Effects of synthetic penicillins on the contractile response of guinea-pig vas deferens

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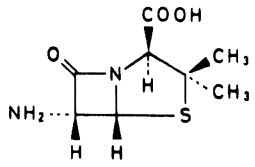
The present study was undertaken to investigate the effects of two synthetic penicillins, ampicillin (ABPC) and cloxacillin (MCIPC), on the contractile responses of isolated guinea pig vas deferens, which has smooth muscle that is under the control of sympathetic nerves. The effects of 6-aminopenicillanic acid (6-APA), the basic component of these penicillins, on contractile response were also investigated. It has been proposed that noradrenaline and adenosine triphosphate (ATP) are simultaneously released from sympathetic nerves in the vas deferens, and act as co-transmitters, while the isolated vas deferens evokes a contractile response by exogenously added noradrenaline as well as exogenously added ATP. ABPC (5×10^{-4} g/ml~2.5×10^{-3} g/ml) and 6-APA (5×10^{-4} g/ml~2.5×10^{-3} g/ml) significantly increased the amplitude of the contractile responses induced by electrical nerve stimulation, while MCIPC (5×10^{-4} g/ml~2.5×10^{-3} g/ml) significantly decreased them. ABPC and 6-APA, each at the concentration of 2.5×10^{-3} g/ml, significantly increased the amplitude of the contractile responses induced by the three treatments, that is, electrical muscle stimulation, exogenously added noradrenaline and exogenously added ATP. However, MCIPC, at the same concentration, significantly decreased them. In the case of electrical nerve stimulation alone, the decrease in the amplitude of the contractile response caused by MCIPC was not completely eliminated even by washing with normal Krebs solution. These results led to the following conclusions: 1) ABPC and 6-APA may act directly on the intramural muscle of the vas deferens so as to increase the amplitude of the contractile response of its muscle and this increase in amplitude is not considered to be mediated via the effects of these agents on the intramural sympathetic nerves of the vas deferens. This increase is a special effect that has been not observed in other organs. 2) MCIPC may act mainly directly on the intramural muscle of the vas deferens so as to decrease the amplitude of the contractile response of its muscle, although the effect of this agent on the intramural sympathetic nerves of the vas deferens is unlikely to be completely negligible. 3) The difference between the effects of ABPC and MCIPC on the contractile response of the vas deferens may be attributable to the difference in the side chain connected to the basic structure of these agents.

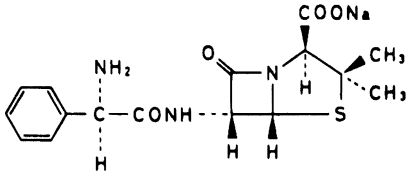
Key words: ampicillin, cloxacillin, vas deferens, contractile response

Introduction

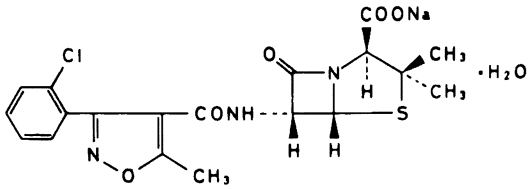
Aratani et al.[1,2] reported that ampicillin (ABPC) and cloxacillin (MCIPC), synthetic penicillins, reduced the spontaneous contractile response of guinea pig intestine and the blood pressure of rabbit. We investigated the effects of ABPC and MCIPC on the smooth muscles of both gallbladder and urinary bladder of the guinea pig, which are under the control of parasympathetic nerves, and suggested that ABPC may affect the intramural cholinergic nerves of these organs as well as the muscles of these organs; MCIPC may affect the muscles of these organs, but its effect on the intramural cholinergic nerves of these organs is unlikely to be negligible[3,4]. We have not found any report concerning the effects of these penicillins on organs



6-APA



ABPC



MCIPC

Fig. 1. Chemical structures of 6-aminopenicillanic acid (6-APA), ampicillin (ABPC) (Na salt) and cloxacillin (MCIPC) (Na salt).

with smooth muscle under the control of the sympathetic nerves. We therefore investigated the effects of ABPC and MCIPC on the guinea pig vas deferens, which has smooth muscle that is under the control of sympathetic nerves. The effects of 6-aminopenicillanic acid (6-APA) on guinea pig vas deferens were also investigated since ABPC and MCIPC have a common basic structure, that is, 6-APA (Fig. 1).

