Korean J. of Pharmacology
Vol. 26, No. 1, pp. 25-33, 1990

Effect of Peptide YY on Vascular Smooth Muscle Contractility

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ABSTRACT

The responsiveness of various arterial smooth muscles isolated from rabbit to peptide YY (PYY) and the calcium source responsible for the muscles to contract were studied *in vitro*.

PYY contracted the muscle strips of femoral, basilar and common iliac arteries more sensitively than renal, superior mesenteric and common carotid arteries. Common carotid and renal arteries were less sensitive to PYY ($p \leq 0.05$) than to NE; and basilar artery was more sensitive to PYY ($p \leq 0.01$) than to NE.

A calcium channel blocker, verapamil and an inhibitor of intracellular calcium release, 3, 4, 5-Trimethoxybenzoic acid 8-(diethylamino)octyl ester [TMB-8] significantly ($p \leq 0.001$) suppressed the concentration-response of the strips from femoral artery to PYY. When both verapamil and TMB-8 existed in normal PSS, the concentration-response to PYY was inhibited almost completely; and a similar suppression was observed when the muscle was incubated in calcium-free, ethyleneglycol-bis-(beta-aminoethyl ether) N,N,N',N'-tetraacetic acid [EGTA] containing PSS.

The results of these experiments suggest that increased PYY activity in circulation may result in the more sensitive increase in the intracranial vascular resistance and the cerebral arterial pressure than the increased sympathetic activity and that both intra- and extracellular calcium are to be utilized for the PYY-induced contraction on arterial smooth muscle.

Key Words: Peptide YY, Norepinephrine, Verapamil, TMB-8

INTRODUCTION

Peptide YY (PYY) is a straight chain polypeptide composed with 36 amino acids (McGuigan, 1989). PYY is secreted by the endocrine cells existing in the mucosal epithelia of intestines (Lundberg *et al.*, 1982; Adrian *et al.*, 1985a; Greeley *et al.*, 1989), especially distal portion including colon and rectum (Adrian *et al.*, 1985a; Sjolund and Ekman, 1988; Calam *et al.*, 1989).

The physiological role of PYY is still uncertain. However, they include the inhibition of gastric (Suzuki *et al.*, 1983; Allen *et al.*, 1984) and small-intestinal (Al Safar *et al.*, 1985) motility, inhibition of gastric secretion (Adrian *et al.*, 1985b; Papas *et al.*, 1986), and inhibition of both secretin- and cholecystokinin-stimulated pancreatic secretion (Tatemoto *et al.*, 1982). Hellstrom *et al.* (1989) observed that PYY increased rectal tone and anal canal pressure. In cardiovascular system, PYY elevated the blood pressures in human (Adrian *et al.*, 1986), cat (Lundberg *et al.*, 1982) and rat (Potter *et al.*, 1989). PYY caused vasoconstrictions in cat intestine (Lundberg *et al.*, 1982), in cat salivary gland (Lundberg and Tatemoto, 1982), in guinea-pig iliac vein (Wahlestedt *et al.*, 1986) and in dog splenic artery (Corder *et al.*, 1987). PYY also constricted feline (Edvinsson, 1985) and rat (Tuor *et al.*, 1988) cerebral arteries. It is very interesting that PYY was mainly found in colonal and rectal mucosa and increased anal canal pressure, and that PYY elevated the blood pressure constricting the cerebral arteries. Here we may ask if there is any relationship between the high rectal pressure as in constipation and the attack of cerebrovascular accident accompanying an intracranial hemorrhage.

* This study was partly supported by a grant from the Ministry of Education of Korea (1988).

The mechanism by which PYY contracts the vascular smooth muscle has not been clearly known yet. Wahlestedt *et al.* (1986) observed that PYY, as Neuropeptide Y (NPY) did, potentiated the contractile response to norepinephrine. Zukowska-Grojec *et al.* (1986) reported that the pressor effect of PYY was antagonized by calcium channel blocker, nifedipine.

