Brazilian Journal of Medical and Biological Research (1998) 31: 1185-1195
ISSN 0100-879X

Endogenous vasopressin and the central control of heart rate during dynamic exercise

L.C. Michelini

Departamento de Fisiologia e Biofísica, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, SP, Brasil

Abstract

The present article contains a brief review on the role of vasopressinergic projections to the nucleus tractus solitarii in the genesis of reflex bradycardia and in the modulation of heart rate control during exercise. The effects of vasopressin on exercise tachycardia are discussed on the basis of both the endogenous peptide content changes and the heart rate response changes observed during running in sedentary and trained rats. Dynamic exercise caused a specific vasopressin content increase in dorsal and ventral brainstem areas. In accordance, rats pretreated with the peptide or the V_1 blocker into the nucleus tractus solitarii showed a significant potentiation or a marked blunting of the exercise tachycardia, respectively, without any change in the pressure response to exercise. It is proposed that the long-descending vasopressinergic pathway to the nucleus tractus solitarii serves as one link between the two main neural controllers of circulation, i.e., the central command and feedback control mechanisms driven by the peripheral receptors. Therefore, vasopressinergic input could contribute to the adjustment of heart rate response (and cardiac output) to the circulatory demand during exercise.

Correspondence
L.C. Michelini
Departamento de Fisiologia e Biofísica, ICB, USP
Av. Prof. Lineu Prestes, 1524
05508-900 São Paulo, SP
Brasil
Fax: 55 (011) 813-0845/818-7285
E-mail: lisete@bmb.icb1.usp.br

Presented at the II International Symposium on Vasoactive Peptides, Ouro Preto, MG, Brasil, October 6-8, 1997.

Publication supported by FAPESP.

Received January 29, 1998
Accepted March 4, 1998

Key words
- Exercise tachycardia
- V_1 receptors
- Brainstem areas
- Peptides
- Blood pressure
- Training
- Rats

Introduction

Mechanisms governing the reflex control of the circulation and their integration at the bulbar level have been extensively studied (see reviews 1-4). Today it is well known that cardiac output, total peripheral resistance and venous capacitance are regulated on a moment-to-moment basis to keep blood pressure (and volume) within a narrow range, maintaining adequate blood supply to different territories in any behavioral condition.

To maintain blood pressure and adjust flow efficiently, the central nervous system (CNS) processes peripheral information about pressure levels, blood gases, pH, blood volume, temperature, etc. conveyed by different sets of receptors such as baroreceptors, chemoreceptors, cardiopulmonary receptors, and others. This information is integrated in different areas and at different levels of the CNS to provide adequate changes of sympathetic and parasympathetic tone to the heart and blood vessels, the main effectors of the circulatory system.

Importance of baroreceptors and the genesis of reflex bradycardia

Among the various mechanisms, the baroreceptors are the major controllers of pressure levels. Baroreceptor afferents or

arterial mechanoreceptors are tonically active at baseline pressure since they are stimulated by the systolic stretching of the vessel during each cardiac cycle. The firing rate of afferents can be increased or decreased instantaneously according to the larger or smaller stretch of the wall, proportional to the transient increase or decrease in pressure from control levels.

Figure 1 shows both the pathways and main bulbar areas (with the respective excitatory and inhibitory amino acid neurotransmitters) involved in the primary circuitry of blood pressure control by baroreceptors. Sinus and aortic nerve afferents (that join the IX and X cranial nerves, respectively) convey the encoded information on blood pressure levels to the nucleus tractus solitarii (NTS), the first synaptic relay in the brainstem. Upon activation by a pressure increase, second-order neurons in the NTS excite: 1) the parasympathetic preganglionic neurons located in the nucleus ambiguus (AMB) and dorsal motor nucleus of the vagus (DMV, not shown) determining an increase in vagal outflow to the heart and bradycardia, and 2) the inhibitory gabaergic neurons in the caudal ventrolateral medulla (CVLM) that project to the rostral ventrolateral medulla (RVLM). The RVLM is a major source of sympathetic premotor neurons projecting to the sympathetic pre-ganglionic neurons located in the intermediolateral cell column (IML) of the spinal cord. Inhibition of RVLM triggered by a pressure increase causes reduction of sympathetic tone to blood vessels and heart, determining an increase in venous capacitance and a decrease in both total peripheral resistance and cardiac output, with a marked bradycardic response. Opposite responses, i.e., a decrease in venous capacitance (with an increase in venous return) and an increase in both total peripheral resistance and cardiac output, are observed dur-

