THE OLFACTORY BULB: AN IGNORED BRAIN STRUCTURE IN THE REGULATION OF CARDIOVASCULAR ACTIVITY

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ABSTRACT
Numerous studies have addressed the participation of the central nervous system in the physiological regulation of blood pressure and in the development and/or maintenance of hypertension. The central nervous system plays a key role in the short-term regulation of blood pressure although recent investigations also support its participation in the long-term modulation. Diverse brain regions and areas like the rostral ventrolateral medulla, the nucleus of the solitary tract, the locus coeruleus, amygdala and hypothalamus are intimately involved in the control of cardiovascular activity. Nevertheless, little is known about the role of the olfactory bulb. This mini review summarizes current knowledge regarding the participation of this telencephalic region in the regulation of cardiovascular activity in physiological and pathophysiological conditions.
Keywords: Olfactory bulb, cardiovascular function, depression, neuropeptides.

RESUMEN
Numerosos estudios han abordado la participación del sistema nervioso central en la regulación fisiológica de la presión arterial y en el desarrollo y / o mantenimiento de la hipertensión arterial. El sistema nervioso central juega un papel clave en la regulación a corto plazo de la presión arterial, aunque investigaciones recientes apoyan su participación en la modulación a largo plazo. Diversas regiones y áreas del cerebro como la médula ventrolateral rostral, el núcleo del tracto solitario, el locus coeruleus, la amígdala y el hipotálamo están íntimamente involucradas en el control de la actividad cardiovascular. Sin embargo, poco se conoce acerca del papel del bulbo olfatorio. Esta breve revisión resume el conocimiento actual en la participación de esta región telencefálica en la regulación de la actividad cardiovascular en condiciones fisiológicas y fisiopatológicas.
Palabras clave: Bulbo olfatorio, función cardiovascular, depresión, neuropéptidos.

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Introduction

The olfactory bulb (OB) is a part of the forebrain located above the nasal cavity. It is the primary information processing center of the olfactory information. In rodents it constitutes 4% of the brain mass whereas in humans it is smaller since it does not rely on the sense of smell to perceive the environment [1]. The OBs (right and left) are brain structures mainly involved in the processing of the sensory inputs coming from the olfactory epithelium [2, 3, 4]. However, there are evidence to supports that this telencephalic region may be implicated in the regulation of the cardiovascular activity [5, 6]. The OBs are structures of complex organization that present several cell layers of concentric arrangement, located from outside to the inside as follows [3, 4, 7] (view Figure 1):

- Glomerular layer
- External glomerular layer
- External plexiform layer
- Mitral cell layer
- Internal plexiform layer
- Internal granular layer
- Granule cell layer

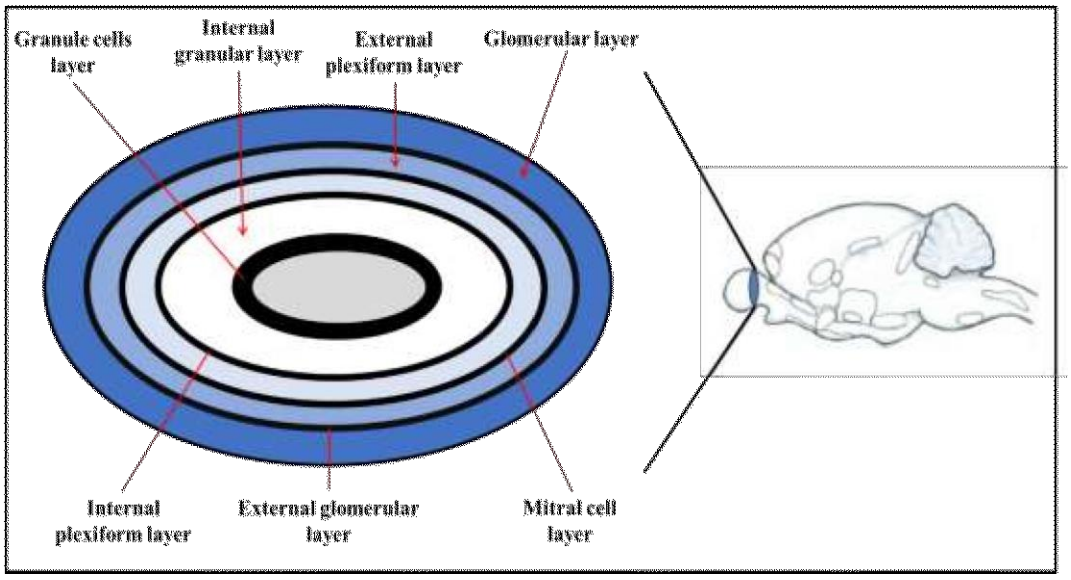

Figure 1. Schematic representation of the coronal section of the olfactory bulb showing the different concentric cell layers.

