Review Article

J Babol Univ Med Sci
23; 2021. P: 412-420

Nerve Centers Affecting the Function of the Cardiovascular System

V. Alikhani (PhD)[1], R. Mohebbati (PhD)[2], M. N. Shafei (PhD)*[2]

1.Department of Physiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, I.R.Iran

2.Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, I.R.Iran

J Babol Univ Med Sci; 23; 2021; PP: 412-420

Received: Dec 11st 2020, Revised: Feb 3rd 2021, Accepted: Feb 24th 2021.

ABSTRACT

BACKGROUND AND OBJECTIVE: The activity of the cardiovascular system is carried out by the Autonomic Nervous System (ANS). ANS itself is controlled by multiple nerve centers. At present, there is little and scattered information about them in Persian language. The aim of this review article is to collect information about nerve centers that control ANS and their relationship with cardiovascular activity in Persian.

METHODS: In this review article, by searching the international and national databases of web of science, Scopus, Google Scholar, PubMed, ISC and Magiran until 2020 and using the keywords cardiovascular system, baroreflex, the rostral ventrolateral medulla (RVLM), the caudal ventrolateral medulla (CVLM), the nucleus tractus solitarius (NTS), the hypothalamic paraventricular nucleus (PVN), the hypothalamic supraoptic nucleus (SON), amygdala, raphe nucleus, the periaqueductal gray (PAG), cuneiform nucleus (CnF), the rostral ventromedial medulla (RVM) and the pedunculopontine tegmental nucleus (PPT), data about Autonomic Nervous System were collected.

FINDINGS: Evaluations have shown that the most important brain centers for regulating blood pressure are the rostral ventrolateral medulla, the nucleus tractus solitarius, the hypothalamic paraventricular nucleus, the periaqueductal gray, and raphe nucleus, which control cardiovascular activity mainly by affecting the sympathetic system.

CONCLUSION: According to the results of this study, the maintenance of basal blood pressure, heart rate regulation and reflex control of blood pressure and heart rate are mainly done by autonomic and especially sympathetic nerve centers.

KEY WORDS: *Cardiovascular System, Brain Nuclei, Autonomic Nervous System, Baroreflex, Blood Pressure*.

Please cite this article as follows:

Alikhani V, Mohebbati R, Shafei MN. Nerve Centers Affecting the Function of the Cardiovascular System. J Babol Univ Med Sci. 2021; 23: 412-20.

***Corresponding Author: M. N. Shafei (PhD)**
Address: Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, I.R.Iran
Tel: +98 51 38828565
E-mail: : ShafeiMN@mums.ac.ir

[DOR: 20.1001.1.15614107.1400.23.1.58.7]
[DOI: 10.22088/jbums.23.1.412]

Introduction

One of the most important factors in regulating the activity of the cardiovascular system is the Autonomic Nervous System (ANS). The ANS system consists of two parts, the sympathetic and the parasympathetic, which have pre and postganglionic neurons. The cell body of sympathetic preganglionic neurons is located in the spinal cord and postganglionic neurons in the sympathetic chain, and their outputs reach target organs such as the heart and arteries. In the parasympathetic system, the preganglionic neurons are located in the sacral and external parts, and their postganglionic neurons are located in the target tissue. The activity of the ANS system is regulated by the supraspinal areas known as the premotor centers. There are many of these centers and they are mainly located in the medulla oblongata, the pons, mesencephalon and hypothalamus and even the cerebral cortex. The most important of these are the rostral ventrolateral medulla (RVLM), caudal ventrolateral medulla (CVLM), nucleus tractus solitarius (NTS), the hypothalamic paraventricular nucleus (PVN), periaqueductal gray (PAG), raphe nucleus, cuneiform nucleus (CnF) and pedunculopontine tegmental nucleus (PPT) (1, 2). This review article provides useful information on cardiovascular activity in these regions.

Methods

This review article was conducted after approval by the ethics committee of Mashhad University of Medical Sciences with the ethics code IR.MUMS.MEDICAL.REC.1398.338. Collected content were collected and analyzed using the keywords cardiovascular system, baroreflex, heart rate, RVLM, CVLM, NTS, PVN, PAG, CnF and PPT in Web of science, Scopus, Google Scholar, PubMed, ISC and Magiran databases by 2020.

Results

There is an important center that regulates cardiovascular activity in the medulla oblongata, known as the vasomotor center (VMC). This center is responsible for maintaining and regulating blood pressure and controlling reflexes. Studies have shown that, first, the center itself includes several areas such as RVLM, CVLM and NTS, and second, other centers such as raphe nucleus, PVN, PAG, CnF and PPT are effective in regulating cardiovascular activity. Table 1 summarizes the inputs and outputs of these areas of the brain involved in cardiovascular activity. In the following sections, the anatomical and physiological characteristics of the regulation of cardiovascular activity are evaluated.