So this study is aimed at observing the sensitivity of various arterial smooth muscles to PYY and to investigate the calcium source utilized by PYY to contract the vascular smooth muscle.

MATERIALS AND METHODS

The rabbits (New Zealand White, male) weighing 3-4kg, were anesthetized by intramuscular injection of ketamine hydrochloride (30 mg/kg) to be exsanguinated by decapitation. The cranium was opened immediately after the exsanguination, and the total brain was removed and immersed in ice-cold Krebs-Hensleit's physiological salt solution (PSS), bubbled with gas mixture of 95% O_2-5% CO_2. The basilar artery was gently isolated from the brain base. Segments of left common carotid artery, superior mesenteric artery, renal artery, common iliac artery and femoral artery were isolated. In the ice-cold PSS saturated with 95% O_2-5% CO_2, the adventitia was cleaned, and the endothelial surface was rubbed with a very fine metal file to destroy the endothelium , and a 1.5mm-wide spiral strip (0.5mm; basilar artery) was obtained with a pair of fine scissors. The 1-1.5cm long muscle strips were tied with silk threads, mounted in Biancani's isolated muscle chambers (Biancani *et al.*, 1984) containing 1ml of PSS, pH 7.4 at 37°C, and aerated with 95% O_2-5% CO_2. Muscle strips were stretched passively to an initial tension of 0.5-2 grams and allowed to sit for 1 hour with continuous dribbling of PSS. The experiments were performed when the muscle strips equilibrated after the perfusion of PSS stopped. The modified Krebs-Hensleit buffer solution was composed of the following (mM): NaCl: 120, $CaCl_2$: 2.5, KCl: 4.6, $NaHCO_3$: 23.8, KH_2PO_4: 1.17, $MgSO_4$: 1.2, Dextrose: 10.

The contractility of the muscle strips was measured with an isometric tension transducer (Grass Force-displacement Strain Gages FT-03, Grass Instrument Co.), and recorded on a physiological recording system (Reorganized Narco Physiograph MK-III-S, Daeyeon Electronics Co. Taegu, Korea).

At the beginning of the experiments, inner surface of the muscle chamber was carefully rinsed with 2.5% bovine serum albumin solution to avoid binding of PYY to the plastic surface. Concentration-response of the vascular smooth muscle strip to PYY was examined by cumulative addition of PYY by half-log-molar concentrations from 10^{-10}M to 10^{-6}M into the muscle chamber in which the muscle strips equilibrated. Cumulative concentration-response to norepinephrine was also examined for a comparison.

The muscle preparations from femoral artery were divided into groups, and several experiments were performed as follows. When a muscle preparation equilibrated, PYY 10^{-6}M was added into the chamber to contract the muscle, followed by an addition of calcium 2.5mM on the top of PYY. At the plateaux of the PYY-induced contraction, verapamil or 3,4,5-Trimethoxybenzoic acid 8-(diethylamino)octyl ester (TMB-8) was added by the cumulative concentrations of 10^{-6}, 10^{-5} and 10^{-4}M for each experimental group. After the additions of verapamil 10^{-4}M or TMB-8 10^{-4}M, calcium 2.5mM was added.

The equilibrated muscle preparation was incubated in PSS added with 10^{-4}M verapamil or TMB-8 in both groups, and 15 minutes later, PYY 10^{-6}M was added, then calcium 2.5mM was added at the top of PYY.

To investigate the effects of the above calcium inhibitors and exclusion of calcium from PSS, cumulative concentration-response to PYY was examined as follows: In normal PSS, in the presence of verapamil 10^{-4}M for a group and TMB-8 10^{-4}M for another, and a combination of both inhibitors for a third; and in calcium-free PSS containing ethyleneglycol-bis-(beta-aminoethyl ether) N,N,N′,N′-tetraacetic acid (EGTA) 0.5mM.