The glomerular zone that has different types of neurons is where the integration of sensory information occurs [3]. To discriminate among the different stimuli, inputs from the olfactory epithelium reach the main OB via the olfactory nerves, wrapped around by supporting cells that exhibit two phenotypes: Shwann cell-like or astrocyte cell-like. These glial cells are of particular interest due to their regenerative capacity, a feature that makes them target for neuronal regeneration research even though they are not typical stem cells [8, 9, 10]. When the olfactory nerves enter the OB, the sensory information is delivered through glutamatergic terminals to the lumen of the olfactory glomeruli. There the signal is processed through GABAergic and dopaminergic periglomerular interneurons, among others. Granulocytic cell projections reach this area and project through the olfactory tract via mitral and tufted cells that relay impulses from the OB to other brain regions. The projections of these cells differ not only in the target site but also in the speed of nerve impulse conduction [11]. The OB connects with different telencephalic, midbrain, diencephalic and brainstem regions, some of which are closely involved in the regulation of cardiovascular activity [12, 13]. In this sense, a relevant projection is that to the nucleus tractus solitarius, at the level of the brainstem, which is considered the primary site for the integration of visceral afferents such as those arising from the baroreflex [14, 15]. In addition, limbic system areas like the amygdala, septum, piriformis, and orbitofrontal cortex also receive inputs from the OB [4, 16].

The OB receives afferences both from the olfactory cortex and other central areas like the locus coeruleus. Noradrenergic fibers from the locus coeruleus innervate the OB, from the central cell layers decreasing the density to the periphery [17, 18]. This centripetal afference represents around 40% of the total extrinsic innervation [18] and it is crucial for the modulation of olfaction and olfactory learning. The OB also receives serotoninergic afferences mainly from the nucleus of the raphe (dorsal and medial) that innervate particularly the glomerular layer. Experiments performed in deafferented animals revealed that serotoninergic stimulation is relevant for olfactory learning but also as a neurotrophic agent. Likewise, cholinergic fibers arising from the horizontal arm of the diagonal band nucleus, prosencephalic basal area also reach OB and innervate mainly the deeper cell layers. These fibers would be involved in the OB neuronal plasticity and the regulation of cell survival [19, 20, 21].

Cortical areas related to olfaction also project to the OB. There is a feedback innervation since brain areas reached by the olfactory nerves send projections back, so the neuronal terminals that come from the olfactory cortex to the OB may arise from the anterior olfactory nucleus, tapeworm tecta, piriform cortex, cortical tonsillar nucleus, and the nucleus of the lateral olfactory tracts. When entering the OB, they selectively release neurotransmitters that act on specific groups of neurons [4, 16, 22]. The sensory input to the main OB triggered by odors arises from the olfactory epithelium and send projections to the piriformis, prefrontal cortex, nucleus tractus solitarius, amygdala and the hypothalamus [23, 24]. The major input to the accessory OB (absent in humans) comes from the vomeronasal organ (vestigial or absent in adult humans) that is involved in the detection of pheromones; the output is sent mainly to the amygdala, nucleus tractus solitary and the accessory olfactory nuclei [25, 26, 27]. The OB efferences originate in the tufted neurons and the mitral cells; the impulses originated in the tufted neurons propagate rapidly to the olfactory to the external and posteroventral part of the olfactory nucleus, the olfactory tubercle and the ventrorostral amygdala whereas those from the mitral cells propagate at a lower speed mainly to the olfactory tubercle (cortical portion), the dorsal anterior olfactory nucleus, the anterior and posterior dorsal piriformis cortex, the lateral entorhinal cortex and the anterior and posterolateral amygdala [3, 4, 7, 11, 22]. Figure 2 shows the complex neuronal circuits between OB and different areas and nuclei of the central nervous system closely related to the control of the cardiovascular function.

