ORIGINAL ARTICLE

UDC: 615.03::616.313-007.272-092.9
DOI: 10.2298/VSP1406571R

Effect of neuropeptide Y on norepinephrine-induced constriction in the rabbit facial artery after carotid artery occlusion

Efekat neuropeptida Y na konstrikciju facijalne arterije kunića izazvane norepinefrinom posle okluzije karotidne arterije

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Abstract

Background/Aim. Atherosclerotic-occlusive changes could be observed in orofacial branches of the external carotid artery. Atherosclerosis-induced ischemia caused alteration in production and release of endothelial factors. The aim of this study was to investigate the influence of carotid artery occlusion (10, 30 and 60 min) on vascular effects of norepinephrine (NOR) and neuropeptide Y (NPY) in the isolated glandular branch of the rabbit facial artery, the main feeding artery for the submandibular gland. **Method.** Changes in isometric tension were recorded in organ bath studies with arterial rings, before and after carotid artery occlusion. **Results.** Concentration-dependent vasocontractile effect of NOR was significantly augmented after 30 and 60 min of carotid occlusion, but only in the rings with intact endothelium. Given alone, NPY showed no effect in isolated glandular branch of the rabbit facial artery, but enhanced NOR vasoconstriction in all the investigated rings. NOR vasocontractile effect enhancement in the presence of NPY was attenuated after 30 and 60 min of carotid occlusion. Also, enhancement of NOR vasoconstriction by NPY was significantly higher in endothelium-intact rings compared to endothelium-denuded rings obtained after 30 and 60 min of carotid occlusion. **Conclusion.** The present investigation provides results of increased vasocontractile effect of NOR and decreased enhancing effect of NPY on NOR vasoconstriction in the rabbit facial artery after carotid occlusion that is related to altered endothelium function.

Key words:
neuropeptides; norepinephrine; carotid arteries; carotid stenosis; rabbits; vasoconstriction.

Apstrakt

Uvod/Cilj. Pokazano je da se okluzivne promene aterosklerotične prirode mogu opaziti na orofacijalnim granama spoljne karotidne arterije. Ishemija izazvana aterosklerozom, dovodi do poremećaja stvaranja i oslobađanja faktora poreklom iz endotela. Cilj ovog istraživanja bio je da se ispita uticaj okluzije karotidne arterije (10, 30 i 60 min) na vazokontraktilne efekte norepinefrina (NOR) i neuropeptida Y (NPY) na izolovanoj žlezdanoj grani facijalne arterije kunića, glavne dovodne arterije za submandibularnu žlezdu. **Metode.** U kupatilu za izolovane krvne sudove ispitivane su izometrijske promene tonusa arterijskih preparata, pre i posle okluzije karotidne arterije. **Rezultati.** Koncentracijski-zavisan vazokontraktilni efekat NOR bio je značajno veći posle 30 i 60 min karotidne okluzije, ali samo na preparatima sa očuvanim endotelom. Primenjen u rastućim koncentracijama, NPY nije imao efekta na tonus izolovane žlezdane grane facijalne aterije kunića, ali je povećao vazokontraktilni efekat NOR na svim ispitivanim preparatima. Povećanje vazokontraktilnog efekta NOR u prisustvu NPY bilo je značajno manje posle 30 i 60 min okluzije. Takođe, efekat NPY posle karotidne okluzije bio je značajno veći na preparatima sa očuvanim endotelom u odnosu na preparate sa uklonjenim endotelom. **Zaključak.** Ovo istraživanje pokazalo je povećanje vazokontraktilnog efekta NOR i smanjenje potencirajućeg efekta NPY na vazokonstrikciju izazvanu NOR na facijalnoj arteriji kunića posle okluzije karotidne arterije koje su povezane sa promenjenom funkcijom endotela.

Ključne reči:
neuropeptidi; noradrenalin; aa. carotis; okluzija; zečevi; vazokonstrikcija.

