REVIEW

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The paraventricular nucleus of the hypothalamus – the concertmaster of autonomic control. Focus on blood pressure regulation

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The autonomic nervous system regulates internal organs and peripheral circulation, which enables the maintenance of homeostasis in vertebrate species. One of the brain regions involved in autonomic and endocrine homeostasis regulation is the paraventricular nucleus of the hypothalamus (PVN). The PVN is a unique site at which multiple input signals can be assessed and integrated. The regulation of the autonomic system by the PVN and, especially, the sympathetic flow, depends upon the integration of inhibitory and excitatory neurotransmitter action. The excitatory neurotransmitters such as glutamate and angiotensin II, and inhibitory neurotransmitters such as γ-aminobutyric acid and nitric oxide, play a key role in the physiological function of the PVN. Moreover, arginine-vasopressin (AVP) and oxytocin (OXT) are important in the regulation of sympathetic system activity. The PVN is also crucial for maintaining cardiovascular regulation, with its integrity being pivotal for blood pressure regulation. Studies have shown that pre-autonomic sympathetic PVN neurons increase blood pressure and the dysfunction of these neurons is directly related to elevated sympathetic nervous system activity under hypertension. Etiology of hypertension in patients is not fully known. Thus, understanding the role of PVN in the generation of hypertension may help to treat this cardiovascular disease. This review focuses on the PVN's inhibitory and excitatory neurotransmitter interactions that regulate sympathetic system activity in physiological conditions and hypertension.

Key words: paraventricular nucleus of the hypothalamus, sympathetic nervous system, hypertension, PVN neurotransmission, blood pressure

INTRODUCTION

Regulation of sympathetic and parasympathetic neural activities to the target organs and peripheral circulation is essential for humans and other vertebrate species to maintain effective homeostasis. The control of physiological functions depends on a neuroendocrine and autonomic nerve-mediated mechanisms, which are regulated *via* specific brain structures. One of the brain regions involved in the regulation of homeostasis is the paraventricular nucleus of the hypothalamus (PVN).

The PVN is a highly conserved brain region present in species from zebrafish to humans. Pharmacological, anatomical, and biochemical studies conducted over the last 20 years described the structure of PVN as a team of central nervous system nuclei, comprising cell bodies of neurons. It is a bilateral structure located on either side of the third ventricle and is an elaboration of the periventricular zone of the hypothalamus. Within this structure, afferent inputs from many regions are translated and integrated into specific autonomic outputs (Patel, 2000; Benarroch, 2005; Kawabe et al., 2009; Pyner 2009; Nunn et al., 2011; Qin et al., 2018; Caba et al., 2020).

The PVN plays an important role in regulating energy homeostasis, fluid balance, stress, growth, reproductive behavior, emotion, sleep-wake balance, and cardiovascular system. This brain region regulates the activity of the

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hypothalamic-pituitary-adrenal axis (HPA), the thyroid axis, and the hypothalamic-pituitary-gonadal axis (HPG). Abnormal development or function of the PVN leads to various diseases such as growth obesity, diabetes mellitus, diabetes insipidus, hypertension, heart failure, and amenorrhea, which was confirmed in experimental animals and humans (Benarroch, 2005; Pyner, 2009; Gabor and Leenen, 2012; Basting et al., 2018; Caba et al., 2020).

This review is dedicated to the description of interactions between the inhibitory neurotransmitters [i.e., nitric oxide (NO) and γ-aminobutyric acid (GABA)] and the excitatory transmitters [i.e., angiotensin II (ANG II) and glutamate (GLU)] in PVN that determine the level of sympathetic activation in the physiological condition. Moreover, we discussed changes in local neurotransmission, which may cause hypertension.

Anatomical description of the PVN

The PVN is a small structure of the forebrain, representing about 1% of the vertebrate brain (Pyner, 2009). It lies adjacently to the third ventricle, from which it derives its name, "paraventricular", meaning "alongside a ventricle". This nucleus is a highly vascularized region of the brain (Rivest, 2002). It is protected by the blood-brain barrier (BBB), although its neuroendocrine neurons extend to sites beyond the BBB (e.g., the posterior pituitary).

The PVN is composed of the magnocellular division, with three distinct parts: anterior, posterior, and medial magnocellular subnuclei, as well as the parvocellular division with five distinct parts: dorsal, lateral, medial, periventricular, and anterior parvocellular subnuclei (Swanson et al., 1980; Qin et al., 2018). Featured parts, in addition to anatomical differences, are also characterized by different functions. The magnocellular division covers the neurons, which project to the posterior pituitary, and their main function is to control oxytocin (OXT) and arginine-vasopressin (AVP) release into the circulation. The parvocellular subdivisions project to the anterior pituitary, where they regulate the activity of the HPA axis, and several structures of the central nervous system that regulate the activity of the autonomic transmission, such as the rostral ventrolateral medulla (RVLM), intermediolateral column of the spinal cord (IML) as well as the nucleus of the solitary tract (NTS) (Benarroch, 2005; Kawabe et al., 2009; Nunn et al., 2011; Quin et al., 2018; Caba et al., 2020).

