Cardiovascular Effects of Felypressin

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Cardiovascular effects of felypressin (FEL) were studied in Wistar rats. Heart rate and mean arterial pressure measurements were taken in awake rats treated with vasopressin (AVP), FEL, or epinephrine (EPI). Each group received either an intravenous (IV) or an intracerebroventricular V_1 receptor antagonist, saline, area postrema removal, or sham surgery. Analysis of variance and Student-Newman-Keuls ($P < .05$) were applied. Felypressin and AVP induced a pressor effect, and bradycardia was inhibited by IV V_1 antagonist. Intracerebroventricular V_1 antagonist and area postrema removal enhanced their pressor effects. Epinephrine induced a higher pressor effect and a similar bradycardia that was not affected by the treatments. It was concluded that FEL depends on V_1 receptors to induce pressor and bradycardic effects, and that it produces a high relationship between bradycardia and mean arterial pressure variation depending on area postrema and central V_1 receptors. These effects are potentially less harmful to the cardiovascular system than the effects of EPI.

Key Words: Anesthesia, local; Vasoconstrictor agents; Blood pressure; Baroreflex; Vasopressin.

Felypressin (FEL), a synthetic analogue of vasopressin (AVP), has been widely used as a substitute for epinephrine (EPI) in anesthetic solutions to promote local vasoconstriction during medical and dental practices.^{1,2} Because it has no interaction with adrenergic receptors, it is suggested that FEL has fewer side effects than EPI.³ Hence, FEL causes fewer cardiovascular⁴ and metabolic⁵ side effects, and it has a higher median lethal dose (LD50)⁶ than EPI. However, the mechanisms and the receptors used by FEL to induce cardiovascular effects are unknown, and very few studies have been conducted on its possible systemic effects.

AVP, as opposed to FEL, has been widely studied. It acts on 2 subtypes of vasopressin receptors (V_1 and V_2 receptors). In physiological conditions, the vascular V_1 receptors promote vasoconstriction when linked to AVP. It has great importance because it helps control arterial pressure by enhancing it, mainly when a reduc-

tion in blood volume occurs.³ Another physiological role for AVP occurs when it is associated with central V_1 receptors, inducing an increase in baroreflex gain (BG).^{7,8} BG may be defined as the degree of effectiveness to which the baroreflex maintains the arterial pressure at near-normal conditions, producing reflex bradycardia and vasodilation after a rapid arterial pressure elevation or permitting tachycardia and vasoconstriction after a decrease in arterial pressure.⁹ Injection of the V_1 receptor antagonist in the area postrema (AP)¹⁰ or AP lesion¹¹ inhibits the ability of peripheral AVP to enhance BG. The V_2 receptors are present in the kidneys, and they promote water retention when they are linked to AVP.³

Because the FEL molecule is similar to the AVP molecule, it is possible that FEL activates cardiovascular mechanisms similar to those of AVP, enhancing the BG through the AP V_1 receptors and inducing an elevation in arterial pressure through the V_1 receptors. In order to test this hypothesis, we injected FEL peripherally combined with either intravenous (IV) or central injection of the V_1 antagonist, or in animals with surgical ablation of AP (APX).

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METHODS

All procedures were performed in the laboratory of pharmacology of Piracicaba Dentistry School of State University of Campinas (UNICAMP), and were approved by the Animal Experimentation Ethics Committee (CEEAB-UNICAMP). A hundred and one male Wistar *spf***** rats (260–300 g) from CEMIB-UNICAMP were kept in cages in a room with a 12 : 12 hour light-dark cycle beginning at 7 AM and a controlled temperature of $23 \pm 2^\circ\text{C}$. Standard food and water were available *ad libitum*.