Materials and Methods

Guinea pigs (300～500 g) were stunned and exsanguinated, and the vasa deferentia were excised, stripped of connective tissue and desheathed. Each segment from the mid portion of the vasa deferentia, approximately 12～15 mm in length, was used as an experimental preparation. Each preparation was immersed in an organ bath containing Krebs solution maintained at 28°C and gassed with 95% O_2 and 5% CO_2 (pH 7.3). The composition of the Krebs solution (mM) was as follows: 133.5 NaCl, 4.7 KCl, 2.5 $CaCl_2$, 0.1 $MgCl_2$, 1.4 NaH_2PO_4, 16.3 $NaHCO_3$ and 7.8 glucose. The end near the testis side of each preparation was fixed with pins and the other end was connected with silk thread to a force displacement transducer. The mechanical response of each preparation induced by electrical stimulation, exogenously added noradrenaline and exogenously added ATP was recorded isometrically under a load of 1 g. Two platinum plates (5 mm×5 mm) were used as stimulus electrodes. The electrodes were placed near the pins that fixed the preparation as described in our previous report[5]. The preparation was electrically stimulated with rectangular pulses (50 volt, 5 Hz) of durations of 0.5 msec and 50 msec for a period of 5 sec.

The drugs used were ampicillin Na salt (ABPC), cloxacillin Na salt (MCIPC) and 6-aminopenicillanic acid (6-APA). These chemical structures are shown in Fig. 1. Other drugs used in this study were adenosine 5'-triphosphate disodium salt (ATP), atropine sulfate, (±)-noradrenaline hydrochloride and tetrodotoxin. The concentrations of drugs used were the final values in the organ bath; these are given in the Results section. Each concentration of ABPC and MCIPC in the organ bath indicates the value which was converted to the potency of the penicillin. The potencies were 853 μg/mg and 906 μg/mg, respectively.

Results

1. Effects of ABPC, MCIPC and 6-APA on contractile response induced by electrical stimulation

The preparation was electrically stimulated with rectangular pulses (50 volt, 5 Hz) of 0.5 msec duration for a period of 5 sec at intervals of 5 min. The preparation showed a contractile response to the stimulation. As shown in Fig. 2, ABPC and 6-APA increased the amplitude of the contractile response. That is to say, the amplitude of the contractile response was significantly increased 4 min after the addition of each agent. The increase, although weakened thereafter, remained nearly stable. The increase was completely eliminated by washing with normal Krebs solution for approximately 30 min (Fig. 2). MCIPC, however, significantly decreased the amplitude of the contractile response (Fig. 2). That is to say, the amplitude of the contractile response was significantly decreased 4 min after the addition of this agent. The decrease, although it became slightly greater thereafter, was nearly stable from 14 to 29 min after the addition of the agent (Fig. 2). This decrease was not completely eliminated even by washing with normal Krebs solution for approximately 30 min

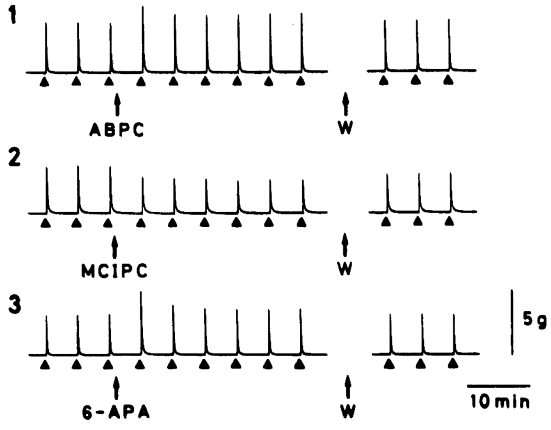


Fig. 2. Effects of ampicillin (ABPC), cloxacillin (MCIPC) and 6-aminopenicillanic acid (6-APA) on the contractile response induced by electrical stimulation.
Electrical stimulation was given with rectangular pulses (50 volt, 5 Hz) of 0.5 msec duration for a period of 5 sec at intervals of 5 min. Electrical stimulation was applied at the triangular dots. 1: effect of ABPC, 2.5×10^{-3} g/ml. 2: effect of MCIPC, 2.5×10^{-3} g/ml. 3: effect of 6-APA, 2.5×10^{-3} g/ml. Each agent (ABPC, MCIPC or 6-APA) was given at the arrow mark. The right side shows the contractile response observed 30~40 min after washing with normal Krebs solution.