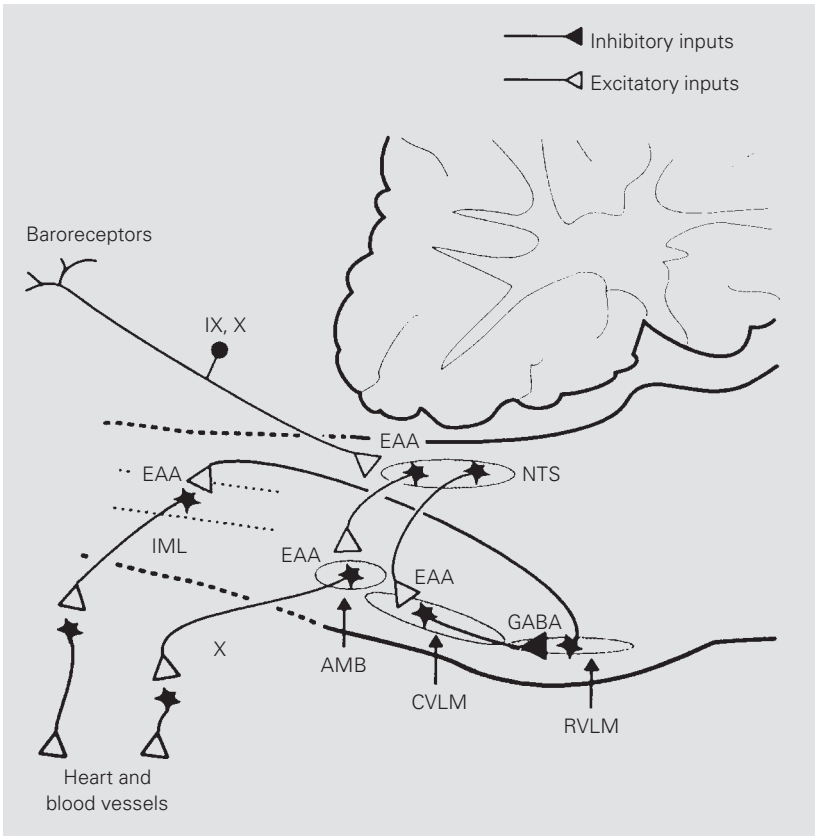


Figure 1 - Schematic representation of afferents, brainstem and spinal cord pathways and efferents that subserve cardiac and vasomotor components of the baroreceptor reflex. Proposed pathways that utilize excitatory (EAA) and inhibitory (Y-aminobutyric acid - GABA) amino acids as neurotransmitters are indicated. AMB = nucleus ambiguus, CVLM = caudal ventrolateral medulla, IML = intermediolateral cell column, NTS = nucleus tractus solitarii, RVLM = rostral ventrolateral medulla. Reproduced from Ref. 4, with permission.

ing a transient pressure decrease. In this case, the reduced or abolished baroreceptor discharge does not stimulate the parasympathetic preganglionic or the inhibitory gabaergic neurons.

It is important to note that activation of baroreceptors by a transient increase in pressure leads to a marked increase in vagal tone and withdrawal of sympathetic tone to the heart, causing strong reflex bradycardia.

Is reflex bradycardia always observed during a pressure increase?

The answer is no. During dynamic exercise, for instance (see Figure 2), there is a moderate (10-20 mmHg) and abrupt increase in pressure, maintained throughout the exercise, that is not accompanied by bradycardia but by a marked tachycardia (increase of 100 beats/min or more). Tachycardia is essential to maintain increased cardiac output (and pressure) that provides appropriate flow for exercising muscles. Flow to skeletal muscles exhibits a large and prompt increase, even at mild exercise intensity (0.4 km/h for rats, see Figure 2), an additional increase being observed at the transition from mild to moderate exercise intensity when the renal circulation (and other parts of the circulation with flow in excess of metabolic activity) starts presenting vasoconstriction, contributing to an increase in flow to active territories.

It has been shown that normal blood pressure, heart rate, cardiac output and systemic vascular resistance responses to exercise require functional arterial baroreceptors (6-9). There is also some experimental evidence demonstrating that baroreceptors are working properly during exercise. In rats, loading of baroreceptors during running on a treadmill produced reflex bradycardia (10) and the sensitivity of the bradycardic response after an acute bout of exercise was of similar magnitude as that seen during the resting period (11). It has been proposed (8,12) that reflex sensitivity is maintained during exercise because the operating point of the arterial baroreflex is reset to higher pressures. However, the mechanism(s) that

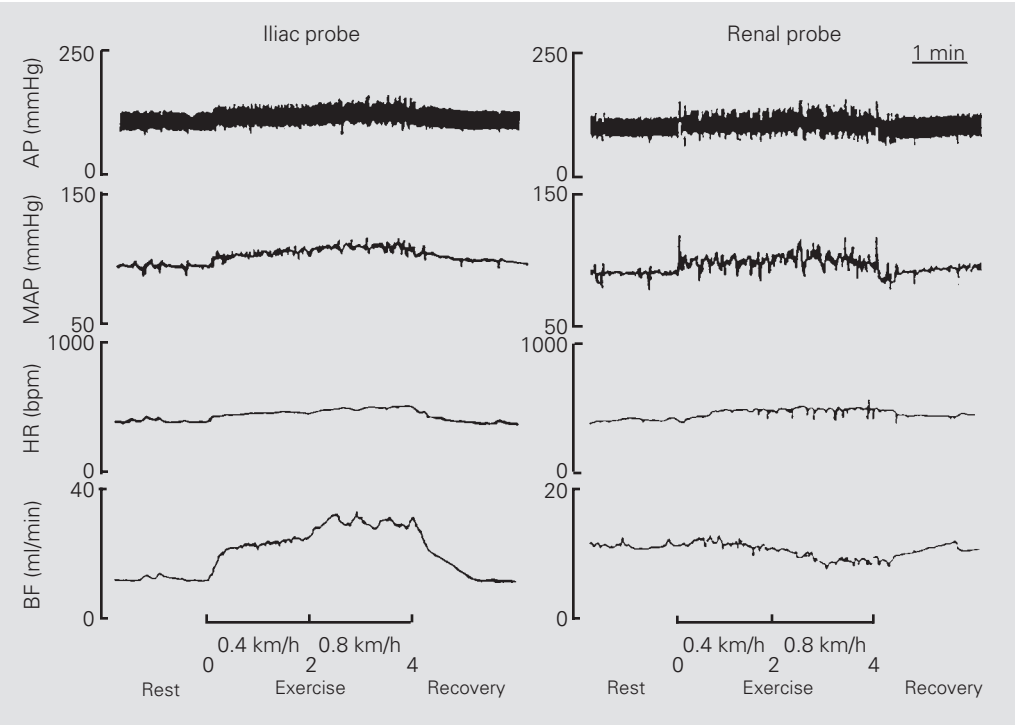


Figure 2 - Recordings of arterial pressure (pulsatile = AP and mean = MAP), heart rate (HR) and iliac (left panel) or renal (right panel) blood flow (BF) in 2 rats under resting conditions, during graded exercise (0.4 and 0.8 km/h) and during recovery. Reproduced from Ref. 5, with permission.

