Int J Clin Exp Med 2017;10(9):13048-13054
www.ijcem.com /ISSN:1940-5901/IJCEM0037685

Review Article

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

Chao-Ying Yan[1], Li-Li Han[2], Jing Kang[3], Jia-Yi Tian[1], Peng Song[1], Zong-Sheng Tian[1], Ming-Xian Li[1]

[1]The First Affiliated Hospital of Jilin University, Changchun 130021, P. R. China; [2]Daxing Hospital of Capital Medical University, Beijing 102600, P. R. China; [3]Jilin Medical University, Jilin 132013, P. R. China

Received August 11, 2016; Accepted November 18, 2016; Epub September 15, 2017; Published September 30, 2017

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

Table 1. Factors that contribute to anti-hypertensive drug resistance [1]

Age
Arterial stiffness
Diabetes
Chronic kidney disease
Salt
Sympathetic nervous system
Systolic blood pressure
Vascular calcification

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 nucleus 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 1-1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate (DiI) in 10 postmortem human fetal midgestational medullae 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

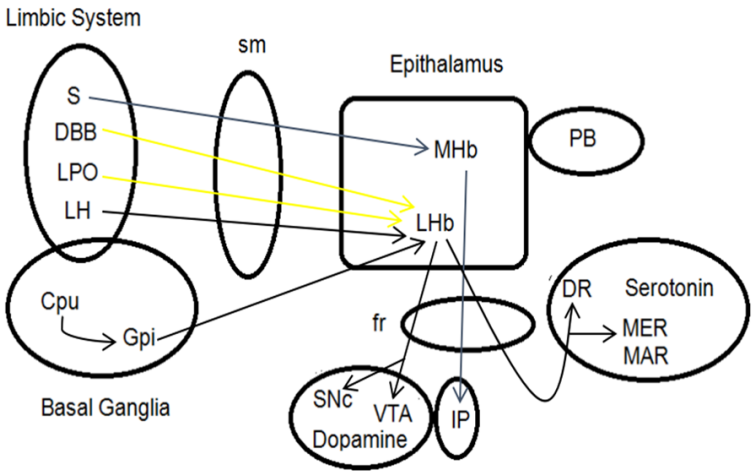

Figure 1. Afferent and efferent connections of the Hb. SNc: substantia nigra pars compacta, VTA: ventral tegmental area, DR: dorsal raphe, MER: medial raphe, MR: magnus raphe, S: septum, DBB: nucleus of diagonal band of Broca, LPO: lateral preoptic area, LH: lateral hypothalamus, GPi: globus pallidus internal segment, CPu: caudate and putamen, sm: stria medullaris, fr: fasciculus retroflexus.

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

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.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (NO. 8167-0080).

Disclosure of conflict of interest

None.

Address correspondence to: Ming-Xian Li, First Affiliated Hospital of Jilin University, 71 Xin Min Street, Changchun 130021, P. R. China. Tel: +86-15804300623; E-mail: limingxian_118@163.com

References

[1] Townsend RR. Pathogenesis of drug-resistant hypertension. Semin Nephrol 2014; 34: 506-513.

[2] Diogo LN and Monteiro EC. The efficacy of antihypertensive drugs in chronic intermittent hypoxia conditions. Front Physiol 2014; 5: 361.

[3] Pensuksan WC, Chen X, Lohsoonthorn V, Lertmaharit S, Gelaye B and Williams MA. High risk for obstructive sleep apnea in relation to hypertension among southeast Asian young adults: role of obesity as an effect modifier. Am J Hypertens 2014; 27: 229-236.

[4] Phillips CL and O'Driscoll DM. Hypertension and obstructive sleep apnea. Nat Sci Sleep 2013; 5: 43-52.

[5] Gueguin M, Le Bouquin-Jeannes R, Faucon G, Chauvel P and Liegeois-Chauvel C. Evidence of functional connectivity between auditory cortical areas revealed by amplitude modulation sound processing. Cereb Cortex 2007; 17: 304-313.