The rats were divided in 13 groups initially containing 7–8 rats each. Because of the critical surgery, some rats died. The groups were: (a) IV saline + IV FEL ($n = 7$); (b) IV saline + IV AVP ($n = 7$); (c) IV saline + IV EPI ($n = 6$); (d) IV β -mercapto- β , β -cyclopentamethylene-propionyl-L-methyl-tyrosine, arginine vasopressin (β MER, a V_1 receptor antagonist) + IV EPI ($n = 6$); (e) intracerebroventricular (ICV) β MER + IV FEL ($n = 8$); (f) ICV β MER + IV AVP ($n = 8$); (g) ICV β MER + IV EPI ($n = 7$); (h) sham surgery of AP removal (APS) + IV FEL ($n = 6$); (i) APX + IV FEL ($n = 6$); (j) APS + IV AVP ($n = 6$); (k) APX + IV AVP ($n = 6$); (l) APS + IV EPI ($n = 6$); and (m) APX + IV EPI ($n = 6$).

For ICV injections, a rat stereotaxic (Kopf) was used to implant a stainless steel guide cannula (12×0.7 mm) in the brain under ketamine anesthesia (100 mg kg^{-1}) intraperitoneally. The opening of the cannula was placed into the top of the fourth ventricle (-2.2 mm from lambda, 5.5 mm from skull surface, and 0.0 mm from sagittal midline; incisor bar 0.0 mm from interaural line).¹² The cannula was secured to the top of the skull with dental cement and fastened with 2 little screws. The insertion of a close-fitting stylet kept the lumen free of debris and clots. A presurgical prophylactic dose of penicillin ($50,000$ IU) was given intramuscularly.

The APX was made using the same stereotaxic tool, the same anesthesia, and the same antibiotic prophylaxis used in the animals submitted to fourth-ventricle cannula implantation. A dorsal neck incision was performed for neck muscle dissection and removal of a part of the occipital bone. The dura mater was incised in order to visualize the cerebellum. Visualization and removal of the AP were performed with the help of a surgical microscope (DF Vasconcelos) and a 30×0.8 -mm-diameter adapted needle that was connected to a suction pump. The APS was performed in a similar manner until the AP could be visualized, and the AP was maintained intact. This was a modified technique.¹³

In order to control blood volume, which may change after AP removal,^{14,15} thus altering pressure and baroreflex responses, the animals submitted to APX were weighed daily, and were tested only when their weight

was the same as that of the APS animals. At this time, similarity was observed in the hematocrit and in the bradycardic response to hypertensive doses of IV EPI in both groups.

Single-pulse ICV injections were applied after replacement of the stylet with an injector that protruded 2.0 mm beyond the tip of the guide cannula and was connected by PE-10 tubing to a $10.0\text{-}\mu\text{L}$ syringe (Hamilton). A total volume of $1.0 \mu\text{L}$ was injected. Stylet and injector were always wiped with cotton soaked in 70% alcohol. After the injection, the injector was removed and replaced by the stylet.

After the experiments, the animals submitted to APX or central injection were profoundly anesthetized with 10% chloral hydrate (0.8 mL rat^{-1}) and perfused with 10% formalin through the left ventricle of the heart. After fixation in 10% formalin, the encephalon was frozen, cut into $50\text{-}\mu\text{m}$ coronal sections, and stained with hematoxylin-eosin. An analysis of the optical microscopic sections enabled us to select only animals correctly injected in the fourth ventricle or with the APX perfectly done.

The drugs used were: AVP, acetate salt (250 ng kg^{-1} , intraperitoneally, Sigma); FEL (240 ng kg^{-1} , IV, or infusion of $10\text{--}640 \text{ ng kg}^{-1} \text{ min}^{-1}$, IV, Polypeptide); EPI, hydrochloride ($2 \mu\text{g kg}^{-1}$, IV, Sigma); and β -Mer, Manning compound ($15 \mu\text{g kg}^{-1}$, IV, and 100 ng , ICV, Sigma). All the drugs were diluted in 0.9% NaCl solution.

Doses of AVP,¹⁶ β -Mer,¹⁰ and EPI¹⁷ were chosen from previous studies that produced satisfactory cardiovascular quantitative results. The FEL dose was equimolar with the AVP dose.

