Central blockade of vasopressin V1 receptors attenuates postexercise hypotension

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Collins, Heidi L., David W. Rodenbaugh, and Stephen E. DiCarlo. Central blockade of vasopressin V1 receptors attenuates postexercise hypotension. Am J Physiol Regulatory Integrative Comp Physiol 281: R375–R380, 2001.—We tested the hypothesis that central arginine vasopressin (AVP) mediates postexercise reductions in arterial pressure (AP) and heart rate (HR). To test this hypothesis, nine spontaneously hypertensive rats (SHR) were instrumented with a 22-gauge stainless steel guide cannula in the right lateral cerebral ventricle and with a carotid arterial catheter. After the rats recovered, AP and HR were assessed before and after a single bout of dynamic exercise with the central administration of vehicle or the selective AVP V1-receptor antagonist d(CH3)5 Tyr(Me)-AVP (AVP-X). AP and HR were significantly decreased below preexercise values with central administration of vehicle (P < 0.05, change (Δ)−21 ± 4 mmHg and Δ−20 ± 6 beats/min, respectively). In sharp contrast, after exercise with central administration of AVP-X, both AP (Δ+8 ± 5 mmHg) and HR (Δ+24 ± 9 beats/min) were not significantly different from preexercise values (P > 0.05). Furthermore, AVP-X at rest did not significantly alter AP (181 ± 11 vs. 178 ± 11 mmHg, P > 0.05) or HR (328 ± 24 vs. 331 ± 22 beats/min, P > 0.05). Thus central blockade of AVP V1 receptors prevented postexercise reductions in AP and HR. These data suggest that AVP, acting within the central nervous system, mediates postexercise reductions in AP and HR in the SHR.

arginine vasopressin; arterial baroreflex resetting; cardiopulmonary baroreflex

Heart disease is the leading cause of death in the United States, and hypertension is a leading risk factor for heart disease. Thus interventions designed to reduce arterial pressure (AP) remain the focus of numerous investigative efforts. A single bout of dynamic exercise reduces postexercise AP for several hours in hypertensive individuals and animals (16, 28). Understanding the mechanisms responsible for the postexercise reduction in AP may lead to measures designed to lower AP in hypertensive individuals. The postexercise hypotension (PEH) requires intact cardiopulmonary (11) and arterial baroreceptors (8). Furthermore, PEH is mediated by a resetting of the operating point of the arterial baroreflex to a lower pressure (9, 21). Arterial baroreflex resetting can occur by facilitation of cardiopulmonary reflexes (5).

Arginine vasopressin (AVP), acting primarily on V1 receptors, enhances both cardiopulmonary (1, 25, 42) and arterial baroreflex function (4, 17, 42) as well as resets the operating point of the arterial baroreflex to a lower pressure (23). Furthermore, Stebbins and colleagues (6, 38) have demonstrated that AVP acts at the area postrema to enhance arterial baroreflex-induced sympathoinhibition during static muscle contraction. Sympathoinhibition also contributes, in part, to PEH (20, 21, 29). Finally, AVP is increased in dorsal brain stem areas during dynamic exercise (32). Taken together, these data support a possible mechanism whereby an AVP-induced facilitation of inhibitory cardiopulmonary reflexes and/or resetting of the operating point of the arterial baroreflex may contribute to PEH. Therefore, this study was designed to test the hypothesis that central administration of a selective AVP V1-receptor antagonist would attenuate postexercise reductions in AP in spontaneously hypertensive rats (SHR).

METHODS

Design. Nine male SHR were weaned at 4 wk of age and housed in standard rat cages at all times. Between 12 and 13 wk of age, all rats were instrumented with a stainless steel guide cannula in the lateral cerebral ventricle. After ~2 wk of recovery, all rats were instrumented with a carotid arterial catheter and were subsequently allowed at least 5 days to recover. After the rats recovered, AP and heart rate (HR) were recorded before and after a single bout of dynamic exercise with the central administration of vehicle or the selective AVP V1-receptor antagonist d(CH3)5Tyr(Me)-AVP (AVP-X). In addition, all rats underwent a sham-exercise protocol that served as a time control. All surgical and experimental procedures were approved by the Institutional Animal Care and Use Committee and were conducted in conformity with the Guide for the Care and Use of Laboratory Animals.

