Arginine-vasopressin mediates central and peripheral glucose regulation in response to carotid body receptor stimulation with Na-cyanide

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Montero, Sergio, Herón Mendoza, Victoria Valles, Mónica Lemus, Ramón Alvarez-Buylla, and Elena R. de Alvarez-Buylla. Arginine-vasopressin mediates central and peripheral glucose regulation in response to carotid body receptor stimulation with Na-cyanide. J Appl Physiol 100: 1902–1909, 2006.—Hypoxic stimulation of the carotid body receptors (CBR) results in a rapid hyperglycemia with an increase in brain glucose retention. Previous work indicates that neurohypophysectomy inhibits this hyperglycemic response. Here, we show that systemic arginine vasopressin (AVP) induced a transient, but significant, increase in blood glucose levels and increased brain glucose retention, a response similar to that observed after CBR stimulation. Comparable results were obtained after intra-cerebral infusion of AVP. Systemic AVP-induced changes were maintained in hypophysectomized rats but were not observed after adrenalectomy. Glycemic changes after CBR stimulation were inhibited by pharmacological blockade of AVP V1α receptors with a V1α-selective receptor antagonist (Jβ-Mercapto-β,β-cyclopentamethylenepropionyl1-O-me-Tyr2, Arg3)-vasopressin). Importantly, local application of micro-doses of this antagonist to the liver was sufficient to abolish the hyperglycemic response after CBR stimulation. These results suggest that AVP is a mediator of the hyperglycemic reflex and cerebral glucose retention following CBR stimulation. We propose that hepatic activation of AVP V1α receptors is essential for this hyperglycemic response.

Recent work suggests that the carotid body receptors (CBR), in addition to their classical role sensing O2, CO2, and pH levels (19, 43), also function as receptors of glucose concentration entering the cephalic circulation (1, 5, 30, 41, 42). Changes in blood glucose concentration in the carotid sinus-body influence the amount of glucose retained by the brain (6), and the injection of sodium cyanide (NaCN) into the local circulation of the carotid sinus induces a rapid hyperglycemic reflex with a rise in brain glucose retention (1). Unloading of carotid baroreceptors also induces rapid glucose adjustments to regulate plasma osmolality during hemorrhage (28). Experimentally induced low-glucose levels increase catecholamine secretion from carotid body glomus cells in a concentration-dependent manner (41), indicating that this structure is very sensitive to glucose concentration.

The efferent pathway for the glycemic reflexes initiated in the carotid sinus region is not fully understood. Previous experiments indicate the participation of the neurohypophysis and adrenal glands, suggesting that the effects of these two glands on CBR hyperglycemic reflexes are humoral (2). A reflex discharge of neurohypophysial secretion occurs after centripetal stimulation of the vagus nerve (23), and it is known that peripheral receptors connected to the vagus nerve (aortic baro- and chemoreceptors) or associated with the glossopharyngeal nerve (carotid baro- and chemoreceptors) mediate some of their effects through the pituitary (44). It is not known, however, what factors secreted by neurohypophysis are required to elicit the hyperglycemic reflexes initiated by CBR stimulation. The neurohypophyseal hormone arginine vasopressin (AVP) stimulates liver glycogenolysis (17) and participates in the central modulation of glucose metabolism. Hypophysectomy (Hypox) leads to adrenal cortical atrophy and hypoglycemia and reduces epinephrine content in adrenal venous blood (23, 50). During stress, as occurs after the perfusion of the carotid sinus with deoxygenated blood, AVP levels rise (47), increasing epinephrine and glucagon levels (21, 52). Acute hypoglycemia stimulates secretion of AVP by the neurohypophysis (11), and this response is accompanied by the activation of specific vasopressinergic hypothalamic neurons (38).

In the present study, we show that systemic or central AVP injections trigger a hyperglycemic response similar to that observed after hypoxic stimulus to the CBR. As with CBR stimulation, the effects of AVP were dependent on the presence of the adrenal glands. The pharmacological blockade of V1α receptors with a selective antagonist (16) abolished the hyperglycemic reflex initiated by hypoxic CBR stimulation. We conclude that AVP is an important mediator of the hyperglycemic reflex and cerebral glucose retention that occurs after CBR stimulation. The results further suggest that AVP may interact with vasopressin receptors located in adrenal and liver cells to stimulate the secretion of catecholamines and glucagon.