[6] Radna RJ and MacLean PD. Vagal elicitation of respiratory-type and other unit responses in basal limbic structures of squirrel monkeys. Brain Res 1981; 213: 45-61.

[7] Castillo DV, Figueroa-Guzman Y and Escobar ML. Brain-derived neurotrophic factor enhanc-

es conditioned taste aversion retention. Brain Res 2006; 1067: 250-255.
[8] Banzett RB, Mulnier HE, Murphy K, Rosen SD, Wise RJ and Adams L. Breathlessness in humans activates insular cortex. Neuroreport 2000; 11: 2117-2120.
[9] Casey KL. Forebrain mechanisms of nociception and pain: analysis through imaging. Proc Natl Acad Sci U S A 1999; 96: 7668-7674.
[10] Kinomura S, Kawashima R, Yamada K, Ono S, Itoh M, Yoshioka S, Yamaguchi T, Matsui H, Miyazawa H, Itoh H, et al. Functional anatomy of taste perception in the human brain studied with positron emission tomography. Brain Res 1994; 659: 263-266.
[11] Martinez JA, Rocha FS, Sobrani E, Galhardo FP and Terra Filho J. Effects of ondansetron on respiratory pattern and sensation of experimentally induced dyspnea. Sao Paulo Med J 2002; 120: 141-145.
[12] Miller AD, Rowley HA, Roberts TP and Kucharczyk J. Human cortical activity during vestibular- and drug-induced nausea detected using MSI. Ann N Y Acad Sci 1996; 781: 670-672.
[13] Schulte T, Brecht S, Herdegen T, Illert M, Mehdorn HM and Hamel W. Induction of immediate early gene expression by high-frequency stimulation of the subthalamic nucleus in rats. Neuroscience 2006; 138: 1377-1385.
[14] Nouwen A, Freeston MH, Cournoyer I, Deschesnes F and Boulet LP. Perceived symptoms and discomfort during induced bronchospasm: the role of temporal adaptation and anxiety. Behav Res Ther 1994; 32: 623-628.
[15] Kou ZY, Huang M and Wang S. Effect of the stimulating the insular cortex on arterial blood pressure and HABENULA neuronal firing activity. Journal of Northeast Normal University Natural Science Edition 2003; 1: 66-69.
[16] Brannan S, Liotti M, Egan G, Shade R, Madden L, Robillard R, Abplanalp B, Stofer K, Denton D and Fox PT. Neuroimaging of cerebral activations and deactivations associated with hypercapnia and hunger for air. Proc Natl Acad Sci U S A 2001; 98: 2029-2034.
[17] Corfield DR, Fink GR, Ramsay SC, Murphy K, Harty HR, Watson JD, Adams L, Frackowiak RS and Guz A. Evidence for limbic system activation during CO2-stimulated breathing in man. J Physiol 1995; 488: 77-84.
[18] Cechetto DF. Central representation of visceral function. Fed Proc 1987; 46: 17-23.