PVN afferent inputs

The PVN receives four major types of inputs: interoceptive, humoral, limbic, and intrahypothalamic (Benarroch, 2005). The interoceptive pathway includes projections from the visceral receptors, nociceptors, and thermoreceptors, which are conducted by spinal afferents that synapse in the dorsal horn and afferent vagal nerve and terminate in the NTS (Patel, 2000; Pyner, 2005). The NTS is the part of the hindbrain that is reached by fibers from cardiopulmonary receptors located on the walls of the atria and ventricles (Patel, 2000; Pyner, 2005). NTS is connected with PVN by axonal junctions, and neurons from this structure are projected to the parvocellular regions of the PVN (pPVN). Transsynaptic viral tracing studies have shown that pPVN neurons formed projections to the kidneys and adrenal medulla. Thus, due to information derived from the peripheral cardiovascular receptors, which arrive at the PVN through NTS, adaptation to specific conditions and regulation of the autonomic nervous system activity is possible. These complex projections enable the maintenance of the homeostasis of the cardiovascular system (Pyner et al., 2000; 2001; 2009). Humoral signals, such as circulating steroids and glucose can reach the PVN directly or through local interneurons (Benarroch, 2005; Ma et al., 2020). Signals can also reach the PVN through an indirect route e.g., angiotensin II (ANG II) acts *via* receptors located on the circumventricular organs that are beyond the BBB and project to the PVN (McKinley et al., 2001). Limbic signals are related to responses to stress and reach the PVN from the prefrontal cortex (PFC) and amygdala (AMG) *via* the bed nucleus of the stria terminalis (BNST) and the dorsomedial nucleus of the hypothalamus (DMH) (Sawchenko et al., 2000). Intrahypothalamic projections include the connection with the dorsomedial nucleus (DMH), the suprachiasmatic nucleus (SCN; critical for circadian control of autonomic and endocrine function), the arcuate nucleus (ARC), and the perifornical area (PFN; involved in the regulation of food intake and energy metabolism) (Benarroch, 2005).

PVN efferent outputs

The PVN neurons can be divided into three main groups (Pyner et al., 2000; 2001; Benarroch, 2005; Ferguson et al., 2008; Caba et al., 2020): i) the magnocellular neuroendocrine neurons, axons of which lead directly to the posterior pituitary and are responsible for the secretion of AVP and OXT into the circulation; ii) the parvocellular neuroendocrine neurons that secrete several hormones transported to the anterior pituitary lobe; they inhibit or stimulate the production of the appropriate hormones from endocrine cells, which potentially play essential roles in controlling the HPA

axis; iii) the preautonomic neurons. Based on Badoer's anatomical findings (2001), three groups of preautonomic neurons are likely to contribute to the ability of the PVN to influence sympathetic nerve activity. To the first group belong PVN neurons that project to the rostral ventrolateral medulla (RVLM) neurons. Excitatory effects of the PVN to the RVLM pathway are mediated *via* glutamate and it is limited by the inhibitory effect of the NTS on the RVLM due to the caudal ventrolateral medullary depressor area (CVLM) (Kawabe et al., 2008; 2009). The second group is represented by PVN neurons that project to the spinal cord and branch to innervate RVLM. The third class of neurons in the PVN project directly to the intermediolateral cell column of the spinal cord (Badoer, 2001; Hardy, 2001). This group of neurons consists of >70% of all neurons (Pyner and Cote, 2000). Up to 2000 neurons project directly from the PVN to the intermediolateral nucleus of the spinal cord. The PVN-spinal projections include neurons expressing either AVP (25-40%) or OXT (20-30%) and, to a lesser extent, endorphin, enkephalin, dopamine, or ANG II. However, projections of the preautonomic PVN neurons may also express more than one neurotransmitter (Nunn et al., 2011). The chemical stimulation (L-glutamate) of this projection causes an increase in blood pressure (BP) and renal sympathetic nerve activity (RSNA) *via* the release of glutamate or vasopressin in the IML (Nunn et al., 2011).

All in all, the PVN neurons can influence sympathetic nerve activity directly *via* the PVN-IML pathway, as well as indirectly, *via* the PVN-RVLM pathway, and both directly and indirectly *via* collaterals to the RVLM and IML.

The PVN's neurotransmitter function under physiological conditions

The PVN serves as an integration center between the neuroendocrine and central/peripheral autonomic nervous systems. Since the PVN plays a substantial role in autonomic regulation and multiple connections with other brain structures, neurotransmission located in this hypothalamic nucleus is highly important. The synaptic control of PVN is immensely complex since over 30 neurotransmitters have been identified in this structure to date (Pyner, 2009).