Materials and methods

Experimental animals and surgical procedures. All procedures in this study were in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (26). Experiments were done on adult male Wistar rats (250–350 g) maintained in a 12:12-h light-dark schedule and temperature-controlled (23–24°C) environment. Food was removed 12 h before surgery, but animals had...

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free access to water containing 10% glucose. Glucose levels under these conditions are more stable during anesthesia than in animals receiving glucose-free water (2, 5). Animals were anesthetized with pentobarbital sodium (3.3 mg/100 g in saline ip), which was supplemented by a continuous intraperitoneal infusion of 0.063 mg/min in saline of the same anesthetic. Under this condition, no pain responses to paw pinching were observed, but the eye-wink reflex was present. Artificial ventilation was provided, and body temperature was controlled at 37 ± 0.1°C. The respiratory rate and tidal volume were based on pH, PCO₂, and PO₂ values of arterial blood obtained during experimental procedures 4 min before protocol manipulations and 8 min afterward (48). Hypox surgeries were performed by a parapharyngeal technique (4) 1 wk before testing. Bilateral adrenalectomy surgeries were performed by a dorsal retroperitoneal approach; 3 days were allowed after surgery for the animals to recover blood Na⁺ levels before starting the experiment (1). In some experiments, a catheter (PE-10, Clay Adams, Parsippany, NJ) was inserted into the coeliac trunk (CT) (22) (Fig. 1A). After the completion of surgical procedures, the rats were provided with buprenorphine (0.03 mg/kg sc every 12 h for the first day) (Temgesic, Schering-Plough, Mexico) for pain relief.

CBR stimulation. CBR stimulation was performed by slowly injecting 5 μg/100 g of NaCN in 0.1 ml of saline through a 27-gauge needle and a thin catheter (PE-10; Clay Adams) into the carotid sinus to avoid baroreceptor stimulation (1). To ensure that responses were due to NaCN reaching only the left carotid sinus of the rat, these receptors were isolated from the cephalic circulation, while the right carotid sinus was denervated (both aortic nerves and the right carotid sinus nerve were sectioned) (Fig. 1A). The technique to isolate the carotid sinus is described in detail in a previous paper (1). Briefly, both the left external carotid artery (beyond the lingual branch) and the internal carotid near the jugular foramen were temporarily occluded (15–20 s); simultaneously, the perfusion liquid that bathed the left carotid body was withdrawn by means of a catheter introduced into the lingual artery (Fig. 1A). With this technique, only the left carotid sinus is exposed to NaCN, and within 15–16 s all the NaCN was washed away from the region.

Intracisternal injections. Intracerebral injections were done into the cisterna magna (CM) (24). To open the atlanto-occipital space, the rat was placed on a plastic stand with the head bent 50° down with respect to the long axis of the body. Once the membrane over the cisterna was exposed, a micromanipulator holding a 23-gauge “butterfly” needle, with attached syringe pump (Baby Bee, BAS, Lafayette, IN) was moved down to slowly penetrate the cerebellomedullary cistern. The correct position was verified by the back flow of clear cerebrospinal fluid observed at the end of each experiment (Fig. 1B).