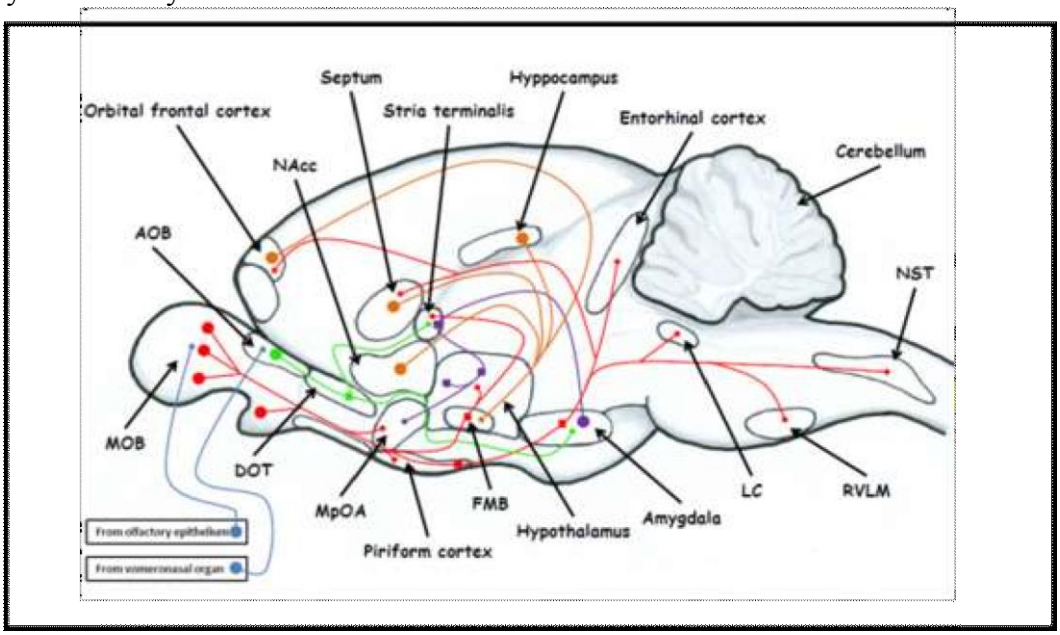

Figure 2. Diagram of a sagittal section of a rat brain showing the olfactory bulb interworking with areas and nuclei with implications in the central regulation of cardiovascular system. References: axonic projection from (●–) or to (–➔) distinct area/nuclei are represented in different colours; main olfactory bulb (MOB); accessory olfactory bulb (AOB); dorsal olfactory tract (DOT); medial preoptic area (MpOA); forebrain medial bundle (FMB); locus coeruleus (LC); rostral ventrolateral medulla (RVLM); nucleus of the solitary tract (NST); nucleus accumbens (NAcc)

OB and cardiovascular function

Diverse studies in experimental animals reveal an association among the sense of smell, the autonomic balance, and cardiovascular physiology [6, 28, 29, 30]. Conscious rats exposed to smoke show changes in blood pressure, breathing and sympathetic activity [31, 32]. It was reported that the changes in vascular and heart physiology correlate with changes in the neurochemistry of various neurotransmitters including norepinephrine in the OB [12, 33].

Nakamura and Hayashida showed that the changes in the cardiovascular response of conscious rats exposed to smoke resulted from both sympathetic and parasympathetic activation [31]. Furthermore, the baroreflex function is likely modulated by parasympathetic firing. Nevertheless, the authors leave open the possibility that an emotional response may be involved [31]. Aromatherapy-based studies in anesthetized rats showed that olfactory stimulation for 10 min with scent of grapefruit oil increases renal sympathetic nerve activity and blood pressure whereas it reduces gastric vagal nerve activity [34]. Furthermore, olfactory stimulation with limonene, a major component of grapefruit oil, also shows similar results in the same experimental model [34]. However, stimulation with lavender oil and its active component linalol, has opposite effects, it reduces renal sympathetic activity and blood pressure while increasing gastric vagal nerve activity [35]. These findings reveal that different essential oils with distinct active component show a differential response on blood pressure and autonomic activity.