The regulation of sympathetic outflow by the PVN is dependent upon the integration of excitatory neurotransmitters such as glutamate (GLU) and angiotensin (ANGII) and inhibitory neurotransmitters such as γ-aminobutyric acid (GABA) and nitric oxide (NO) (Savic et al., 2022). An overview of the neurotransmitters involved in the PVN-dependent cardiovascular regulation is presented in Table 1. Below, we will describe the role of the above-mentioned neurotransmitters located in the PVN.

Excitatory neurotransmitters that determine the sympathetic tone: glutamate (GLU) and angiotensin II (ANG II)

Immunohistochemical and pharmacological studies in rats show that the PVN is one of the areas containing high levels of glutamate (GLU) and ionotropic glutamate receptors (NMDA) (Gören et al., 2000; Herman et al., 2000; Basting et al., 2018). The PVN neurons projecting spinally receive an excitatory glutamatergic input that arises from interneurons within the PVN and other regions, including extrahypothalamic subnuclei (Herman et al., 2000; Li and Pan, 2006). An excitatory amino acid is likely to be the neurotransmitter that is involved in PVN-induced cardiovascular responses. Indirect projections from the PVN to the RVLM and from the RVLM to the IML are presumably also involved in these responses (Kawabe et al., 2009). Electrical and chemical stimulation of the PVN (Table 1) in conscious and anesthetized rats elevated heart rate, as well as arterial blood pressure and sympathetic activity together with an increase in plasma epinephrine and norepinephrine levels (Martin and Haywood, 1998; Zhang et al., 1998; Gören et al., 2000; Li et al., 2001; 2006; Kawabe et al., 2008; Busnardo et al., 2009; Grzęda et al., 2011, 2017). These pressor responses were blocked by microinjections of a few NMDA receptor antagonists into the PVN (Gören et al., 2000; Li et al., 2001; 2006). On the other hand, NMDA receptor antagonists abolished the pressor responses which were a consequence of the administration of $GABA_A$ receptor antagonist bicuculline (Li and Pan, 2001) or *NOS* inhibitor, L-NMMA (Li and Pan, 2006).

ANG II is a component of the renin-angiotensin-aldosterone system (RAAS) which, in addition to its effects on blood pressure, regulates water and electrolyte management. Circulating ANG II does not exceed the BBB. The PVN and RVLM are regions where ANG II is synthesized, and where their receptors (mainly AT_1) are present (Allen et al., 1999; Sriramula et al., 2011; Sharma et al., 2012). Additionally, ANG II neurotransmission was confirmed in intra-PVN projections. ANG II acts as a neurotransmitter on the neurons, which project from the subfornical organ (SFO) to the PVN. The excitatory SFO input to the PVN is mediated by ANG II, which acts both directly *via* AT_1 receptors on PVN neurons, and indirectly, *via* increased release of glutamate from local interneurons (Latchford et al., 2004). In the parvocellular region of PVN, which is especially important for autonomic control, the expression of AT_1 receptors is high (Numm et al., 2011). In-

Table 1. An overview of the neurotransmitters involved in the PVN-dependent cardiovascular regulation.

Neurotransmitter	mRNA in PVN	Ligands	Blood pressure	Heart rate	Sympathetic activity	References
Glutamate				NMDA receptors		
	+	NMDA (+)	↑	↑	↑	Busnardo et al., 2009 Goncharuk et al., 2002 Gören et al., 2000 Grzęda et al., 2017 Kawabe et al., 2008 Li and Pan, 2007b Li et al., 2001 Li et al., 2006
		L-Glutamate (+)	↑	↑	↑	Busnardo et al., 2009 Goncharuk et al., 2002 Li et al., 2006
		AP 5 (-)	↓ NMDA/L-Glu L-NMMA/ Bicuculline	↓ NMDA/L-Glu L-NMMA/ Bicuculline	↓ NMDA/L-Glu L-NMMA/ Bicuculline	Busnardo et al., 2009 Goncharuk et al., 2002 Li and Pan, 2007a Li et al., 2001 Li et al., 2006
		LY 235959	–	↓ L-Glu	↓ L-Glu	Busnardo et al., 2009
		Kynurenic acid (-)	↓ and ↓ L-Glu	↓ and ↓ L-Glu	↓ and ↓ L-Glu	Cruz and Machado, 2009 Li and Pan, 2007a
		AAV2-flex-ta CASP3-TEVp (-)	↓	-	↓	Basting et al., 2018
				AMPA receptors		
		AMPA (+)	↑	↑	↑	Gören et al., 2000
GABA				$GABA_A$ receptors		
	+	Muscimol (+)	↓ and ↓ L-NAME	↓ and ↓ L-NAME	↓ and ↓ L-NAME	Abreu et al., 2009 Wang et al., 2009 Zhang and Patel, 1998
		Bicuculline (-)	↑ L-NAME	↑ L-NAME	↑ L-NAME	Abreu et al., 2009 Cruz and Machado, 2009 Li and Pan, 2006 Li et al., 2003 Schlenker et al., 2001* Wang et al., 2009 Zhang and Patel, 1998
				$GABA_B$ receptors		
	+	Baclofen (+)	↓	↓	↓	Badoer and Merolli, 1998 Wang et al., 2009
		CGP 52432 (-)	↑	↑	↑	Li and Pan, 2006
		CGP 35348 (-)	↑	↑	↑	Wang et al., 2009
NO				NO		
	+	SNP (+)	↓	↓	↓	Busnardo et al., 2010 Patel, 2000 Zhang and Patel, 1998
		L-NAME (-)	↑	↑	↑	Cruz and Machado, 2009 Zhang and Patel, 1998
		L-NMMA (-)	↑	↑	↑	Li et al., 2001
		N-Propyl	↓ L-Glu	↓ L-Glu	↓ L-Glu	Busnardo et al., 2010
ANG II				AT_1		
	+	ANG II (+)	↑	↑	↑	Chitravanshi et al., 2012 Sharma et al., 2012* Sriramula et al., 2011
		ACE2 (-)	↓ANG II	↓ ANG II	↓ANG II	Sharma et al., 2012*
		Losartan (-)	↓ANG II	↓ ANG II	↓ ANG II	Chitravanshi et al., 2012