Blood sampling and measurements. Blood samples were obtained without interrupting the circulation (1) by using heparin-filled catheters inserted into the abdominal aorta (via the femoral artery) and jugular sinus (via the right external jugular vein) (Fig. 1A). Samples were collected after the cannulas were washed three times with blood. The correct placement of the catheters was verified at the end of each experiment. Blood sampling was as follows: in those experiments in which only one drug was injected or infused, two control-basal
samples were taken at time \( t = -4 \) min and at \( t = -2 \) min [i.e., 4 and 2 min before the administration of the drug or the beginning of the infusion \( t = 0 \)], and three experimental samples were taken at \( t = 4 \) min, \( t = 8 \) min, and \( t = 16 \) min. When a combined administration of two drugs was done, the infusion of the first drug began 5 min before time \( 0 \) \( (t = -5 \) min), and the second drug injection was done at \( t = 0 \) min; two basal samples were taken at \( t = -4 \) min and at \( t = -2 \) min, and three experimental samples were taken during the following 16 min at \( t = 4 \) min, \( t = 8 \) min, and \( t = 16 \) min. As in our laboratory’s previous experiments, blood flow values did not change after CBR stimulation (1). For brain glucose retention, arterial-venous glucose differences across the brain were estimated in micromoles per milliliter. Since blood glucose levels in abdominal aorta were indistinguishable from those in carotid artery at each sampling time, 0.10 ml of arterial blood (abdominal aorta) and 0.10 ml of venous blood (jugular sinus) were collected from the cannulated vessels; in a complete sampling period, 1.2 ml of blood were taken (<8% of total blood volume in rats) (16). To compensate for fluid loss, the rats received an injection of 0.3 ml of saline after each pair of samples was taken (1, 5). Blood glucose concentration was measured by the glucose-oxidase method (Beckman Autoanalyzer, Fullerton, CA) in micromoles per milliliter. Plasma glucagon concentration was measured in duplicate by double antibody immunoassay (Diagnostic Products, Los Angeles, CA) (39) in samples collected into tubes containing 500 KIU Trasylol/ml plasma (Bayer AG, Leverkusen, Germany) and expressed in picograms per milliliter; the lower limit of this assay was 13.7 pg/ml and the coefficient of variation was 6.5%. Epinephrine concentration in plasma was determined by HPLC (36) in picograms per milliliter. Arterial gases (\( P_{O_2} \), \( P_{CO_2} \)) and pH levels were determined by a gas analyzer (Micro 13, Instrumentation Laboratory, Lexington, MA) in mmHg and absolute units, respectively. All measured glucose, glucagon, or epinephrine levels were within the ranges of curves prepared from commercial standards.

**Drugs and drug application.** The drugs used in this study were as follows: 1) NaCN (Baker, Phillipsburg, NJ) in a dose of 5 \( \mu \)g/100 g in 0.1 ml of saline into the isolated carotid sinus; 2) AVP (Sigma, St. Louis, MO) in a dose of 15 pmol/100 g in 0.4 ml of saline as a bolus injection in the jugular sinus or AVP in a dose of 5 pmol/100 g/min in 0.1 ml of saline for constant infusion into the CM during 16 min; 3) AVP antagonist (\( \beta \)-mercaptop-\( \beta \)-cyclopentamethylenepropionyl\( \beta \), O-Me-Tyr\( \beta \), Arg\( \beta \))-vasopressin (Sigma), hereto referred to as VP1-A, in a dose of 120 pg \( \cdot \)100 g \( \cdot \)1 min \( ^{-1} \) in 0.4 ml of saline for constant infusion during 21 min into the CT. The antglycogenolytic potency of VP1-A has been previously defined in liver cells (29). Compounds were dissolved immediately before application. For control experiments, identical volumes of saline were injected.

**Experimental protocol and number of animals in each experiment.** The following conditions were tested: 1) CBR stimulation with NaCN in the isolated carotid sinus \( (n = 10) \) or saline control in the isolated carotid sinus, \( (n = 5) \), all in normal rats; 2) bolus injection of AVP into the jugular sinus in normal rats \( (n = 5) \), in Hypox rats \( (n = 5) \), and in adrenalectomized (ADX) rats \( (n = 5) \); 3) CBR stimulation with NaCN in the isolated carotid sinus during a VP1-A infusion \( (n = 5) \) or during a saline control infusion \( (n = 5) \) above the CT all in normal rats; 4) as in the CBR stimulation but with the VP1-A infusion below the CT; 5) constant infusion of AVP \( (n = 5) \) or saline control \( (n = 5) \) into the CM in normal rats.

**Statistical analysis.** The data were expressed as means \( \pm \) SE. We used the SPSS statistical package for our analysis (SPSS, Chicago, IL). In Figs. 2 and 3, comparisons between treatments over time were made by repeated-measures ANOVA utilizing Tukey’s test for post hoc comparisons. In Fig. 4, comparisons between treatments over time were made by repeated measures. Basal arterial blood glucose values in our anesthetized animals at \( t = -4 \) min and \( t = -2 \) min were stable and ranged between 7.5 and 8.5 mmol/ml. Significance level was set at \( *P < 0.05 \).