The response of the muscle preparation to PYY was expressed as the mean ± S.E. of the increment of tension (ΔT, g) by the addition of PYY to the bathing solution, i.e., developed tension minus resting tension. The maximal effects (Emax) and median effective concentration (EC50) of concentration-responses to PYY and norepinephrine were computed by the method of double-reciprocal plot introduced by Tallarida and Murray (1987). To evaluate the statistical significance of differences between means of experimental and control groups, the unpaired Student's t-test in Stat Works TM (Version 1.2, written by Rafferty J. *et al.*, Cricket Software, Inc. Philadelphia, PA, USA) was used.

The following materials were used in this study: peptide YY (porcine, lyophilized, from SIGMA CHEMICAL Co. St., Louis, MO, U.S.A) was reconsituted by addition of demineralized water, and the aliquots of 20 μl of stock solution were stored in a deep freezer of −80°C to be diluted for daily use.

Norepinephrine, Verapamil, TMB-8 and EGTA were also ordered from SIGMA Chemical Co. For concentration-response studies, the serially diluted drugs were added into 1 ml bath by 20 μl of stock solutions for each concentration with micropipette to obtain the final concentrations in baths. And most of the reagents were ordered from Shinyo pure chemical (Osaka, Japan).

RESULTS

The vascular smooth muscle preparations isolated from various rabbit arteries contracted in response to the cumulative additions of PYY into the bathing PSS in concentration-dependent manners. As shown on Fig. 1, femoral artery tended to contract most strongly, and the net contractile response of basilar artery was very weak. Table 1 shows the EC50s computed from each concentration-response curve to PYY. Femoral artery ($10^{-7.91}$M) was the most sensitive and significantly different from carotid artery ($10^{-6.19}$M, $p \leq 0.001$), from superior mesenteric artery ($10^{-6.47}$M, $p \leq 0.05$) and from renal artery ($10^{-6.53}$M, $p \leq 0.05$). EC50 of basilar artery was very low, significantly lower than that of carotid artery ($p \leq 0.001$), superior mesenteric artery ($p \leq 0.01$) or renal artery ($p \leq 0.01$). Common iliac artery responded to PYY with the EC50 of $10^{-7.31}$M, which was not significantly different from that of the superior mesenteric, renal, femoral or basilar artery, but significantly different ($p \cap 0.05$) from the EC50 of common carotid artery.

On Table 2, the responsiveness of the arterial smooth muscle preparations to PYY were compared to those to norepinephrine (NE). All the smooth muscles tested contracted by NE in concentration-dependent manners. The maximal conctractions of muscle strips responding to NE (Emax revealed as ΔT(g) by mean ± S.E.) were variable as 1.43 ± 0.170

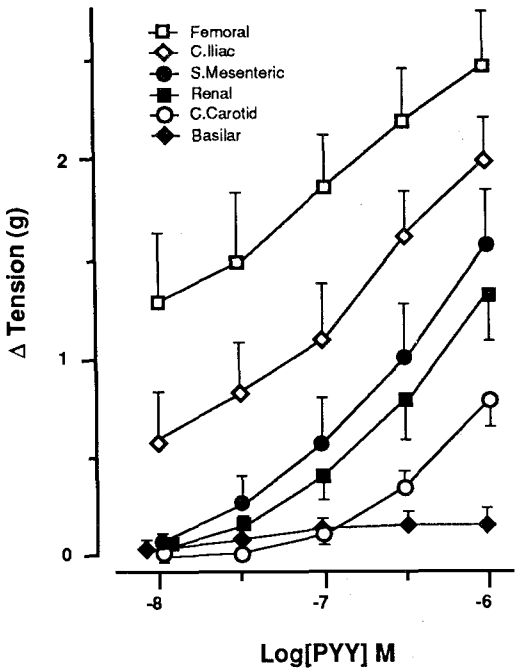

Fig. 1. Concentration-responses to PYY of the vascular smooth muscle strips isolated from various arteries of rabbit.
The value represents mean ± S.E. of the increment (△) in tension from the resting state by cumulative additions of PYY.

