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Interaction between orexin and N-Methyl-D-Aspartate (NMDA) receptors in hypertensive and normotensive rats: an insight into predictive biomarkers for hypertension

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Abstract

High Blood Pressure also known as hypertension (HTN) is one of the most common lifestyles based chronic diseases. HTN is a high-risk contributing factor towards stroke or any other cerebrovascular disorder (CVD). Many endogenous chemicals are involved in HTN such as orexin (also known as hypocretin), which is a neuropeptide produced by the neurons located mainly in the hypothalamus. Other areas of the brain such as Locus coeruleus (LC) and Rostral ventrolateral medulla (RVLM) and endogenous chemicals such as neurotransmitters, hormones and enzymes are also directly or indirectly involved in the regulation of HTN.

We are essentially focusing on the orexin neurons that are activated by a type of glutamate receptor known as N-Methyl-D-Aspartate (NMDA). This review will discuss the role of molecules such as m-calpain and Jacob, produced because of the interaction between orexin and NMDA receptors in spontaneous hypertensive rats (SHR) and normotensive Wistar Kyoto (WKY) rats.

Keywords: Hypertension; Biomarkers; SHR and WKY rats; LC and RVLM regions; Orexin; NMDA; m-Calpain and Jacob

1. Introduction

Blood pressure is the force required for the distribution of blood in the body. However, an excessive increase in blood pressure (BP), i.e., hypertension (HTN) is detrimental to the cardiovascular system as well as multiple other systems of the body. Essential or primary hypertension leads to an increased level of cholesterol in the blood. High cholesterol levels may result in build-up of a plaque inside the arteries. Excessive plaque formation increases the chances of heart attack and/or stroke [1]. Hypertension is likely to be the consequence of an interaction between environmental and genetic factors, and if left unmanaged may lead to secondary hypertension in later stages of life. Some amendable risk factors are high salt and alcohol intake, smoking, lack of physical activity, excessive saturated fat intake, stress and obesity [2]. The World Health Organization (WHO) rates hypertension as one of the main causes of premature death worldwide and this rate continues to increase alarmingly [3].

In 2013, it was estimated that 40.6% of the people with HTN receive antihypertensive drugs for treatment but only 13.2% achieve controlled levels of BP[4]. Thus, a large number of hypertensive people are living with uncontrolled blood pressure, which means that they are at a greater risk of having ischemic attacks and developing cardiovascular diseases [4].

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According to a recent report, 31.1% of the world's adult population suffers from HTN [5]; it has also been suggested that there is a widening health disparity in HTN prevalence worldwide [5]. Out of an estimated figure of 1.39 billion hypertensive people, 349 million arose from high income and 1.04 billion from low and middle income countries [5]. It has been estimated that by 2025 there will be 1.56 billion adults worldwide living with high blood pressure [6].

There is a continuous decline in the mortality rate of HTN-gated cardiovascular diseases due to a better understanding of its underlying mechanisms in animal models [7]. In addition, the development of novel methods for the prevention of cerebrovascular diseases [8] has helped to restore this situation. Similarly, new chemicals are synthesized for the neuroprotection [9] that helped in preventing the occurrence of hypertension and related conditions such as post stroke [10]. However, more research is needed to reduce the incidences of excitotoxicity in the neurons and in the ischemic brain [11, 12] leading to a better management of the cerebrovascular attack such as stroke [13], [14].

Scientific studies have established that hypertension needs to be reduced in order to control cardiovascular and cerebrovascular diseases [15]. At present, many laboratories around the world are exploring a plethora of biomarkers, as early indicators of hypertension [16] ' [17].

The literature reports the presence of high concentrations of orexin in the spontaneously hypertensive rat (SHR), as compared to the normotensive Wistar Kyoto (WKY) rat's brain [18]. The SHR strain is considered to be the most appropriate animal model to study HTN and is readily translated to humans [19]. Moreover, the cause of rising blood pressure (BP) is not clearly understood in SHRs, which is also true in humans. Hence, SHRs have been extensively used for more than 50 years to study cardiovascular and cerebrovascular diseases, and WKY rats are used as controls in the studies using SHRs [20]. The literature also provides evidence that NMDA receptor activation could have distinct consequences on neuronal disorders depending on their location at and around synapses [21].

