concomitant release of vasopressin in the circulation and to increase sympathetic outflow. They found that somatodendritically released vasopressin activates V1aR in the parvocellular part to enhance sympathetic outflow. In agreement with these findings, Lozić et al. [29•] reported that adenovirally driven overexpression of V1aRs in the PVN decrease baroreflex sensitivity under baseline conditions and potentiate the increase of blood pressure and heart rate short-term variability during stress. Bearing in mind that decreased baroreflex sensitivity together with increased cardiovascular variability are recognized risk factors for cardiovascular disorders [38–40], it can be suspected that the greater density of V1aRs in the PVN may imply the greater proneness to cardiovascular events. This is further supported by the finding that centrally injected V1a antagonist to the rat minimized the harm of experimentally induced myocardial ischemia [41–43].

Central Vasopressin V1b Receptors

It is well established the brain V1bR plays a key role in the regulation of the hypothalamo-pituitary-adrenocortical axis and the stress response. During acute exposure to stress, vasopressin secreted from parvocellular neurons of the PVN and released into the portal circulation modulate ACTH release in the anterior pituitary, directly by the stimulation of V1bR on pituitary corticotrophs and by potentiating the effects of corticotrophin releasing factor (CRF) [44]. More importantly V1bRs were found to be critically involved in the process of adaptation to stress [44, 45]. In addition to the identification of V1bRs on pituitary corticotrophs and hypothalamic PVN and SON, they were detected in abundance in the limbic circuitry, olfactory bulb, hippocampus, amygdala, cerebellum, prefrontal cortex and the septum [46, 47]. Physiological and pharmacological experimentation have demonstrated that in these structures, V1bRs affect behavior: social motivation, recognition, memory [48, 49], aggression [50], anxiety and depression [51]. Moreover, selective vasopressin V1bR antagonists have been shown to exert antidepressant and anxiolytic activity [52] but they failed to be introduced into clinical practice. In this context, it is noteworthy to mention that hipothalamo-pituitary adrenocortical axis and the limbic dysfunction are key attributes of psychopathology such as depression, and depression is found to be associated with increased risk of cardiovascular pathology [53]. However, the mechanism linking these pathologies remains largely unknown. The possibility is that V1b may be this link. Rossi et al. [54] suggested a concept that PVN and V1bR activation may be implicated in the mediation of enhanced sympathetic outflow toward the cardio-renal system.

Cotransmission and Vasopressin Release

Vasopressin neurons co-express a number of other neuropeptides including apelin, dynorphin and galanin as well as the purine, adenosine triphosphate and NO [55–57]. Each of these has been demonstrated to influence the activity of vasopressin neurons and might be involved in autocrine feedback regulation of somatodendritic release [57]. Apelin is a peptide that induces elevation in mean arterial blood pressure and enhances sympathethic nervous system activity when microinjected into the parvocellular compartment of the PVN, the RVLM or into the rat brain ventricles [58–60]. The mechanism by which apelin induces sympathoexcitation is still under debate, but there are strong indices that the interplay between apelin and vasopressin systems [61] may be partly responsible for the sympathetic overdrive. Novel findings by Griffiths et al. [62•] confirm previous notions. In experiments in normotensive rats, they have demonstrated that apelin-induced sympatho-excitation at the level of RVLM is dependent upon V1aRs.

Neuroinflammation and Vasopressin Release

PVN and vasopressin were also found to be the involved in neurogenic hypertension induced by neuro-inflammation. Shen and collaborators [63] reported recently that in experimentally induced hypertension, neuroinflammation occurs and increases the expression of the NMDA receptor in the PVN resulting in increased vasopressin release and peripheral sympathoexcitation. A growing body of recent evidence supports a major role of astrocytes in the regulation of SON/PVN neuronal function. A variety of mechanisms, including the release of neuroactive substances, such as ATP, taurine, D-serine, and nitric oxide, the activity of neurotransmitter transporters responsible for uptake of glutamate as well as astrocyte controlled crosstalk between NMDA and $GABA_A$ postsynaptic receptors on magnocellular neurons, were invoked [64–66]. Some of these mechanisms were already reported to undergo compensatory changes in experimental neurogenic hypertension and heart failure in order to dampen enhanced glutaminergic activity and sympathetic over-excitation [64–66]. Figure 2 shows factors involved in autocrine