Table 1. Comparison of the responsivenesses to peptide YY of the smooth muscle strips isolated from various arteries of rabbit by means of median effective concentration (EC50)

Arteries	n=	EC50 (10^{-n}M)	Significance				
Common carotid	9	6.19 ± 0.132	c				
Superior mesenteric	6	6.47 ± 0.199	ns	c			
Renal	7	6.53 ± 0.180	ns	ns	c		
Common iliac	8	7.31 ± 0.414	*	ns	ns	c	
Basilar	7	7.61 ± 0.254	***	**	**	ns	c
Femoral	6	7.91 ± 0.447	***	*	*	ns	ns

Values are revealed as Mean ± SE.
c: the target of comparison
ns: non-significant difference from the artery indicated by "c" on the same column.
* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$; significantly different from "c"

Table 2. Comparison of the responsiveness of various arterial smooth muscle strips isolated from rabbit to peptide YY and to norepinephrine by means of maximal effect (Emax) and median effective concentration (EC50)

Arteries	Emax (ΔT, g)		EC50 (10^{-x}M)	
	NE	PYY	NE	PYY
Common carotid (N=6, P=9)	1.43±0.170	1.30±0.215	6.99±0.231	6.19±0.132*
Superior mesenteric (N=4, P=6)	3.87±0.834	2.72±0.448	6.73±0.369	6.47±0.199
Renal (N=6, P=7)	2.21±0.247	1.78±0.327	7.40±0.154	6.53±0.180*
Common iliac (N=7, P=8)	3.10±0.394	2.89±0.499	7.94±0.169	7.31±0.414
Femoral (N=6, P=6)	3.77±0.270	2.84±0.394	8.21±0.82	7.91±0.447
Basilar (N=6, P=7)	0.14±0.039	0.21±0.038	6.14±0.139	7.61±0.254***

Values are revealed as Mean±SE.

ΔT, g: The increment of tension as the maximal response.

* p≤0.05, ** p≤0.01: Significantly different from the corresponding value of norepinephrine group.