Double-blind and randomized aromatherapy-based studies were also performed in humans, that have a weak sense of smell as compared to rodents. Angelucci and coworkers compiled reports in the literature regarding the effect of various fragrances like lavender, lemon, and patchouli among others on the autonomic balance and blood pressure [36]. Conclusion were rather controversial, since various reports failed to find a correlation. In this sense, Kiecolt-Glaser and coworkers compared the stimulation with lemon aroma and lavender relaxant with odorless water in 57 individuals exposed to stressful stimuli like low temperatures, the peeling of an adhesive tape on the skin, etc. and the results were not conclusive. These authors showed that inhaling lemon oil improves positive mood and also increases norepinephrine release, however, it does not present any other physiological or health-related benefits. Furthermore, both lemon and lavender appeared to depress delayed hypersensitivity responses to Candida relative to water (control group), suggesting that the immunomodulatory effects of these odors were negative, at least for this aspect of the immune response [37]. Other reports provided data on the relevance of subjectivity and prediction of the expected response to inhaled essential oils. In this sense, these authors conclude that the perceived physiological changes in blood pressure, heart rate and heart rate variability only reflect changes in alertness, but do not correlate with real changes in the respective vegetative states [38]. Therefore, the role of olfaction in cardiovascular activity is still a matter of debate, although diverse avenues have elucidated how these functions would be linked.

Olfactory disturbances generally lead to poor food intake choices, reduced appetite, and eventually weight loss, malnutrition, impaired immune response, and worsening of illnesses. Patients with an altered sense of smell use higher amounts of sugar and salt to enhance the flavors thus leading to health deterioration and enhanced risk of diabetes and hypertension. These patients usually increase the use of table salt and exhibit a deep craving for salty foods following olfaction loss but do not have any consistent taste abnormality [39].

Several works in patients reveal a strong link between depression and cardiovascular diseases as well as between depression and the OB [40, 41, 42]. Depression may affect the pathogenesis of cardiovascular diseases. In fact, patients with major depression have altered hemodynamic parameters. The prevalence of depression in patients with cardiovascular diseases ranges from 15 to 20%. In those with acute myocardial infarction is 19.8% (31.1% had previous clinically significant depression) whereas in hypertensive patients is approximately 40.1%. The incidence of depression is very high in hypertensive patients, 63.4% and 36.6% in women and men, respectively [42].

Bilateral bulbectomy is a well-established and accepted model of depression that exhibits modifications in sympathetic activity and cardiovascular function and has been used to screen

different antidepressant agents [5, 12, 43]. Rats with bilateral bulbectomy show increased exploratory behavior, hyperactivity, and decreased sexual behavior as well as changes in temperature, endocrine and immune responses, and cardiovascular physiology [5, 12, 43]. Some authors consider that the cardiovascular responses are related to variations in the autonomic nervous system regulation [44, 45]. The changes following bulbectomy are associated with alterations in one or more neurotransmitters like norepinephrine, acetylcholine, serotonin, GABA and glutamate [12, 43]. In addition, it was reported that the integrity of the OB is necessary for the brain to generate a normal sympathetic excitatory response to a series of physiological stimuli, including the baroreflex [5]. The ablation of OB produces the modification in the neurochemistry of different neurotransmitters in various regions and areas of the central nervous system [46, 47]. Pioneering investigations by Allen showed that olfactory stimulation in mammals is accompanied by changes in respiration and blood pressure [48].

Works from our laboratory showed for the first time that noradrenergic activity is enhanced in the OB of DOCA-salt hypertensive rats. Norepinephrine content as well tyrosine hydroxylase (the enzyme that catalyzes the rate limiting step in catecholamine biosynthesis) activity are significantly elevated [33]. Increased catecholamine biosynthesis correlates with enhanced norepinephrine neuronal release in the OB of DOCA-salt rats [33]. Although the OB does not have noradrenergic neuron bodies, it receives fibers from the locus coeruleus that release norepinephrine [18, 49]. Previous studies showed that cholinergic and/or noradrenergic stimulation of noradrenergic neurons in the locus coeruleus of normotensive animals increases norepinephrine content in the OB [50]. Norepinephrine release in the OB induces changes in the reproductive and exploratory behavior, the detection and sensitivity to odors and blood pressure [5, 51, 52, 53]. Another relevant finding is that the activity and the plasma membrane expression of the neuronal norepinephrine transporter are decreased in the OB of DOCA-salt hypertensive animals [33]. Taken together these findings imply that norepinephrine turnover is enhanced and further support the hypothesis that the OB is a sympathoexitatory region given that the release of norepinephrine elevates blood pressure [5, 51]. Other authors suggest that the imbalance of the neuronal norepinephrine transporter contributes to the development of hypertension and other cardiovascular diseases [54, 55, 56, 57].