Synaptic NMDA receptor activation is neuroprotective, whereas extra synaptic NMDA receptors[22] trigger neuronal death and/or neurodegenerative processes[23] through cell signalling molecules such as Jacob and Calpain [24]. This antagonistic role of NMDA receptors with the orexin neurons may open many venues for the future investigations regarding their relationship with hypertension.

Over the last few decades, researchers have identified several biomarkers such as triglycerides [25], c-reactive proteins[26] and fibrinogen [27] present in the blood for the detection of HTN. Despite exhaustive research in this area, the rate of HTN is increasing alarmingly worldwide [3]. At present, all the identified biomarkers for HTN are simply categorizing its damaging effects. Either these biomarkers are produced because of HTN or due to the diseases associated with HTN; therefore, they cannot be classified as predictive biomarkers. Hence, this review will recognize the molecules, which may act as predictive biomarkers for HTN before the establishment of the disease.

2. Biomarkers of Hypertension

Several kinds of biomarkers have been identified for the detection of hypertension. Some of the well-known biomarkers of cardiovascular diseases including hypertension are triglycerides, C-reactive protein, fibrinogen, serum albumin, uric acid, homocysteine and intracellular adhesion molecule-1(ICAM-1) [28]. In general, the term 'biomarker' refers to a measurement variable associated with the outcome of a disease. Whereas, a 'predictive biomarker' is calculated mathematically between independent and dependent variables, with the goal of predicting a future outcome [29].

We are focusing on the two major endogenous chemicals i.e., Orexin and NMDA, which when they act together certain molecules are produced that may act as predictive biomarkers for HTN. Several studies have reported the involvement of the neuropeptide orexin in the regulation of blood pressure [30]'[31]. There are two isoforms of orexin, orexin A and orexin B, which bind to their corresponding G protein-gated receptors, orexin receptor 1 (OrxR-1) and orexin receptor-2 (OrxR-2), respectively [32]'[33]. The neuropeptides orexin-A and B are derived from prepro-orexin, which is mainly present in the tubal part of the hypothalamus and to a lesser extent in the testes, adrenal glands[34] and myenteric plexus [35]. Orexin-A is present across mammalian species, whereas orexin-B is present in rats and humans [36]. However, both the orexins A and B are located throughout the central nervous system as well as in the small intestine. Previous studies have also reported the cardiovascular and neuroendocrine effects of orexins [33].

Another endogenous chemical, NMDA, which is a type of glutamate receptor, is reported to be involved in the activation of orexin neurons [37]' [38]. Hypertension can also be regulated chemically by using the NMDA antagonist 1-amino cyclo propane carboxylic acid (ACPC) [39].

Extrasynaptic NMDA receptors play an important role in regulating orexin-gated hypertension [40]. Research indicates that the activation of synaptic NMDA receptors is neuroprotective; whereas, the stimulation of extrasynaptic NMDA promotes cell death [41]. Cell signalling proteins such as Jacob [42] and Calpain [43] are involved in producing hypertension through the g-protein gated cell signalling system, using the cyclic AMP transduction method [44, 45]. Interaction of NMDA receptors with that of orexin results in hypertension [46]. Recent findings indicate that the serotonin receptor along with NMDA is involved in hypoxia [47] indicating the importance of glutamatergic transmission and the role of extra synaptic NMDAR in neurodegeneration [48] and hypertension [49]'[50].

3. Possible pathways for identifying biomarkers for hypertension

At present there are certain cell signaling pathways and neurotransmitters such as the Rho-kinase [51] pathway, NMDA [52] and gamma aminobutyric acid (GABA) [53] are involved in blood pressure regulation [54, 55] and these molecules could be used as therapeutic targets. Synergistic effects of many neurotransmitters such as NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)[56-58] and several phosphorylation enzymes such as casein kinase-1 [59], casein kinase-2 [60], protein kinase CK2 [61] and phosphatases [50] are involved in the pathology of hypertension.