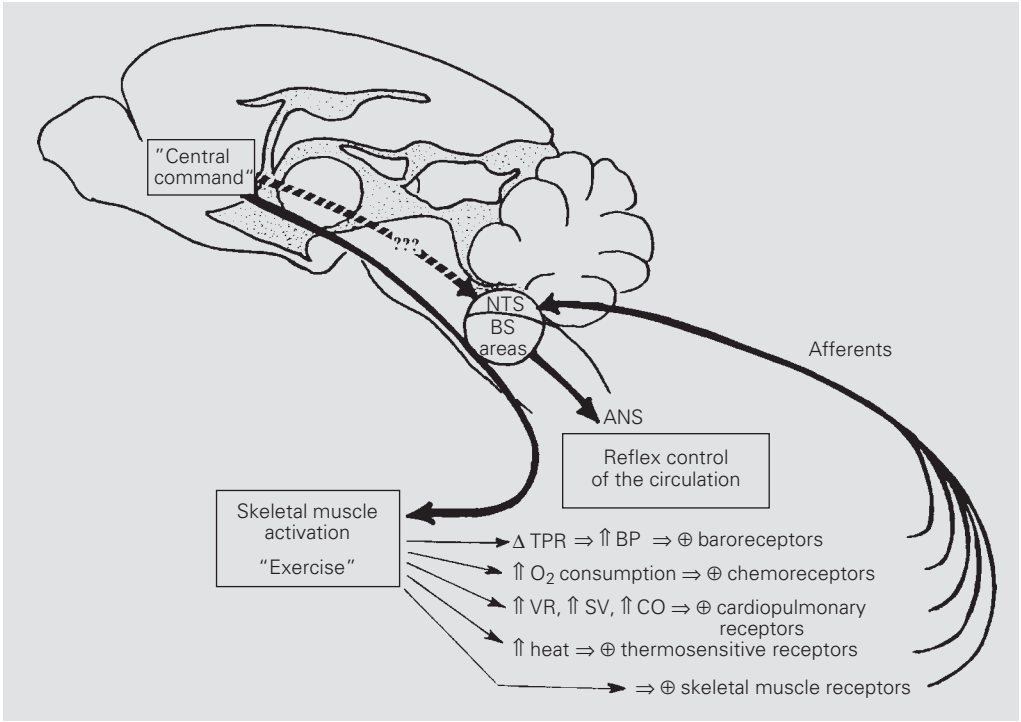


Figure 3 - Schematic presentation of the two neural mechanisms that control circulation during exercise: the "central command" and the feedback control mechanisms, driven by different receptors from cardiovascular areas and active muscles. The hypothesized pathway that integrates both mechanisms is represented by the dashed line. NTS = Nucleus tractus solitarii; BS = brainstem; TPR = total peripheral resistance; BP = blood pressure; VR = venous return; SV = stroke volume; CO = cardiac output; ANS = autonomic nervous system.

would permit the coexistence of marked tachycardia with a moderate increase in blood pressure during exercise without changing the bradycardic protective response in the case of a further pressure challenge is (are) not known.

According to current theory, the circulatory control during exercise is governed by two main neural mechanisms: a "central command" and a feedback control mechanism driven by the receptors from cardiovascular areas and active muscles (9,12,13). As shown schematically in Figure 3, the "central command" is a feed-forward control to set the basic pattern of motor activity for the skeletal muscles. Skeletal muscle activation stimulates receptors located within the muscles themselves and causes, directly or indirectly, changes in total peripheral resistance, leading to an increase in pressure which is accompanied by an increase in oxygen consumption, a reduction of venous capacitance with an increase in venous return, and by heat production. These changes are continuously monitored by the baroreceptors, chemoreceptors, cardiopulmonary and thermosensitive receptors, respectively, which, together with the receptors located in active muscles, regulate the circulation in a reflex manner, determining appropriate changes in the autonomic control to the heart and vessels. Although it is likely that both feed-forward and feedback controllers of circulation should interact to regulate the arterial pressure and heart rate response during exercise, very little is known about this possible interaction. An attractive hypothesis, under investigation in our laboratory, is that central projections from integrative centers, such as those from the hypothalamus to the cardiovascular relay areas in the brainstem would serve as links between the "central command" and the feedback control driven by peripheral receptors (see dashed arrow in Figure 3).

Among the modulatory centers in the hypothalamus, the supraoptic (SON) and particularly the paraventricular nucleus (PVN) are of great importance in cardiovascular control. The PVN is a complex nucleus

with two distinct regions (14,15): the magnocellular region synthesizes vasopressin and oxytocin which are released into the blood via the neurohypophysis (16), while the neurons of the parvocellular region project to the brainstem areas (NTS, DMV, RVLM, IML) involved in the autonomic control of heart and vessels (17-22).

On the other hand, the NTS is a heterogeneous cell group containing different types of neurons in the brainstem. It appears to be an important candidate site for the proposed interaction between feed-forward and feedback controllers of the circulation during exercise because: 1) it is the first synaptic relay of all peripheral afferents in the CNS (4,22,23); 2) it projects to brainstem areas controlling parasympathetic and sympathetic outflow (2,4); 3) it projects directly (and indirectly via bulbar, pontine and midbrain groups) to PVN and SON nuclei, amygdala and cortex (4,24-26), and 4) interestingly, it receives monosynaptic projections from the PVN (17-20). The reciprocal direct NTS → PVN, PVN → NTS innervation provides a prompt feedback control loop through which the PVN, an important hypothalamic integrative center involved in autonomic and neuroendocrine control, could also modulate afferent cardiovascular inputs (level, type, distribution, etc.) coming from the periphery to the NTS (26).

The long-descending monosynaptic projections from the PVN to the NTS have been shown to contain vasopressin, oxytocin, enkephalins and somatostatin (20-22). Most importantly, the PVN has been shown to be the only source of vasopressinergic projections to the NTS (19,20); inside the NTS vasopressin is contained only in fibers which make axo-somatic and axo-dendritic connections with NTS neurons (27), an arrangement characteristic of a modulatory circuitry.

