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Study on Relaxing Effect of Oxybutynin on the Contractile Response of Arterial Smooth Muscle

Jae Ki Ko* and Yung Hong Baik**

*Department of Internal Medicine, College of Medicine, Chonbuk National University, Chonju 520, Korea and
**Department of Pharmacology, Chonnam University Medical School, Kwangju 500, Korea

ABSTRACT

Pharmacological actions of an antispasmodic agent, oxybutynin were investigated in the isolated procine coronary arteries. The coronary rings were contracted by acetylcholine (ACh) and KCl in a dose-dependent fashion. The ACh-induced contractions were significantly potentiated by removal of endothelium and $EC_{50}=0.52$ μM of intact endothelial rings was about 2 times greater than $EC_{50}=0.28$ μM of rings without the endothelium. These results suggest that the endothelium plays an inhibitory role in ACh-induced contraction. Oxybutynin and atropine inhibited dose-dependently 1.0 μM ACh-induced contraction and atropine inhibited dose-dependently 1.0 μM ACh-induced contraction and the IC_{50s} were 11.0 nM and 0.47 nM, respectively. Atropine did not affect 35 mM KCl-induced contraction but oxybutynin inhibited the contraction to the basal tension in a dose-dependent manner. The IC_{50} of oxybutynin on the KCl-induced contraction was 49.7 μM. The dose-response curve to ACh was parallelly shifted to the right by pretreating coronary rings with IC_{50} of atropine (0.47 nM) or oxybutynin (11.0 nM) but the curve to KCl was rightward shifted in a noncompetitive manner under pretreatment with IC_{50} of oxybutynin (49.7 μM). Oxybutynin inhibited 0.1 μM Bay K 8644-induced contraction to the basal tension in a dose dependent manner, but 35 μM histamine-induced contraction was inhibited to only 50% of the original level even in maximal concentration (5×10^{-4} M) of oxybutynin.

These results suggest that oxybutynin causes antispasmodic action through sensitive blocking action on muscarinic receptors and inhibitory action on calcium influx in the procine coronary artery.

Key Words: Oxybutynin, Porcine coronary artery, Acetylcholine, Calcium influx
Abbreviations: ACh; acetylcholine, EDRF: endothelium-derived relaxing factor

INTRODUCTION

Antispasmodics of smooth muscles are generally classified into neurotropic and myotropic agents. The former is represented by anticholinergic agents, while the latter by papaverine which causes increase of cyclic AMP by inhibition of tissue phosphodiesterase. However, there are some agents which have the anticholinergic effect, but also the myotropic effect in higher concentration (Kubo *et al.*, 1981). And also there are other myotropic agents which do not inhibit phosphodiesterase and related to the calcium transfer (Takayanagi *et al.*, 1980).

Generally speaking, contractile agents cause contraction by increasing intracellular calcium concentration $[Ca^{2+}]i$, and relaxant agents elicite relaxation by direct action on contractile system or by decreasing $[Ca^{2+}]i$ (Filo *et al.*, 1965; Somlyo and Somlyo, 1965; Goodman, 1979; Tamita *et al.*, 1985; Rueggand Pfitzer, 1985). Accordingly, it is considered that the neurotropic type of smooth muscle relaxants results from decrease of $[Ca^{2+}]i$ and the myotropic type from direct action on contractile protein.

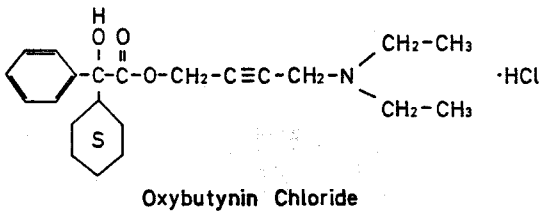
Since the agents which decreased $[Ca^{2+}]i$ had

** To whom reprint requests should be addressed.

been termed as "calcium antagonists" by Fleckenstein (1977), many investigators reported that various smooth muscle relaxants selectively inhibited calcium influx into cells. And these agents have been referred to as "calcium channel blockers" (Triggle, 1981; Cauvin *et al.*, 1983). The compounds which inhibit the influx of extracellular calcium ions formed a new field as therapeutic agents on diseases of cardiac and smooth muscle system. Therefore the mechanism of various agents used as antispasmodics of intestinal and urinary system in clinic was reinvestigated. It is confirmed that papaverine, benactyzine and aspaminol known as antispasmodics, and oxybutynin and flavoxate known as anticholinergic drugs in the past are related to calcium transfer (Takayanagi *et al.*, 1977; 1979; Anderson and Fredericks, 1977).