Similarly, hypertension is also modulated by polyamines such as spermidine [62] and spermine [62],[63] and peptides, for example arginine vasopressin[64],[65] through their actions on NMDA receptors.

The literature indicates that not only neurotransmitters but also the hormones such as angiotensin II [66, 67] are involved in regulating blood pressure. While, enzymes such as Src-kinase potentiates interaction between post and presynaptic NMDA receptors, thus affecting the blood pressure [68]. Blood pressure is mainly dysregulated due to the expression of different subunits in pre-and post-synaptic NMDA receptors [69]. Similarly, various regions of the brain regulate blood pressure by monitoring different chemicals, such as corticotropin releasing factor (CRF) in RVLM[70]; and catecholamine in the nucleus of the solitary tract [54] and the locus coeruleus [71].

The importance of biomarkers for hypertension must be viewed together with a thorough understanding of the brain areas along with the endogenous chemicals involved in the regulation of HTN.

4. Brain areas and chemicals involved in the regulation of blood pressure

The LC nucleus is in the dorsal wall of the brain stem, but its projections are widespread from the cortex to the spinal cord [72]. The LC is the major site of noradrenaline production, which participates in sympathetic activities such as increased heart rate and blood pressure. The LC plays a major role in regulating many other activities like the sleep wakefulness cycle, arousal and the stress response [73]. There are two types of adrenergic receptors α1 and α2 present in LC neurons. Stimulation of α1 adrenoceptors is excitatory whereas α2 receptors, which are located pre synaptically, are autoreceptors that play an important role in negative feedback. Excessive release of adrenaline in the brain automatically activates the α2 receptors, which in turn stops postsynaptic receptor activity, like an auto cut-off. These auto-receptors are widely distributed in the brain and have an important role in modulating noradrenaline release from its presynaptic terminal [74].

RVLM also contains adrenergic neurons and participates in an increase in blood pressure (BP), either directly or indirectly. There are bulbospinal neurons in RVLM that are sympathoexcitatory in nature, which contribute directly to hypertension [75]. Moreover, RVLM projections in LC may contribute to hypertension, by activating adrenoceptors due to spillage of noradrenaline from the dendrites of LC neurons. Indirectly, RVLM projections to the sympathetic neurons of the Intermediolateral cell column (IML) in the spinal cord activate preganglionic neurons to release glutamate, which in turn causes vasoconstriction and an increase in BP [75]. Some of the RVLM neurons have an intrinsic pacemaker, which helps in maintaining the normal rhythm of the heartbeat and thus helps in regulating BP. An increase in BP triggers the activation of baroreceptors located mainly in the neck. This activity stimulates the solitary tract nucleus (STN) which in turn triggers GABAergic neurons in the caudal ventrolateral medulla (CVLM) to inhibit RVLM activity. This whole process works as a negative feedback reaction, thus balancing the increased cardiac rhythm linked to sympathetic activity [76],[77].

Besides, the hypothalamus, orexin neurons are also densely present in the locus coeruleus [72]. Similarly, orexin fibers are present in the septal nuclei, the paraventricular, the zona incerta, the sub thalamic nucleus, the substantia nigra, the raphe nuclei, and the nucleus of the solitary tract, fewer projections are also found in cortical regions and in the olfactory bulb [78]. Higher levels of OrxR1 mRNA are present in *tenia tecta*, the hippocampus, dorsal raphe, and locus coeruleus.

Whereas, OrxR2 mRNA is mainly expressed in the cerebral cortex, nucleus accumbens, subthalamic and paraventricular thalamic nuclei [78]. Orexin receptors are widely distributed in the brain, especially in the areas of brain stem such as the rostral ventrolateral medulla (RVLM) and locus coeruleus (LC) [78]. RVLM is involved in the facilitation of cardiovascular responses such as blood pressure by the stimulation of peripheral chemoreceptors, present on the carotid body [79, 80]. Similarly, other areas of the brain such as the hypothalamic paraventricular nucleus (PVN) are also involved in controlling blood pressure through both inhibitory and excitatory neurotransmitters [46], such as GABA and glutamate (NMDA).