↑ or ↓ - increase or decrease; ↑ ligand's name or ↓ ligand's name – ligands increase or decrease; (+) – agonist; (-) – antagonist; * – conscious rats; AAV2-flex-taCASP3-TEVp – cre-dependent caspase-lesioned glutaminergic neurons, ACE2 – angiotensin-converting enzyme 2, AMPA – AMPA receptor agonist, AP-5 – NMDA receptor antagonist, Baclofen – $GABA_B$ receptor agonist, Bicuculline – $GABA_A$ receptor antagonist, CGP-35348 – $GABA_B$ receptor antagonist, CGP52432 – $GABA_B$ receptor antagonist, GABA – γ-aminobutyric acid, L-Glu – L-glutamate, Kynurenic acid – ionotropic glutamate receptor antagonist, L-NAME – nitric oxide synthase inhibitor, L-NMMA – inhibitor of all three isoforms of NOS, NO – nitric oxide, LY235959 – NMDA receptor antagonist, Muscimol – $GABA_A$ receptor agonist, NMDA – N-methyl-D-aspartic acid, N-Propyl – nNOS inhibitor, SNP – NO donor.

trathecal (Allen et al., 2002) and intra-PVN ANG II administration (Chitrvanshi et al., 2011; Sriramula et al., 2011; Sharma et al., 2012) results in an AT_1-dependent increase in blood pressure and sympathetic activity in laboratory rats. Additionally, this effect is attenuated after the administration of losartan – an AT_1 receptor antagonist (Chitrvanshi et al., 2011).

Inhibitory neurotransmitters that determine the sympathetic tone: γ-aminobutyric acid (GABA) and nitric oxide (NO)

Wang et al. (2009) showed the mRNA expression of $GABA_A$ and $GABA_B$ receptor subtypes in the PVN. In physiological conditions, the PVN is under the potent inhibitory influence of GABA and NO, as demonstrated by the striking increase in the sympathetic drive that can be elicited by local injection of $GABA_A$ receptor antagonist – bicuculline or inhibitors of nitric oxide synthase (Schlenker et al., 2001; Li and Pan, 2006; Wang et al., 2009; Abreu et al., 2009; Cruz et al., 2009, Ferreira-Junior et al., 2019). On the other hand, microinjection of muscimol – an agonist of $GABA_A$, promotes sympathetic inhibition in anesthetized rats (Zhang and Patel, 1998; Abreu et al., 2009; Wang et al., 2009). The inhibitory effects of GABA in the PVN are mediated primarily by $GABA_A$ receptors (Li and Pan, 2006; Wang et al., 2009; Czell et al., 2012). The PVN is under tonic inhibition by GABA *via* the $GABA_A$ receptor and NO and these effects are synergistic.

The PVN is one of the central sites containing nitric oxide (NO)-positive neurons. It was also found that NO inhibits the activity of the sympathetic system and regulates the functions of the circulatory system (Hojna et al., 2010; Lu et al., 2015). Moreover, inhibition of NO activity generates overactivity of the sympathetic nervous system observed in hypertension (Zhou et al., 2014). In the PVN, three neuronal nitric oxide synthase (*NOS*) isoforms are present: neuronal (*nNOS*), endothelial (*eNOS*), and inducible (*iNOS*) (Hojna et al., 2010, Lu et al., 2015, Patel 2000). Furthermore, it was confirmed that in PVN *nNOS* and *eNOS* are involved in sympathoexcitation in renovascular hypertensive rats (Zhou et al., 2014), and *iNOS* is responsible for the increased activity of the sympathetic nervous system in a rat restraint stress model or application of the corticotropin-releasing factor (Yamaguchi et al., 2009; 2010).