Oxybutynin chloride (Fig. 1) was one of a series of acetylenic amino esters synthetized by Majewski *et al.*, (1965). Lish *et al.* (1965) reported that major pharmacological actions of oxybutynin are anticholinergic and local anesthetic action. Since then oxybutynin has been used as a therapeutic agent in bladder spasm, enuresis, neurogenic bladder and vesicoureteral reflex (Hock, 1967; Diokno and Lapides, 1972; Thompson and Lauvetz, 1976, Buttarazzi, 1977; Wein *et al.*, 1978; Homsy *et al.*, 1985; Maizels and Rosenbaum, 1985). On the other hand, the mechanism of oxybutynin has been studied by several investigators and it is reported that the durg has anticholinergic and local anesthetic effects on intestinal and urinary tract, slight inhibition to phosphodiesterase and inhibitory effect on calcium influx, (Fredericks *et al.*, 1978; Levin and Wein, 1982; Perales *et al.*, 1986).

Lately, it is known that some of calcium channel blockers elicite relaxation of vascular smooth muscle, so we attempted to investigate pharmacological effects of oxybutynin on the porcine coronary artery.



Oxybutynin Chloride

Fig. 1. Structural formula of a tertiary ammonium compound, oxybutynin chloride.

METHODS

Porcine hearts were obtained from a local slaughterhouse near Kwangju and immersed in cold (2~4℃) physiological salt solution (PSS) within 5 min after death. The right coronary artery was removed from the heart and trimmed clean of connective and adipose tissue under a stereoscope. The cleaned artery was then cut into two rings (4~5 mm long). In some cases, the endothelium was removed by gentle rubbing with an angular metal rod inserted into the lumen of the arterial ring. The endothelium-removed rings were only used in the experiment to compare the contractile response to acetylcholine (ACh) with the response to ACh in the intact endothelial rings. In other experiments the intact endothelial rings were used. A ring was mounted in each of four muscle baths by sliding each ring over two parallel 21-gauge stainless steel pins. The lower pin was anchored rigidly in a support foot at the bottom of the bath and the upper was suspended from an isometric transducer (Grass FTO3)connected to a polygraph (Grass 7D). Volume of bath was 20 ml and bath fluid was saturated with 95% O_2 and 5% CO_2 at 37℃ (pH=7.3). The composition of the PSS was as follows: NaCl, 126.9: KCl, 4.7; $CaCl_2$, 1.6; $MgSO_4$, 1.17; KH_2PO_4, 1.18; $NaHCO_3$, 18.0; glucose, 5.5 mM. The rings were equilibrated in PSS for 1.5~2.0 hrs and maintained a resting tension of 5 g. After this equilibration peroid, all rings were tested for viability and reproducibility by challenging with 35 mM KCl two or three times. When the 35 mM KCl-induced contraction was uniform, main experiments were started. Drugs were cumulatively administered into baths and data were represented with % of maximal or control contraction. The dose-response curve was obtained by iterative, nonlinear, least squares computer program of De Lean *et al.*, (1978). EC_{50} (effective concentration of 50%), EC_{80} (effective concentration of 80%), IC_{50} (inhibitory concentration of 50%) and the slope of the curve were obtained from the above program, too. Comparisons of two data were made using grouped or paired t-test. A p value < 0.05 was accepted as statistically significant.

Drugs used are oxybutynin hydrochloride

(Marion Lab.), acetylcholine bromide (Sigma), histamine hydrochloride (Sigma), atropine sulfate (Sigma) and Bay K 8644 (methyl-1, 4-dihydro-2, 6-dimethyl-3-nitro-4- (2-trifluoromethylphenyl)-pyridine-5-carboxylate) (Bayer). The stock solution of Bay K 8644 was dissolved in 95% ethanol and others were prepared in distilled water.