Surgical procedures. All instrumentation was performed using aseptic surgical procedures. Rats were anesthetized with an intramuscular injection of ketamine hydrochloride (40 mg/kg), xylazine (8 mg/kg), and chlorpromazine hydrochloride (4 mg/kg). Subsequently, each rat was placed into a cranial stereotaxic instrument (Kopf, Tujunga, CA), and a guide cannula was inserted into the lateral right cerebral ventricle (Kopf stereotaxic coordinates: 2 mm ventral, 0 mm lateral, 10 mm anterior relative to the bregma). After placement of the guide cannula, the surgical incision was closed with 4-0 nylon suture. After surgery, rats were allowed at least 1 wk to recover. After recovery, rats were placed in a restraint cage and exercised using a cyclic treadmill protocol (30). After exercise, AP and HR were recorded using a CAM II Data acquisition system (Kent Scientific, Torrington, CT). AP was recorded from a femoral arterial catheter, and HR was recorded from the lead II electrocardiographic signal.

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Results from this study support the conclusion that central AVP contributes, in part, to PEH. In this study, a single bout of dynamic exercise reduced postexercise AP and HR (Δ−21 ± 4 mmHg and Δ−20 ± 6 beats/min, respectively). This postexercise reduction in AP and HR is similar in magnitude to that recently reported for hypertensive rats (8, 9, 11, 29). Importantly, central administration of a selective AVP V1-receptor antagonist prevented postexercise reductions in AP and HR. The effect of AVP-X was limited to the central nervous system because the central dose used in this study (100 ng) (27) is significantly below that required for peripheral blockade (10–14 μg/kg) (39). Furthermore, central administration of AVP-X at rest did not significantly alter AP or HR. Similarly, sham exercise had no significant effect on resting AP or HR. Taken together, these data demonstrate that AVP, acting within the central nervous system, has a major role in the mechanisms mediating PEH.

DISCUSSION

Several investigators have reported a statistically and clinically significant reduction in resting AP and HR following a single bout of dynamic exercise in individuals and animals with hypertension (16, 28). The PEH is associated with elevations in cardiac output as well as reductions in peripheral resistance (22).
and sympathetic nerve activity (20, 29). The postexercise sympathoinhibition is mediated by an enhanced inhibitory influence of the cardiopulmonary baroreflex as well as a decrease in gain and leftward shift of the arterial baroreflex function curve (9, 11).

It is well known that AVP modulates arterial and cardiopulmonary baroreflex function. Specifically, endogenously released AVP enhances the arterial and cardiopulmonary baroreflex inhibition of sympathetic nerve activity as well as reduces the gain and shifts the operating point of the arterial baroreflex to a lower pressure (23). AVP mediates its effect on baroreflex function through V1 vasopressin receptors in the central nervous system, specifically the area postrema. Thus it was reasonable to postulate that PEH may be mediated, in part, by AVP. Although the mechanisms responsible for the AVP-induced PEH were not investigated, several studies have reported that AVP activates neurons in the area postrema that project to the nucleus of the solitary tract (NTS) (Fig. 3A). These area postrema neurons sensitize NTS neurons to baroreceptor afferent signals. This response enhances processing of baroreceptor input (Fig. 3B) and resets the operating point of the arterial baroreflex to a lower pressure (Fig. 3C). Thus this effect of AVP is dependent on afferent input from peripheral baroreceptors (34). Importantly, it has been shown that sinoaortic denervation prevents PEH and sympathoinhibition in hypertensive rats (8). Furthermore, a single bout of dynamic exercise resets the operating point of the arterial baroreflex to lower pressures (9, 21). These data support a mechanism whereby AVP could mediate PEH by enhancing NTS responsiveness to baroreceptor input (37).

**Fig. 1.** Mean arterial pressure (MAP) before and after exercise with central administration of vehicle (A) or central blockade of vasopressin V1 receptors (d(CH3)5 Tyr(Me)-arginine vasopressin (AVP) (AVP-X); B). C: MAP before and after a 40-min session of sham exercise (resting on the treadmill). A significant reduction in MAP following exercise [postexercise hypotension (PEH)] was observed with the central administration of vehicle (Δ−21 ± 4 mmHg; A). In sharp contrast, after exercise with central administration of AVP-X, arterial pressure was not different from preexercise values (Δ+8 ± 5 mmHg; B). Finally, a 40-min session of sham exercise did not significantly alter arterial pressure (Δ+4 ± 5 mmHg; C). These data support the conclusion that central vasopressin contributes, in part, to PEH. *P < 0.05.