Based on these neuroanatomical/immunohistochemical data, on the demonstration that vasopressin receptors are present at high density in the NTS (28-31), on the knowledge that vasopressin has important cardiovascular effects (32,33), and on our previous observations that peripheral and central vasopressin administration produced hypertension but quite different heart rate responses (34-36), our next question was:

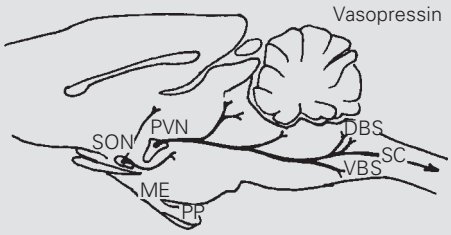
Is vasopressin in the NTS involved in baroreceptor reflex control of heart rate?

To answer this question, some years ago we developed a technique to chronically cannulate the dorsal brainstem and to administer peptides in the NTS of freely moving rats (37). Administration of a suppressor dose of vasopressin restricted to the NTS (mimicking stimulation of the long-descending vasopressinergic projections to this area) did not change the sensitivity of the baroreceptor reflex control of heart rate, but displaced the set point of the reflex toward higher heart rate values (37). This response contrasts with both the potentiation of the bradycardic response after intravenous vasopressin (38,39) and the blunting of reflex bradycardia following injection of vasopressin into the cerebrospinal fluid of conscious rats (26,39, see also Table 1). The peripheral hormone vasopressin sensitizes

Table 1 - Vasopressin effects on baroreceptor reflex (BRS) control of heart rate in conscious rats.

NTS, Nucleus tractus solitarii.

Site of administration	BRS effect	Receptor involved	References
iv	↑ gain	V_2	38,39
Lateral ventricle	↓ gain	V_1	39
4th ventricle	↓ gain	not determined	26
NTS	gain unchanged changes set point	V_1	37



VP content immediately after acute exercise

	S rats	T rats
PVN	ns	ns
SON	ns	ns
ME	ns	ns
PP	ns	ns
DBS	ns (+1.2 x)	⇑ 43 x*+
VBS	ns (+3.2 x)	⇑ 6 x*+
SC	ns	ns
Plasma	ns	ns

Figure 4 - Schematic representation of extra-hypothalamic vasopressinergic pathways arising from parvicellular regions of the supra-optic (SON) and paraventricular (PVN) nuclei in the hypothalamus and of the other central areas in which vasopressin content was measured. The main changes in vasopressin (VP) content induced by acute exercise in sedentary (S) and trained (T) rats are shown below. Training itself did not change the basal content of vasopressin in plasma and brain areas, except for a tendency (not significant) to a reduction in vasopressin levels in the dorsal brainstem (DBS) when compared to S rats at rest. ME = Median eminence; PP = posterior pituitary; SC = spinal cord; VBS = ventral brainstem; ns, nonsignificant. Original data in Ref. 40. *P<0.05 *vs* rest, +P<0.05 *vs* S rats.

the baroreceptor reflex through V_2 receptors accessible from the blood, while neuronal V_1 receptors show highly specific responses such as inhibition of the reflex bradycardia by the neurohormone released into the cerebrospinal fluid, but displacement of the operating point of the reflex by the neurotransmitter vasopressin released directly in the NTS upon stimulation of projections originating in the PVN. In addition, the lack of sensitivity for the bradycardic response during a pressure increase (gain not different from zero) observed after pretreatment of the NTS with a V_1 blocker (37) indicates that tonic activity of these projections is essential for the proper function of baroreceptor reflex control of heart rate.

Therefore, the reply to this question is yes. Although neurohormonal vasopressin (as well as the peripheral hormone) could also influence the reflex control of the heart, it appears that vasopressinergic projections to the NTS are of major importance because they constitute a pathway by which the PVN could directly modulate baroreceptor function (26). In addition, by shifting the operating point of the baroreflex control of the heart toward higher heart rate values, the vasopressinergic input modulates the bradycardic response to pressure challenges: during small pressure increases within a range of 10-20 mmHg (similar to that observed during dynamic exercise, see Figure 2) there was no bradycardic response, i.e., pressure increased without changes in basal heart rate (26,37). This effect is consistent with and not opposite to the appearance of exercise tachycardia during 10-20 mmHg pressure increase, as observed in Figure 2. On the other hand, in the same range of pressure change reflex bradycardia was significantly increased after endogenous blockade of V_1 receptors in the NTS (26,37).

Based on these observations, one may speculate that an increased discharge of vasopressinergic neurons in the NTS during exercise may be relevant to the problem of the genesis of centrally mediated exercise tachycardia.

Are there changes in the vasopressinergic input to the NTS during exercise?

To deal with this query we quantitated the vasopressin content in different areas of the CNS and plasma of sedentary and trained rats sacrificed at rest or after acute exercise tests on a treadmill (40). The results obtained are summarized in Figure 4. Immediately after the acute exercise tests, which resulted in maximal HR in both the sedentary and trained groups (increases of 150-170 beats/min over baseline values), we observed specific increases in vasopressin content only in the dorsal (DBS) and ventral brainstem (VBS) areas, corresponding to the solitarii-vagal complex and ventrolateral medulla, respectively. There were no changes in the spinal cord, PVN, SON, median eminence, posterior pituitary and plasma vasopressin levels after exercise in the sedentary and trained groups. Exercise-induced changes in DBS and VBS vasopressin content during exercise were observed in both sedentary and trained groups, but

were significantly higher only in trained rats.

These results clearly demonstrate that vasopressinergic projections to the NTS are activated during dynamic exercise. Furthermore, the specific increases of vasopressin content in DBS and VBS, with no detectable changes in the biosynthetic areas or in the magnocellular pathways to neurohypophysis or plasma levels (40), emphasize that the central vasopressin system exerts a differential and specific control in special situations. Exercise has been shown to affect mostly the parvicellular vasopressinergic pathways from PVN to brainstem (40).