Table 1. The following table summarizes the inputs and outputs of the brain areas involved in cardiovascular activity, along with neurotransmitters and their location.

Brain nucleus	Location	The most important neurotransmitter	Cardiovascular function	Input	Output
RVLM	Anterior medulla (3)	(Glutamate, GABA, Angiotensin II) (4)	Sympathetic and vascular stimulators, regulation of blood pressure, chemoreflexes, baroreflex (4)	NTS, CVLM, PAG, PVN, Kölliker-Fuse/Parabrachial complex, amygdala, cuneiform nucleus, raphe nucleus	The intermediolateral nucleus (4)
CVLM	Medulla	GABA, glutamate	Blood pressure reduction by inhibiting RVLM	NTS	RVLM (5)
NTS	Posterior medulla	Glutamate, acetylcholine, adenosine triphosphate	Baroreceptors and Chemoreceptors	Baroreceptor afferent fibers, carotid body afferents	Nucleus ambiguus, RVLM, CVLM
PVN	Either side of the third ventricle	Vasopressin, oxytocin	Regulation of blood pressure, emotional control of the cardiovascular system	Nucleus tractus solitarius	Preganglionic neurons, enlargement of the pituitary gland, nucleus tractus solitarius, limbic system and amygdala, brainstem
Raphe nucleus	Medulla	Serotonin	Baroreflex, blood pressure regulation	Arc-shaped fiber	RVLM, spinal cord
PAG	Mesencephalon	Glutamate	Modulation of pain (6), baroreflex, regulation of blood pressure, cardiovascular activity	Hypothalamus, basal forebrain, cuneiform nucleus, substantia nigra, reticular formation, raphe magnus (7)	NTS ،RVMM ،RVLM
CnF	Mesencephalon	Glutamate, acetylcholine	Cardiovascular control, pain modulation, blood pressure regulation	Inserta region, amygdala, hypothalamus, superior colliculus, PAG, substantia nigra, anterior cuneiform nucleus	RVLM, gigantocellular reticular nucleus, vagus nerve, nucleus tractus solitarius, limbicsystem, Kölliker-Fuse/Parabrachial complex
PPT	Upper pons (8)	Glutamate, acetylcholine, GABA (8)	Autonomous regulation (9), Regulation of blood pressure (10)	Basal ganglia, extrapyramidal system (8)	Subthalamic nucleus, substantia nigra pars compacta, internal globus pallidus (11)

[DOR: 20.1001.1.15614107.1400.23.1.58.7]
[DOI: 10.22088/jbums.23.1.412]

The rostral ventrolateral medulla (RVLM): The RVLM is located between the facial nerve nuclei at the front, the trigeminal nerve on the side of the head, and the nucleus ambiguus, and was first shown by Ross et al. to play an important role in controlling cardiovascular activity (12). Chemical and electrical stimulation of RVLM causes a sharp increase in blood pressure and heart rate, as well as bilateral destruction or chemical inactivation, and the blood pressure drops to the point of spinal cord injury (13). Deactivation of RVLM also inhibits baroreflex reactions (14), chemical and cardiac reflexes (4), which indicates the important role of RVLM in tonic and phasic control of blood pressure. The RVLM region is a sympathetic stimulus and its neurons project directly to the sympathetic preganglionic neurons of the spinal cord and increase their activity (3, 12, 15).

The RVLM region is a heterogeneous tissue and two groups of C1 and non-C1 neurons with different chemical properties have been identified in it and the number of C1 neurons is higher (16). Although C1 neurons make up about 50-70% of the neurons entering the spinal cord, they do not play a major role in maintaining and regulating blood pressure (17, 18). Their destruction reduces the compressive effect of glutamate stimulation by about 40%. Therefore, although this group of neurons is involved in stimulating blood pressure, it is not necessary to maintain basal blood pressure and vascular tone (14) but is involved in regulating reflex responses from baroreceptors and other cardiovascular reflexes. Group C1 also has projections to the parasympathetic, noradrenergic neurons of the central nervous system, and hypothalamic structures such as the PVN, and the median preoptic region (4).