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Introduction

Salivary gland blood flow, mainly controlled by the parasympathetic and sympathetic nervous system, significantly contributes to salivary secretion. Cholinergic neurotransmitter, acetylcholine (ACh) and adrenergic, norepinephrine (NOR), are mainly responsible for vasodilatory and vasoconstrictory responses in salivary glands, but also for the important role in vascular regulation has non-adrenergic noncholinergic system involving: vasodilators such as vasoactive intestinal polypeptide (VIP) and nitric oxide (NO), and vasoconstrictors such as neuropeptide Y (NPY) and adenosine triphosphate (ATP) [1–3]. Immunohistochemistry revealed NPY to be present around blood vessels and secretory parts in rat and human submandibular gland, colocalized with NOR in sympathetic nerves [4, 5]. Previous studies showed that NPY acts as vasoconstrictor and enhances the response to various constrictor substances in a number of animal and human arterial beds [6–8] . Moreover, some studies emphasize the significance of NPY as a mediator strongly activated under conditions of oxygen deprivation such as in ischemic coronary artery disease [9, 10] . It is important to note that in nonischemic tissues, vascular effect of NPY is mainly a result of activation of NPY Y1 receptors, but under ischemia there was an induction and upregulation of NPY Y2 receptors, mainly involved in non-vasocontractile and angiogenic activities of NPY [3, 11] .

Cellular function depends upon adequate oxygen supply. Oxygen deprivation as the result of ischemia of the human vascular tissue plays the critical role in development and progression of ischemic disorders [12]. It is interesting to note that atherosclerotic-occlusive changes could be observed in human orofacial arteries which maintain local blood flow in salivary glands , such as facial, maxillary and lingual arteries, branches of external carotid artery. Under experimental conditions, Vág et al. [14] have shown that carotid artery occlusion is followed by a decrease of submandibular blood flow in rat, and associated with decreased NO synthesis/release in intraglandular blood vessels. Ischemia affects vascular function in terms of impairment of endothelial function and alteration in production and release of endothelium-derived vasodilators and vasoconstrictors, in favor of the last one [15–18]. A previous study in isolated glandular branch of rabbit facial artery (feeding artery for submandibular gland), after acute carotid occlusion, revealed a decreased responsiveness to both, ACh-endothelium-dependent and VIP-endothelium-independent vasorelaxation after carotid occlusion as a result of impairment of transduction signals including NO, prostaglandins and cAMP [19].

Having in mind the impact of ischemia on endothelial cell function and impairment of vasodilatory responses to ACh and VIP in rabbit facial artery, we hypothesized that acute ischemia would change sympathetic control of vascular tone causing potentiation of vasocontractile responses of NOR and NPY in isolated glandular branch of rabbit facial artery. To test this hypothesis, we investigated the impact of 10, 30 and 60 min of carotid occlusion on vasocontractile effects of NOR and NPY, as well as involvement of endothelium in these effects.

Methods

Animals and organ bath studies

The study was approved by the Ethical Committee of the Faculty of Dental Medicine at the University of Belgrade. The experiments were conducted on Chincilla rabbits (17 males and 5 females), aged 3 months, weighing 2.5–3.0 kg. The animals were anesthetized using urethane (1g/kg *iv*). Experimental ischemia was induced by left or right common carotid artery occlusion by cords for 10, 30 or 60 min. After the mentioned periods, the segments of occluded glandular branch of facial artery and contralateral, nonoccluded (controls) were dissected out and placed in Krebs-Ringer bicarbonate solution (37°C, pH = 7.4 gassed with 95% O_2 and 5% CO_2). The endothelium was removed in some rings by wire. After 60 min of equilibration, 1.0 g tension was applied and segments stabilized for further 30 min. A Hugo Sachs model MC 6621 recorder was used for isometric tension changes registration.

Experimental protocol

Endothelium removal and functional integrity of arterial segments were confirmed by the inability of segments to relax (< 70%) to ACh (10 μM) and by the ability to contract to potassium-rich Krebs-Ringer solution (KCl = 60 mM). Concentration-response curves to NOR (0.1–10 μM), alone, and 30 min after incubation with NPY (0.1 μM), were obtained in endothelium-intact and endothelium-denuded arterial segments. In another group of experiments, vascular effect of cumulative concentrations of NPY (0.01–0.3 μM) was investigated.

Drugs

All the compounds were obtained from Sigma–Aldrich, St. Louis, USA. All the drugs were dissolved in distilled water and prepared as the final concentrations for the 150 μL of bath solution.