In parentheses: N=; number of strips in norepinephrine group,

P=; *number of strips in peptide YY group.*

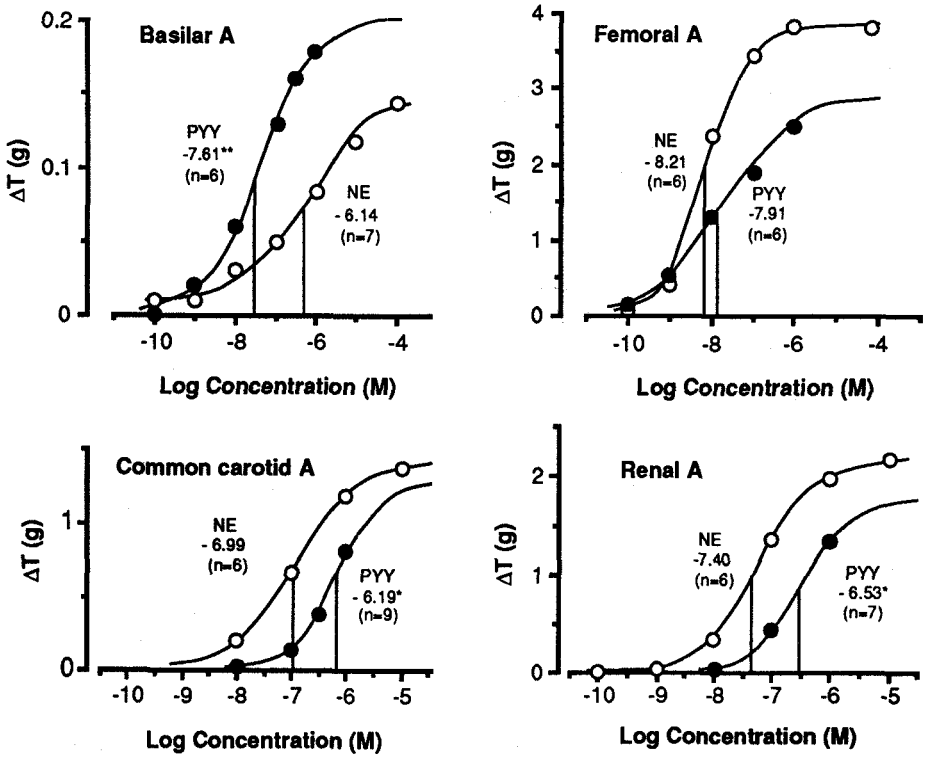

Fig. 2. Comparison of the responsiveness of various rabbit vascular smooth muscle strips to PYY and to NE. Values are revealed as mean±S.E. of the increment in tension (ΔT) from the resting state. The negative values next to the names of groups are the exponential number of 10 representing the EC50 of each concentration-response curve. * p≤0.05, ** p≤0.01; significantly different from the other group.

of common carotid artery, 3.87±0.834 of superior mesenteric artery, 2.21±0.247 of renal artery, 3.10±0.394 of common iliac artery, and 3.77±0.270 of femoral artery. These values were similar to or likely to be a little higher than the Emaxs evoked by PYY as 1.30±0.215 of common carotid artery, 2.72±0.448 of superior mesenteric artery, 1.78±0.327 of renal artery, 2.89±0.499 of common iliac artery and 2.84±0.394 of femoral artery. The only exception was the Emax of basilar artery, i.e., 0.21±0.038 by PYY inclined to be higher than 0.14±0.039 by NE. EC50s of PYY and NE on various arteries were also compared on Table 2. When they were revealed as the mean±S.E. of X of 10^{-x}M, in superior mesenteric artery, common iliac artery and femoral artery, the EC50 in response to NE showed 6.73±0.369, 7.94±0.169 and 8.21±0.082 respectively, which showed no significant difference to those in response to PYY which were 6.47±0.199, 7.31±0.414 and 7.91±0.447. The EC50s of PYY on common carotid artery (6.19±0.132) and renal artery (6.53±0.180) were significantly higher than those of NE on common carotid artery (6.99±0.231, $p \leq 0.05$) and renal artery (7.40±0.154, $p \leq 0.05$). In contrast, on basilar artery, the EC50 of PYY (7.61±0.254) was significantly ($p \leq 0.01$) lower than that of NE (6.14±0.139). These data are shown on Fig. 2.

Fig. 3 exhibits the interactions between PYY, calcium, and verapamil, the well known calcium channel blocker or TMB-8 which inhibits the calcium release from sarcoplasmic reticulum (Baracos *et al.*, 1986; Ganz *et al.*, 1988). In normal calcium PSS, PYY-induced contraction of the smooth muscle preparation isolated from femoral artery was reinforced by addition of calcium 2.5mM (Fig. 3, A). Verapamil reduced the PYY-induced contraction in a concentration-dependent manner, and at the concentration of 10^{-4}M, addition of calcium 2.5mM

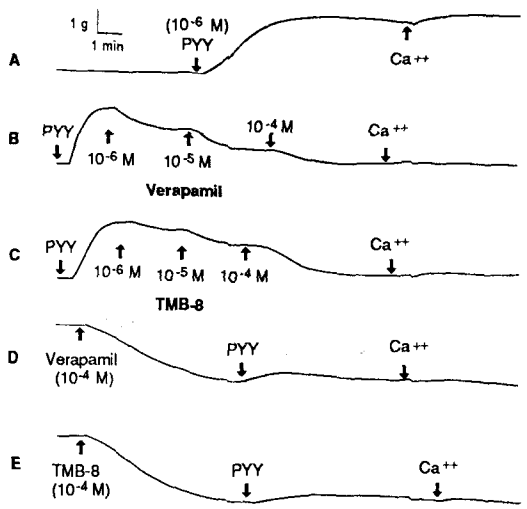

Fig. 3. Diagramtic representation of the inhibitory effects of verapamil and TMB-8 on the PYY-induced contraction of vascular smooth muscle isolated from the rabbit femoral artery. The additional calcium increased the final concentration of calcium in the muscle chamber to 5mM which was twice as high as normal concentration.