Mean arterial pressure (MAP) and heart rate (HR) were measured at least 5 days post-fourth-ventricle cannula implantation or at least 15 days after APX or APS. A catheter was inserted into a femoral vein to inject drugs and another into a femoral artery to measure arterial pressure and HR under 10 mg kg^{-1} ketamine anesthesia. After recovery and at least 18 hours post-catheter implantation, the artery catheter was connected to a transducer (P-1000B, Narco-Biosystems Inc) that was connected to a physiograph (Physiograph 6-B, Narco-Biosystems Inc). AVP, FEL, or EPI were injected into the vein catheter after 1 of the following 5 treatments in different animals: (a) IV injection of 0.9% NaCl solution; (b) IV injection of β -Mer; (c) ICV injection of β -Mer; (d) APX; and (e) APS. An interval of 10 minutes was maintained between injecting 2 drugs or saline, and a baseline of 5 minutes was maintained prior to any injection.

Data were expressed as mean $\pm$ SD. Variance analysis followed by Student-Newman-Keuls post hoc test was used to compare the groups. The significance level was set for $P < .05$.

Figure 1. Mean and SEM of mean arterial pressure of the rats submitted to intravenous (IV) injection of 240 ng kg⁻¹ of felypressin (FEL), 250 ng kg⁻¹ of vasopressin (AVP), or 2 μg kg⁻¹ of epinephrine (EPI) after IV injection of 0.9% NaCl, IV injection of 15 μg kg⁻¹ of β-mercapto-β,β-cyclopentamethylenepropionyl-L-methyl-tyrosine, arginine vasopressin (β-MER), intracerebroventricular (ICV) injection of 100 ng of B-mer, or removal (APX) or sham removal (APS) of area postrema. Different letters mean a statistical difference ($P < .05$) between different treatments of the same group. * $P < .05$ versus EPI group.

RESULTS

Because no difference was observed in baselines for MAP or HR, a particular baseline containing all results was described; baselines were respectively 117 ± 4 mm Hg and 391 ± 7 beats per minute (bpm), $n = 101$.

The IV injection of FEL enhanced MAP to 149 ± 9 mm Hg and reduced HR to 296 ± 20 bpm ($n = 7$), $P < .05$ versus baseline. The IV AVP induced similar modifications: 157 ± 9 mm Hg and 297 ± 28 bpm ($n = 7$), $P < .05$ versus baseline. The IV injection of EPI induced an elevation in MAP that differed from the increase induced by FEL and AVP ($P < .05$): 224 ± 8 mm Hg and a reduction of HR to 280 ± 9 bpm ($n = 6$), $P > 0.05$ versus FEL and AVP groups. The duration of the FEL and AVP hypertensive effects was longer (120 seconds) than the duration of EPI, which ceased immediately after injection.

The IV β-Mer completely inhibited the modifications induced by FEL, for which values were 127 ± 6 mm Hg and 407 ± 18 bpm ($n = 9$), and by AVP, for which values were 116 ± 5 mm Hg and 372 ± 10 bpm ($n = 7$), but not the modification induced by EPI, for which values were 203 ± 13 mm Hg and 297 ± 9 bpm ($n = 6$).

The ICV injection of β-Mer enhanced the pressor effect induced by IV injection of FEL, 173 ± 5 mm Hg ($P < .05$), but did not modify its bradycardic effect, HR = 334 ± 10 bpm, $n = 8$. The ICV β-Mer injection induced similar modifications in the group that received AVP, 182 ± 7 mm Hg and 298 ± 22 bpm ($n = 8$), but did not modify the effect of EPI on MAP or HR, 248 ± 7 mm Hg and 281 ± 10 bpm ($n = 6$).

The APS did not modify the effect of IV injection of FEL, 151 ± 4 mm Hg and 300 ± 34 bpm ($n = 6$), or of AVP, 153 ± 6 mm Hg and 243 ± 15 bpm ($n = 6$). The APX enhanced the pressor effect induced by FEL, 177 ± 4 mm Hg, and did not modify its bradycardic effect, 308 ± 8 bpm. The APX also enhanced the pressor effect of AVP, 188 ± 5 mm Hg, $P < .05$ versus APS + IV AVP, but did not alter its bradycardic effect, 310 ± 8 bpm. Neither APS nor APX modified the cardiovascular changes induced by EPI, 227 ± 6 mm Hg and 289 ± 17 bpm, for APS ($n = 6$), and 242 ± 13 mm Hg and 277 ± 5 bpm for APX ($n = 6$). All results are plotted in Figures 1 and 2.