Studies have shown that stimulation of central chemoreceptors (increased CO2) as well as increased blood pressure activates RVLM neurons, which indicates their involvement in chemical and compressive reflexes (14). Based on this, it can be said that RVLM is a cardiovascular information relay center to the peripheral sympathetic nerves that receives inputs from pressure, chemical and cardiopulmonary receptors as well as several brain areas including NTS, CVLM (4), PAG (2), PVN (19), Kölliker-Fuse/Parabrachial complex (12), raphe nucleus (20), amygdala (21), CnF (22) and PPT and other areas and then sends its projections to sympathetic preganglionic neurons of the spinal cord (4). Numerous neurotransmitters such as glutamate, γ-aminobutyric acid (GABA), norepinephrine, angiotensin II, acetylcholine, serotonin, endogenous opioids, and nitric oxide (NO) have been identified in RVLM. However, most of its output neurons (about 80%) are glutamatergic. Of the three types of glutamate transmitters (VGLUT1, VGLUT2, and VGLUT3), type VGLUT2 is related to the axon terminal of descending neurons in RVLM. This vector is present in both C1 and non-C1 neuronal groups and shows that both neuronal groups in RVLM have a glutamatergic pathway and use glutamate as a neurotransmitter to regulate cardiovascular activity (23). Glutamate and (γ-aminobutyric acid) GABA are also present as inhibitory neurotransmitters in RVLM. Sympathetic currents activated by RVLM depend mainly on the balance between excitatory and inhibitory neurotransmitters glutamate, GABA, and angiotensin II (19). Figure 1 shows the major routes associated with RVLM.

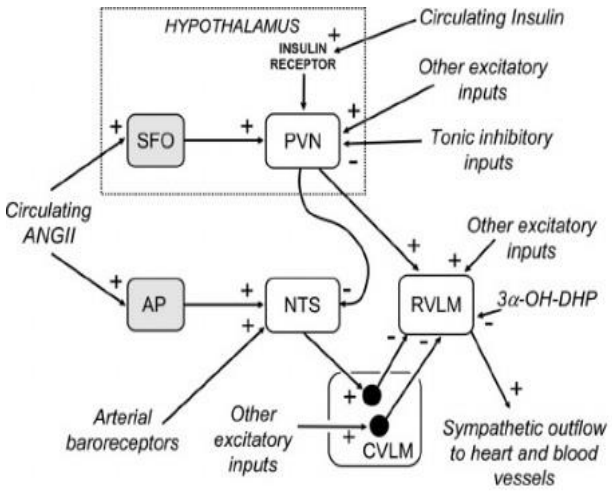

Figure 1. RVLM inputs and outputs. The RVLM area receives excitatory input from the nucleus tractus solitarius, raphe nucleus, and paraventricular nucleus and receives the inhibitory input from CVLM. It then affects the heart and arteries by sending neurons to the IML.

The caudal ventrolateral medulla (CVLM): The CVLM region is located behind the RVLM and its stimulation with glutamate reduces blood pressure (24). CVLM contains a large number of GABAergic neurons that project to RVLM, and induce a strong inhibitory effect on sympathetic activity and arterial pressure (5, 25). The CVLM region is an important part of the baroreflex system; it receives excitatory inputs from the NTS and inhibits RVLM through its GABAergic neurons by increasing the activity of the baroreflex (25, 26). Inhibition of RVLM does not appear to be entirely dependent on excitatory inputs to the CVLM GABAergic neurons; in the absence of baroreceptor

[DOR: 20.1001.1.15614107.1400.23.1.58.7]
[DOI: 10.22088/jbums.23.1.412]

inputs, non-CVLM-dependent GABAergic inputs greatly inhibit the activity of RVLM neurons. Therefore, this non-baroreceptor-dependent input plays an important role in regulating blood pressure in the absence of baroreceptor reflex (25).

The nucleus tractus solitarius (NTS): The NTS nucleus is located in the posterior part of the medulla oblongata and plays an essential role in compression and chemical reflexes (27). The NTS region is the site of the first synapse of afferent fibers originating from baroreceptors, chemoreceptors, and the heart (27, 28). These afferents form synapses in the NTS. Baroreceptor afferents terminate in medial nuclei and chemoreceptor afferents terminate in internal NTS subnuclei (2). The neurotransmitter of these afferents is glutamate, which binds to non-NMDA receptors in the NTS, although NMDA receptors may also play a role. NTS neurons project these data to several areas, including the brainstem and spinal cord (2, 29).

To regulate cardiovascular function, the NTS region sends its axons to the cell body of parasympathetic preganglionic neurons in the dorsal motor nucleus of the vagus nerve, nucleus ambiguous, and GABAergic neurons in the CVLM, partly the RVLM, as well as the forebrain. Therefore, activation of baroreceptors leads to vagus increase and sympathetic decrease in the heart and finally bradycardia, decreased cardiac output, decreased sympathetic flow to arteries, increased venous capacity and decreased vascular resistance (30).

The hypothalamic paraventricular nucleus (PVN): The hypothalamus is one of the most important centers for regulating cardiovascular activity. The lateral and ventral parts as well as the paraventricular nucleus (PVN) are the areas involved in the regulation of vasomotor neurons. The most important feature of the PVN is that it has direct and indirect projections to the spinal cord and innervates the sympathetic preganglionic neurons and is involved in the production of sympathetic vascular tone in response to fluctuations in cardiovascular regulation (31).

