Review Article
New insights into limbic system roles in the myocardial effects of hypertension

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Abstract: There is a strong association between abnormalities in central nervous system structure and function and increased risk for the development of hypertension. Comprehensive clinical studies and research using animal models, including brain imaging studies, have revealed effects of insula metabolites on hypertension associated with OSA. Alterations in the limbic system of the central nervous system are closely linked both to hypertension status and to myocardial changes that result from pressure overload. While therapy, including continuous positive airway pressure, have shown excellent results, new studies delineating mechanisms of action are needed. This review article summarizes current concepts regarding central nervous system connections to hypertension and cardiac pathology associated with obstructive sleep apnea (OSA). The limbic system provides one such novel mechanism for resistant hypertension and related cardiac diseases that may be amenable to treatment in the setting of OSA.

Keywords: Review, insular cortex, habenula nucleus, raphe nucleus, resistant hypertension, sleep apnea

Introduction
Resistant hypertension is often encountered in the clinic, and is characterized by chronic elevation of blood pressure that is non-responsive to a variety of currently used anti-hypertensive medications. Although the pathogenesis of drug-resistant hypertension remains unclear, potential contributors are listed in Table 1 [1]. A relationship between obstructive sleep apnea/hypopnea syndrome (OSAHS) and cardiovascular complications has been known since the 1980’s. In OSAHS patients, treatment-resistant hypertension was attributed to chronic intermittent hypoxia (CIH), endothelial dysfunction, systemic inflammation, sympathetic nervous system abnormalities, oxidative stress and obesity. The consequence of these mechanisms resulting from sleep disorders has led to an increased incidence of vascular diseases that contribute to a significant increase in overall cardiovascular risk. For example, oxygen desaturation complex sequence plus a typical pattern of most respiratory events correlates to increased incidence of cardiovascular disease [2]. Continuous positive airway pressure (CPAP) treatment for OSAHS has led to an effective lowering of sleep-apnea related high blood pressure [3, 4]. Although CPAP is effective in lowering blood pressure, there are reports that the effect of CPAP on blood pressure in patients with OSAHS may be limited. Therefore, reducing blood pressure for some of these patients remains difficult [2].

The limbic system includes the insular cortex and habenula. In this review, we discuss the relationship between the limbic system of the nuclear island cortex, habenula, and closely associated raphe nucleus nerve structure and function of the central nervous system with cardiovascular disease. We provide new ideas for understanding the pathogenesis of resistant hypertension, which may provide insight into novel therapeutic targets.

Insular cortex and cardiovascular disease
The lobus insularis is located at the edge of the basal structure of the cortex in the native secondary cortex of the temporal cortex, which is a part of the temporal lobe cortex involved in the sorting and storage of information to process taste. The lobus insularis connects with a wide
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**Table 1. Factors that contribute to anti-hypertensive drug resistance [1]**

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<th>Factor</th>
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<tr>
<td>Age</td>
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<tr>
<td>Arterial stiffness</td>
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<td>Diabetes</td>
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<td>Chronic kidney disease</td>
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<td>Salt</td>
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<td>Sympathetic nervous system</td>
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<td>Systolic blood pressure</td>
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<td>Vascular calcification</td>
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range of other neural structures in the brain including the lobus fromatis, lobus parietalis and lobus temporalis [5, 6]. The breathing adjustment unit is located in the insular cortex and the amygdala, and the hippocampus participates in awakening during apneic episodes [7].

Vagus nerve stimulation in the airways and lung cortex activates the lobus insularis. The insular cortex regulates temperature, taste, pain, nausea, breathing, inner environmental stability and the basic sense of survival [8-13]. The insular cortex receives nerve inputs from the thalamus and hypothalamus. Electrical stimulation of the insular cortex in rats increases blood pressure. Stimulation of the cortex of the lobus insularis regulates excitement responses from the basolateral amygdala and habenula nucleus to the raphe nuclei, which may participate in regulating nerve activity during sleep [9, 14, 15].