The negative ratio between the variation in HR and the variation in MAP ($-\Delta\text{HR } \Delta\text{MAP}^{-1}$) of the experimental groups are expressed in the Table.

Table 1. Negative Ratio Between Variation in HR and MAP in RATS*

	Treatment†					
	IV SAL + IV FEL (n = 7)	IV SAL + IV AVP (n = 7)	IV SAL + IV EPI (n = 6)	IV βMER + IV EPI (n = 6)	ICV βMER + IV FEL (n = 8)	ICV βMER + IV AVP (n = 8)
−ΔHR ΔMAP ^{−1}	3.1 ± 0.3 A	2.6 ± 0.4 A	1.1 ± 0.1 B	1.1 ± 0.1 B	1.0 ± 0.1 B	1.2 ± 0.2 B

	Treatment†					
	ICV βMER + IV EPI (n = 7)	APS + IV FEL (n = 6)	APX + IV FEL (n = 6)	APS + IV AVP (n = 6)	APX + IV AVP (n = 6)	APX + IV EPI (n = 6)
	0.9 ± 0.1 B	2.6 ± 0.2 A	1.2 ± 0.1 B	3.1 ± 0.2 A	1.0 ± 0.1 B	0.9 ± 0.1 B

* Rats received IV injection of 240 ng FEL, 250 ng AVP, or 2 μg kg^{−1} EPI, previously treated with IV injection of SAL (0.9% NaCl), IV Injection of 15 μg kg^{−1} βMER, ICV injection of 100 ng βMER, APS, or APX.

† Values are mean ± SD. HR indicates heart rate; MAP, mean arterial pressure; IV, intravenous; FEL, felypressin; AVP, vasopressin; EPI, epinephrine; SAL, saline; βMER, β-mercapto-β,β-cyclopentamethylenepropionyl-0 methyl-tyrosine, arginine vasopressin; ICV, intracerebroventricular; APS, sham surgery of area postrema removal; APX, surgery of area postrema removal; and −ΔHR ΔMAP^{−1}, negative ratio between variation in heart rate and mean arterial pressure. Different letters indicate a statistical difference.

Figure 2. Mean and SEM of heart rate of the rats submitted to intravenous (IV) injection of 240 ng kg^{−1} of felypressin (FEL), 250 ng kg^{−1} of vasopressin (AVP), or 2 μg kg^{−1} of epinephrine (EPI) after IV injection of 0.9% NaCl, IV injection of 15 μg kg^{−1} of β-mercapto-β,β-cyclopentamethylenepropionyl-0 methyl-tyrosine, arginine vasopressin (β-MER), intracerebroventricular (ICV) injection of 100 ng of B-MER, or removal (APX) or sham removal (APS) of area postrema. Different letters mean a statistical difference (*P* < .05) between different treatments of the same group.

DISCUSSION

The BG is of great value in measuring the power of the cardiovascular system to buffer rapid variations in arterial pressure.^{8,10,18} In this study, we have tried to attribute to FEL not only any characteristic related to the enhancement of the baroreflex gain, but also the potential to promote elevation in arterial pressure only when it is administered in high doses. Because AVP and FEL are analogues, we have tried to compare cardiovascular effects between both drugs.