(Fig. 2). ABPC and 6-APA at concentrations of 5×10^{-4}g/ml to 2.5×10^{-3}g/ml showed the above-mentioned effect of increasing the amplitude of the contractile response, but at the concentration of 1×10^{-4} g/ml, they had no effect on amplitude (Table 1). MCIPC at the concentration of 5×10^{-4} g/ml to 2.5×10^{-3} g/ml showed the above-mentioned effect of decreasing the amplitude of the contractile response, but at the concentration of 1×10^{-4} g/ml had no effect on its amplitude (Table 1). The above phenomena produced by ABPC, MCIPC and 6-APA were also observed in the presence of atropine at the concentration of 1×10^{-6} M (data not shown).

2. Effects of ABPC, MCIPC and 6-APA on contractile response induced by electrical stimulation in the presence of tetrodotoxin

The preparation, in the presence of tetrodotoxin (3×10^{-7} M), was electrically stimulated with rectangular pulses (50 volt, 5 Hz) of 50 msec duration for a period of 5 sec. The preparation showed a contractile response to the stimulation. As shown in Fig. 3, ABPC and 6-APA, at the concentration of 2.5×10^{-3} g/ml, increased the amplitude of the contractile response. That is to say, the amplitude

Table 1. Effect of ampicilln, cloxacillin and 6-aminopenicillanic acid on the contractile response induced by electrical stimulation

Agent	Concentration (g/ml)	N	Amplitude of contractile response (% of control)	
			Time after addition of an agent	
			4 min	29 min
ABPC	1×10^{-4}	6	100±1	100±2
	5×10^{-4}	8	107±4**	104±2*
	1×10^{-3}	10	111±7***	106±4**
	2.5×10^{-3}	7	122±13**	108±6**
MCIPC	1×10^{-4}	6	100±1	100±1
	5×10^{-4}	8	97±2**	96±2***
	1×10^{-3}	15	95±4***	93±5***
	2.5×10^{-3}	15	74±10***	67±11***
6-APA	1×10^{-4}	6	101±2	100±1
	5×10^{-4}	6	108±4**	103±4*
	1×10^{-3}	10	113±26***	106±5*
	2.5×10^{-3}	10	135±26***	109±9**

The preparation was stimulated with rectangular pulses (50 volt, 5 Hz) of 0.5 msec duration for a period of 5 sec. N indicates the number of preparations used. Each value represents the mean±SD of the amplitudes of the contractile responses observed 4 min and 29 min after the addition of an agent.
*, **, and *** indicate significant difference from the value before the addition of an agent, namely the control, at $P<0.05$, $P<0.01$ and $P<0.001$, respectively.
ABPC: amicillin, MCIPC: cloxacillin, 6-APA: 6-aminopenicillanic acid

of the contractile response was significantly increased 4 min after the addition of each agent. This increase, although weakened thereafter, remained as long as 29 min after the addition of the agent (Fig.3). As shown in Fig. 3, MCIPC, at the concentration of 2.5×10^{-3} g/ml, decreased the amplitude of the contractile response. This decrease remained to a similar degree even 29 min after the addition of the agent as that at 4 min after its addition (Fig.3). The increases caused by ABPC and 6-APA and the decrease caused by MCIPC in the amplitude of the contractile response was eliminated by washing with normal Krebs solution containing tetrodotoxin for approximately 30 min (Fig.3).

3. Effects of ABPC, MCIPC and 6-APA on contractile response induced by exogenously added noradrenaline

As shown in Fig. 4, the preparation showed a contractile response to exogenously added noradrenaline (1×10^{-5} M). Its amplitude was significantly increased 4 min after the addition of ABPC (2.5×10^{-3} g/ml) or 6-APA (2.5×10^{-3} g/ml). The increase, although weakened thereafter, remained even 29

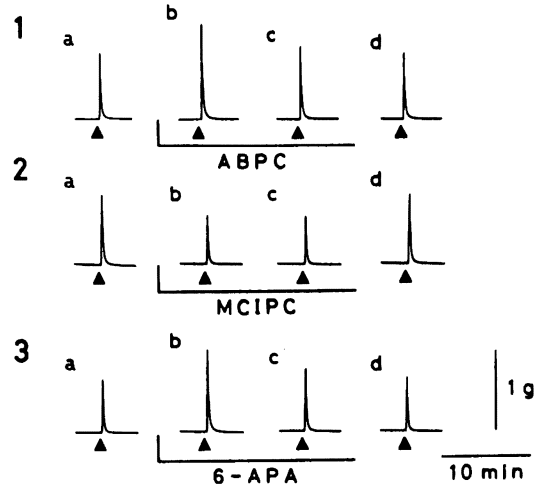


Fig. 3. Effects of ampicillin (ABPC), cloxacillin (MCIPC) and 6-aminopenicillanic acid(6-APA) on the contractile response induced by electrical stimulation in the presence of tetrodotoxin.