5. Neurotransmitters and HTN

The literature indicates that GABAergic activity in the hypothalamic arcuate nucleus (ARCN) modulates blood pressure and increases mean arterial pressure (MAP) and heart rate (HR) due to the impaired baroreflex function. Whereas NMDA in ARCN decreases MAP and increases HR [53].

Glutamate is a major excitatory neurotransmitter in the central nervous system, which plays a significant role in ischemic stroke through its ionotropic NMDA receptors. Cerebral endothelial cells respond to glutamate by altering their protein expression profile and may be important vascular targets in better understanding of the pathogenesis of ischemic stroke [81]. Components of oxidative stress may account for selective neurodegenerative disorders through glutamatergic receptors [82].

There is also a close relationship between AMPA and orexin receptors as they are present close to each other on the same postsynaptic receptor. An application of antagonists of AMPA receptors before applying orexin results in partial attenuation of anxiety-like symptoms [83], leading to HTN in future.

The glutamatergic and orexinergic interactions are diverse in different regions of the brain

[81]·[84]. Orexin not only interacts with glutamate but also communicates with dopamine neurons[85] of the nucleus accumbens[86]. Orexin plays an important role in narcolepsy, like dopamine in Parkinson's disease and acetylcholine in early Alzheimer's disease [87]. Similarly, orexin regulates metabolism and influences reward- based feeding due to its sensitivity to blood glucose levels [88].

Certain hormones, discussed below, have been reported to regulate NMDA and orexin levels and their interactions.

6. Hormones and HTN

The literature illustrates that NMDA significantly increases arterial blood pressure [89], levels of catecholamine, arginine vasopressin (AVP) and subsequent behavioral changes [64]. Similarly, angiotensin II (AngII) increases blood pressure and reproductive hormonal changes, which influence receptor movement in cardiovascular circuitry and contribute to hypertension. This cycle is mainly due to increased postsynaptic NMDA receptor activity in the PVN [84].

The estrogen receptors β (ERβs) that are present in PVN neurons influence the NMDA receptor NR1 subunit trafficking in ERβ-containing PVN neurons. These findings suggest that NR1 density is decreased in ERβ-PVN dendrites, thus reducing NMDA receptor activity, and preventing hypertension. Conversely, in the absence of estrogen, NR1 density is upregulated in ERβ-PVN dendrites and ultimately leads to the neurohormonal dysfunction resulting in hypertension Adaptive changes in glutamatergic signalling within PVN neurons may play an important role in the neurohumoral dysfunction, which results in hypertension induced by angiotensin II (ANG II) [67].

Likewise, enzymes also play an important role in the NMDA-orexin interaction and resultant changes in blood pressure.

6.1. Endogenous factors and HTN

The activities of protein kinases and phosphatases increase the NMDA receptor (NMDAR) function leading to hypertension. This modulatory effect of NMDAR is because of increased phosphorylation of these receptors due to the interaction of the enzyme casein kinase-1 with casein kinase-2. Therefore, it has been suggested that reducing the phosphorylation of the NMDAR may help in the treatment of neurogenic hypertension [59]. Inhibition of protein kinase CK2 normalizes phosphorylation and decreases NMDAR activities [60]. These findings suggest that augmented CK2 activities elevates sympathetic vasomotor tone causing essential hypertension [61].

Gases such as carbon monoxide are capable of inhibiting tumor necrosis factor-α mediated brain inflammatory disease [90], thus contributing to cytoprotection against HTN gated cerebrovascular diseases [91]. However, in the late stages of cerebral ischemia large amounts of nitric oxide (NO) produced by the inflammatory cells contribute to brain injury [92].