[19] Li MX, Wang JH and Wang S. Blockage of the habenular nucleus can eliminate dyspnea induced by electrostimulation of the insular cortex. Neural Regen Res 2010; 5: 1025-1029.
[20] Oppenheimer SM and Cechetto DF. Cardiac chronotropic organization of the rat insular cortex. Brain Res 1990; 533: 66-72.
[21] Scheitz JF, Erdur H, Haeusler KG, Audebert HJ, Roser M, Laufs U, Endres M, Nolte CH. Insular cortex lesions, cardiac troponin, and detection of previously unknown atrial fibrillation in acute ischemic stroke: insights from the troponin elevation in acute ischemic stroke study. Stroke 2015; 46: 1196-201.
[22] Yang SQ, Han LL, Dong XL, Wang CY, Xia H, Liu P, Wang JH, He PP, Liu SN and Li MX. Maleffects of obstructive sleep apnea on the heart. Sleep Breath 2012; 16: 717-722.
[23] Brunoni AR, Vanderhasselt MA, Boggio PS, Fregni F, Dantas EM, Mill JG, Lotufo PA and Bensenor IM. Polarity- and valence-dependent effects of prefrontal transcranial direct current stimulation on heart rate variability and salivary cortisol. Psychoneuroendocrinology 2013; 38: 58-66.
[24] Scheitz JF, Erdur H, Haeusler KG, Audebert HJ, Roser M, Laufs U, Endres M and Nolte CH. Insular cortex lesions, cardiac troponin, and detection of previously unknown atrial fibrillation in acute ischemic stroke: insights from the troponin elevation in acute ischemic stroke study. Stroke 2015; 46: 1196-1201.
[25] Harper RM, Macey PM, Henderson LA, Woo MA, Macey KE, Frysinger RC, Alger JR, Nguyen KP and Yan-Go FL. fMRI responses to cold pressor challenges in control and obstructive sleep apnea subjects. J Appl Physiol (1985) 2003; 94: 1583-1595.
[26] Menteer J, Macey PM, Woo MA, Panigrahy A and Harper RM. Central nervous system changes in pediatric heart failure: a volumetric study. Pediatr Cardiol 2010; 31: 969-976.
[27] Woo MA, Macey PM, Fonarow GC, Hamilton MA and Harper RM. Regional brain gray matter loss in heart failure. J Appl Physiol (1985) 2003; 95: 677-684.
[28] Woo MA, Stevenson WG, Moser DK, Trelease RB and Harper RM. Patterns of beat-to-beat heart rate variability in advanced heart failure. Am Heart J 1992; 123: 704-710.
[29] Cui L, Wang JH, Wang M, Huang M, Wang CY, Xia H, Xu JG, Li MX and Wang S. Injection of L-glutamate into the insular cortex produces sleep apnea and serotonin reduction in rats. Sleep Breath 2012; 16: 845-853.
[30] Aizawa H. Habenula and the asymmetric development of the vertebrate brain. Anat Sci Int 2013; 88: 1-9.
[31] Wang J, Wang M, Wei Z, Li M, Huang M and Wang S. The lateral habenular nucleus mediates signal transduction from the insular cor-