Interactions between vasopressin content and baroreceptor function were already documented in a previous study (41) in which afferent input to the NTS region was interrupted via surgical denervation. Sinoaortic denervation produced differential changes in hypothalamic and brainstem vasopressin levels, with an increase in the brainstem and a decrease in the PVN and SON. It is not known whether alterations in peptide content are associated with changes in the local (DBS/VBS) secretion of vasopressin, or whether the DBS and VBS changes in vasopressin content observed during exercise are associated with cardiovascular responses to acute exercise. Since our previous results showed that exogenous administration and endogenous blockade of arginine peptide (AVP) in the NTS were able to shift the operating point of the reflex during a transient pressure increase, resulting in a smaller bradycardic response and an increased bradycardic response, respectively, we next investigated the role of AVP in exercise tachycardia.

Vasopressin in the NTS and its modulatory effect on exercise tachycardia

To determine whether changes in vasopressin content in the NTS are associated with cardiovascular responses to acute exercise we studied the blood pressure and heart rate response to exercise of chronically instrumented freely moving trained and sedentary rats after pretreatment of the NTS with vasopressin or a V_1 blocker (26,40). Administration of exogenous vasopressin in the NTS (mimicking an increased release into this area) specifically potentiated the tachycardic response without any change in blood pressure response during exercise. This effect was observed in both sedentary and trained rats. Most importantly (see Figure 5), in rats pretreated with a V_1 blocker the exercise tachycardia was significantly blunted without any change in the pressure response. Blunting of the tachycardic response was observed in both sedentary and trained rats but was significantly larger in the trained rats (40; see Figure 6). Therefore, the functional results are consistent with vasopressin content, since the peptide was significantly increased in the DBS of trained rats immediately after acute exercise and endogenous blockade of vasopressin at this level caused a significantly larger decrease in the exercise tachycardia of trained rats.

It was also shown (40) that the effect of vasopressin in the NTS is mediated by V_1 receptors and is specific for the tachycardic response during exercise because V_1 receptor blockade did not change control levels of heart rate or mean arterial pressure (observed during the rest period) nor did it change the pressor response to exercise. During dynamic exercise, specific adaptive responses of the heart without any change in the pressure response were also observed in trained spontaneously hypertensive rats (SHR) when compared with sedentary control rats (42).

Specific modulation of the heart rate response during exercise constitutes a very precise and selective mechanism for maintaining adequate cardiac output and blood flow to active muscles. It has been shown that during exercise the sympathetic outflow to the heart was the largest in the body and was increased by 17-fold, an increment at

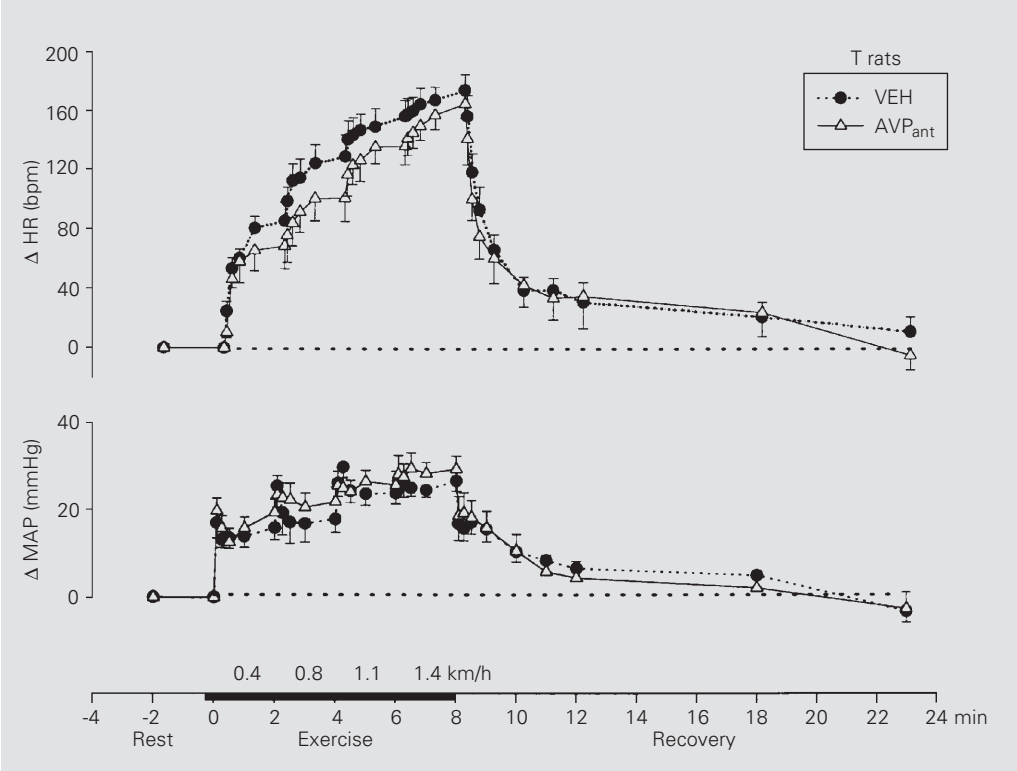


Figure 5 - Heart rate (HR) (upper panel) and mean arterial pressure (MAP) responses (lower panel) during progressive exercise (0.4 up to 1.4 km/h) in 7 trained rats pretreated with vehicle (VEH) or a V_1 blocker (AVP_{ant}) into the NTS. Reproduced from Ref. 40, with permission.

least 5 times higher than any other outflow tested (43). This is a clear demonstration of the importance of the central control of the heart (heart rate, contractility, cardiac output) during exercise. In addition, our results concerning the changes in brainstem vasopressin content and specific potentiation or blunting of the heart rate response after vasopressin or V_1 blocker treatment in the NTS (40) suggest that vasopressinergic projections from the PVN to the NTS are part of the central mechanism that specifically modulates heart rate control during exercise.

It should be noted that immediately after acute exercise vasopressin content was also increased in the VBS. Although it is possible that suprabulbar vasopressinergic pathways could modulate heart rate control by a combined action on dorsal (afferent input) and ventral (efferent output) brainstem areas, the functional effects of vasopressin in the ventral brainstem remain to be determined.