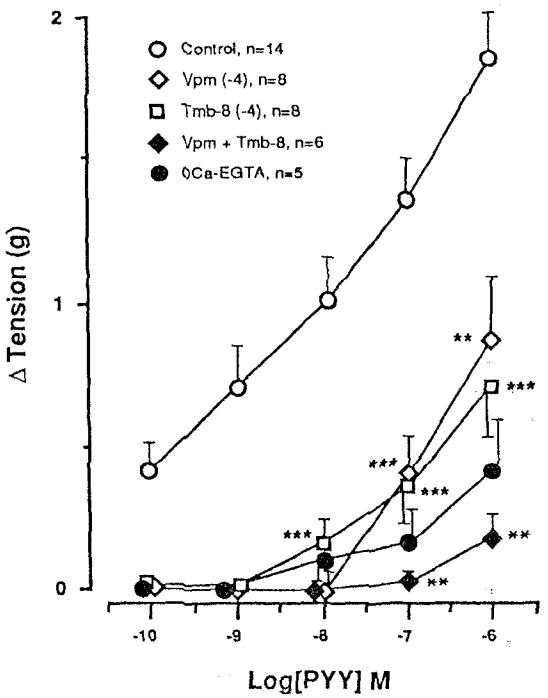

Fig. 4. Effects of verapamil, TMB-8 and the exclusion of calcium from PSS on the PYY-induced contraction of vascular smooth muscle isolated from the rabbit femoral artery. Values are revealed as mean±S.E. of the increment (Δ) in tension from resting state.

★★ $p \leq 0.01$, ★★★ $p \leq 0.001$; significantly different from control

** $p \leq 0.01$; Δ tension was significantly lower than those of verapamil alone or TMB-8 alone. The values of 0Ca-EGTA group were not significantly different from that of verapamil + TMB-8 group.

could not reverse this verapamil inhibition (Fig. 3, B). TMB-8 also reduced the PYY-induced contraction in a concentration-dependent manner, and at the concentration of 10^{-4}M, addition of calcium 2.5mM could not reverse this TMB-8 inhibition (Fig. 3, C). In the presence of verapamil (10^{-4}M, Fig. 3, D) or TMB-8 (10^{-4}M, Fig. 3, E), PYY 10^{-6}M contracted the muscle but less than in normal condition, and reinforcement of the contractility by additional calcium 2.5mM was negligible. For a quantitative presentation of above mentioned phenomena, concentration-response to PYY under various conditions were examined, and the results are shown on Fig. 4.

In normal PSS, the cumulative concentration-response to PYY in femoral artery reached the level of 1.86 ± 0.170g at 10^{-6}M in control group. In the presence of verapamil 10^{-4}M, the 10^{-6}M PYY-induced contraction was significantly inhibited (0.88 ± 0.225g, $p \leqslant 0.01$); and the same concentration of TMB-8 inhibited the PYY-induced contraction more significantly (0.72 ± 0.190g, $p \leqslant 0.001$) than verapamil. When the muscle preparations were incubated in the presence of both verapamil 10^{-4}M and TMB-8 10^{-4}M, the 10^{-6}M PYY-induced contraction was almost abolished (0.18 ± 0.083g), and the value was significantly lower ($p \leqslant 0.01$) than in the presence of verapamil or TMB-8 alone. In calcium-free PSS containing EGTA 0.5mM, the increment of tension induced by 10^{-6}M PYY was very low (0.43 ± 0.191), and it was not significantly different from the value when both verapamil and TMB-8 were present.

DISCUSSION

The physiological role of PYY in cardiovascular system has not been extensively investigated. Recently, some authors reported the vasoconstrictor effect of PYY reducing the blood flow to spleen (Corder *et al.*, 1987), to jejunum and ileum (Buell and Harding, 1989), pancreas (Inoue *et al.*, 1988), and liver (Corder and Withrington, 1988). Besides, PYY also constricted cerebral vessels (Edvinsson, 1985; Tuor *et al.*, 1988).