Moreover, glutamatergic and GABAergic mechanisms in the PVN are modulated by NO. In the central nervous system (CNS), NO can be generated by *nNOS* in response to the activation of NMDA receptors (Santini et al., 2013). The microinjection of a non-selective nitric oxide synthase inhibitor – L-NMMA or L-NAME – into the PVN induced increase in blood pressure and heart rate and, additionally, enhanced the sympathetic response to ionotropic glutamate receptor activation (Zhang and Patel, 1998; Li et al., 2001; Hirooka et al., 2011). The sympathoexcitatory effect of L-NMMA was blocked by prior local microinjection of bicuculline (Li et al., 2001). Furthermore, microinjection of the NO donor sodium nitroprusside into the PVN leads to a decrease in sympathetic tone (Zhang and Patel, 1998; Busnardo et al., 2010) that can be prevented by prior microinjection of bicuculline at the same site (Zhang et al., 2001). NO microdialysis in the PVN produced an increase in GABA release (Cruz et al., 2009). The presented results indicate that NO effects are dependent on GABA. Moreover, a dual effect of NO is observed in the PVN: on the one hand, it reduces the glutamate-mediated excitation and on the other hand, it enhances the inhibitory effect of GABA.

Neuropeptides: vasopressin (AVP) and oxytocin (OXT)

The paraventricular nucleus of the hypothalamus is a place of synthesis of AVP and OXT, which are secreted into the peripheral circulation and perform their neuroendocrine roles. The biological effects of vasopressin are mediated by the three subtypes of receptors: $V_{1a}R$, $V_{1b}R$, and V_2R, whereas oxytocin activates its own OXTR and $V_{1a}R$ receptors. AVP and OXT receptors are present in the peripheral organs and in several regions of the brain, including PVN (Szczepańska-Sadowska et al., 2021). The pharmacological studies have confirmed that the AVP and OXT act as neurotransmitters in the projection from the PVN to the IML (Yang et al., 2002; Szczepanska-Sadowska, 2006; Savic et al., 2022). The electrical and chemical stimulation of PVN neurons results in an increase in sympathetic nerve activity and arterial blood pressure, and these effects were prevented after treatment with V_{1a} receptor antagonist ($d(CH2)5$ [$Tyr(me)^2$,arg^8] vasopressin) (Malpas and Coote, 1994; Numm et al., 2011). Tachycardia, which occurs after stimulation of PVN, was inhibited by several oxytocin receptor antagonist ($d(CH_2)_5$[$Tyr(Me)^2$, Orn^8]-oxytocin and L-368,899) injection (Yang et al., 2009). Furthermore, the intrathecal injections of AVP have been reported to increase renal sympathetic nerve activity and PVN-induced increase in MAP and RSNA were blocked by the intrathecal injections of a V_1 vasopressin receptor antagonist (Kawabe et al., 2009).

Role of the PVN neurotransmitters in the generation of hypertension

The etiology of hypertension in patients is not fully known. Thus understanding the role of PVN in

the generation of hypertension may help to treat this cardiovascular disease. It is estimated that 26% of the world's population is burdened with hypertension. The prevalence of the disease is expected to increase to 29% by 2025. The high prevalence of hypertension exacts a tremendous public health burden. Moreover, hypertension is one of the most powerful modifiable risk factors for cardiovascular and cerebrovascular diseases. Although the underlying mechanism is complex and still under investigation, it is well-accepted that the sympathetic nervous system plays a central role. Functional investigation indicates that the hyperactivity of PVN neurons may be involved in the elevated sympathetic vasomotor tone in hypertension (Fig. 1) (Zhang et al., 2002; Li and Pan, 2007a; Qin et al., 2018; Wang et al., 2020). Bilateral inhibition (chemical and electrolytic lesions) of the PVN in spontaneously hypertensive and Dahl salt-sensitive hypertensive rats produces a substantial decrease in arterial pressure (Allen, 2002; Ito et al., 2003). A certain form of hypertension – one kidney, one clip (1K1C) – is abolished in rats with a performed electrolytic lesion of the PVN (Earle et al., 1995). Of particular interest for the current review is the modification of the PVN-integrated neuronal circuitry which may play a significant role in the pathology of hypertension (Felder et al., 2003; Li and Patel, 2003).