Baroreflex maintains arterial pressure near normal values after a rapid variation in basal arterial pressure.⁹ Some mechanisms used to achieve this effect are changes in HR and in vasoconstriction, because of modifications of the peripheral sympathetic or vagal activity.⁹ Because BG may be defined as the effectiveness with which baroreflex performs its function, the larger the HR and vascular responses to the same arterial pressure variation, the larger the BG. Taking this into consideration, some authors¹⁸ have measured the BG as being the negative variation in heart rate divided by the variation in arterial pressure ($-\Delta\text{HR} \Delta\text{MAP}^{-1}$). Using this ratio, others¹⁰ have shown that AVP is 3 times more potent than phenylephrine in inducing bradycardia, after its pressure effects. In the present study, we used this ratio to compare the potency of AVP, FEL, and EPI in enhancing bradycardia produced by an increase of arterial pressure. We found that FEL and AVP induced a higher $-\Delta\text{HR} \Delta\text{MAP}^{-1}$ ratio, about 3 times greater than that EPI. FEL increases MAP only in high doses, and reduces HR, and these effects are similar to the ones produced by AVP¹⁰ and by FEL in dogs.¹⁹

The high ratio of $-\Delta\text{HR}$ to ΔMAP (suggesting promotion of a high BG and a buffer in arterial pressure variation), associated with the enhancement of arterial pressure only in high doses, is a desirable characteristic of FEL, particularly because it is widely used clinically. Furthermore, this characteristic may be an advantage in case of intravascular injection, overdose, or injection into an especially sensitive patient. The doses of both FEL and EPI used in this study should be compared to the ones used with local anesthesia so that this advantage of FEL over EPI can be therapeutically demonstrated. Therefore, using the quantity of vasoconstrictor administered in local anesthesia with 1 cartridge as a parameter, the dosage of FEL used in this study was about 4 times larger than the dosage of EPI, but produced a smaller pressor effect (about 3 times less).

Another part of this study attempted to show that the cardiovascular responses to FEL are V_1 receptor dependent. To test this hypothesis, we used β -Mer, a V_1 antagonist, peripherally. The present experiments have shown that β -Mer was able to inhibit the cardiovascular

effects of FEL, namely hypertension and bradycardia. The β -Mer effect is specific to V_1 receptors, because it does not alter the pressor and the bradycardic effects induced by EPI. Before this study, the only author²⁰ who used FEL as a V_1 agonist observed its effects in the endocrine system, and no data were available to show the dependence of V_1 receptors on FEL in promoting its cardiovascular effects. This information may be important should any antagonist be used to prevent or treat undesired FEL effects.

The APX and ICV injection of β -Mer enhanced the pressor effect induced by both FEL and AVP and resulted in $-\Delta\text{HR} \Delta\text{MAP}^{-1}$ ratio values similar to those of the EPI group. These results show that the lower pressor effect induced by AVP and FEL, but not by EPI, is dependent on the V_1 central receptors and AP. Because the AP is devoid of a blood-brain barrier,⁸ FEL, when injected peripherally, may easily reach it to modulate arterial pressure and HR. The ability of AVP to inhibit the peripheral sympathetic activity,^{8,10,21} as well as an increase in BG⁸ dependent on the AP V_1 receptors, has been previously demonstrated.^{7,8,10,11}

It has already been demonstrated that anesthesia with EPI in humans causes more hazardous hemodynamic changes than anesthesia with FEL,⁵ which also has a higher LD50 value than EPI.⁶ The smallest modification in arterial pressure produced by FEL may be mediated by AP and V_1 receptors, because the ICV injection of V_1 antagonist and APX enhances the hypertensive effect of FEL. This mechanism used by FEL could explain the advantages of FEL over EPI in maintaining arterial pressure to near-normal values, and in having a higher LD50 and less hemodynamic changes.

In relation to FEL's central effects, the present results conflict with those of others²² who have demonstrated that AVP, not FEL, regulated cardiovascular parameters when injected intracisternally in anesthetized dogs. However, 3 items should be considered when comparing the study by those authors with this study: (a) the anesthesia they used may have modified the cardiovascular response in dogs; (b) the intracisternal injection may not have reached the V_1 receptors to induce HR modulation, and the modulation observed after intracisternally injecting AVP may have been caused by the activation of a V_1 receptor's independent mechanism, probably a V_2 receptor-dependent mechanism; and (c) they used dogs, a different species.