The insular cortex plays a crucial role during breathe difficulty such as after strenuous exercise, in high altitude or other hypoxic conditions, and during acute anxiety or other emotional situations. This suggests that the insular cortex may provide a neural basis for breathing difficulties that occur during OSAHS [16, 17].

A wide variety of stimulations can each produce insular cortex-related breathing disorders. In animal studies, stimulation of the insular at the rear and tail of the cortex induced cardiac dysfunction, as monitored by echocardiography; and this cardiac dysfunction was accompanied by increased blood pressure and respiration rates. These changes may be late effects after the development of apnea and severe hypoxemia [18, 19]. This effect was blocked by adrenergic receptor blockers, but not by atropine administration. Oppenheimer and colleagues revealed an association between the stimulation of the insular cortex and cardiac arrhythmias, which occurred through the activation of the lateral area of the hypothalamus to the insular cortex. The relevant neurotransmitter may be glutamic acid [20].

Scheitz and colleagues found that insular cortex involvement, higher admission high-sensitivity cardiac troponin T, older age, hypertension, and longer monitoring associated with the new detection of AF during in-hospital ECG monitoring. Patients with higher high-sensitivity cardiac troponin T or insular cortex involvement may be candidates for prolonged ECG monitoring [21].

In OSA patients, left ventricular ejection fraction (LVEF), fractional shortening (FS) and the ratio of early to late diastolic filling (E/A) in patients with severe OSAHS were lower than in patients with moderate OSAHS and in healthy controls. Tissue Doppler imaging derived Tei index and pulmonary artery systolic pressure also increased along with the severity of OSAHS. LVEF and FS decreased in patients who suffered from OSAHS for >10 years, compared with patients who suffered from OSAHS for a shorter period of time. LVEF and FS in patients with secondary hypertension have significantly decreased relative to non-hypertensive OSAHS patients and healthy controls. E/A decreased in OSAHS patients whether they had secondary hypertension or not [22].

Alterations in brain parenchymal function influence emotion, personality and short-term memory. Pediatric heart failure patients revealed a significant reduction in cerebral gray matter volume, which may be related to the downregulation of multiple nerve pathways [23, 24]. The structural and functional abnormalities of the insular cortex associate with sudden cardiac death and heart failure, and may be involved in the formation of acute ischemic stroke and hypertension after paroxysmal atrial fibrillation (AF). OSAHS patients with heart failure in the insular cortex region have significant gray matter loss. These patients show high sympathetic nerve tone, which suggest that brain structural damage effect the autonomic nervous system, and is consistent with the clinical manifestations of OSAHS [25-28].
Habenula nucleus function and role is very important

The habenula nucleus is an important part of the limbic system, which is located in the limbic forebrain and brainstem. In addition to receiving afferent fibers into the forebrain regions, the habenula nucleus also issues efferent fiber projections to the dorsal raphe nucleus, substantia nigra and hypothalamus [29]. Due to the location of the habenular nucleus in the central nervous system and the relationship with other major neural structures, the habenular nucleus is involved in pain, sleep, endocrine, respiratory, cardiovascular and other physiological functions; in particular, cognitive function [30].

The habenular is related closely with OSA incidence. The habenular nucleus including the medial habenula and lateral habenula contains a variety of cells that respond to neurotransmitters such as acetylcholine. The habenular nucleus is closely connected with sleep. Furthermore, stimulation of the habenular nucleus disrupts breathing patterns similar to that observed during OSAHS. The habenular nucleus inhibits the release of 5-hydroxytryptophan (5-HT) through cells of the raphe nuclei, which can affect cardiovascular function [31]. The habenular nucleus promotes the psychological stress of hypertension [32].