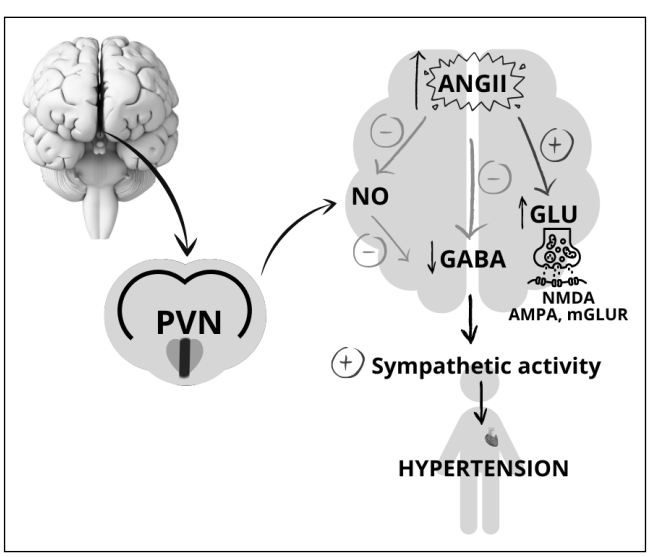

Fig. 1. The effect of PVN's excitatory and inhibitory synaptic neurotransmission imbalance in hypertension. Impaired GABA/NO-ergic transmission and ANG II-dependent GLU release result in overactivation of NMDA, AMPA, and mGLU receptors, which leads to hyperactivity of PVN and elevated sympathetic tone in hypertension. PVN – the paraventricular nucleus of the hypothalamus, GABA – γ-aminobutyric acid, NO – nitric oxide, ANGII – angiotensin II, GLU – glutamate, NMDA – ionotropic glutamate receptors, AMPA – AMPA receptors, mGLUR – metabotropic glutamate receptors.

In physiological conditions, the PVN is under the potent inhibitory influence of the GABA-NO pathway, however, this feedback loop is disturbed in hypertension. This dysfunction results in the oversecretion of GLU, ANG II, and other excitatory neurotransmitters.

Excitatory neurotransmitters that determine the sympathetic tone: glutamate (GLU) and angiotensin II (ANG II)

Increased glutamatergic neurotransmission in the PVN contributes to the elevated sympathetic vasomotor tone in SHR and the deoxycorticosterone acetate-salt model of hypertension (DOCA-salt) in mice (Li and Pan 2007a; 2017; Basting at al. 2018). The ionotropic glutamate receptor blockage (both NMDA and non-NMDA antagonists) in the PVN decreases the excitability of PVN presympathetic neurons and sympathetic outflow in spontaneously hypertensive (SHR), but not in normotensive Wistar-Kyoto (WKY) rats (Li and Pan, 2007a; 2017). Partial lesions of the PVN glutamatergic neurons [by Cre-dependent caspase (AAV-flex-taCasp3-TEVp) injections] resulted in an attenuated rise in BP following DOCA-salt treatment in mice. Noradrenaline level, as an index of sympathetic activity, was significantly reduced after DOCA-salt treatment in the animals with lesioned PVN compared to wild-type groups (Basting et al., 2018).

Consequently, intra-PVN administration of AP5 (a specific NMDA receptor antagonist) and CNQX (a selective non-NMDA receptor antagonist) caused a decrease in mean blood pressure, but only in SHRs (Li and Pan, 2007a). Additionally, the activity of group II mGluRs at the glutamatergic terminals in the PVN increased in SHR rats and this can restrain the excitability of PVN presympathetic neurons and sympathetic vasomotor tone in hypertension (Ye et al., 2013). Zhou et al. (2020) showed that activation of presynaptic group III mGluRs inhibits the excitability of PVN presympathetic neurons to attenuate sympathetic vasomotor activity. These results suggest that under physiological conditions, the glutamatergic system in the PVN does not perform a significant role in maintaining the relevant activity of the sympathetic tone. However, the inhibitory effects of inotropic receptor antagonists in SHRs indicate that ionotropic and metabotropic glutamate receptors were involved in the overactivation of the glutamatergic transmission in the PVN, which determines the elevated sympathetic tone in experimental hypertension.

The RAS is one of the most complex regulatory systems, which has a role in the regulation of cardiovascular system function. The systemic role of the RAS in the regulation of blood pressure and in the pathophysiology of hypertension has been targeted for many years.

All of the RAS components are present in the PVN (Miller and Arnold, 2019; Vargas Vargas et al., 2022).

In SHRs, there is an enhanced response in blood pressure and SFO neuron activity caused by the intracarotid injection of ANG II. This may explain the increased response to circulating angiotensin in hypertension, which is critical for the activation of the sympathoadrenal responses. ANG II has been present in elevated central concentrations in the hypothalamus and expression of the AT_1 receptors was also elevated in the PVN of SHR rats (Meyer et al., 1990). Central infusion (i.c.v.) of an AT_1 receptor blocker abolishes the increase in blood pressure in various types of experimental hypertension: in DOCA-salt rats (Park and Leenen, 2001), rats with increased plasma aldosterone (Xue et al., 2011), a high-salt diet in Dahl rats, and SHR rats (Gabor and Leenen, 2012). Raquel et al. (2022) showed that exercise training in SHR rats reduces the angiotensin levels in the PVN, thus normalizing the activity of the autonomic system and blood pressure. Moreover, PVN administration of angiotensin 1-7 (ANG 1-7, biologically active peptide of the RAS) increases blood pressure in renovascular hypertensive rats, and an increased density of Mas receptors (ANG 1-7 G protein-coupled receptor) in the PVN in hypertensive rats has also been described (Sun at al., 2012). On the other hand, inhibition of ANG 1-7 in the PVN attenuates sympathetic activity and reduces blood pressure in salt-induced hypertension (Yu et al., 2019).