**RESULTS**

**CBR stimulation in normal rats.** In these experiments, blood gases and \( \rho \)H were within normal range (48) and did not change significantly between \( t = -4 \) min and \( t = 8 \). The values obtained varied between 119 \( \pm \)1 and 127 \( \pm \)6 Torr for \( P_{O_2} \), between 31.6 \( \pm \)2 and 38.2 \( \pm \)4 Torr for \( P_{CO_2} \), and between 7.39 \( \pm \)0.01 and 7.42 \( \pm \)0.02 for \( \rho \)H. CBR stimulation in normal anesthetized rats \( (n = 10) \) with NaCN (5 \( \mu \)g/100 g) injected locally into the circulation of the carotid sinus induced an increase in arterial glucose concentration and brain glucose retention (5). Arterial glucose concentration progressively increased at 4, 8, and 16 min after CBR stimulation (Fig. 2A), whereas brain glucose retention increased at 4 and 8 min postinjection reaching a maximum at 8 min after CBR stimulation (Fig. 2E). CBR stimulation in normal rats consistently evoked an increase in epinephrine and glucagon concentrations in plasma \( (P < 0.05) \) (Table 1). Control saline injections showed no significant effects on circulating glucose levels (data not shown).

**AVP into the jugular sinus in normal, Hypox, and ADX rats.** A bolus injection of AVP (15 pmol/100 g in 0.4 ml of saline) into the jugular sinus in normal anesthetized rats \( (n = 5) \) elicited an increase in arterial glucose concentration similar to that observed after CBR stimulation (Fig. 2B). Arterial glucose rose from 6.2 \( \pm \)0.4 to 8.9 \( \pm \)1.0 \( \mu \)mol/ml. When these effects were expressed as arterial-venous glucose differences, values were similar to those observed after NaCN stimulation (Fig. 2E). To test whether the pituitary and adrenals had a role in brain glucose retention, AVP was injected in Hypox and ADX rats. Arterial glucose concentration in Hypox rats rose from 6.0 \( \pm \)0.2 to 8.9 \( \pm \)0.5 \( \mu \)mol/ml 8 min after AVP injection. Brain glucose retention also increased in Hypox rats after injection of NaCN into the CBR or after systemic AVP injections. These values were similar to those observed in intact rats (Fig. 2E). In contrast, the same dose of AVP into the jugular sinus of ADX rats \( (n = 5) \) failed to induce significant changes in arterial or venous blood glucose concentrations (Fig. 2D). Glucose levels before and after AVP-treatment in ADX rats were significantly lower compared with controls \( (P < 0.05) \) (Fig. 2E).

**AVP injections into the jugular sinus evoked increases in epinephrine and glucagon concentrations in plasma \( (P < 0.05) \) that were very similar to those observed after CBR stimulation (Table 1). After saline injection, epinephrine and glucagon concentrations did not change significantly. In ADX animals, AVP injections failed to increase epinephrine plasma levels, but a significant increase in glucagon plasma levels was observed (Table 1).

**CBR stimulation in normal rats during an infusion of VP1-A or saline into the CT.** When CBR stimulation with NaCN (5 \( \mu \)g/100 g) was applied simultaneously with a pharmacological blockade of V1a receptor sites in the liver [using an infusion of micro-doses of VP1-A (120 pg \( \cdot \)100 g \( \cdot \)1 min \( ^{-1} \) in 0.4 ml of saline) above the CT for 21 min] (29) the hyperglycemic response to CBR stimulation was abolished \( (n = 5) \). Glucose concentrations in these rats were significantly lower compared with rats in which VP1-A was substituted for saline \( (n = 5) \) \( (P < 0.05) \) (Fig. 3A). In experiments injecting VP1-A below the CT simultaneously with CBR stimulation, no differences were observed in arterial glucose levels compared with saline.
control experiments (n = 5) (Fig. 3A). When brain glucose retention was calculated, a significant decrease was observed at t = 4, t = 8, and t = 16 min post-CBR stimulation when VP1-A was applied above the CT compared with saline control-injected rats (P < 0.05) (Fig. 3B). The same dose of VP1-A injected below the CT did not alter brain glucose retention evoked by CBR stimulation, indicating that the observed effects of VP1-A were most likely due to its action in the liver and not to systemic effects (Fig. 3B). These results suggest that vasopressin activation of V1a receptors is essential for the liver glycogenolytic responses observed after CBR stimulation.