The PVN nucleus is located on either side of the third ventricle of the brain and contains magnocellular and parvocellular neurosecretory neurons. Magnocellular neurons project to the posterior pituitary gland and are responsible for secreting the hormones vasopressin and oxytocin, but parvocellular neurosecretory neurons project to centers involved in controlling the body's autonomic activity (32). Although vasopressin-containing neurons involved in cardiovascular control and neuroendocrine activity are anatomically distinct, they act in a coordinated manner in response to physiological challenges that require a hemostatic response (32). PVN contains inhibitory and excitatory neurons that balance sympathetic tone. Studies use c-fos gene expression to show that PVN neurons in the spinal cord, although involved in the body's hemostatic control in response to hypoxia and hypotension, are not major centers. Some researchers believe that PVN pathways are involved in cognitive control and cardiovascular control (33).

Neurons originating from the PVN nucleus are glutamatergic and establish synapses with dopamine terminals. Electrical stimulation of PVN stimulates the release of dopamine in the nucleus accumbens. While the presynaptic release of dopamine by PVN is unknown, dopamine release can have a motivating effect on behavior by facilitating the transfer of information in the nucleus accumbens (34). Changes in arterial pressure and changes in blood volume cause the expression of the c-fos gene in brainstem neurons that project to the PVN (35). A study showed that hemorrhagic hypotension also induces c-fos gene expression in a number of hypothalamic nuclei, including PVN (36).

The raphe nuclei: The role of the raphe nuclei in controlling cardiovascular activity is well specified (37-39). This nucleus is located in the midline of the medulla oblongata and has several subgroups. The raphe nuclei located at the tail end of the midline include Pallidus, Obscurus, and Magnus and have projections to the spinal cord (40). Most hematopoietic nucleus neurons contain serotonin and are therefore called serotonergic neurons (41). Under basal conditions, raphe neurons do not have much effect on sympathetic tonic activity and can have different effects depending on the injection site (42).

Chemical and electrical stimulation of the nucleus has been shown to increase and decrease blood pressure and sympathetic activity, depending on the site of stimulation. Neurons that project to the spinal cord IML are activated by stimulation of baroreceptors and appear to be sympathetic inhibitors, and neurons that reach the forebrain regions act through RVLM and are sympathetic stimuli (43). Serotonergic neurons that project to RVLM through 5-HT1A receptors facilitate the activity of sympathetic cardiovascular reflexes in RVLM (41). Furthermore, according to immunohistochemical studies, c-fos gene expression in serotonergic neurons that project to spinal cord IML does not occur in response to changes such as

[DOR: 20.1001.1.15614107.1400.23.1.58.7]
[DOI: 10.22088/jbums.23.1.412]

hypotension, hypovolemia, and hypoxia (41). Inactivation of the ventromedial region of the raphe nucleus worsens the condition of hypotension and slows the return of blood pressure and heart rate, while inactivation of dorsal raphe nucleus delays the onset of hypotension (41). In addition to serotonin, other neuropeptides such as substance P, thyroid-releasing hormone, and enkephalin have also been identified in these neurons (44).

The periaqueductal gray (PAG): The PAG area is located in the midbrain and plays an important role in defense responses, Fight-or-Flight Response, pain, anxiety, reproduction, and cardiovascular and respiratory activity. Anatomically, PAG is divided into four regions with different functions: dorsomedial (dmPAG), dorsolateral (dlPAG), lateral (lPAG), and ventrolateral (vlPAG) (45). Local stimulation of different PAG regions, depending on the injection site, induces different cardiovascular responses. For example, stimulation of the dorsal lPAG increases blood pressure with severe contraction of skeletal muscle and stimulation of the end tail causes a sharp increase in renal artery contraction with little effect on skeletal muscle. Depressive responses and PAG bradycardia are related to different parts of vlPAG that preferentially innervate skeletal and renal vascular muscles (46).

Injection of acetylcholine into vlPAG reduces blood pressure without changing heart rate (47), while injection of noradrenaline into this area increases blood pressure with bradycardia (48). In addition, it has been shown that the activity of vlPAG glutamatergic projections can cause cardiovascular changes through RVLM. These results highlight the role of vlPAG in cardiovascular function (2). In addition, dPAG modulates the sympathetic component of the baroreceptor reflex. On the other hand, electrical or chemical stimulation of PAG increases heart rate and blood pressure (2).

The results showed that dlPAG nitrogen neurons have a stimulatory effect on cardiovascular activity. In summary, direct injection of SNP and L-Arg significantly increased blood pressure, while L-NAME had no significant effect on the parameters. Therefore, the synthesis of NO in dlPAG causes a pressure response and baroreflex bradycardia, but its effect of increasing pressure is greater (49). Studies have also shown that PAG exerts its sympathetic effects through its association with the medulla oblongata, brain bridge, and hypothalamus. The most important PAG pathway is in the medulla oblongata, so most of its output is to the RVLM. The PAG pathway to RVLM appears to be an important pathway for controlling PAG cardiovascular activity (50).