Increased ANG II-dependent production of reactive oxygen species (ROS), for example, superoxide anions or hydroxyl radicals in the SFO-PVN-RVLM pathway is the most compiling mechanism underlying the generation of hypertension (Campese et al., 2007). Oxidative stress induced by high angiotensinergic system activity is important in the induction of the increase in blood pressure and the activation of the sympathetic nervous system in hypertension. Microinjection of ANG II (i.c.v.) leads to an increase in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-mediated superoxide production and Fra-like activity through enhanced expression of the AT_1 receptor, which indicates neuronal activity in PVN in hypertensive/SHR and two-kidney, one clip (2K1C) rats. The NADPH oxidase is a major factor in the increase in the cerebral production of ROS in hypertension (Campese et al., 2007). Additionally, gene expression of AT_1 receptors and NADPH oxidase subunits was elevated in the PVN in rats with renovascular hypertension (Oliveira-Sales et al., 2009). The angiotensin II-dependent complex mechanisms enhancing ROS production are presented in Fig. 2. Furthermore, interactions between NO and the intensity of oxidative stress have been reported in the rat brain. The superoxide derived from NADPH oxidase causes the inactivation of NO and, on the other hand, NO reduces the superoxide (Hirooka et al., 2011). Kishi et al. (2002) described that an elevated level of NO in the RVLM resulted in a decrease in blood pressure and sympathetic system activity to a greater degree in hypertensive (SHR) than in control rats.

Evidence for participation of oxidative stress in the pathogenesis of hypertension is provided by the studies in which the central microinjection of radical scavengers (Tempol) or NADPH oxidase inhibitor (apocynin) decreased blood pressure, reduced superoxide production and PVN neuronal excitation in SHR, but not in control rats (Kishi et al., 2004; Wang, 2020).

Inhibitory neurotransmitters that determine the sympathetic tone: γ-aminobutyric acid (GABA) and nitric oxide (NO)

Furthermore, neuronal activity of the PVN is strongly intensified when the GABA-NO feedback loop is blocked by both GABA antagonist and NOS inhibitor (Patel et al., 1996; 2000; Zhang et al., 1998). In rats with experimental hypertension induced by renal wrap

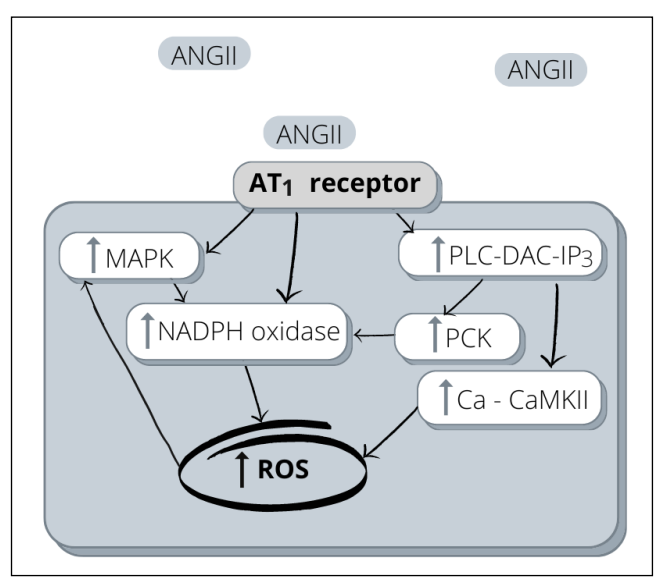

Fig. 2. ANG II-dependent mechanisms of reactive oxygen species (ROS) production (modified from Braga et al. 2011, Hirooka et al. 2011). Increased excitability of AT1 receptors leads to increased secretion of NADPH oxidase, which enhances the ROS production and activation of the MAPK and the PLC-DAG-IP3 pathway. This pathway, in turn, activates protein kinase C (PKC) leading to an increase in the NADPH oxidase activity and elevation in the intracellular concentration of calcium, and CaMKII activation. Furthermore, ROS increases the activity of NADPH oxidase by MAPK-dependent mechanisms, which finally stimulates the production of ROS. (ANG II) angiotensin II, (CaMKII) Ca2+/calmodulin-dependent protein kinase II, (MAPK) mitogen-activated protein kinase, (NADPH) nicotinamide adenine dinucleotide phosphate, (PLC-DAG-IP3) phospholipase C-diacylglycerol and inositol trisphosphate pathway, (ROS) reactive oxygen species.