1~3: The preparation, in the presence of tetrodotoxin (3×10^{-7} M), was stimulated with rectangular pulses (50 volt, 5 Hz) of 50 msec duration at the triangular dots for a period of 5 sec. 1: effect of ABPC, 2.5×10^{-3} g/ml. 2: effect of MCIPC, 2.5×10^{-4} g/ml. 3: effect of 6-APA, 2.5×10^{-3} g/ml. Each "a" in 1~3 indicates the contractile response in the presence of an agent (ABPC, MCIPC or 6-APC), namely the control. Each "b" in 1~3 indicates the contractile response observed 4 min after the addition of an agent. Each "c" in 1~3 indicates the contractile response observed 29 min after the addition of an agent. Each "d" in 1~3 indicates the contractile response observed 30 min after washing with Krebs solution containing tetrodotoxin (3×10^{-7} M).

min after the addition of the agent (Fig.4). This increase was eliminated by washing with normal Krebs solution for approximately 30 min (data not shown). The amplitude of the contractile response induced by noradrenaline was significantly decreased 29 min after the addition of MCIPC at the concentration of 2.5×10^{-3} g/ml (Fig.4). This decrease was also eliminated by washing with normal Krebs solution for approximately 30 min (data not shown).

4. Effects of ABPC, MCIPC and 6-APA on contractile response induced by exogenously added ATP

As shown in Fig. 5, the preparation showed a contractile response to exogenously added ATP (1×10^{-5} M). The amplitude of the response was significantly increased 4 min after the addition of

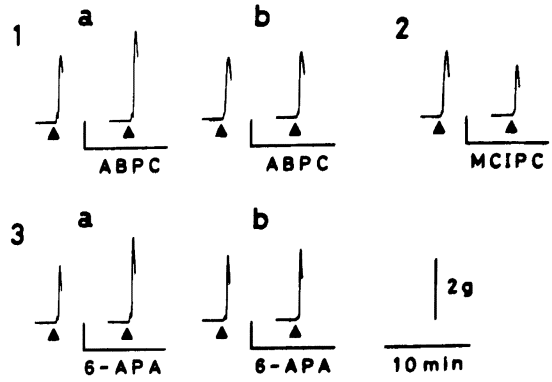


Fig. 4. Effects of ampicillin (ABPC), cloxacillin (MCIPC) and 6-aminopenicillanic acid(6-APA) on the contractile response induced by exogenously added noradrenaline.

1: effect of ABPC, 2.5×10^{-3} g/ml. 2: effect of MCIPC, 2.5×10^{-4} g/ml. 3: effect of 6-APA, 2.5×10^{-3} g/ml. In all tracings, noradrenaline was applied at triangular dots. Each left side tracing of "a and b" in 1 and 3 and 2 indicates the contractile response in the absence of each agent, namely the control. Each right side tracing of "a" in 1 and 3 indicates the contractile response observed 4 min after the addition of each agent. Each right side tracing of "b" in 1 and 3 and 2 indicates the contractile response observed 29 min after the addition of each agent. "a and b" in 1 and 3: different preparations, respectively.

ABPC (2.5×10^{-3} g/ml) or 6-APA (2.5×10^{-3} g/ml). The increase, although weakened thereafter, remained even 29 min after the addition of the agent (Fig.5). This increase was eliminated by washing with normal Krebs solution for approximately 30 min (data not shown). The amplitude of the contractile response induced by ATP was significantly decreased 29 min after the addition of MCIPC at the concentration of 2.5×10^{-3}g/ml (Fig. 5). This decrease was also eliminated by washing with normal Krebs solution for approximately 30 min (data not shown).