The cuneiform nucleus (CnF): The CnF nucleus is a sympathetic excitatory nucleus located in the mesencephalon and is associated with the central components involved in the regulation of cardiovascular activity, including RVLM, NTS, PAG, and the Kölliker-Fuse/Parabrachial complex and is involved in cardiovascular regulation (22, 51-52). The CnF nucleus is involved in the control of various functions, the most important of which are analgesic effects and cardiovascular control (53).

CnF is reported to be located in the orbital center, which is involved in regulating sympathetic and parasympathetic activity related to the heart and arteries. The CnF nucleus sends outputs to the gigantocellular reticular nuclei, the vagus motor nuclei, and the NTS. These projections are probably related to the bradycardic responses of this nucleus. In addition, CnF has outputs to the limbic region, the Kölliker-Fuse/Parabrachial complex, the RVLM, and the spinal cord IML. The major inputs of this nucleus are from the midbrain and forebrain structures, the central amygdala nucleus, the lateral hypothalamic regions, the PAG, and the opposite cuneiform nucleus. It has been shown that the cardiovascular effect of this nucleus is mainly mediated by RVLM. This pathway is polysynaptic and the Kölliker-Fuse (KF) and PAG nuclei are involved in this transmission (51).

Glutamate, acetylcholine and NO are the most important neurotransmitters affecting cardiovascular activity in CnF (22, 53-56). Injection of glutamate into the nucleus causes a short- and long-term increase in blood pressure, and inactivation of the KF nucleus greatly reduces the short-term response (55). In addition, microinjection of acetylcholine in this nucleus reduces blood pressure without affecting the heart rate, which is done by muscarinic receptors (50). Another study showed the role of the nucleus in hemorrhagic hypotension. The role of serotonin receptor type 1a (5-HT1A) in this nucleus in controlling cardiovascular activity under normal conditions and bleeding has also been shown (49). The inhibitory effect of the nitrergic system of this nucleus on cardiovascular responses has been reported (22).

The pedunculopontine tegmentum nucleus (PPT): The PPT nucleus is a heterogeneous region consisting of several neuronal groups located above the cerebral bridge and divided into two parts of dense with large neuronal groups (containing cholinergic neurons) and

[DOR: 20.1001.1.15614107.1400.23.1.58.7]
[DOI: 10.22088/jbums.23.1.412]

retiform with small and medium neurons (containing glutamatergic neurons and noncholinergic neurons) (8). The PPT nucleus has many afferent and efferent projections into the cerebral cortex, thalamus, basal ganglia, cerebellum, and spinal cord. 80 to 90% of dense part neurons contain cholinergic neurons. The neurons in the non-dense part are mainly glutaminergic and partly cholinergic. Both neuronal parts also contain GABAergic inhibitory neurons. The inputs to PPT are from the cerebral cortex, through the basal ganglia and the extrapyramidal system (8), and the cardiovascular-related outputs are to the RVLM, NTS, and PAG (9, 57). The most important neurons in this area are cholinergic, GABAergic and glutamatergic. However, other less important neurons, such as nitrergic neurons, have also been identified (58).

The PPT nucleus is involved in activities such as movement, sleep, breathing regulation, and pain and reward. Its role in cardiovascular activity is also well defined (7, 11, 57). In our previous studies, the role of the cholinergic, GABAergic and nitrergic systems of the nucleus on cardiovascular activity has been demonstrated (10, 58, 59). The effect of this nucleus on the regulation of cardiovascular activity due to hemorrhage has also been shown (60).

Discussion

The function of the cardiovascular system is regulated by nervous, hormonal and local factors, and the role of the nervous system is more important. The nerve centers that play a role in regulating basal cardiovascular activity are located mainly in the brainstem and other areas, including the cerebral cortex, and their environmental effect is through the autonomic nervous system (sympathetic and parasympathetic) (4). In addition, the nerve centers that affect cardiovascular function in conditions such as hypertension, bleeding, stress and exercise are also different and have different neural pathways (30). In this study, our aim was to identify the most important neural centers that control cardiovascular activity without considering neural pathways in various conditions.

The results of this study showed that the most important areas regulating cardiovascular activity include RVLM, NTS, CVLM, PVN, Raphe nuclei as well as CnF and PPT. Among these areas, the RVLM region, as the most important center of sympathetic stimulation, plays the main role in regulating the basal activity of the cardiovascular system. There are also several nerve centers that are involved in regulating cardiovascular activity in a variety of conditions.

Acknowledgment

We would like to thank the Vice Chancellor for Research and Technology of Mashhad University of Medical Sciences.