RESULTS

Contractile Effects of Acetylcholine and KCl

ACh produced concentration-dependent contractions in both rings with and without endothelium (Fig. 2). The ACh-induced contractions were significantly potentiated by removal of the endothelium. EC_{50} of the deendothelized ring was 0.28 ± 0.03 μM and that of the intact endothelial ring was 0.52 ± 0.04 μM. The former EC_{50} was significantly smaller than the latter ($P < 0.01$), but each slope of two curves was equal as 1.15. Both rings were contracted by KCl in a dose-dependent fashion. The KCl-induced contractions showed a slight tendency to increase in rings without the endothelium, but there are no significanct difference between EC_{50s} of intact endothelial (27 ± 1.8 mM) and deendothelial (22 ± 2.1 mM) rings.

Effects of Oxybutynin and Atropine on Acetylcholine- and KCl-induced Contraction

Oxybutynin and atropine itself slightly reduced the resting tension of 5 g less than 0.5 g. In this experiment EC_{80s} of ACh and KCl were 1 μM and 35 mM, respectively, and effects of oxybutynin and atropine on these doses-induced contractions were investigated.

The 1 μM ACh-induced contraction was not maintained in steady-state and slowly relaxed after maximal contraction. So effects of oxybutynin and atropine on the 1 μM ACh-induced contraction were investigated as in Fig. 3. The rings were pretreated with several doses ($10^{-11} \sim 10^{-7}$ M) for 15 min. The 1 μM ACh was then delivered to both test and control tissues. The ACh-induced contraction was reduced to the

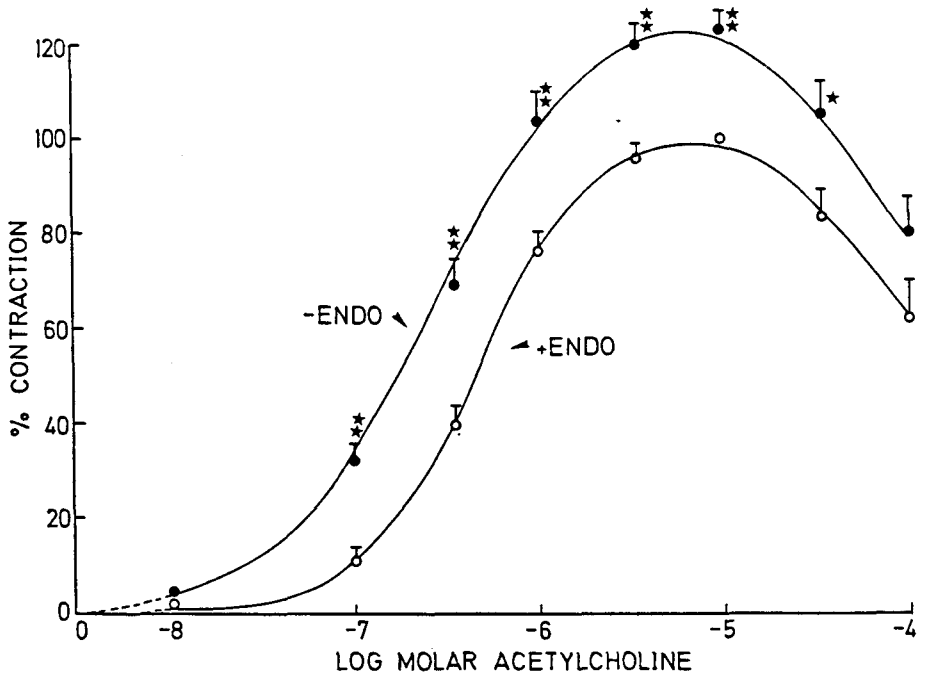


Fig. 2. Dose-response curves to acetylcholine in tissues with (○) and without (●) endothelium. Acetylcholine was added to the muscle bath in a cummulative fashion ; when equilibrium tension was obtained, the next dose was added. Each point represents the mean response ± S.E.M. of 6–10 rings. Where the S.E.M. bar is absent, the S.E.M. is < the size of the data point.

basal tension in a dose-dependent fashion by both blockers. Each slope of inhibitory curves of oxybutynin and atropine was −1.54 and −1.41, respectively and there was no significant difference between both slopes (Fig. 3). IC_{50} of atropine was 0.47±0.046 nM and IC_{50} of oxybutynin was 11±0.84 nM. The atropine IC_{50} was about 23 -fold lower than the oxybutynin IC_{50}.