There are some undesired cardiovascular effects produced by FEL that can be commented on. One was shown in this study: the duration of its hypertensive effect was about 120 seconds. However, as was demonstrated, this hypertensive effect can be reached only in very high doses of FEL; these doses are not likely in clinical cases, even after an accidental intravascular in-

jection. Another side effect of FEL is the reduction of coronary blood flow, cardiac index, and myocardial oxygen tension in dogs,¹⁹ showing that one should be careful with FEL for patients with myocardial or coronary disease.

Working with patients with essential hypertension, Sunada et al²³ observed an increase in blood pressure when these patients were administered anesthesia with moderate doses of FEL. It is well known that in hypertensive rats, as well as in humans with essential hypertension, there is an increase in the peripheral sympathetic activity that includes reduction in BG,^{24–29} and maybe FEL has a different interaction with these special patients. However, these authors did not compare the effect of EPI and FEL in these patients, and EPI may be more hazardous than FEL in these situations, because it has a smaller ratio of $-\Delta\text{HR}$ to ΔMAP than FEL. A similar study in spontaneously hypertensive rats could be helpful in showing the interaction of FEL with the cardiovascular system in hypertensive conditions. Despite the results reached by Sunada et al,²³ one may say that FEL has less worrisome cardiovascular effects compared to EPI in conditions where essential hypertension does not exist.

Another situation to be studied concerns the fact that FEL could produce different results in Brattleboro rats or in patients with diabetes insipidus, both deficient in AVP and with the possibility of V_1 receptor physiological alterations.

A comparison of the effects of FEL with AVP investigated in this study demonstrated qualitative and quantitative similarity. Hence, this study not only shows the pharmacological identity of the 2 drugs, but also discloses the aspects related to the systemic effects and the receptors used by FEL to promote its effects in the cardiovascular system.

In short, the present study indicates that FEL induces cardiovascular effects similar to AVP: arterial pressure enhancement only in high doses, bradycardia, and a high relationship between bradycardia and enhancement in arterial pressure, all effects dependent on V_1 receptors, and the central effect depends on AP. These effects show that in normal conditions, FEL produces less effect on the cardiovascular system than EPI.

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REFERENCES

1. Brahma AK, Pemberton CJ, Ayeko M, Morgan LH. Single medial injection peribulbar anaesthesia using prilocaine. *Anaesthesia*. 1994;49:1003–1005.
2. Coulthard P. Local anesthetic use among GDPs. *Br Dent J*. 2005;199:778.
3. Jackson EK. Vasopressina e outros agentes que afetam a conservação renal de água. In: Goodman GA, ed. *As Bases Farmacológicas da Terapêutica*. 9th ed. Rio de Janeiro, Brazil: McGraw Hill; 1996:523–535.
4. Meechan JG. The effects of dental local anesthetics on blood glucose concentration in healthy volunteers and in patients having third molar surgery. *Br Dent J*. 1991;170:373–376.
5. Meechan JG, Cole B, Welbury RR. The influence of two different dental local anesthetic solutions on the haemodynamic responses of children undergoing restorative dentistry: a randomized, single-blind, split-mouth study. *Br Dent J*. 2001;190:502–504.
6. Volpato MC, Ranali J, Amaral IM, Demetrio CG, Chalita LV. Acute toxicity (LD50 and CD50) of lidocaine and prilocaine in combination with adrenaline and felypressin. *Indian J Dent Res*. 1999;10:138–144.
7. Barazanji MW, Cornish KG. Vasopressin potentiates ventricular and arterial reflexes in the conscious nonhuman primate. *Am J Physiol*. 1989;256:1546–1552.
8. Hasser EM, Bishop VS, Hay M. Interactions between vasopressin and baroreflex control of the sympathetic nervous system. *Clin Exp Pharmacol Physiol*. 1997;24:102–108.
9. Guyton AC, Hall JE, eds. *Tratado de Fisiologia Médica*, 10th ed. Rio de Janeiro, Brazil: Guanabara Koogan, 2002.
10. Hasser EM, Bishop VS. Reflex effect of vasopressin after blockade of v_1 receptors in the area postrema. *Circ Res*. 1997;67:265–271.
11. Applegate RJ, Hasser EM, Bishop VS. Vagal cold block in area postrema-lesioned dogs. The interaction of vasopressin and the sympathetic nervous system. *Am J Physiol*. 1987;252:153–141.
12. König JFR, Klippel RA. *The rat brain. A stereotaxic atlas*. New York, NY: Univ of Chicago Press; 1963.
13. Collister JP, Osborn JW. The area postrema does not modulate the long term salt sensitivity of arterial pressure. *Am J Physiol*. 1998;275:1209–1217.
14. Johnson AK, Loewy A. Circumventricular organs and their role in visceral functions. In: Loewy AD, Spyer K, eds. *Central Regulation of Autonomic Functions*. New York, NY: Oxford Univ Press; 1990.
15. Johnson AK, Gross PM. Circumventricular organs and brain homeostatic pathways. *FASEB J*. 1993;7:678–686.
16. Tarpey SB, Bennett T, Randall MD, Gardiner SM. Differential effects of endotoxaemia on pressor and vasoconstrictor actions of angiotensin II and arginine vasopressin in conscious rats. *Br J Pharmacol*. 1998;123:1367–1374.
17. Benkuski NA, Lewis SJ, Kooy NW. Peroxynitrite-mediated attenuation of α and β adrenoceptor agonist-induced