Relationship between raphe nucleus and OSAHS

The raphe nuclei are located in the medulla of the mesencephalic reticular formation, contain 5-HT neurons, and are divided into the dorsal raphe nucleus and nuclei raphe magnus nucleus. The dorsal raphe nucleus and its two subnuclear portions are located in the dorsal lateral and ventral sides [33]. The nucleus raphe magnus is the main structure of the descending inhibitory pathway in the raphe nucleus, in which the dorsal raphe nucleus is mainly excited [34]. The raphe nucleus is continuously inhibited by the habenula [35].

The raphe nucleus receives inputs from the optic chiasm, hypothalamus, periaqueductal gray, brainstem reticular formation and the trigeminal spinal nucleus. The raphe nucleus regulates self-discipline, somatic sensory inputs, and motor and endocrine functions [36, 37]. The nucleus of the solitary tract (nTS) is a major site of brainstem control of vital functions (e.g., cardiovascular reflexes and respiration). Zec examined anatomic relationships of the human nucleus of the solitary tract, using a bidirectional lipophilic fluorescent tracer 1'-dioctadecyl-3,3',3'-tetramethylindocarbocyanine perchlorate (DiI) in 10 postmortem human fetal midgestational medulna oblongatae [38].

There are interactions between the 5-HT neurons and GABA neurons in the brain cortex and raphe nuclei. The raphe nucleus is the main structure involved in sleep regulation, and is dysregulated during sleep apnea. The dorsal raphe nucleus is involved in the central regulation in the genioglossus. Electrical stimulation of the dorsal and ventral raphe nucleus enhanced genioglossus muscle activity, suggesting that neuron excitement in the raphe nucleus region may maintain concentrations of genioglossus muscle stimulating factor. Exodic nerves may differ from the raphe nuclei as a mechanism to coordinate brain activity in response to sleep [38, 39]. In rabbits, respiratory motion changes occurred when the habenular nucleus was electrically stimulated [40].

Limbic system pathology causes OSAHS and hypertension, arrhythmias, and sudden death

The raphe and habenular nucleus are closely intermingled in the regulation of sleep activity and wakefulness, both under normal conditions and during OSAHS. Yadav and colleagues found that adult obstructive sleep apnea decreases with bilateral N-acetyl aspartate and increased inositol metabolites in the left anterior insular lobe, which is an activated glial state and may exert an anti-inflammatory effect. This could lead to greater neuronal injury, and it was suggested that protecting glial cells and neurons may be a therapeutic target for relief of OSAHS symptoms [41]. OSAHS in the marginal system can lead to nocturnal anoxia, sleep fragmentation, sympathetic nerve excitability and inflammation, as the cardiovascular system is very sensitive to hypoxia [42].

Long-term OSA associated sequelae include hypertension, atrial enlargement and fibrosis, ventricular hypertrophy, and coronary artery disease. These complications also predispose a patient to cardiac arrhythmias, as they can lead to reduction in atrial effective refractory
period, triggered and abnormal automaticity, or promote slowed and heterogeneous conduction, all of which are mechanisms that increase the persistence of re-entrant arrhythmias and prolong the QT interval.

Cardiac electrical and structural remodelling observed in OSA animal models can progress the arrhythmogenic substrate to further enhance arrhythmia generation. Future investigations clarifying the contributions of specific OSA-related mechanistic pathways to arrhythmia generation may allow targeted preventative therapies to mitigate OSA-induced arrhythmogenicity [43]. The presence and severity of obstructive sleep apnea (OSA) in patients with congenital long QT syndrome (LQTS) is associated with increased QT prolongation corrected for heart rate, which is an important biomarker of sudden cardiac death [44].

**Regulation of the cardiovascular system by the limbic system**

Recent progress has been made in our understanding of how blood pressure is regulated. The limbic system is central to cardiovascular activity regulation, and the habenular nucleus connected to the limbic forebrain and brainstem provides an important relay station that accepts signals from the limbic forebrain [45]. Limbic neural pathway function and the structural barriers itself can cause dysfunction of the cardiovascular system. This provides a new treatment idea for patients who have not successfully responded to current medication regimens.