Conclusions

In summary, we observed that vasopressin is released in the NTS during acute exercise (40) and that increased content of vasopressin in the NTS by acting on V_1 receptors caused both a shift of the operating point of the arterial baroreflex toward higher heart rate values (determining a smaller bradycardic response during pressure increases without changing baroreflex sensitivity; 37) and a larger tachycardic response during exercise (26,40). It is not known whether these responses are caused by subtraction of the vagal output and/or by an increase in sympathetic output. Preliminary results (Michelini LC, unpublished observations) on loading of baroreceptors in the presence of sympathetic or vagal blockade (propranolol or atropine *iv* treatment, respectively) showed that vasopressin administration into the NTS was able to displace the bradycardic response toward

higher heart rate values only in rats blocked with atropine (intact sympathetic outflow), suggesting that vasopressin in the NTS facilitates the sympathetic pathway or favors the inhibition of sympathetic withdrawal that usually occurs during transient blood pressure increases. It was also shown that tachycardia during dynamic exercise was due to instantaneous withdrawal of parasympathetic tone followed by a maintained increase of sympathetic tone (44-47). Possible contributions of vagal and/or sympathetic tone to the modulation of exercise tachycardia by central vasopressinergic input remain to be determined.

We may clarify that the vasopressinergic system of the NTS is not the only central mechanism involved in the genesis of exercise tachycardia (and/or central adaptations to training) because an AVP antagonist (AVP_{ant}) in this area did not block the heart rate response but only caused a partial blunting (Figure 5). Several peptides have been identified in the solitarii-vagal complex (22) and some of them were shown to be present in the projections from the hypothalamus to this area (20). It is likely that other peptidergic systems may be involved in the genesis of exercise tachycardia. Kregel et al. (48) showed that corticotropin-releasing factor is important since a partial blunting of the tachycardic response was observed after intracerebroventricular administration of its receptor antagonist. The oxytocinergic system has also been shown to be involved in stress-induced tachycardia (49) and to interact with the central vasopressinergic system in cardiovascular control (50,51). Preliminary results with oxytocin (52) administered into the solitarii-vagal complex showed that the peptide caused a significant blunting of the tachycardic response during dynamic exercise. Although the V_1 blocker used in our experiments is 100 times more potent as an antivasopressor than as an antioxytocic, we could not exclude possible effects due to a partial blockade of oxytocin in the brainstem. However, stimulation of oxytocin receptors did not seem to be involved in the potentiation of exercise tachycardia since oxytocin administration into the solitarii-vagal complex (52) caused a significant blunting of the tachycardia during dynamic exercise, a response opposite to that observed with AVP. Therefore, during dynamic exercise oxytocinergic projections to the NTS should be less activated or not activated at all and the mechanism underlying exercise tachycardia seems to be different from that determining stress tachycardia.

Taken together, the anatomic, immunohistochemical, radioautographic, biochemi-

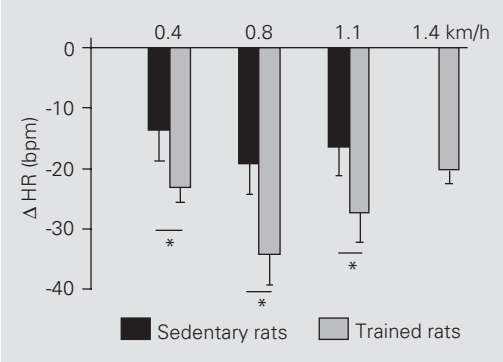


Figure 6 - Comparison of maximal heart rate (HR) reduction during exercise in sedentary and trained rats pretreated with the V_1 blocker. Bars represent the differential effect of administration of the antagonist (AVP_{ant} minus vehicle response) into the NTS. *P<0.05 *vs* sedentary group. Reproduced from Ref. 40, with permission.

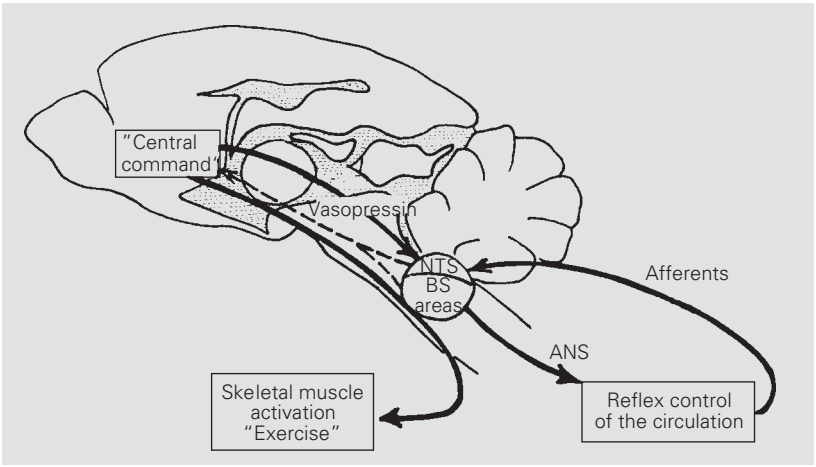


Figure 7 - Proposed vasopressinergic link to adjust the feed-forward ("central command") and feedback controllers of the circulation during exercise. The dashed line represents the peripheral encoded information (from afferents) from cardiovascular effectors conveyed by the nucleus tractus solitarii (NTS) and other brainstem areas (BS) to suprabulbar integrative centers. ANS, Autonomic nervous system.

cal and functional data summarized in this review indicate that the long-descending projections from the PVN to the NTS in the brainstem are part of the central mechanism modulating baroreceptor reflex control of heart rate during exercise. As illustrated in Figure 7, we propose that the vasopressinergic pathway to the nucleus tractus solitarii serves as one link between the "central command" and the reflex control of the heart and of the circulation, contributing to the adjustment of the heart rate response (and cardiac output) to the circulatory demand during dynamic exercise.