Statistics

The vasoconstriction induced by each concentration of NOR and NOR+NPY was expressed as a percent constriction of Krebs-Ring solution (KCl = 60mM)-induced maximal constriction. The maximal effect (E_{max}) and the concentration of the agonist which produced half of E_{max} (pEC_{50} = - log EC_{50}) for each concentration-response curve were obtained in nonlinear regression analysis (GraphPad Prism software). The results were expressed as $\bar{x} \pm$ S.E.M.; n refers to the number of experiments. The results of comparison of vascular effects of NPY, in the control and the occluded rings, were calculated as differences of area under the concentration–response curves (AUC) for NOR, obtained in the presence or absence of NPY, in control and experimental situation. In this way, we were able to integrate effects of NPY and carotid occlusion, both affecting vasoconstriction. The AUC was calculated from each cumulative concentra-

tion-response curve before, and after 10, 30 and 60 min of carotid occlusion (GraphPad Prism software). The results were analyzed using Student's *t*-test for paired and unpaired observations and analyses of variance (one way ANOVA followed by a Dunnet's *post hoc* test or two way ANOVA followed by a Bonferroni's correction). The significance was considered from a value of $p < 0.05$.

Results

NOR (0.1–10 μM) induced concentration-dependent constriction in the rabbit facial arterial rings with and without endothelium is shown in Figure 1. The maximal vasocontractile effect of NOR (10 μM) was significantly augmented in endothelium-denuded compared to endothelium-intact rings but with no change in pEC_{50} (100.5 ± 5.5%; pEC_{50} = 6.07 ± 0.07 compared to 76.0 ± 4.2%; pEC_{50} = 5.91 ± 0.02, respectively). After 30 and 60 min of carotid occlusion, significant augmentation of maximal vasocontractile effect (E_{max}) to NOR was observed in endothelium-intact but not in denuded rings, while pEC_{50} remain unchanged (Tables 1 and 2). The values of AUC for NOR-induced vasoconstriction in endothelium-intact rings were augmented also in rings after 30 and 60 min, but not after 10 min of occlusion (Figure 2).

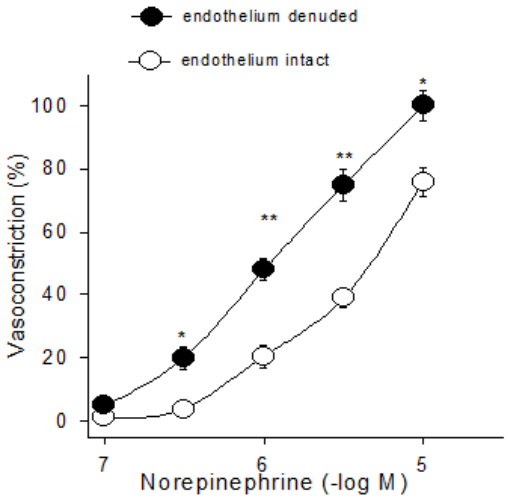

Fig. 1 – Concentration-response curves for norepinephrine (NOR) in the rabbit facial arterial rings with the intact (○) and denuded endothelium (●). Each point represents the x̄ ± S.E.M from 5 experiments. The responses are expressed as percent contraction of maximal contraction induced by 60 mM KCl. *$p < 0.05$; **$p < 0.01$ endothelium-denuded in comparison with endothelium-intact rings (Student's *t* test for unpaired observations).

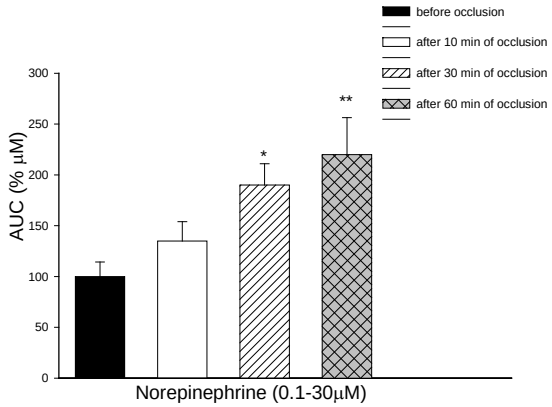

Fig. 2 – The area under curve (AUC) values for norepinepheine (NOR) on endothelium-intact rabbit facial arterial rings before and after 10, 30 and 60 min of carotid occlusion. Each column represents the x̄ ± S.E.M. from 5 experiments. *$p < 0.05$; **$p < 0.01$ compared to the AUC for NOR vasoconstriction obtained in rings before carotid occlusion (one-way ANOVA with Dunnet's *post hoc* test).