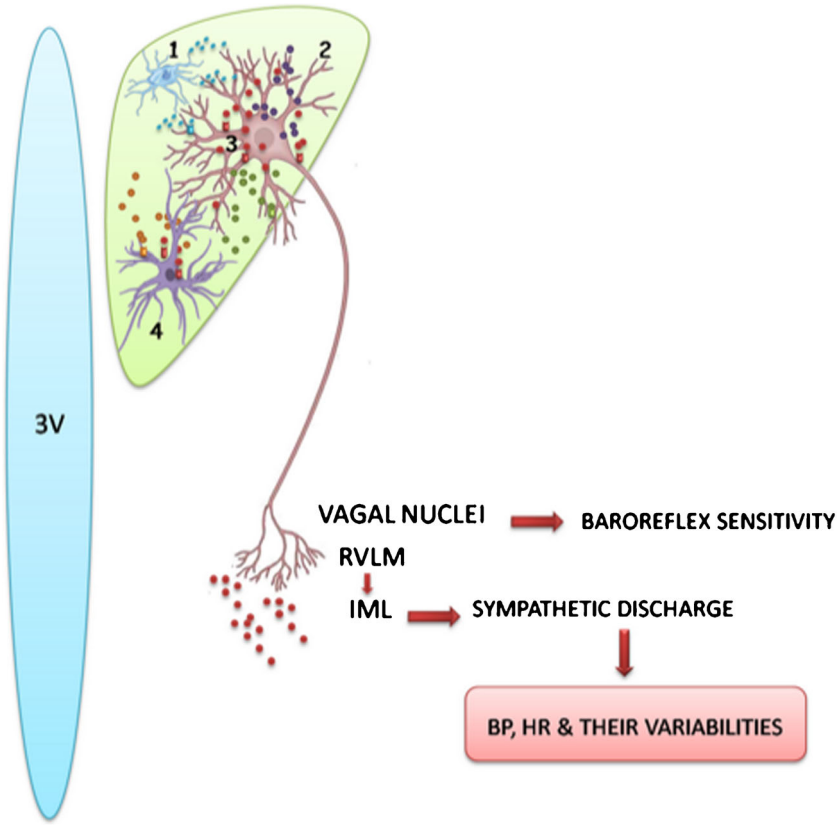

Fig. 2 Factors in local regulation of PVN-mediated sympathetic discharge. 1. Microglia and neuroinflammation; 2. Somatodendritic co-release of neurotransmitters and active substances; 3. Vasopressin receptors and other receptors; 4. Astrocytes. RVLM: rostral ventrolateral medulla; IML: intermediolateral column of the spinal cord. BP: blood pressure; HR: heart rate

and paracrine regulation of the vasopressinergic neurons in the PVN.

Conclusions

The neuropeptide vasopressin, synthesized mostly in the PVN and SON of the hypothalamus, is an important mediator of neuroendocrine regulation of the circulation and the stress response. Recent advances in basic research discovered that PVN and SON neurons co-expresses V1a and V1b receptors, and that vasopressin may act in autocrine /paracrine fashion to modulate the activity of parvocellular neurons and hence sympathetic outflow. V1aRs were found to be involved in sympathoexcitation by hyperosmotic challenges and stress. Experimental evidence also pinpoints V1b receptors in PVN as a possible link between stress-induced psychopathologies and cardio-renal sympathoexcitation. A number of neurotransmitters are co-released with vasopressin in the PVN. Apelin is one of them and it was found to enhance sympathetic outflow involving descending vasopressinergic pathways. Hypertension is characterized by neuroinflamation in the PVN and this was reported to endorse neuronal excitation and sympathoexcitation. It has been suggested that astrocytes play a role of a key compensatory mechanisms in the control of PVN neuronal activity and to undergo remodeling in experimental hypertension and heart failure.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance.
- •• Of major importance

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