References

1. Kirchheim HR (1976). Systemic arterial baroreceptor reflexes. *Physiological Reviews*, 56: 100-176.
2. Palkovits M (1980). The anatomy of central cardiovascular neurons. In: Fuke K, Goldstein M, Hökfelt B & Hökfelt T (Editors), *Central Adrenalin Neurons: Basic Aspects and their Role in Cardiovascular Functions*. Pergamon Press, Oxford, 3-17.
3. Chalmers J & Pilowsky P (1991). Brainstem and bulbospinal neurotransmitter systems in the control of blood pressure. *Journal of Hypertension*, 9: 675-694.
4. Dampney RAL (1994). Functional organization of central pathways regulating the cardiovascular system. *Physiological Reviews*, 74: 323-364.
5. Amaral SL & Michelini LC (1997). Validation of transit-time flowmetry for chronic measurements of regional blood flow in resting and exercising rats. *Brazilian Journal of Medical and Biological Research,* 30: 897-908.
6. Ludbrook J (1983). Reflex control of blood pressure during exercise. *Annual Review of Physiology,* 45: 155-168.
7. DiCarlo E & Bishop VS (1990). Exercise training enhances cardiac afferent inhibition of baroreflex function. *American Journal of Physiology,* 258 (*Heart and Circulatory Physiology,* 27): H212-H220.
8. DiCarlo E & Bishop VS (1992). Onset of exercise shifts operating point of arterial baroreflex to higher pressures. *American Journal of Physiology,* 262 (*Heart and Circulatory Physiology*, 31): H303-H307.
9. Rowell LB (1992). Reflex control of the circulation during exercise. *International Journal of Sports Medicine*, 13 (Suppl I): S25-S27.
10. Krieger EM, Brum PC & Negrão CE (1998). Role of arterial baroreceptors during acute and chronic exercise. *Biological Research* (in press).
11. Silva GJ, Brum PC, Negrão EC & Krieger EM (1997). Acute and chronic effects of exercise on baroreflexes in spontaneously hypertensive rats. *Hypertension*, 30 (Part 2): 714-719.
12. Rowell LB & O'Leary DS (1990). Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *Journal of Applied Physiology,* 69: 407-418.
13. Mitchell JH (1990). Neural control of the circulation during exercise. *Medicine and Science in Sports and Exercise*, 22: 141-154.
14. Swanson LW & Kuypers HGJM (1980). The paraventricular nucleus of the hypothalamus: Cytoarchitectonic subdivisions and organization of projections to the pituitary, dorsal vagal complex and spinal cord as demonstrated by retrograde fluorescence double-labeling methods. *Journal of Comparative Neurology*, 194: 555-570.
15. Swanson LW & Sawchenko PE (1980). Paraventricular nucleus: A site for the integration of neuroendocrine and autonomic mechanisms. *Neuroendocrinology,* 31: 410-417.
16. Morris JF, Chapman DB & Sokol HW (1987). Anatomy and function of the classic vasopressin secreting hypothalamus-neurohypophyseal system. In: Gash DM & Boer GI (Editors), *Vasopressin. Principles and Properties*. Plenum, New York, 1-89.
17. Buijs RM, Swaab DF, Dogterom J & van Leeuwen FW (1978). Intra and extrahypothalamic vasopressin and oxytocin pathways in the rat. *Cell and Tissue Research,* 186: 423-433.
18. Nilaver G, Zimmerman EA, Witkins J, Michaels J, Hoffman D & Silverman AJ (1980). Magnocellular hypothalamic projection to the lower brain stem and spinal cord of the rat. Immunocytochemical evidence for predominance of the oxytocin-neurophysin system compared to the vasopressin-neurophysin system. *Neuroendocrinology,* 30: 150-158.
19. Sofroniew MV & Schrell U (1981). Evidence for a direct projection from oxytocin and vasopressin neurons in the hypothalamic paraventricular nucleus to the medulla oblongata: immunohistochemical visualization of both the horseradish peroxidase transported and the peptide produced by the same neurons. *Neuroscience Letters,* 22: 211-217.
20. Sawchenko PE & Swanson LW (1982). Immunohistochemical identification of neurons in the paraventricular nucleus of the hypothalamus that project to the medulla or to the spinal cord in the rat. *Journal of Comparative Neurology,* 205: 260-272.
21. Palkovits M (1984). Distribution of neuropeptides in the central nervous system: A review of biochemical mapping studies. *Progress in Neurobiology,* 23: 115-189.
22. Van Giersbergen PLM, Palkovits M & De Jong W (1992). Involvement of neurotransmitters in the nucleus tractus solitarii in cardiovascular regulation. *Physiological Reviews,* 72: 789-824.
23. Miura M & Reis DJ (1969). Termination and secondary projections of carotid sinus nerve in the cat brain stem. *American Journal of Physiology*, 217: 142-153.
24. Sawchenko PE & Swanson LW (1981). Central noradrenergic pathways for the integration of hypothalamic neuroendocrine and autonomic responses. *Science,* 214: 685-687.
25. Palkovits M (1988). Neuronal circuits in central baroreceptor mechanism. In: Saito H, Parvez H, Parvez S & Nagatsu T (Editors), *Progress in Hypertension*. Vol. 1. VSP, Utretch, 387-409.
26. Michelini LC (1994). Vasopressin in the nucleus tractus solitarius: a modulator of baroreceptor reflex control of heart rate. *Brazilian Journal of Medical and Biological Research,* 27: 1017-1032.
27. Weindl A & Sofroniew M (1985). Neuroanatomical pathways related to vasopressin. In: Ganten D & Pfaff D (Editors),