Discussion

Electrical stimulation with rectangular pulses of 0.5 msec duration evoked a contractile response (Fig.2). As shown in our previous paper[5], the contractile response may be due to the release of transmitter from intramural postganglionic sympathetic nerve endings of the preparation as a result of electrical current stimulation of the intramural nerves of the preparation (electrical nerve stimulation). On the other hand, electrical stimulation with rectangular pulses of 50 msec duration in the

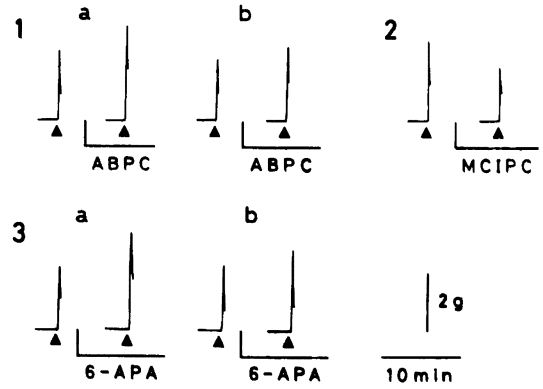


Fig. 5. Effects of ampicillin (ABPC), cloxacillin (MCIPC) and 6-aminopenicillanic acid (6-APA) on the contractile response induced by exogenously added ATP.

1: effect of ABPC, 2.5×10^{-3} g/ml. 2: effect of MCIPC, 2.5×10^{-3} g/ml. 3: effect of 6-APA, 2.5×10^{-3} g/ml. In all tracings, ATP was applied at triangular dots. Each left side tracing of "a and b" in 1 and 3 and 2 indicates the contractile response in the absence of each agent, namely the control. Each right side tracing of "a" in 1 and 3 indicates the contractile response observed 4 min after the addition of each agent. Each right side tracing of "b" in 1 and 3 and 2 indicates the contractile response observed 29 min after the addition of each agent. "a and b" in 1 and 3: different preparations, respectively.

presence of tetrodotoxin, a neuron blocker, evoked a contractile response (Fig.3). As shown in our previous paper[5], again, the contractile response is not mediated by a stimulus effect of the electrical current on the intramural nerves of the preparation, but is mediated by a direct stimulus effect of the electrical current on the muscle of the preparation (electrical muscle stimulation). It has been proposed, moreover, that noradrenaline and ATP are simultaneously released from sympathetic nerves in the tissue, and act as co-transmitters[6~8]. Exogenously added noradrenaline and ATP have been shown to act, respectively, at α_1-adrenoceptors and P_2-purinoceptors of muscle in the vas deferens wall, and to mediate the contractile response of muscle[6~8]. That is to say, they act directly on muscle in the vas deferens wall.

We then observed the effects of ABPC, MCIPC and 6-APA on the contractile responses of the preparation induced by electrical nerve stimulation, electrical muscle stimulation, exogenously added noradrenaline and exogenously added ATP. ABPC (5×10^{-4} g/ml~2.5×10^{-3} g/ml) and 6-APA (5×10^{-4} g/ml~2.5×10^{-3} g/ml) significantly increased the amplitude of the electrical nerve stimulation-induced contractile response (Fig. 2 and Table 1), whereas MCIPC (5×10^{-4} g/ml~2.5×10^{-3} g/ml) significantly decreased it (Fig. 2 and Table 1). Aratani et al.[1] suggested that ABPC exerted cholinergic action on organs that have smooth muscle. Aratani et al.[2] again suggested that MCIPC acted mainly paralytically on such organs, but its cholinergic action was unlikely to be negligible. However, the increasing effect of ABPC and 6-APA and the decreasing effect of MCIPC on the amplitude of the contractile response in the present study were also observed in the presence of atropine (1×10^{-6} M). The intramural cholinergic nerves of the vas deferens may therefore be unrelated to these effects. The effects of ABPC, MCIPC and 6-APA at the concentration of 2.5×10^{-3} g/ml on the amplitude of the contractile response induced by electrical muscle stimulation, exogenously added noradrenaline and exogenously added ATP were similar to those on the amplitude of the contractile response induced by electrical nerve stimulation (Figs. 2~5). From the above-described results, it is reasonable to conclude that ABPC and 6-APA may act directly on the intramural muscle of the vas deferens so as to increase the amplitude of the contractile response of its muscle, and this increase in amplitude is not considered to be mediated via the effects of these agents on the intramural nerves of the vas deferens. It can be assumed, moreover, that MCIPC acts directly on the intramural muscle of the vas deferens so as to decrease the amplitude of the contractile response of the muscle, although the effect of this agent on the intramural sympathetic nerves of the vas deferens is unlikely to be completely negligible, since the decrease caused by MCIPC was not completely eliminated even by washing with normal Krebs solution only in the case of electrical nerve stimulation. The difference between the effects of ABPC and MCIPC on the contractile response of the preparation may be attributable to the difference in the side chain connected to the basic structure of these agents, since ABPC and MCIPC have a common basic structure, that is, 6-APA. On the other hand, both ABPC and MCIPC decrease the contractile response of intestine, gallbladder and

urinary bladder of the gainea pig[1~4], and 6-APA decreases the contractile response of gallbladder and urinary bladder of the guinea pig[3,4]. The effects of ABPC and 6-APA as observed in our present study are, therefore, special effects which have not been observed in other organs.