In this study, we observed that common iliac or femoral arteries which supply the blood to lower extremity were contracted by PYY more strongly and more sensitively than the superior mesenteric or renal arteries which supply splanchnic organs. It was also observed that common carotid artery responded to PYY much less sensitively not only than the arteries to extremities but also than basilar artery which supplies the brain stem, cerebellum and posterior cerebrum. The net increases in tensions (ΔT, g) of the arterial strips induced by PYY were variable, and tended to be similar to those induced by NE in most preparations from various arteries. Basilar artery showed very weak contractile responses to both PYY and NE. But it should be taken into account that the diameter of basilar artery is short, and the wall is very thin. However, the net increment of tension by PYY was inclined to be higher than that by NE.

Regarding the sensitivities of the arterial smooth muscles to PYY and NE inferred from the EC50, we observed that the arteries supplying the extremities and mesentery responded to PYY similarly to NE; left common carotid artery which mostly supply the brain responded to PYY less sensitively ($p \leqslant 0.05$) than to NE as well as the renal artery; only basilar artery, an intracranial artery responded to PYY much more sensitively ($p \leqslant 0.01$) than to NE. Although the role of autonomic nervous system, with some controversy, appeared not to be a major component in the control of cerebral circulation (Traystman, 1981), Moskalenko *et al.* (1977) suggested that cerebral cortical vessels were sensitive to NE at the same concentrations as in normal physiological conditions and that vasoconstriction developed in response to sympathetic activation. Thus, we may take a serious view of the fact that PYY contracted a cerebral artery more sensitively than NE. On the other hand, some recently-discovered peptides attract the attentions of some investigaters. Mejia *et al.* (1988) reported that neuropeptide Y (NPY) caused potent contractions of cerebral vessels, and calcitonin gene-related peptide (CGRP), substance P (SP) and capsaicin caused relaxation of precontracted cerebral arteries. NPY is one of the members of pancreatic polypeptide (PP) family including PP, NPY, and PYY; and these three peptides have structural similarities among them. Suzuki *et al.* (1989) suggested that NPY and CGRP released from nerve fibers innervating blood vessels could function as long acting modulators of cerebral blood flow. In our sutudy, PYY evoked a more sensitive contractile response than NE on basilar artery, and a less sensitive response than NE on renal and common carotid artery. Thus, it can be presumed that increased PYY activity in circulation increasing the peripheral resistance will consequently elevate the blood pressure by a similar way to the increase in sympathetic activity, but a relatively larger proportion of circulating blood volume will strive to distribute to the kidneys and brain for the sensitivity of vasoconstrictions in extremities and mesentery are not significantly different from that to NE, but

carotid and renal arteries responds less sensitively to PYY than to NE. The result of such a volume distribution to the brain in conjunction with the cerebral vasoconstriction may lead to an increase in the intracranial arterial pressure to a higher extent. Tuor *et al.* (1988) reported that no reductions in brain blood flow (28 regions) were observed *in vivo* although PYY infusion elevated arterial blood pressure by 15-25% without influencing heart rate, suggesting an increase in peripheral resistance. Even if we excluded the possibility of volume shifting toward the brain under the effect of PYY accounting the fact that another larger portion than in NE would strive to distribute to the kidneys, it is distinct that an increase in systemic arterial pressure without reduction of cerebral blood flow accompanied with cerebral vasoconstriction may be a serious precipitation for a hemorrhagic cerebrovascular accident.

The role of calcium in the contraction mechanism of vascular smooth muscle is well known to be very important. But in the action mechanism of PYY, the role of calcium has not been deeply investigated. Edvinsson (1985) reported that NPY and PYY contracted feline cerebral artery, and NPY mediated contraction of cerebrovascular smooth muscle via a mechanism that is dependent on the concentration of extracellular calcium. Zukowska-Grojec *et al.* (1986) observed that NPY and PYY mediated nonadrenergic vasoconstriction, which was antagnoized by calcium channel blocker, nifedipine. These reports suggested that PYY-induced vasoconstriction is mediated by a mechanism which depends totally or at least partially on the extracellular calcium influx.