In separate experiments, 35 mM KCl produced a steady-state tension. Following the development of steady-state KCl-induced tension, cummulative dose-response curves were constructed for atropine and oxybutynin (Fig. 4). Even if concentration of atropine was increased up to 1 mM, atropine did not affect the KCl-induced tension at all. However oxybutynin relaxed the KCl-induced tension to the baseline, in a dose-dependent fashion. The slope of the inhibitory curve for oxybutynin was −1.36±0.07 and IC_{50} was 49.7± 3.90 μM. The oxybutynin IC_{50} (49.7 μM) for the KCl-induced tension was 4,500-fold greater than the oxybutynin IC_{50} (11.0 nM) for the ACh-induced contraction. The dose-response curve for ACh was shifted about 5-fold to the right by pretreatment with the oxybutynin IC_{50} and about 8-fold to the right by pretreatment with the atropine IC_{50} (Fig. 6).

Each EC_{50} for ACh was 0.52±0.04 μM in control, 2.8±0.15 μM in oxybutynin-pretreated and 4.5±0.31 μM in atropine pretreated group, respectively. There are no differences among slopes and maximal contractions in three curves. These results indicate that ACh-induced contractions are competitively inhibited by atropine and oxybutynin. In contrast to the ACh-induced contraction, KCl-induced contractions were non-competitively inhibited by pretreatment with the oxybutynin IC_{50}=49.7 μM and the maximal contraction of KCl in oxybutynin-pretreated group was reduced to 27% of control group (Fig. 7).

Effect of Oxybutynin on Bay K 8644- and Histamine-induced Contraction

EC_{80s} for Bay K 8644 (0.1 μM) and histamine (35 μM) were quoted in other papers (Dube *et al.*, 1985, Williams *et al.*, 1987). Effect of

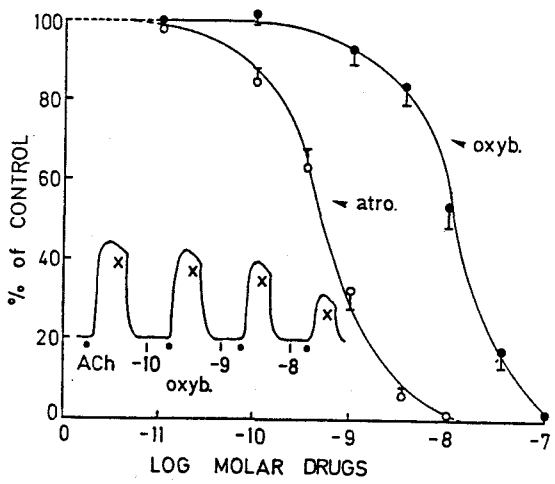


Fig. 3. Dose-response curve to atropine and oxybutynin in acetylcholine-induced contraction. Rings were contracted by 1.0 μM acetylcholine in the presence of different concentrations of atropine (○) or oxybutynin (●) as described in text. Each point represents the mean ± the S.E.M. of 4–6 rings. Where the S.E.M. bar is absent, the S.E.M. is < the size of the data point.
Insert : A trace showing the experimental protocol to test effect of oxybutynin on 1.0 uM acetylcholine-induced contraction.