In rats, breathing rates and blood pressure increased after electrical stimulation of the habenular nucleus. Similarly, breathing rates and blood pressure decreased after injury to the raphe nucleus, which prevented 5-HT release [46]. This finding indicates the habenular nucleus is a strong regulator for breathing and blood pressure through the transmission of neural signals from the raphe nucleus [47]. The effect of stimulating the raphe nucleus was decreased by lidocaine administration into either side of the habenular nucleus, revealing an important interaction between the habenular and raphe nucleus. Habenular stimulation itself causes high blood pressure and reduce habenular excited 5-HT, which lead to apnea, hypoxemia, sympathetic nerve and other reactions caused by secondary high blood pressure [48-50].

Using lidocaine to block the effects of stimulation of the locus coeruleus or lateral parabrachial nucleus, the habenular nucleus releases L-glutamic acid to increase blood pressure and heart rate (Figure 1). Evidence suggests that regulating the habenular nucleus is more effective in controlling blood pressure than treatments to regulate the locus coeruleus or lateral parabrachial nucleus [51]. Preventing habenular nucleus stimulation elevates arterial blood pressure, concomitant with nucleus of solitary tract neuron discharge [52]. Pressor response induced by stimulation of habenular nucleus neurons belongs to the defense reaction category of response, similar to the response that occurs in the hypothalamus. Neurotransmitters are dopamine and 5-HT. The habenular nuclei and their circuitry control the dopamine and 5-HT systems [53].

Biancardi and colleagues found that in spontaneously hypertensive rats, the hypothalamic...
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The paraventricular nucleus of solitary tract nucleus and the medullary reticular structure are involved in the hypertension response to neurohumoral activation. Angiotensin II mediates a feed-forward mechanism in hypertension by increasing blood circulation in the blood brain barrier and increasing blood brain barrier permeability [54].

The insular cortex receives visceral afferents and interacts with the structure of limbic system, and such plays an important role in the integration of visceral afferent and autonomic behavior, particularly with regard to the regulation of the cardiovascular system. Electrical stimulation to some locations within the INS can propagate to the nuclei by stimulating nerve impulses through descending pathways, which triggers an elevation in blood pressure. This indicates that the habenular nucleus is an important stopover from the limbic forebrain to the brainstem dorsal pathway. Stress exposure caused a 60% greater pressor response in Schlager inbred hypertensive (BPH/2J) mice. Stress-induced cardiovascular responses are also associated with greater neuronal activation, as detected by c-Fos expression, in the medial nucleus of the amygdala (MeAm), dorsomedial hypothalamus (DMH) and marginally in the rostral ventrolateral medulla. Mice regulate their blood pressure by activating the sympathetic nervous system, indicating the regulatory function of the amygdala, hypothalamus and medulla [55].

Single photon emission computed tomography (SPECT) was used to measure the activation of the insular cortex, thalamus and the anterior cingulate cortex in subjects under hypnosis [56]. Blocking the insular cortex of the habenula in rats revealed that habenular nucleus is one of the main pathways involved in the stimulation of the island. In addition, the amygdala and hypothalamus are also involved in this reaction, particularly the lateral hypothalamus. Electrical stimulation of the central nucleus of the amygdala increased arterial blood pressure, which was prevented by lidocaine administration. Infusion of artificial cerebrospinal fluid into the habenular nucleus had no effect on electrical pressor response to amygdala stimulation. Selective stimulation of midbrain dopamine neurons by designer receptors exclusively activated by designer drugs reduced the forced swimming test in a manner similar to that observed with lateral habenular nucleus inhibition [57]. This confirmed that LHb is a flux point of the signaling pathway.

In conclusion, there is a clear correlation between OSA and cardiovascular diseases, particularly hypertension and arrhythmias. Animal models and radiographic imaging have demonstrated that the limbic system is closely related to OSA. The concept that the limbic system is important to the development of resistant hypertension provides a new direction for the future treatment of sleep related diseases.

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Disclosure of conflict of interest

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