(Martin and Haywood, 1998; Northcott et al., 2012) or by chronic infusion of ANGII (Da Silva et al., 2011), the tonic GABA-ergic inhibition of PVN sympathoexcitatory neurons is reduced. Additionally, the frequency and amplitude of GABA-ergic spontaneously inhibitory postsynaptic currents were decreased in SHR rats (Li and Pan, 2007b; Ferreira-Junior et al., 2019). Moreover, $GABA_A$ receptor binding sites measured by quantitative autoradiography, endogenous hypothalamic GABA concentrations, and density of muscimol (a potent, selective agonist for the $GABA_A$ receptor) binding to hypothalamic membranes were significantly lower in the PVN of SHR rats compared to normotensive control (Li et al., 2006). While injection of bicuculline ($GABA_A$ receptor antagonist) increased blood pressure in normotensive rats, in SHR rats this effect was attenuated (Li and Pan, 2007b). However, microinjection of baclofen ($GABA_B$ receptor agonist) into the PVN decreased blood pressure only in SHR animals. Blockade of the PVN $GABA_B$ receptors increases the activity of the PVN-RVLM output neurons and blood pressure in hypertensive SHRs but not in normotensive rats (Li and Pan, 2007b). According to the research described above, it follows that in hypertensive rats the function of $GABA_A$ receptors is attenuated, but the function of $GABA_B$ receptors is enhanced, in the PVN. Ferreira-Junior (2019) showed that, in both normotensive and hypertensive rats (SHR), exercise training induces an early and maintained increase in the expression of GABAergic input to presympathetic PVN neurons, which is accompanied by the reduction of sympathetic activity. Given the fact that GABA is a dominant inhibitory neurotransmitter in the hypothalamus, it was hypothesized that the reduced inhibition of GABA on sympathetic outflow contributes to the pathogenesis of hypertension. Reduced tonic GABA-ergic inhibition of the neurons may, in turn, cause a reduction in NO production, which is an important factor that leads to hypertension. The arginine-NO pathway is disturbed (mRNA expression levels of *nNOS* are reduced) in the hypothalamus of SHR and renovascular hypertensive rats (Hirooka et al., 2011). Therefore, an increase in sympathetic activity is a consequence of reduced GABA/NO inhibition, which causes an increase in the excitation mediated by NMDA and/or AT_1 receptors (Li and Pan, 2007b; Basting at al., 2018). The abnormal changes in neuronal activity also significantly increased in hypertensive versus normotensive rats. The expression of c-Fos family proteins, which has been used as markers of chronically activated neuronal populations, was enhanced in rats with various types of experimental hypertension (e.g., SHR) (Palmer and Printz, 2002) or induced by DOCA treatment (Pietranera et al., 2001).

Neuropeptides: vasopressin (AVP) and oxytocin (OXT)

AVP and OXT are the peptides that participate peripherally and centrally in the circulatory system function, including blood pressure regulation. However, their action is not fully understood (Japundžić-Žigon et al., 2020; Wsol et al., 2020).

In SHR rats and hypoxia-induced hypertension, AVP levels were elevated (Moriguchi et al., 1994; Szczepańska-Sadowska et al., 1998). Elevated levels of APV in the hypothalamus can generate overactivation of the sympathetic nervous system (Japundžić-Žigon et al., 2020). It seems that increased activity of the RAS system may cause hyperactivity of the vasopressin system in the case of hypertension (Szczepańska-Sadowska et al., 2021). Data from animal-derived models indicate that OXT may play a beneficial role in the regulation of cardiovascular functions in hypertension (Higa-Taniguchi et al., 2009; Wsol et al., 2020; Szczepańska-Sadowska et al., 2021). Hypertension is associated with altered expression of OXT receptors in the central nervous system, including the PVN in SHR rats (Martins et al., 2005; Higa-Taniguchi et al., 2009). Higa-Taniguchi et al. (2009) showed that hypertension in rats (SHR) and exercise training have opposite effects on oxytocin system activity in the PVN. The action of OXT neural projections from PVN to NTS was reduced in SHR, but physical activity improved OXT system function and corrected the hypertension-induced deficits. Additionally, the use of stressors (such as social, sensory, and environmental stress) in rats resulted in increased blood pressure in WKY and SHR, and this effect was stronger in hypertensive rats. Moreover, the stress-induced rise in blood pressure was reduced by the chronic central administration of OXT in both groups (Wsol et al., 2020).

CONCLUSIONS

In conclusion, the PVN has emerged as one of the most important autonomic control centers in the brain, playing an essential role in the maintenance of homeostasis. Moreover, the PVN is a central nervous system site, in which multiple excitatory and inhibitory input signals can be assessed and integrated. On the other hand, the complex multifactorial autonomic output can also be generated there.

The presented data documented that PVN has been implicated in the specific central mechanisms of both the regulation of important physiological cardiovascular processes as well as the pathophysiology of many diseases e.g., hypertension. Studies discussed in this review have supported the role of the PVN in the reg-

ulation of the sympathetic system. Furthermore, interactions between the inhibitory neurotransmitters (i.e., NO and GABA), and the excitatory transmitters (i.e., ANG II and GLU) significantly affect the level of sympathetic activation. Moreover, endogenous, centrally acting AVP and OXT may play an essential role in the mechanisms responsible for the generation of hypertension. Changes in neuronal excitability within the PVN are a cause of alterations in sympathetic activity in cardiovascular diseases, and thus, the PVN can be a potential target for the integrative treatment of various autonomic dysfunctions.

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