[DOR: 20.1001.1.15614107.1400.23.1.58.7]
[DOI: 10.22088/jbums.23.1.412]

References

1.Deuchars SA, Lall VK. Sympathetic preganglionic neurons: properties and inputs. Compr Physiol. 2015;5(2):829-69.
2.Lagatta DC, Ferreira-Junior NC, Deolindo M, Corrêa FM, Resstel LB. Ventrolateral periaqueductal grey matter neurotransmission modulates cardiac baroreflex activity. Euro J Neurosci. 2016;44(11):2877-84.
3.Dampney RA, Goodchild AK, Robertson LG, Montgomery W. Role of ventrolateral medulla in vasomotor regulation: a correlative anatomical and physiological study. Brain Res. 1982;249(2):223-35.
4.Guyenet PG, Stornetta RL, Holloway BB, Souza GM, Abbott SB. Rostral Ventrolateral Medulla and Hypertension. Hypertension. 2018;72(3):559-66.
5.Dupont AG, Légat L. GABA is a mediator of brain AT 1 and AT 2 receptor-mediated blood pressure responses. Hypertens Res. 2020:43(10):995-1005.
6.Dampney R. Emotion and the cardiovascular system: postulated role of inputs from the medial prefrontal cortex to the dorsolateral periaqueductal gray. Front Neurosci. 2018;12:343.
7.Beitz AJ. The organization of afferent projections to the midbrain periaqueductal gray of the rat. Neuroscience. 1982;7(1):133-59.
8.French IT, Muthusamy KA. A Review of the Pedunculopontine Nucleus in Parkinson's Disease. Front Aging Neurosci. 2018;10:99.
9.Topchiy I, Waxman J, Radulovacki M, Carley DW. Functional topography of respiratory, cardiovascular and pontine-wave responses to glutamate microstimulation of the pedunculopontine tegmentum of the rat. Respir Physiol Neurobiol. 2010;173(1):64-70.
10.Pasandi H, Abbaspoor S, Shafei MN, Hosseini M, Khajavirad A. $GABA_A$ receptor in the Pedunculopontine tegmental (PPT) nucleus: Effects on cardiovascular system. Pharmacol Rep. 2018;70(5):1001-9.
11.Garcia-Rill E. The pedunculopontine nucleus. Prog Neurobiol. 1991;36(5):363-89.
12.Ross CA, Ruggiero DA, Park DH, Joh TH, Sved AF, Fernandez-Pardal J, et al. Tonic vasomotor control by the rostral ventrolateral medulla: effect of electrical or chemical stimulation of the area containing C1 adrenaline neurons on arterial pressure, heart rate, and plasma catecholamines and vasopressin. J Neurosci. 1984;4(2):474-94.
13.Babic T, Ciriello J. Medullary and spinal cord projections from cardiovascular responsive sites in the rostral ventromedial medulla. J Comp Neurol. 2004;469(3):391-412.
14.Kimmerly DS. A review of human neuroimaging investigations involved with central autonomic regulation of baroreflex-mediated cardiovascular control. Auton Neurosci. 2017;207:10-21.
15.Oshima N, Onimaru H, Yamagata A, Ito S, Imakiire T, Kumagai H. Rostral ventrolateral medulla neuron activity is suppressed by Klotho and stimulated by FGF23 in newborn Wistar rats. Auton Neurosci. 2020;224:102640.
16.Dash KE, Stornetta RL, Holloway BB, Guyenet PG. Do Non-C1 Cells In The Rostral Ventrolateral Medulla Increase Blood Pressure?. FASEB J. 2017;31(S1):827-30.
17.Madden CJ, Sved AF. Rostral ventrolateral medulla C1 neurons and cardiovascular regulation. Cell Mol Neurobiol. 2003;23(4-5):739-49.
18.Madden CJ, Sved AF. Cardiovascular regulation after destruction of the C1 cell group of the rostral ventrolateral medulla in rats. Am J Physiol Heart Circ Physiol. 2003;285(6):H2734-48.
19.Lozić M, Tasić T, Martin A, Greenwood M, Šarenac O, Hindmarch C, et al. Over-expression of V1A receptors in PVN modulates autonomic cardiovascular control. Pharmacol Res. 2016;114:185-95.
20.Bago M, Marson L, Dean C. Serotonergic projections to the rostroventrolateral medulla from midbrain and raphe nuclei. Brain Res. 2002;945(2):249-58.
21.Kalin NH, Shelton SE, Davidson RJ. The role of the central nucleus of the amygdala in mediating fear and anxiety in the primate. J Neurosci. 2004;24(24):5506-15.
22.Farrokhi E, Shafei MN, Khajavirad A, Hosseini M, Ebrahimzadeh Bideskan AR. Role of the nitrergic system of the cuneiform nucleus in cardiovascular responses in Urethane-Anesthetized male rats. Iran J Med Sci. 2017;42(5):473-80.