In this study, muscle strips from femoral artery were selected to study the calcium related mechanism since they responded most strongly and most sensitively to PYY. The calcium channel blocker, verapamil (Conen *et al.*, 1987) and an intracellular calcium inhibiter, TMB-8 (Baracos *et al.*, 1986) were employed for an investigation of the calcium source mobilized by PYY to contract the vascular smooth muscle. Verapamil reduced the PYY-induced contraction from the sustained state of contraction and prevented the muscle to contract under the stimulation of PYY. TMB-8 also relaxed the muscle precontracted by PYY, and inhibited the PYY contraction from the resting state. When both the extracellular calcium influx and intracellular calcium release were blocked by the coexistence of verapamil and TMB-8, the PYY-induced contraction was almost totally abolished, and the little net increment of tension (ΔT) was significantly ($p \leq 0.01$) lower than those when verapamil or TMB-8 was exsisted alone. Once either or both of the calcium inhibitors employed in this study was/were present in the bathing PSS, additional calcium could not reinstate the muscle to contract in response to PYY. Thus it is presumed that both the extracellular and intracellular calcium should be utilized not only to initiate but also to maintain the PYY-induced contraction. To support this hypothesis, the concentration-response to PYY was tested in calcium-free PSS containing calcium chelater, EGTA 0.5mM. When the muscle was incubated in calcium-free condition longer than 30 minutes, the contractile response of the muscle to PYY was suppressed, and the ΔT was similar to those in the presence of both verapamil and TMB-8. In fact, an exclusion of free calcium from the extracellular fluid by any means leads to the calcium efflux from the cytosol for an equilibrium, and a subsequent depletion of intracellular calcium store results (Rega, 1986; Lee *et al.*, 1989). Blocking both the influx of extracellular calcium and the release of intracellular calcium may be the same as depleting both intra- and extra-cellular calcium from a viewpoint of preventing the maintenace of enough cytosolic free calcium concentration to contract the muscle.

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=국문초록=

Peptide YY의 혈관 평활근 수축성에 미치는 효과

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가토의 적출동맥평활근 절편에 대한 peptide YY(PYY)의 수축작용을 관찰하고, PYY의 수축기전상 동원되는 칼슘의 기원을 조사하여 다음과 같은 결과를 얻었다.

각 동맥의 나선형 절편은 PYY의 실험조내 첨가에 의하여 농도의존적인 수축반응을 보였다. 그중 대퇴동맥이 가장 강력하고 예민한 수축경향을 보였으며, 그 다음은 대뇌의 기저동맥, 총장골동맥, 상장간막동맥, 신동맥, 총경동맥의 순으로 예민하였다.

PYY에 대한 반응성을 Norepinephrine(NE)에 대한 반응성과 비교해볼때, 총경동맥과 신동맥은 PYY보다 NE에 대해서 유의하게($P \leqslant 0.05$)예민하였고, 기저동맥은 NE보다 PYY에 더 예민하였다($p \leqslant 0.05$).

대퇴동맥 절편에서 칼슘통로봉쇄제인 verapamil과 세포내 저장칼슘유리를 억제하는 3,4,5-Trimethoxybenzoic acid 8-(diethylamino)octyl ester「TMB-8」는 각각 PYY에 의한 수축을 억제하였는데 ($p \leqslant 0.05$), verapamil과 TMB-8이 동시에 존재할 때는 PYY에 의한 수축은 거의 완전히 억제되었고, ethyleneglycol-bis-(beta-aminoethyl ether), N,N,N',N'-tetraacetic acid「EGTA」0.5mM를 첨가한 칼슘배제용액 내에서도 PYY에 의한 수축은 거의 완전히 억압되었다.

이상의 결과를 종합하면, 혈중 PYY가 증가했을 때는 교감신경계흥분시보다 강한 뇌혈관의 수축이 일어날 수 있으며, 뇌동맥압은 교감신경계 흥분시보다 더 높을 수가 있으리라 추정된다. 또 PYY에 의한 혈관 평활근 수축에는 세포외액의 칼슘과 세포내저장칼슘의 이용이 공히 필수적이라고 생각된다.