tex in OSA rats. Sleep Breath 2014; 18: 491-497.
[32] Descarries L, Watkins KC, Garcia S and Beaudet A. The serotonin neurons in nucleus raphe dorsalis of adult rat: a light and electron microscope radioautographic study. J Comp Neurol 1982; 207: 239-254.
[33] Yu P, Song G, Liu L and Liu YX. [Effects of stimulation at different areas of nucleus raphe dorsalis on genioglossus and diaphragm activities]. Sheng Li Xue Bao 1998; 50: 106-110.
[34] Wang S and Liu MZ. Spontaneous discharges of habenular nucleus and its inhibitory action on nucleus raphe magnus. Science Bulletin 1980; 25: 83-88.
[35] Nogueira MI, de Rezende BD, do Vale LE and Bittencourt JC. Afferent connections of the caudal raphe pallidus nucleus in rats: a study using the fluorescent retrograde tracers fluorogold and true-blue. Ann Anat 2000; 182: 35-45.
[36] Bagdy E, Kiraly I and Harsing LG Jr. Reciprocal innervation between serotonergic and GABAergic neurons in raphe nuclei of the rat. Neurochem Res 2000; 25: 1465-1473.
[37] Schwartz AR, Bennett ML, Smith PL, De Backer W, Hedner J, Boudewyns A, Van de Heyning P, Ejnell H, Hochban W, Knaack L, Podszus T, Penzel T, Peter JH, Goding GS, Erickson DJ, Testerman R, Ottenhoff F and Eisele DW. Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. Arch Otolaryngol Head Neck Surg 2001; 127: 1216-1223.
[38] Zec N and Kinney HC. Anatomic relationships of the human nucleus of the solitary tract in the medulla oblongata: a DiI labeling study. Auton Neurosci 2003; 105: 131-144.
[39] Wang YT, Wang N, Li RF and Liu L. [Inspiratory-facilitated effects due to electrical stimulation of the nucleus raphe dorsalis in rabbits]. Sheng Li Xue Bao 1987; 39: 248-254.
[40] Cragg BG. The role of the habenula in the respiratory response of the rabbit to warmth or to restraint. Exp Neurol 1961; 4: 115-133.
[41] Jasmin L, Burkey AR, Granato A and Ohara PT. Rostral agranular insular cortex and pain areas of the central nervous system: a tract-tracing study in the rat. J Comp Neurol 2004; 468: 425-440.
[42] Yadav SK, Kumar R, Macey PM, Woo MA, Yan-Go FL and Harper RM. Insular cortex metabolite changes in obstructive sleep apnea. Sleep 2014; 37: 951-958.
[43] Lv Y, Ma D, Meng H, Li C and Lin W. Habenula regulates cardiovascular activities in the insula cortex in a rat model of epilepsy. Int J Neurosci 2012; 122: 314-323.
[44] May AM, Van Wagoner DR, Mehra R. OSA and cardiac arrhythmogenesis: mechanistic insights. Chest 2017; 151: 225-241.
[45] McCombe A, Touma F, Jackson D, Canniffe C, Choudhary P, Pressley L, Tanous D, Robinson PJ, Celermajer D. Sudden cardiac death in adults with congenitally corrected transposition of the great arteries. Open Heart 2016; 3: e000407.
[46] Yang SN and Wang S. Chemical stimulation of habenula caused respiratory effects in rats. Act Zool Sin 1993; 39: 181-184.
[47] Yu L, Li H and Huang M. Dorsal raphe nucleus mediated reins check respiration and behavior of rats. Chin J Clin Rehab 2005; 9: 75-77.
[48] Peng L, Wang J, Zhang L, Liu P, Wang M, Huang M, Liu S, He P, Cui L, Li M and Wang S. Role of 5-hydroxytryptamine expression in cerebellar Purkinje cells in obstructive sleep apnea syndrome. Neural Regen Res 2012; 7: 606-610.
[49] Meng H, Wang Y, Huang M, Lin W, Wang S and Zhang B. Chronic deep brain stimulation of the lateral habenula nucleus in a rat model of depression. Brain Res 2011; 1422: 32-38.
[50] Pan YZ, Wang XM, Wu SS and Wang S. [Effect of losartan on arterial blood pressure and unit discharging of neurons in LHb and MHb of rat]. Zhongguo Ying Yong Sheng Li Xue Za Zhi 2002; 18: 23-25.
[51] Yang LM, Yu L, Jin HJ and Zhao H. Substance P receptor antagonist in lateral habenula improves rat depression-like behavior. Brain Res Bull 2014; 100: 22-28.
[52] Yamaguchi N and Okada S. Cyclooxygenase-1 and -2 in spinally projecting neurons are involved in CRF-induced sympathetic activation. Auton Neurosci 2009; 151: 82-89.
[53] Ouyang M and Wang S. Dexamethasone attenuates the depressor response induced by neuropeptide Y microinjected into the nucleus tractus solitarius in rats. Br J Pharmacol 2000; 129: 865-870.
[54] Stephenson-Jones M, Floros O, Robertson B and Grillner S. Evolutionary conservation of the habenular nuclei and their circuitry controlling the dopamine and 5-hydroxytryptophan (5-HT) systems. Proc Natl Acad Sci U S A 2012; 109: E164-173.
[55] Biancardi VC, Son SJ, Ahmadi S, Filosa JA and Stern JE. Circulating angiotensin II gains access to the hypothalamus and brain stem during hypertension via breakdown of the blood-brain barrier. Hypertension 2014; 63: 572-579.
[56] Davern PJ, Jackson KL, Nguyen-Huu TP, La Greca L and Head GA. Cardiovascular reactivity and neuronal activation to stress in Schlager genetically hypertensive mice. Neuroscience 2010; 170: 551-558.
[57] Nair SG, Strand NS and Neumaier JF. DREADDing the lateral habenula: a review of methodological approaches for studying lateral habenula function. Brain Res 2013; 1511: 93-101.