**Fig. 2.** Heart rate (HR) before and after exercise with central administration of vehicle (A) or central blockade of vasopressin V1 receptors (AVP-X; B). C: HR before and after a 40-min session of sham exercise (resting on the treadmill). After exercise with central administration of vehicle, HR was significantly below the preexercise level (Δ−20 ± 6 beats/min; A). With central administration of AVP-X, HR was not significantly different from the preexercise level (Δ+24 ± 9 beats/min; B). Finally, a 40-min session of sham exercise did not alter HR (Δ+10 ± 7 beats/min; C). *P < 0.05.
An interesting and important question is how could the effects of AVP persist 60 min after the stimulus (exercise) for its release was completed? AVP has a systemic half-life of ~3–4 min. Although the half-life is probably longer in the central nervous system, it is reasonable to question how the effects of AVP could still be around 60 min after exercise. The mechanisms mediating the long-lasting effects of AVP [at least 60 min after the stimulus for its release (exercise) was completed] are unknown and were not investigated in this study. However, several investigators have reported a long-lasting effect of AVP in the central nervous system. For example, alterations in the HR response to dynamic exercise were observed 2 days after AVP was microinjected into the NTS of conscious rats (19). Furthermore, these investigators reported that repeated exposure to AVP (mediated by a daily exercise-induced release of AVP) caused a long-lasting sensitization to AVP. Similarly, central exposure to AVP potentiated the pressor (30) and behavioral (2, 36) responses to subsequent exposures to this peptide. This potentiation was mediated by V1 receptors and was reported to persist for days (36). Finally, AVP has a major role in memory (12), further supporting its long-lasting effects.

It has been suggested that the long-lasting effects of AVP were due to postreceptor mechanisms (15, 36) because no changes in V1-receptor density or affinity were observed. In addition, the long-lasting effect of AVP may be due, in part, to enhancing NTS responsiveness to baroreceptor afferent signals by a phenomenon termed “wind-up” (14, 18). Repetitive stimulation of unmyelinated baroreceptor afferents may result in hyperexcitability of NTS neurons via a poststimulatory facilitation mechanism (33). The influence of AVP on the poststimulatory facilitation mechanism (“wind-up”) has not been investigated and merits further research.

In addition to the effect of AVP on the arterial baroreflex, this hormone also enhances the cardiopulmonary baroreflex regulation of the circulation. Specifically, endogenously released AVP enhances the reflex inhibitory response to activation of the cardiopulmonary baroreflex (24). Importantly, several studies have demonstrated that a single bout of dynamic exercise enhances the inhibitory influence of the cardiopulmonary baroreflex on the sympathetic nervous system (3, 11, 13). The postexercise facilitation of inhibitory cardiopulmonary baroreflexes may be due to AVP acting on the area postrema (Fig. 3A). In this situation, AVP could augment reflex sympathoinhibition in response to cardiopulmonary input and contribute, in part, to PEH.

Postexercise facilitation of inhibitory cardiopulmonary baroreflexes may also contribute to PEH by resetting the operating point of the arterial baroreflex to a lower pressure (5). Cardiopulmonary baroreflex afferents exert a tonic inhibitory influence on the arterial baroreflex such that the gain is reduced and the arterial baroreflex function curve is shifted to the left (10, 26). Furthermore, increasing cardiopulmonary baroreflex afferent activity further decreases the gain and shifts the arterial baroreflex function curve to the left (10). Thus the level of cardiopulmonary activity influences the gain and position of the arterial baroreflex function curve.

**Limitations.** With the use of the intracerebroventricular injection technique, we can only state that the effect is centrally mediated. Unfortunately, we cannot identify the specific central site(s) of action. In addi-
tion, it is possible that AVP-X is acting at multiple sites that have opposing responses. However, the intracerebroventricular injection technique is a reasonable first approach. Now that we are confident that the effect is centrally mediated, future investigations will focus on techniques for discrete microinjections into specific nuclei of conscious animals (19, 32).

Perspectives

AVP is a complex hormone that has multiple effects including water reabsorption at the distal and collecting tubules of the kidney as well as vascular smooth muscle constriction. Peripheral AVP also contributes to an increase in AP and redistribution of cardiac output during dynamic exercise via its vasoconstrictor actions (39–41). Importantly, AVP also interacts with arterial and cardiopulmonary baroreceptors to regulate cardiovascular function at rest and during exercise. Specifically, AVP acts at the area postrema to enhance arterial baroreflex-induced sympathoinhibition during static exercise (6). This effect of AVP may be due to a resetting of the operating point of the arterial baroreflex to a lower pressure. Resetting of the operating point of the arterial baroreflex to a lower pressure may be the same mechanism by which AVP mediates PEH. Specifically, AVP-induced facilitation of NTS processing of baroreceptor afferent input would mediate sympathoinhibition and shift the operating point of the arterial baroreflex to a lower pressure.

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