Neurobiology of Vasopressin. Springer-Verlag, Berlin, 137-195.
28. Dogterom J, Snijdewint FGM & Buijs RM (1978). The distribution of vasopressin and oxytocin in the rat brain. *Neuroscience Letters*, 9: 341-346.
29. Van Leeuwen FW, Van der Beek EM, Van Heerikhuize JJ, Wolters P, Van der Meulen G & Wan Y-P (1987). Quantitative light microscopic autoradiographic localization of binding sites labelled with [^{3}H] vasopressin antagonist d(CH_2)$_5$Tyr(Me)VP in the rat brain, pituitary and kidney. *Neuroscience Letters,* 80: 121-126.
30. Tribollet E, Barberis C, Jard S, Dubois-Dauphin M & Dreifuss JJ (1988). Localization and pharmacological characterization of high affinity binding sites for vasopressin and oxytocin in the rat brain by light microscopic autoradiography. *Brain Research,* 442: 105-118.
31. Phillips PA, Abrahams JM, Kelly J, Paxinos G, Grzonka Z, Mendelsonhn FAO & Johnston CI (1988). Localization of vasopressin binding sites in rat brain by *in vitro* autoradiography using a radioiodinated V_1 receptor antagonist. *Neuroscience,* 27: 749-761.
32. Cowley Jr AW, Liard JF, Skelton MM, Quinlen Jr EW, Osborn Jr JW & Webb RL (1985). Vasopressin-neural interactions in the control of cardiovascular function. In: Schrier RW (Editor), *Vasopressin*. Raven Press, New York, 1-10.
33. Cowley Jr AW & Liard JF (1987). Cardiovascular actions of vasopressin. In: Gash DM & Boer GJ (Editors), *Vasopressin: Principles and Properties*. Plenum, New York, 389-433.
34. Michelini LC, Barnes KL & Ferrario CM (1983). Arginine vasopressin modulates the central action of angiotensin II in the dog. *Hypertension*, 11: I-75-I-79.
35. Ferrario CM, Mikami H, Michelini LC, Kawano Y & Brosnihan KB (1985). Interaction of vasopressin with central neurogenic mechanisms of blood pressure regulation. In: Schrier RW (Editor), *Vasopressin*. Raven Press, New York, 47-57.
36. Michelini LC, Barnes KL & Ferrario CM (1986). Area postrema lesions augment the pressor activity of centrally administered vasopressin. *Clinical and Experimental Hypertension, Theory and Practice*, A8: 1107-1125.
37. Michelini LC & Bonagamba LGH (1988). Baroreceptor reflex modulation by vasopressin microinjected into the nucleus tractus solitarii of conscious rats. *Hypertension*, 11 (Suppl I): I-75-I-79.
38. Imai Y, Nolan PL & Johnston CI (1983). Restoration of suppressed baroreflex sensitivity in rats with hereditary diabetes insipidus (Brattleboro rats) by arginine vasopressin and DDAVP. *Circulation Research*, 53: 140-149.
39. Unger T, Rohmeiss P, Demmert G, Ganten D, Lang RE & Luft FC (1986). Differential modulation of the baroreceptor reflex by brain and plasma vasopressin. *Hypertension*, 8 (Suppl II): II-157-II-162.
40. Dufloth DL, Morris M & Michelini LC (1997). Modulation of exercise tachycardia by vasopressin in the nucleus tractus solitarii. *American Journal of Physiology*, 273 (*Regulatory, Integrative and Comparative Physiology*, 42): R1271-R1282.
41. Alexander N & Morris M (1988). Effects of chronic sinoaortic denervation on central vasopressin and catecholamine systems. *American Journal of Physiology,* 255 (*Regulatory, Integrative and Comparative Physiology*, 24): R768-R733.
42. Veras-Silva AS, Mattos KC, Brum PC, Negrão CE & Krieger EM (1998). Effect of exercise training on hemodynamic responses during exercise in spontaneously hypertensive rats. *American Journal of Physiology* (in press).
43. Esler M, Jennings G, Lambert G, Meredith I, Horne M & Eisenholfer G (1990). Overflow of catecholamine neurotransmitters to the circulation: Source, fate and functions. *Physiological Reviews,* 70: 963-985.
44. Maciel BC, Gallo Jr L, Marin-Neto JA, Lima Filho EC & Martins LEB (1986). Autonomic nervous control of the heart rate during dynamic exercise in normal man. *Clinical Science,* 71: 457-460.
45. Gallo Jr L, Maciel BC, Marin-Neto JA & Martins LEB (1989). Sympathetic and parasympathetic changes in heart rate control during dynamic exercise induced by endurance training in man. *Brazilian Journal of Medical and Biological Research,* 22: 631-643.
46. Arai Y, Saul JP, Albrecht P, Hartley LH, Lilly LS, Cohen RJ & Colucci WS (1989). Modulation of cardiac autonomic activity during and immediately after exercise. *American Journal of Physiology,* 256 (*Heart and Circulatory Physiology*, 25): H132-H141.
47. Negrão CE, Moreira ED, Brum PC, Denadai MLDR & Krieger EM (1992). Vagal and sympathetic control of heart rate during exercise by sedentary and exercise-trained rats. *Brazilian Journal of Medical and Biological Research,* 25: 1045-1052.
48. Kregel KCJ, Overton M, Seals DR, Tipton CM & Fisher LA (1990). Cardiovascular responses to exercise in the rat: role of corticotropin-releasing factor. *Journal of Applied Physiology,* 68: 561-567.
49. Morris M, Callahan MF & Lucion AB (1995). Central oxytocin mediates stress-induced tachycardia. *Journal of Neuroendocrinology*, 7: 455-459.
50. Poulin P & Pittman QJ (1993). Oxytocin pretreatment enhances arginine vasopressin-induced motor disturbances and arginine vasopressin-induced phosphoinositol hydrolysis in rat septum: a cross sensitization phenomenon. *Journal of Neuroendocrinology*, 5: 33-39.
51. Poulin P, Komulainen A, Takahashi Y & Pittman QJ (1994). Enhanced pressure responses to *icv* vasopressin treatment with oxytocin. *American Journal of Physiology*, 266 (*Regulatory, Integrative and Comparative Physiology*, 35): R592-R598.
52. Michelini LC, Pontes Jr FL & Braga DC (1995). Modulation of heart rate response by oxytocin in the solitarii-vagal complex. *Hypertension,* 25: 1412 (Abstract).