vascular responses in vivo. *Eur J Pharmacol.* 1999;364:151–158.

18. Farah VMA, Moreira ED, Pires MD, Irigoyen MCC, Krieger EM. Comparison of three methods for the determination of baroreflex sensitivity in conscious rats. *Braz J Med Biol Res.* 1999;32:361–369.

19. Miyachi K, Ichinohe T, Kaneko Y. Effects of local injection of prilocaine-felypressin on the myocardial oxygen balance in dogs. *Eur J Oral Sci.* 2003;111:339–345.

20. Buckingham JC. Vasopressin receptors influencing the secretion of ACTH by the rat adenohypophysis. *J Endocrinol.* 1987;113:389–396.

21. Suzuki S, Takeshita A, Imaizumi T, et al. Central nervous system mechanisms involved in inhibition of renal sympathetic nerve activity induced by arginine vasopressin. *Circ Res.* 1989;65:1390–1399.

22. Montastruc P, Dang Tran L, Montastruc JL. Reduction of vagal pressor reflexes by neurohypophyseal peptides and related compounds. *Eur J Pharmacol.* 1985;117:355–361.

23. Sunada K, Nakamura K, Yamashiro M, Sumitomo M, Furuya H. Clinically safe dosage of felypressin for patients with essential hypertension. *Anesth Prog.* 1996;43:108–115.

24. Abboud FM. The sympathetic system in hypertension: state of the art review. *Hypertension.* 1982;4(suppl 2):208–225.

25. Mancina G, Mark AL. Arterial baroreflexes in humans. In: Shepherd JTF, Abboud, M, eds. *Handbook of Physiology*. Bethesda, MD: American Physiological Society; 1983:755–793.

26. Schorer-Apelbaum D, Weinstock M, Ben-Ishay D. Sympathetic component of baroreflex control of heart rate is impaired in hypertension-prone (sbh) sabra rats. *J Hypertens.* 1984;2:257–260.

27. Stepniakowski K., Budzikowski A, Lon S, Szczepanska-Sadowska E. Central cardiovascular effects of avp and anp in normotensive and spontaneously hypertensive rats. *J Auton Nerv Syst.* 1994;47:33–43.

28. Mancina G, Grassi G, Ferrari AU. Reflex control of the circulation in experimental and human hypertension. In: Zanchetti A, Mancina G, eds. *Handbook of Hypertension*. Amsterdam, The Netherlands: Elsevier Science; 1997:568–601.

29. Rossi NF, O'Leary DS, Woodbury D, Chen H. Endothelin-1 in hypertension in the baroreflex intact SHR: a role independent from vasopressin release. *Am J Physiol.* 2000; 279:18–24.