AVP or saline infusion into the CM in normal rats. The above results indicated that AVP in the systemic circulation requires intact adrenals to have a stimulatory role. Since it is well known the AVP receptors are extensively distributed throughout the brain (40), we investigated the role for AVP in the central system. When AVP (5 pmol·100 g⁻¹·min⁻¹) was introduced directly into the brain by infusion into the CM for 16 min (n = 5), arterial glucose concentration and brain glucose retention were significantly higher compared with rats in which saline was infused for 16 min into the CM (n = 5) (P < 0.05) (Fig. 4, A and B). At 8 min from the beginning of AVP infusion, arterial glucose concentration reached a maximum value of 9.9 ± 0.8 μmol/ml with a small significant decrease observed at 16 min. Glucose concentration in venous blood did not increase significantly. Brain glucose retention increased at t = 4, t = 8, and t = 16 min when compared with saline-infused control rats (P < 0.05) (Fig. 4C). Glucagon levels also increased significantly (P < 0.05) after central AVP infusions from 57.2 ± 9 to 102.5 ± 13 pg/ml. In control experiments, neither glucose nor glucagon concentrations changed after saline infusion (Table 1).

DISCUSSION

Following CBR stimulation, there is a rapid hyperglycemic response that results from an increased glucose output from the
liver (2). The present study substantiates this previous observation and shows that AVP activation of hepatic V1a receptors is essential for the liver glycogenolytic response after CBR stimulation. The neurohypophysis can directly induce glycogenolysis by the secretion of AVP (17). Consistently, in Hypox rats, CBR stimulation does not result in a hyperglycemic response (2). AVP injections, in contrast, increased arterial glucose concentration and brain glucose retention initiated by CBR stimulation (2, 3). Glucose retention by the brain is likely mediated by 10.220.33.4 on July 5, 2017 http://jap.physiology.org/ Downloaded from

![Fig. 3: Arterial (a) and venous (v) plasma glucose concentrations and brain glucose retention evoked by CBR stimulation during an infusion of β-mercapto-β,β-cyclopentamethylenepropionyl1-O-Me-Tyr2, Arg8-vasopressin (VP1-A) or saline into the coeliac trunk. A: VP1-A (120 pg·100 g⁻¹·min⁻¹) (n = 5). B: saline (n = 5). C: brain glucose retention (as in Fig. 2). The data are expressed as mean ± SE. Comparisons between treatments over time were made by repeated measures ANOVA utilizing Tukey’s test for post hoc comparisons. *P < 0.05.](image)

3A). This inhibition was not seen when antagonist was injected below the hepatic circulation. Results suggest that AVP is an important mediator of the hyperglycemic response induced by CBR stimulation and that it acts in liver. Although plasma AVP appears to have a fundamental role in this response, we cannot exclude that direct neural signals from the ventromedial hypothalamus (VMH) to the liver may also contribute to this response (7, 49).

The hypothalamus appears to integrate information arising from multiple glucose-sensitive areas, including regions within the VMH (31) or peripheral receptors within the mesenteric circulation (14, 35). For example, work of Donovan et al. (14) and Moore et al. (35) shows that activation of portal vein glucose sensors plays a central role in sympathoadrenal and insulin responses to hypoglycemia. The VMH also regulates autonomic functions and energy metabolism, which are closely linked to glucose homeostasis (7, 18). Sensory impulses conveyed by both the vagus and glossopharyngeal nerves after CBR activation increase the firing rate of the VMH neurons, likely resulting in AVP secretion (32). It will be very interesting to determine whether glucose-sensitive regions in the brain or mesenteric region can modulate the secretion of AVP initiated after CBR stimulation and whether this level of integration occurs in the VMH. It will be also interesting to determine whether AVP is involved in the homeostatic responses initiated by other glucose receptors (52).

Our results indicate that the adrenal glands are required for the hyperglycemic response in liver after CBR stimulation. In addition to its role in liver glucose secretion, AVP could induce stimulus-specific changes in catecholamine concentration in plasma (8). This pathway could stimulate adrenomedullary receptors, activate the secretion of epinephrine, and also contribute to hepatic glycogenolysis (34, 51). Under physiological and stressful conditions (hypoxia), these levels of epinephrine in blood may be sufficient to increase circulating glucose (49). Systemic injection of AVP in ADX animals failed to increase circulating glucose. Similar results have been obtained after local infusion of AVP directly into liver (unpublished observations). We do not know how the adrenal gland participates in this response. Its contribution may be mediated indirectly by epinephrine and corticoids. The lack of hyperglycemic response to AVP observed in ADX rats could be explained by a requirement of normal levels of circulating corticosterone for the expression of V1a receptors in liver (37) as well as to a decrease in glycogen stores observed in these rats (13).