An unexpected finding showed by Abramoff et al in the OB of DOCA-salt rats is the existence of an asymmetry in noradrenergic activity, given that the right OB and not the left OB exhibits the changes in noradrenergic transmission [33]. The pathophysiological significance of this asymmetry in this animal model is presently unknown. Nevertheless, some authors propose that the right hemiportion of other regions of the central nervous system like the hypothalamus has greater impact the regulation of cardiovascular function [58, 59].

Vasoactive peptides like angiotensin II, natriuretic peptides, bradykinin, and endothelin (ET) are expressed in the OB and changes in their function have been related to cardiovascular impairment. In the OB of spontaneously hypertensive rats, altered properties and function of the natriuretic peptide receptor A (NPR-A) was reported suggesting that it may be implicated in the pathogenesis of hypertension [60]. Studies from our laboratory show changes in the endothelinergic system in this telencephalic region in DOCA-salt hypertensive rats. We showed increased ET type A receptor (ET_A) and diminished ET type B receptor (ET_B) expression in the OB of hypertensive animals. Furthermore, confocal microscopy studies showed that ET_A receptors colocalize with tyrosine hydroxylase positive neurons, and both ET receptors are increased in these catecholaminergic neurons. These findings show a clear association in the OB between changes in the endothelinergic and catecholaminergic systems and salt dependent hypertension [61].

In previous works we reported the role of the central endothelinergic system in the maintenance of blood pressure in DOCA-salt hypertension through the ET_A receptor activation. The acute intracerebroventricular infusion of an ET_A antagonist or a specific ET_B agonist significantly attenuates blood pressure and other hemodynamic parameters [61, 62]. Normotensive animals also exhibit decreased hemodynamic parameters, but such reduction results considerably lower. These findings show that DOCA-salt hypertensive animals have a higher brain endothelinergic tone mediated by ET_A

receptor activation. These observations correlate with changes in noradrenergic transmission at the level of the OB. The hemodynamic modifications are compatible with observations in other brain sympathoexcitatory areas. In this sense, it was reported that BQ610 (ET_A antagonist) or IRL1620 (ET_B selective agonist) acutely applied to the brain (1 h) significantly reduces the activity of tyrosine hydroxylase activity and the expression of its phosphorylated forms (protein and mRNA) [61, 62]. Moreover, chronic infusion of either BQ610 or IRL1620 (7 days) to DOCA-salt animals reduces systolic blood pressure without changes in the heart rate. These results show that the brain ET_A receptor is coupled to a pressor response whereas the ET_B receptor would counteract this response [63].

The catecholaminergic response in the OB shows that the chronic treatment of hypertensive rats with an ET_A antagonist (BQ610) reduces tyrosine hydroxylase activity in the right hemoportion of the OB without changes in the left OB [63]. However, ET_B activation, modifies neither the activity nor the expression of tyrosine hydroxylase (unpublished data). Recent findings from our laboratory show that the acute administration of BQ610 into the OB ventricle, decreases systolic blood pressure in hypertensive rats but elicits no changes in normotensive animals (Figure 3).