Both ABPC and MCIPC have been orally administered to humans at a clinical dosage of 500 mg, and the concentration of each agent in blood measured[9~12]. The highest concentrations of ABPC in the blood were 4.4×10^{-6} g/ml (Ichikawa et al.)[9] and 3.4×10^{-6} g/ml (Higuch et al.)[10], and those of MCIPC were 3.0×10^{-6} g/ml~3.5×10^{-6} g/ml (Okubo et al.)[11] and 4.6×10^{-6} g/ml (Shioda et al.)[12]. However, we have not found any report from the clinical point of view concerning the effects of these agents on organs with smooth muscle under the control of the sympathetic nerves. As shown in our present study, ABPC, MCIPC and 6-APA at low concentrations had almost no effect on the contractile response of tissue, but at high concentrations induced a significant effect. This result is compatible with the observation of Aratani et al[1,2].

Our conclusions are as follows: 1) ABPC and 6-APA may act directly on the intramural muscle of the vas deferens so as to increase the amplitude of the contractile response of its muscle, this increase is not considered to be mediated via the effects of these agents on the intramural sympathetic nerves of the vas deferens. The increase is a special effect that has not been observed in other organs. 2) MCIPC may act mainly directly on the intramural muscle of the vas deferens so as to decrease the amplitude of the contractile response of the muscle, although its effect on the intramural sympathetic nerves of the vas deferens is unlikely to be completely negligible. 3) The difference between the effects of ABPC and MCIPC on the contractile response of the vas deferens may be attributable to the difference in the side chain connected to the basic structure of these agents.

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モルモット輸精管の収縮反応におよぼす合成 penicillin の影響

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合成 penicillin である ampicillin (ABPC) および cloxacillin (MCIPC) ならびにこれら penicillin の母核である 6-aminopenicillanic acid (6-APA) の摘出モルモット輸精管の収縮反応におよぼす影響について研究した。輸精管は，主に交感神経の支配を受けている。Noradrenaline と adenosine triphosphate (ATP) は，輸精管の交感神経から同時に放出され，組織の筋に co-transmitter として作用することが知られているが，外来性に noradrenaline を加えても，外来性に ATP を加えても，輸精管は収縮反応を示す。ABPC (5×10^{-4} g/ml～2.5×10^{-3} g/ml) および 6-APA (5×10^{-4} g/ml～2.5×10^{-3} g/ml) は，電気的神経刺激 (50 volt, 0.5 msec の矩形波にて，5 Hz の頻度で 5 sec 間刺激) により惹起される輸精管の収縮反応の高さを明らかに増強したが，MCIPC (5×10^{-4} g/ml～2.5×10^{-3} g/ml) は，その収縮反応の高さを明らかに減弱させた。ABPC (2.5×10^{-3} g/ml) および 6-APA (2.5×10^{-3} g/ml) は，電気的筋刺激 (tetrodotoxin 存在下で，50 volt, 50 msec の矩形波にて，5 Hz の頻度で 5 sec 間刺激)，外来性に加えた noradrenaline および ATP により惹起される収縮反応の高さを明らかに増強したが，MCIPC (2.5×10^{-3} g/ml) は，それら収縮反応の高さを明らかに減弱させた。MCIPC (2.5×10^{-3} g/ml) の電気的神経刺激により惹起される収縮反応の高さに対する減弱効果だけは，正常 Krebs 液で洗浄しても完全には消失しなかった。上記の事実より，ABPC および 6-APA の輸精管収縮反応の高さ増強効果は，輸精管壁内の筋肉に対するこれら penicilline 系被験薬物の直接作用に起因しており，これら penicilline 系被験薬物の輸精管壁内神経 (sympathetic) に対する作用は考え難い。なお，このような収縮反応の高さ増強効果は，他の臓器ではまだ観察されていない特殊な効果である。MCIPC の輸精管収縮反応の高さ減弱効果は，輸精管壁内神経 (sympathetic) に対する MCIPC の作用を完全に無視することはできないが，主に MCIPC の輸精管壁内の筋に対する直接作用に起因するものと推定される。なお，輸精管の収縮反応に対する ABPC と MCIPC の作用態度の違いは，両者の側鎖の相違によるものと思われる。

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