Given in increasing concentrations, NPY (0.01–0.3 μM) showed no effect on the resting tone of the isolated glandular branch of the rabbit facial artery, before and after carotid artery occlusion, regardless the endothelium presence.

Table 1

Maximal effect (E_{max}) of norepinephrine in endothelium-intact and -denuded rings before and after 10, 30 and 60 min of carotid artery occlusion

Carotid artery occlusion (min)	E_{max} (%), x̄ ± S.E.M.	
	endothelium-intact rings	endothelium-denuded rings
0	76.0 ± 4.2	100.5 ± 5.5†
10	82.6 ± 4.5	108.7 ± 6.3†
30	131.5± 5.6†*	90.4± 4.5
60	145.5 ± 4.5†**	107.4 ± 6.5

***$p < 0.05$; **$p < 0.01$ (rings before *vs* rings after carotid occlusion); †$p < 0.05$ (endothelium-intact *vs* -denuded rings).**

Table 2

pEC_{50} values of norepinephrine in endothelium-intact and -denuded rings before and after 10, 30 and 60 min of carotid artery occlusion

Carotid artery occlusion (min)	pEC_{50}	
	endothelium-intact rings	endothelium-denuded rings
0	5.91 ± 0.02	6.07 ± 0.07
10	5.90 ± 0.05	6.00 ± 0.03
30	6.00 ± 0.04	5.86 ± 0.07
60	6.09 ± 0.03	5.95 ± 0.03

EC_{50} – concentration producing half of maximal effect (E_{max})

In the presence of NPY (0.1 μM), vasocontractile effect to NOR was significantly enhanced in all the investigated rings obtained before and after 10, 30 and 60 min of carotid occlusion (data not shown). The comparison of dAUC values showed that enhancement of NOR vasocontractile effect in the presence of NPY was attenuated after 30 and 60 min of occlusion, in endothelium-denuded rings, as well as after 60 min of occlusion in endothelium-intact rings. Also, enhancing effect of NPY was significantly higher in endothelium-intact compared to endothelium-denuded rings obtained after 30 and 60 min but not after 10 min of carotid occlusion (Figure 3).

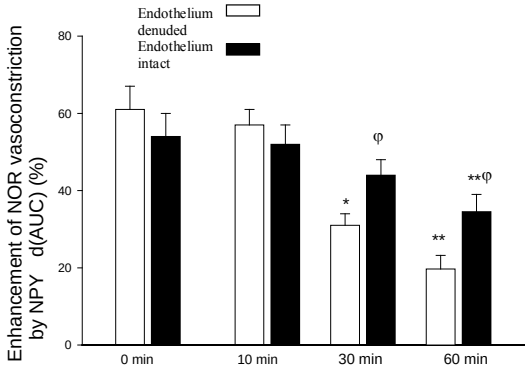

Fig. 3 – Potentiation of norepinepheine (NOR)-mediated vasoconstriction in rabbit facial arterial rings [calculated as the percentual differences of the area curve (AUC) for NOR] in the presence of neuropeptide Y (NPY), before and after 10, 30 and 60 min of carotid artery occlusion. Each column represents the $\bar{x} \pm$ S.E.M. from 6 experiments. *$p < 0.05$, **$p < 0.01$ compared to d (AUC) (%) obtained in the rings before carotid artery occlusion; $^{\varphi}p < 0.05$ endothelium-denuded in comparison with endothelium-intact rings (two-way ANOVA with Bonferroni correction).