Glucagon is known to play a role in counteracting hypoglycemia (18). In contrast to previous studies (30), here we show that CBR stimulation or systemic AVP injections produced an increase in glucagon plasma levels. Interestingly, these effects were independent of the adrenals in a similar way as in AVP-perfused rat pancreas (52). The failure of glucagon alone to induce an increase in plasma glucose levels in ADX rats is probably due to deficient glycogen stores, as loss of the hepatic glycogen-binding subunit of protein phosphatase underlies deficient glycogen synthesis in ADX rats (13). Koyama et al. (30) suggest that glucagon is not critical for maintenance of basal glucose production.

Whereas the hypophysis and adrenals are required for the hyperglycemic reflex (2), these glands are not required for increased brain glucose retention initiated by CBR stimulation (2, 3). Glucose retention by the brain is likely mediated...
centrally. Interestingly, the glucose transporter GLUTX1 is specifically found in vasopressin-expressing cells (25). Hormones from hypothalamic origin, including AVP, are present in CSF under physiological conditions (12). CBR stimulation may not only result in increased levels of circulating AVP but also within the brain, where it would reach the cerebrospinal fluid and VMH. It will be of interest to further study the source and mode of distribution of endogenously secreted central AVP.

Intracisternal infusion of AVP resulted in a significant increase in brain glucose retention. We do not know exactly where AVP injected into the CM ends up in the brain to

Table 1. Arterial plasma epinephrine and glucagon levels after carotid body receptors stimulation or a bolus injection of AVP in the jugular sinus in normal and adrenalectomized rats

<table>
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<th>Minute</th>
<th>Normal rats</th>
<th>ADX rats</th>
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<td>Saline (5)</td>
<td>NaCN (10)</td>
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Values are means ± SE, with no. of animals per experiment in parentheses. Carotid body receptors (CBR) stimulation was performed by an injection of sodium cyanide (NaCN; 5 g/100 g in 0.1 ml of saline) in the isolated carotid sinus. ADX, adrenalectomized; Saline, 0.1 ml saline was injected in the isolated carotid sinus; AVP, arginine vasopressin (15 pmol ⋅ 100 g⁻¹ ⋅ 0.4 ml saline⁻¹); E, epinephrine (pg/ml); G, glucagon (pg/ml). *P < 0.05, different from its basal sample (time = -4 min).
produce the rapid observed response. Substances injected intracistermally diffuse rapidly, reaching many parts of the brain, especially regions close to the brain ventricles (20). Drug-diffusion experiments (9) suggest that what we inject into the CM should reach the periventricular hypothalamus and the nucleus tractus solitarii (NTS). V1a receptors are extensively associated with paraventricular nucleus (40). Interestingly, vasopressinergic neurons localized also in the paraventricular nucleus receive information from the CBR (47). These same regions have a prominent AVP-ergic projection to the NTS (15), and the NTS receives an afferent projection from the CBR (10). Direct administration of microdoses of AVP into the NTS in awake rats increases brain glucose retention (51). Central AVP infusion may also activate sympathoadrenal outflow, enhancing cortisol and catecholamine secretion (21), to trigger protective counterregulatory neurohormonal responses. The results obtained in the present study were not due to peripheral leakage of AVP; at the concentrations we used, AVP does not leak into the circulation for at least 30 min after the beginning of intracerebral infusion (27).

It is becoming increasingly evident that CBRs have an important physiological role in the regulation of glucose homoeostasis and that a hypoxic stress exerts a tonic influence on secretion of AVP. Since the changes in glucose homoeostasis after AVP paralleled the effects obtained after CBR stimulation and since AVP antagonists in the liver inhibited peripheral glucose responses to CBR stimulation, we conclude that AVP, acting directly on the liver, is an important mediator of CBR-induced changes in circulating glucose. AVP also increases catecholamine and glucagon secretions to further induce hepatic glycogenolysis. This work adds to our understanding of the mechanism by which the CBRs and AVP contribute to the complex network of regulatory mechanisms that control blood glucose levels. 

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