[DOR: 20.1001.1.15614107.1400.23.1.58.7]
[DOI: 10.22088/jbums.23.1.412]

23.Abbott SB, Holloway BB, Viar KE, Guyenet PG. Vesicular glutamate transporter 2 is required for the respiratory and parasympathetic activation produced by optogenetic stimulation of catecholaminergic neurons in the rostral ventrolateral medulla of mice in vivo. Eur J Neurosci. 2014;39(1):98-106.
24.Sved AF, Ito S, Madden CJ. Baroreflex dependent and independent roles of the caudal ventrolateral medulla in cardiovascular regulation. Brain Res Bull. 2000;51(2):129-33.
25.Mandel DA, Schreihofer AM. Glutamatergic inputs to the CVLM independent of the NTS promote tonic inhibition of sympathetic vasomotor tone in rats. Am J Physiol Heart Circ Physiol. 2008;295(4):H1772-9.
26.Soares ER, Barbosa CM, Campagnole-Santos MJ, Santos RA, Alzamora AC. Hypotensive effect induced by microinjection of Alamandine, a derivative of angiotensin-(1-7), into caudal ventrolateral medulla of 2K1C hypertensive rats. Peptides. 2017;96:67-75.
27.Zoccal DB, Furuya WI, Bassi M, Colombari DS, Colombari E. The nucleus of the solitary tract and the coordination of respiratory and sympathetic activities. Front Physiol. 2014;5:238.
28.Saha S. Role of the central nucleus of the amygdala in the control of blood pressure: descending pathways to medullary cardiovascular nuclei. Clin Exp Pharmacol Physiol. 2005;32(5-6):450-6.
29.MacDonald AJ, Ellacott KL. Astrocytes in the Nucleus of the Solitary Tract: Contributions to Neural Circuits Controlling Physiology. Physiol Behav. 2020;223:112982.
30.Michelini LC. The NTS and integration of cardiovascular control during exercise in normotensive and hypertensive individuals. Curr Hypertens Rep. 2007;9(3):214-21.
31.Pyner S. The paraventricular nucleus and heart failure. Exp Physiol. 2014;99(2):332-9.
32.Stern JE. Neuroendocrine-Autonomic Integration in the Paraventricular Nucleus: Novel Roles for Dendritically Released Neuropeptides. J Neuroendocrinol. 2015;27(6):487-97.
33.Cho JH, Moon JB, Park CW, Ohk TG, Shin MC, Won MH. Differential activation of c-Fos in the paraventricular nuclei of the hypothalamus and thalamus of the rat following myocardial infarction. Resuscitation. 2016;106(Suppl 1):E90.
34.Kirouac GJ. Placing the paraventricular nucleus of the thalamus within the brain circuits that control behavior. Neurosci Biobehav Rev. 2015;56:315-29.
35.Krukoff TL, MacTavish D, Harris KH, Jhamandas JH. Changes in blood volume and pressure induce c-fos expression in brainstem neurons that project to the paraventricular nucleus of the hypothalamus. Mol Brain Res. 1995;34(1):99-108.
36.Jin G-S, Li X-L, Jin Y-Z, Kim MS, Park BR. Role of peripheral vestibular receptors in the control of blood pressure following hypotension. Korean J Physiol Pharmacol. 2018;22(4):363-8.
37.Arami MK, Mirnajafi Zade J, Komaki A, Amiri M, Mehrpooya S, Jahanshahi A, et al. Nitric oxide in the nucleus raphe magnus modulates cutaneous blood flow in rats during hypothermia. Iran J Basic Med Sci. 2015;18(10):989-92.
38.Kirouac GJ, Li S, Mabrouk G. GABAergic projection from the ventral tegmental area and substantia nigra to the periaqueductal gray region and the dorsal raphe nucleus. J Comp Neurol. 2004;469(2):170-84.
39.Moazzami A, Tjen-A-Looi SC, Guo Z-L, Longhurst JC. Serotonergic projection from nucleus raphe pallidus to rostral ventrolateral medulla modulates cardiovascular reflex responses during acupuncture. J Appl Physiol (1985). 2010;108(5):1336-46.
40.Hettigoda NS, Fong AY, Badoer E, McKinley MJ, Oldfield BJ, Allen AM. Identification of CNS neurons with polysynaptic connections to both the sympathetic and parasympathetic innervation of the submandibular gland. Brain Struct Funct. 2015;220(4):2103-20.
41.Kung L-H, Glasgow J, Ruszaj A, Gray T, Scrogin KE. Serotonin neurons of the caudal raphe nuclei contribute to sympathetic recovery following hypotensive hemorrhage. Am J Physiol Regul Integr Comp Physiol. 2010;298(4):R939-53.
42.Zaretsky DV, Zaretskaia MV, Samuels BC, Cluxton LK, DiMicco JA. Microinjection of muscimol into raphe pallidus suppresses tachycardia associated with air stress in conscious rats. J Physiol. 2003;546(Pt 1):243-50.
43.Rahmouni K. Cardiovascular regulation by the arcuate nucleus of the hypothalamus: neurocircuitry and signaling systems. Hypertension. 2016;67(6):1064-71.