Discussion

The results of the present functional study add new insights into the impact of different time of carotid artery occlusion duration as well as of endothelium on vascular effects to NOR and NPY in the glandular branch of the rabbit facial artery. Our study showed that NOR-induced concentration-dependent vasoconstriction in the glandular branch of the isolated rabbit facial artery was significantly enhanced in endothelium-denuded compared to endothelium-intact arterial rings. These results suggest that under non-ischemic conditions in this artery, the presence of endothelium influences the effect of NOR and partly masks it, most probably as a result of endothelium release of vasodilator substances, as seen in other arterial beds [20, 21]. Carotid artery occlusion affects the vasocontractile effect of NOR only in endothelium-intact rings and time-dependently: 10 min was without effect while it was most pronounced after 60 min of carotid occlusion. In the endothelium-intact rings, but not in the denuded, after 30 and 60 min of carotid occlusion vasocontractile effect of NOR was found to be significantly enhanced compared to the matched rings obtained before carotid occlusion. Furthermore, the present results show that carotid occlusion affected responsiveness, measured by E_{max}, but no sensitivity, measured by pEC_{50}, to NOR. It implies that ischemic enhancement of the effect of NOR is rather a result of altered signalling in dysfunctional endothelium than an alteration at the receptor level suggesting the significant role of ischemia-altered endothelium in vasoconstriction induced by NOR in rabbit facial arterial rings after carotid occlusion. Moreover, the fact that in endothelium-denuded rings the effect of carotid artery occlusion on NOR vasoconstriction was not observed, implies that vascular smooth muscle-derived vasoconstrictors are not involved in the observed ischemic alteration of the effect of NOR.

It is well-known that, under physiological conditions, the resting arterial tone is under the control of endothelium and balanced release of vasodilators and vasoconstrictors derived from endothelium, while under conditions of ischemia, this balance is altered in favor of vasoconstrictors due to endothelial dysfunction [22]. Recently, in the glandular branch of the rabbit facial artery, the results showed that 30 and 60 min of carotid occlusion resulted in the impairment of endothelium function and decreased ACh-endothelium-dependent vasorelaxation [19]. The suggested underlying mechanism included a decrease in endothelial NO production/release and a concomitant increased involvement of cyclooxygenase (COX) [19].

Having in mind the increased function of NPY under ischemic conditions [9] we investigated the impact of experimentally-induced ischemia on NPY effect in the glandular branch of the rabbit facial artery. In the present investigation, NPY, given alone in increasing doses, had no effect in the glandular branch of facial artery neither before nor after carotid occlusion. However, NPY significantly increased NOR effect in this artery, under ischemic and non-ischemic conditions, regardless of endothelium presence. Thus, NPY alone is not a potent vasoconstrictor in the rabbit facial artery, but requires a tone to contract, similarly to some other arterial beds such as mesenteric artery of rat and ear artery of rabbit [23, 24]. Comparison of dAUC values showed that under ischemia, enhancing effects of NPY on NOR vasoconstriction decreased in the isolated rabbit facial artery. One possible reason for this could be lying in the fact that under ischemia, expression and activity of NPY Y2 receptors in vascular smooth muscle are increased [11] and that, contrary to activation of NPY Y1, activation of these receptors opposes constriction [25]. Although NPY-mediated enhancement of NOR vasocontractile effect shows no difference in rabbit endothelium-intact compared to denuded facial rings before carotid occlusion, after 30 and 60 min of occlusion, enhancement of NOR vasoconstriction by NPY is higher in endothelium intact compared to denuded rings. This could be due to increased endothelium-release of vasoconstrictors which could contribute to NPY effect , but some studies also point out the fact that endothelium *per se* could synthesize NPY or internalize sympathetically-derived NPY and release it under some circumstances, such as artery occlusion [26, 27].

Conclusion

Having in mind the significance of sympathetically-regulated salivary gland blood flow for salivary gland function, our results provide some new findings concerning NOR and NPY vascular effects on the main feeding artery for submandibular gland under ischemic conditions. This could be important for clarifying mechanisms of endothelial dysfunction underlying salivary gland diseases related to ischemic circulatory disorders.

Acknowledgements

This study was supported by the Serbian Ministry of Education, Science and Technological Development, Grant No. 175021.

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Received on March 13, 2013.
Revised on April 10, 2013.
Accepted on April 11, 2013.