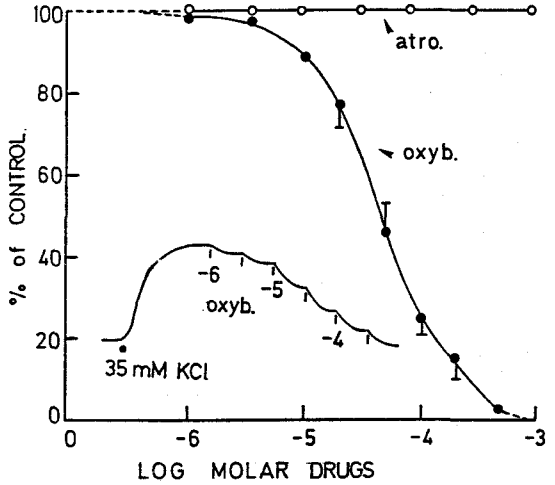


Fig. 4. Dose-response curve to atropine and oxybutynin in KCl-induced contraction. Rings were precontracted by 35 mM KCl, then atropine (○) or oxybutynin (●) was added to the muscle bath in a cummulative fashion as described in text. Each point represents the mean ± S.E.M. of 4–6 rings. Where the S.E.M. bar is absent, the S.E.M is < the size of the data point.
Insert : A trace showing the experimental protocol to test effect of oxybutynin on 35 mM KCl-induced contraction.

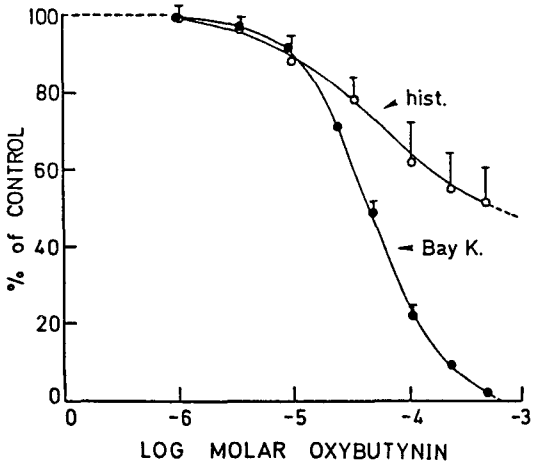


Fig. 5. Dose-response curve to oxybutynin in Bay K 8644— and histamine-induced contraction. In "Bay K" curve, rings were precontracted by 0.1 μM Bay K 8644 (●), then oxybutynin was added to the muscle bath in a cummulative fashion. In "hist" curve, rings were contracted by 35 μM histamine (○) in the presence of different concentractions of oxybutynin as described in text. Each point represents the mean ± S.E.M. of 4—6 rings. Where the S.E.M. bar is absent, the S. E. M. is < the size of the data point.

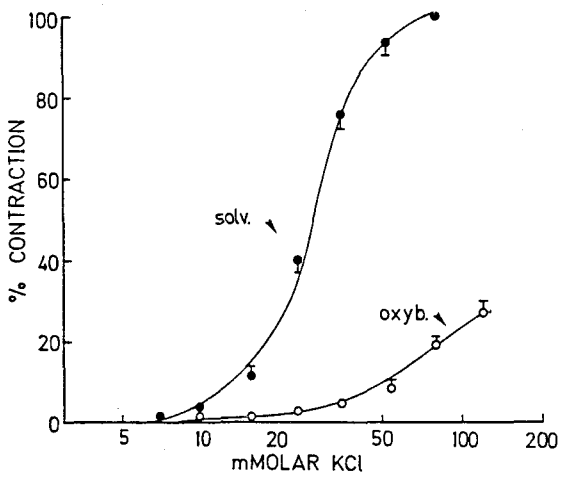


Fig. 7. Effect of oxybutynin on the KCl dose-response curve. Rings were pretreated for 20 min with solvent (●) or oxybutynin (○). After this pretreatment period, the resting tension which had been altered by the solvent or the drug were restored to the original 5g base-line tension by mechanical adjustment of the rings. KCl was then delivered to both test and control rings in a cummulative fashion. Each point represents the mean ± S.E.M of 4—8 rings.