[DOR: 20.1001.1.15614107.1400.23.1.58.7]
[DOI: 10.22088/jbums.23.1.412]

44.McClintick JN, McBride WJ, Bell RL, Ding Z-M, Liu Y, Xuei X, et al. Gene expression changes in serotonin, GABA-A receptors, neuropeptides and ion channels in the dorsal raphe nucleus of adolescent alcohol-preferring (P) rats following binge-like alcohol drinking. Pharmacol Biochem Behav. 2015;129:87-96.
45.Keay KA, Bandler R. Periaqueductal gray. In: Paxinos G, editor. The Rat Nervous System, 4th ed. Elsevier; 2015. p. 207-21.
46.O'Callaghan EL, McBryde FD, Burchell AE, Ratcliffe LE, Nicolae L, Gillbe I, et al. Deep brain stimulation for the treatment of resistant hypertension. Curr Hypertens Rep. 2014;16(11):493.
47.Deolindo MV, Pelosi GG, Busnardo C, Resstel LBM, Corrêa FMA. Cardiovascular effects of acetylcholine microinjection into the ventrolateral and dorsal periaqueductal gray of rats. Brain Res. 2011;1371:74-81.
48.Pelosi GG, Corrêa FMA. Cardiovascular effects of noradrenaline microinjected into the dorsal periaqueductal gray area of unanaesthetized rats. Eur J Neurosci. 2005;22(12):3188-94.
49.NejadShahrokhAbadi R, Zangouei AS, Mohebbati R, Shafei MN. Determining the cardiovascular effects of nitric oxide in the dorsolateral Periaqueductal Gray (dlPAG) in anaesthetised rats. J Taibah Univ Med Sci. 2020;15(6):502-8.
50.Hao Y, Liu T-T, He Z-G, Wu W, Xiang H-B. Hypothesis: CeM-PAG GABAergic circuits may be implicated in sudden unexpected death in epilepsy by melanocortinergic signaling. Epilepsy Behav. 2015;50:25-8.
51.Korte SM, Jaarsma D, Luiten PG, Bohus B. Mesencephalic cuneiform nucleus and its ascending and descending projections serve stress-related cardiovascular responses in the rat. J Auton Nerv Syst. 1992;41(1-2):157-76.
52.Verberne AJ. Cuneiform nucleus stimulation produces activation of medullary sympathoexcitatory neurons in rats. Am J Physiol. 1995;268(3 Pt 2):R752-8.
53.Shafei MN, Nasimi A, Alaei H, Pourshanazari AA, Hosseini M. Role of cuneiform nucleus in regulation of sympathetic vasomotor tone in rats. Pathophysiology. 2012;19(3):151-5.
54.Lam W, Verberne AJ. Cuneiform nucleus stimulation-induced sympathoexcitation: role of adrenoceptors, excitatory amino acid and serotonin receptors in rat spinal cord. Brain Res. 1997;757(2):191-201.
55.Shafei MN, Nasimi A. Effect of glutamate stimulation of the cuneiform nucleus on cardiovascular regulation in anesthetized rats: Role of the pontine Kolliker-Fuse nucleus. Brain Res. 2011;1385:135-43.
56.Shafei MN, Niazmand S, Enayatfard L, Hosseini M, Hasanzade Daloee M. Pharmacological study of cholinergic system on cardiovascular regulation in the cuneiform nucleus of rat. Neurosci Lett. 2013;549:12-7.
57.Padley JR, Kumar NN, Li Q, Nguyen TB, Pilowsky PM, Goodchild AK. Central command regulation of circulatory function mediated by descending pontine cholinergic inputs to sympathoexcitatory rostral ventrolateral medulla neurons. Circ Res. 2007;100(2):284-91.
58.Shafei MN, Nikyar T, Hosseini M, Niazmand S, Paseban M. Cardiovascular effects of nitrergic system of the pedunculopontine tegmental nucleus in anesthetized rats. Iran J Basic Med Sci. 2017;20(7):776-82.
59.Nikyar T, Hosseini M, Niazmand S, Shafei MN. Evaluation of nicotinic receptor of pedunculopontine tegmental nucleus in central cardiovascular regulation in anesthetized rat. Iran J Basic Med Sci. 2018;21(4):376-81.
60.Mohebbati R, Hosseini M, Khazaei M, Khajavirad A, Shafei MN. The Effects of Inactivation of Pedunculopontine Tegmental Nucleus by Cobalt (II) Chloride on Cardiovascular Responses in Hemorrhagic Hypotensive Rats. Basic Clin Neurosci. 2019;10(3):235-44.

[DOR: 20.1001.1.15614107.1400.23.1.58.7]
[DOI: 10.22088/jbums.23.1.412]