Similarly, salts like magnesium lithospermate B can protect neurons, both from NMDA and kainic acid-induced neurodegeneration and thus raises the possibility of using this salt as a potential neuroprotective agent [93]. Recent studies suggest that activation of Endothelin-1 receptors during Type 1 diabetes plays an important role in the dilation of cerebral arterioles [94].

Neurotransmitters, hormones, enzymes and other endogenous factors, trigger both upstream and downstream cell signaling pathways to activate the neuronal receptors leading to HTN and related cardio and cerebrovascular diseases.

The Rho/Rho–kinase pathway in the central nervous system is involved in the maintenance of dendritic spines, which form the postsynaptic contact sites of excitatory synapses. Inhibition of the Rho–kinase pathway in neurons promotes growth of dendritic spines or branches. In contrast, activation of the Rho/Rho–kinase pathway reduces dendritic spines or branches, suggesting that morphological changes of dendritic spines occur rapidly. Spine morphology is associated with glutamate sensitivity and inhibition of the Rho-kinase activity in the nucleus of the solitary tract (NTS) enhances glutamate sensitivity[51].

7. Jacob and mCalpain proteins as HTN biomarkers

Calpain is a calcium- dependent cytosolic proteolytic enzyme with different isoforms[95] such as μ-calpain and m-calpain, which are activated by synaptic and extra-synaptic NMDA receptors respectively.

Studies have indicated that the activation of μ-calpain is important for cell-survival and stimulation of m-calpain initiates toxic effects and cell death.

Under stressful conditions excessive release of corticotropin-releasing hormone (CRH) activates NMDA receptors resulting in an influx of Ca2+ molecules, which enhance the activity of mCalpain. Thus, a vicious cycle of excitotoxicity is maintained, resulting ultimately in cell-death.

As orexin is one of the well-known endogenous neuropeptides, which directly and/or indirectly stimulates extrasynaptic NMDAR, resulting in HTN, mCalpain could be considered as a significant predictive biomarker for HTN.

Jacob is a protein which discloses the origin of NMDA receptor signal and defines the communication from the synapse to the nucleus. When synaptic NMDAR get stimulated then the extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) phosphorylates the protein, Jacob. Whereas, the activation of extrasynaptic NMDARs fail to phosphorylate Jacob instead they help in translocation of Jacob to the nucleus [96]. The phosphorylated or non-phosphorylated state of Jacob determines whether it promotes cell survival and enhances synaptic plasticity or induces cell death.

These diverse functions require the regulation of gene expression and, hence, synapse-to-nucleus communication is the key factor modulated by Jacob. Activation of synaptic NMDARs induces the expression of cell survival and plasticity gene and the activation of extrasynaptic NMDARs primarily drives the expression of cell-death genes.

Overexpression of Jacob results in the gene expression that induces neurodegeneration, whereas suppression has the opposite effect. Therefore, a balanced expression of Jacob protein can play a pivotal role in protecting the neurons from the future damaging effects, thus may act as a potential biomarker for HTN.

8. Conclusion

All the biomarkers identified to date such as Interleukin- 6, intercellular adhesion molecule-1 (ICAM –1) and homocysteine cannot be classified as causative agents (predictive biomarkers) of HTN. These chemicals represent either the damaging effect of HTN or the resultant toxins due to HTN related diseases.

Until the causative agents are identified, diseases such as HTN and /or other cerebrovascular disorders cannot be cured. Several studies have indicated the direct involvement of orexin and NMDA receptors and their regulator proteins such as Jacob and Calpain in the modulation of HTN which is the leading cause of cerebrovascular diseases.

This review focussed on the molecules, such as Jacob and m-Calpain, which are produced due to the interaction between the neuropeptide orexin and extra synaptic NMDA receptors. Such molecules, which can act as predictive biomarkers, need to be investigated in further. Once these endogenous chemicals are established as causative biomarkers, then the antagonists of these molecules may be used as therapeutic agents for the treatment of HTN.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors report no conflicts of interest.

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