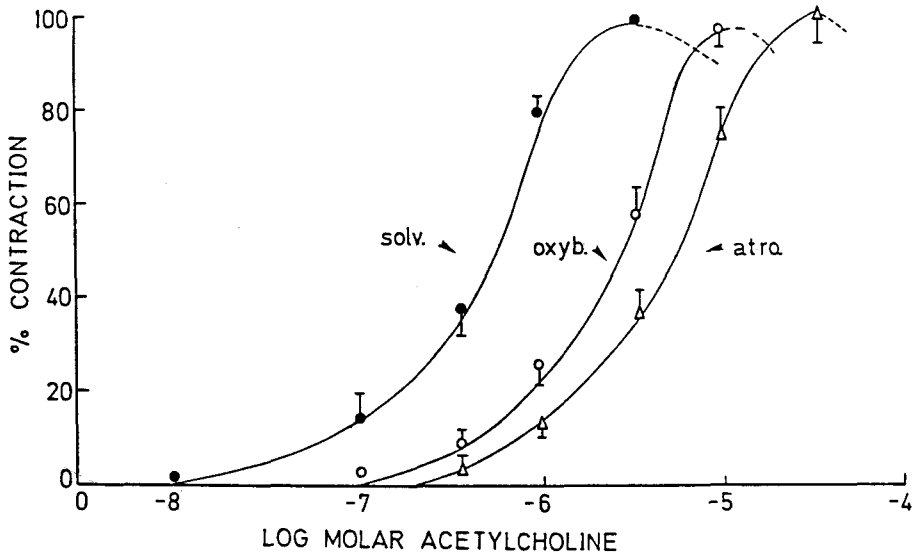


Fig. 6. Effect of oxybutynin and atropine on the acetylcholine dose-response curve. Rings were pretreated for 20 min with solvent (●), IC_{50} = 11.0 nM of oxybutynin (○), or IC50 = 0.47 nM of atropine (△). After this pretreatment period, the resting tensions which had been altered by the solvent or the drugs were restored to the original base-line tension by mechanical adjustment of the rings. Acetylcholine was then delivered to both test and control rings in a cummulative fashion. Each point represents the mean ± S.E.M of 4—6 rings. Where the S.E.M. bar is absent, the S.E.M is < the size of the data point.

oxybutynin on 0.1 μM Bay K 8644 and 35 μM histamine-induced contraction was investigated. The Bay K 8644 induced tension was relaxed by oxybutynin to the baseline, in a dose-dependent manner (Fig. 5). The histamine-induced contraction was also dose-dependently inhibited by oxybutynin but not relaxed to the baseline. The maximal inhibition of the histamine contraction by oxybutynin was about 50%. Slopes of oxybutynin-inhibitory curves for the Bay K 8644- and histamine-induced contraction were -1.22 ± 0.08 and -0.95 ± 0.07, respectively. There is no difference between both slopes of oxybutynin-inhibitory curves for the KCl-and Bay K 8644-induced contraction but significant difference between slopes of oxybutynin-inhibitory curves for Bay K 8644-and histamine-induced contraction ($P<0.05$).

DISCUSSION

It is well known that a parasympathetic neurotransmitter, ACh decreases peripheral vascular resistance in in vivo but produces frequently contraction of isolated blood vessels in in vitro experiments. This inconsistency has been discussed between scholars for long time. Furchgott and his colleagues (1980, 1981, 1983) reported that vascular relaxation by ACh is not a direct action and results from release of endothelium-derived relaxing factor (EDRF) by ACh from vascular endothelium.

In this experiment, ACh produced concentraction-dependent increases in tension in rings both with and without endothelium. The contractile responses to ACh were significantly potentiated in rings without endothelium than in intact endothelial rings. Williams *et al.* (1987) also observed the calcium channel agonists, Bay K 8644-and (+)-S202-791 [Isopropyl 4-(2,1,3-benzyoxadiazol-4-yl)-1, 4-dihydor-2, 6-dimethyl-5-nitro-3-pyridine carboxylate]-induced contraction were potentiated by removal of endothelium in porcine coronary artery. Their explanation for the potentiation phenomenon was that the calcium agonists produced contraction of smooth muscle, but may also release EDRF which will reduce the contraction. A possible explanation for action of ACh on porcine coronary artery in this study takes into account reports that contractile responses to norepinephrine and ACh in rabbit thoracic aorta were potentiated by removal of endothelium (Elgleme *et al.*, 1984; shin, 1986) and that relaxant effect of ACh in intact endothelial tissue was antagonized by atropine (Furchgott 1983). The ACh produced contraction of porcine coronary artery via a direct action on muscarinic receptors, and also relaxation by release of EDRF from the endothelium. When the endothelium was removed, release of EDRF by ACh is abolished, and the full contraction of ACh is seen. This appears to be a potentiation of the ACh-induced contraction.