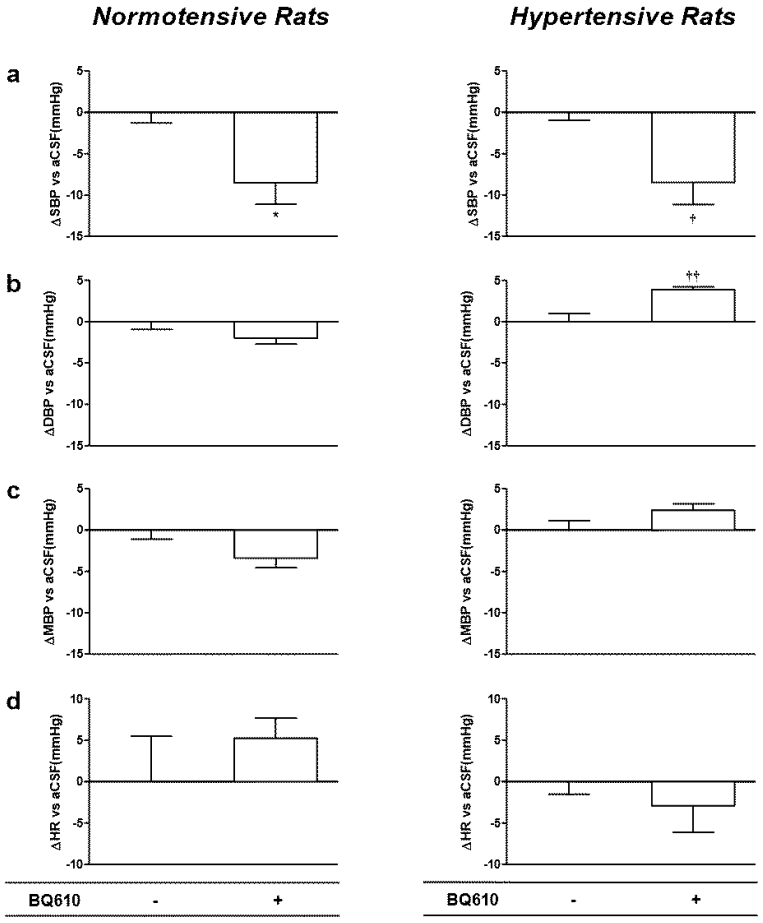

Figure 3. Effects of BQ-610 administration into the olfactory bulb of Control (normotensive) and DOCA-Salt hypertensive animals. *, **: $p<0.05$ and 0.01 vs Control; †, ††: $p<0.05$ and 0.01 vs DOCASalt. Number of animals: 4 per experimental group.

In another study normotensive and DOCA-salt hypertensive rats were subjected to bilateral bulbectomy at week 5. We show that systolic blood pressure is significantly reduced in hypertensive rats as compared with sham-operated animals. However, no changes are observed in normotensive rats with bilateral bulbectomy (Figure 4). These findings support the role of the OB in the maintenance of blood pressure elevation in salt dependent hypertension.

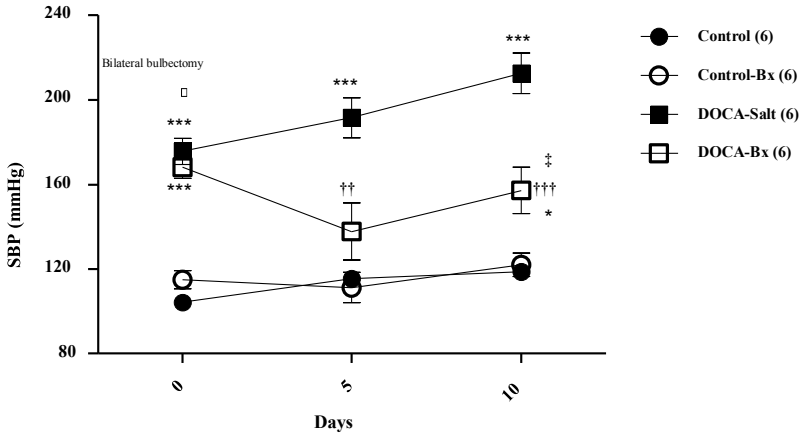

Figure 4. Effects of bilateral bulbectomy (Bx) on systolic blood pressure. ***, *: p<0.001 and 0.05 vs Control; †††, ††: p<0.001 and 0.01 vs DOCA-Salt; ‡: p<0.05 vs Control-Bx.

Summary

The association between the OB and mood disorders is well documented, as well as a bidirectional relationship between depression and cardiovascular diseases. Likewise, there is a close connection between the OB and the limbic system, and the areas related to the control of cardiovascular function. In this brief review, we summarized the current knowledge that support the existence of a relationship between the OB and the regulation of cardiovascular function, with focus on hypertension. The OB would be part of a complex puzzle that is the brain regulation of the cardiovascular function, which is not presently completely understood. Several questions remain regarding the OB and cardiovascular regulation: - Is the OB a main or a supporting actor? - What are the pathways and neurotransmitters involved? - What is the precise role of other vasoactive peptide systems expressed in the BO in the regulation of cardiovascular function?

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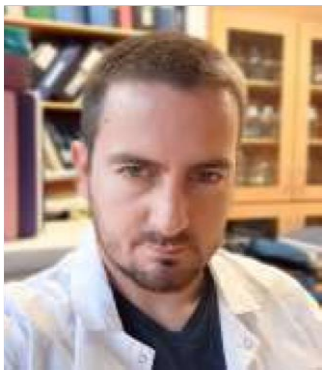

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