The dose-response curve for ACh was competitively shifted to the right by pretreatment with oxybutynin as well as atropine. Each slope of control, atropine-pretreated and oxybutynin pretreated groups was similar and no difference among them. However IC_{50} of atropine for 1.0 μM ACh-induced contraction was 23-fold weaker than that of oxybutynin. These results suggest that inhibitory potencies of atropine and oxybutynin on the ACh-induced contraction are different each other but the mechanism of the inhibition may be the same, i.e. blocking action on muscarinic receptors. This hypothesis is supported by reports that oxybutynin has anticholinergic action in intestinal and bladder muscle (Lish *et al.*, 1965; Anderson and Fredericks, 1977).

Vascular smooth muscle has potential-operated channel (POC) and receptor-operated channel (ROC) involving calcium influx (Hurwitz and Suria, 1971). Representative agonists for POC are KCl, Bay K 8644 and (+)-S202-791, and agonists for ROC are neurohumoral agents causing contractile response (Droogmans *et al.*, 1977; van Breemen *et al.*, 1981; 1982; Schramm *et al.*, 1983, Hof *et al.*, 1985; Dube *et al.*, 1985). KCl and Bay K 8644 as agonists for POC and histamine as an agonist for ROC were used in this experiment. Atropine did not affect the KCl-induced contraction at all but oxybutynin inhibited the KCl-and Bay k 8644-induced contraction in a dose-dependent fashion. IC_{50s} of oxybutynin for KCl-and Bay k 8644-induced tension were 49.7 μM and 63.0 μM, respectively and there was no difference between them. These data suggest that atropine has no effect on calcium influx via POC but oxybutynin inhibits calcium influx via POC. Oxybutynin inhibited also histamine-induced contraction by increase of calcium influx via ROC. The slope of inhibitory curve for the histamine contraction was different from those for the KCl

and Bay K 8644 contraction. This means the inhibitory mechanism of oxybutynin on the histamine contraction is different to that on the KCl contraction.

Conclusively these results suggest that oxybutynin has anticholinergic effect and blocking action on ROC in higher concentraction as well as POC in porcine coronary artery.

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═ 국문초록 ═

동맥근 수축에 대한 Oxybutynin의 이완효과에 관한 연구

*전북대학교 의과대학 내과학교실
**전남대학교 의과대학 약리학교실

고 재 기*·백 영 홍**

돼지 우관상동맥을 적출하여 항경련제인 oxybutynin의 약리작용을 조사하였다.

1. Acetylcholine (ACh)과 KCl은 관상동맥을 수축시켰고 이 수축효과는 용량의존적이였다. ACh의 수축효과는 내피손상표본 (EC_{50}=0.28 μM)에서 내피표본 (EC_{50}=0.52 μM)보다 약 2배 강화되었으나 KCl의 수축효과는 양군간에 차이가 없었다.

2. ACh (1.0 μM)의 수축효과는 oxybutynin과 atropine에 의하여 용량의존적으로 억제되었고 두 약물의 IC_{50}는 각각 11.0 nM과 0.47 nM로 atropine이 약 23배나 더 예민하였다. 그러나 KCl (35 mM)의 수축효과는 atropine으로는 전혀 영향받지 않았고 oxybutynin으로는 용량의존적으로 억제되었으며 IC_{50}=49.7 μM이였다.

3. ACh의 용량반응곡선은 oxybutynin (IC_{50}=11 nM) 및 atropine (IC_{50}=0.47 nM) 전처리하에서 우측으로 평행이동되었고, KCl의 용량반응곡선은 oxybutynin (IC_{50}=49.7 μM) 전처리하에서 우측으로 비상경적 이동을 일으켰다.

4. Oxybutynin은 Bay K 8644 (0.1 μM)의 수축효과를 용량의존적으로 억제하였고 IC_{50}=63.0 μM이었으며, histamine (35 μM)의 수축효과는 oxybutynin의 최대량 (500 μM)으로 부분억제(최대 50%)만을 일으켰다.

이상의 성적으로 적출돼지 관상동맥에서 내피세포는 ACh에 의한 수축반응에 억제적 영향을 미치며, oxybutynin은 강력한 muscarine receptor 차단작용과 calcium influx 억제작용에 의하여 혈관근 이완을 일으킨다고 추론하였다.