# Effects of aminoglycoside antibiotics on the contractile response of guinea—pig vas deferens

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The present study was undertaken to investigate the effects of kanamycin (KM), bekanamycin (AKM) and ribostamycin (RSM), aminoglycoside antibiotics, on the contractile response of isolated guinea pig vas deferens. The contractile response of isolated vas deferens induced by electrical stimulation with rectangular pulses (50 volt, 5 Hz) of 0.5 msec duration for a period of 5 sec was abolished by guanethidine and tetrodotoxin, but was not affected by hexamethonium. Therefore, the intramural nerves supplying the vas deferens are undoubtly the postganglionic sympathetic nerves, and the above-mentioned contractile response may be due to a stimulus effect of the electrical current on the intramural nerves of the vas deferens (electrical nerve stimulation). Further, the contractile response of isolated vas deferens induced by electrical stimulation with rectangular pulses (50 volt, 5 Hz) of 50 msec duration for a period of 5 sec in the presence of tetrodotoxin may be due to a stimulus effect of the electrical current on the muscle of the vas deferens (electrical muscle stimulation). It has been proposed, moreover, that noradrenaline and adenosine triphosphate are simultaneously released from sympathetic nerves in the vas deferens, and act as co-transmitters, while the isolated vas deferens evoked a contractile response by exogenously added noradrenaline as well as exogenously added adenosine triphosphate. KM ($1\times10^{-5}$ g/ml—$1\times10^{-3}$ g/ml), AKM ($5\times10^{-6}$ g/ml—$1\times10^{-3}$ g/ml) and RSM ($5\times10^{-5}$ g/ml—$1\times10^{-3}$ g/ml) reduced the amplitude of the contractile response induced by electrical nerve stimulation in a concentration-dependent manner. KM, AKM and RSM, each at a concentration of $5\times10^{-4}$ g/ml, reduced, with much approximation, the amplitudes of contractile responses induced by the three treatments, that is, electrical muscle stimulation, exogenously added noradrenaline and exogenously added adenosine triphosphate. However, each of these antibiotics at the concentration mentioned was exceedingly potent in reducing the effect on the amplitude of the contractile response induced by electrical nerve stimulation. All these findings may bring about a conclusion that KM, AKM and RSM affect both intramural sympathetic nerves and muscle of the vas deferens. It also seems possible that the effects of these antibiotics are greater on the former than they are on the latter.

**Key words**: aminoglycoside antibiotics, contractile response, vas deferens

## INTRODUCTION

In general, aminoglycoside antibiotics are not metabolized in the body and are excreted intact in urine[1]. Several reports concerning the effects of these antibiotics on organs with smooth muscle have suggested that they act directly on muscle to reduce its contractile response[2~5]. We investigated the effects of aminoglycoside antibiotics on the

smooth muscle of the guinea pig urinary bladder, which is under the control of parasympathetic nerves, and suggested that the aminoglycoside antibiotics may affect the intramural cholinergic nerves of the urinary bladder as well as its muscle[6]. We have not found any report concerning the effects of these antibiotics on organs with smooth muscle under the control of the sympathetic nerves. We, therefore, investigated the effects of aminoglycoside antibiotics (kanamycin, bekanamycin and rebostamycin) on the guinea pig vas deferens, which has smooth muscle that is under the control of sympathetic nerves.

## MATERIALS AND METHODS

Guinea pigs (300—500 g) were stunned and exanguinated, and the vasa deferentia were excised, stripped of connective tissue and desheathed. Each segment from the midportion 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 by silk thread to a force displacement transducer. The mechanical response of each preparation induced by electrical stimulation, exogenously added noradrenaline and exogenously added adenosine triphosphate 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. That is to say, the preparation was placed between two electrodes which were set parallel and face to face with each other. The space between the preparation and one electrode was approximately 2 mm. The other electrode was placed very close to the preparation, nearly touching it. The preparation was electrically stimulated with rectangular pulses (50 volt, 5 Hz) of durations ranging from 0.5—50 msec for a period of 5 sec.

The drugs used were adenosine 5'-triphosphate disodium salt, guanethidine sulfate, hexamethonium chloride, (±)-noradrenaline hydrochloride, tetrodotoxin, kanamycin sulfate, bekanamycin sulfate and ribostamycin sulfate.

The concentrations of drugs used were the final values in the organ bath; these are given in the Results section. Each concentration of kanamycin (KM), bekanamycin (AKM) and ribostamycin (RSM) in the organ bath indicates the value which was converted to the potency of the antibiotic. The potencies of KM, AKM and RSM used in this experiment were 673 μg/mg, 714 μg/mg and 686 μg/mg, respectively.

The results are expressed as means±SD, and Student's t-test was used to evaluate the significance of differences.

## RESULTS

### 1. Effects of pharmacological antagonists on the contractile response induced by electrical stimulation

As shown in Fig. 1, electrical stimulation with rectangular pulses (50 volt, 5 Hz) of 0.5 msec duration for a period of 5 sec evoked a contractile response. We then observed the effects of pharmacological antagonists on these contractile responses. Guanethidine ($5\times10^{-6}$ M) almost abolished the contractile response (Fig. 1-1). Guanethidine ($1\times10^{-5}$ M) abolished it (data not shown), as did tetrodotoxin ($3\times10^{-7}$ M) (Fig. 1-2). Hexamethonium ($1\times10^{-4}$ M) did not affect the contractile response (Fig. 1-3).

### 2. Effects of KM, AKM and RSM on the contractile response induced by electrical stimulation

We observed the effects of KM, AKM and RSM on the contractile response induced by rectangular pulses (50 volt, 5 Hz) of 0.5 msec duration for a period of 5 sec at intervals of 5 min. As shown in Fig. 2, KM, AKM and RSM all immediately reduced the amplitude of the contractile response. That is to say, the reduction of its amplitude reached the maximum level 4 min after the addition of each antibiotic and remained on the same level thereafter. This reducing effect was observed at any concentration of antibiotic which produced a reduction in the contractile response (data not shown). KM ($1\times10^{-5}$ g/ml—$1\times10^{-3}$ g/ml), AKM ($5\times10^{-6}$

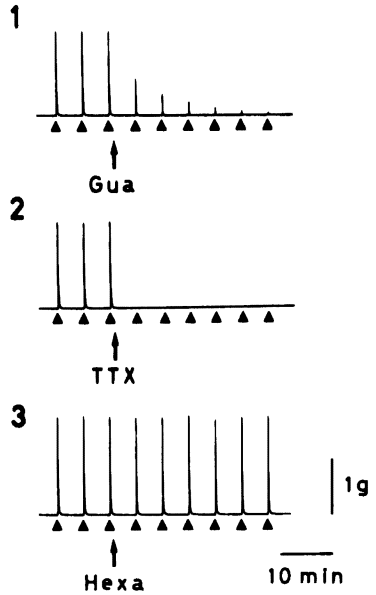


Fig. 1. Effects of pharmacological antagonists on the contractile response induced by electrical stimulation.

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. 1: Effect of guanethidine (Gua), $5\times10^{-6}$ M. 2: Effect of tetrodotoxin (TTX), $3\times10^{-7}$ M. 3: Effect of hexamethonium (Hexa), $1\times10^{-4}$ M. Electrical stimulation was applied at the triangular dots. Each agent was given at the arrow mark.

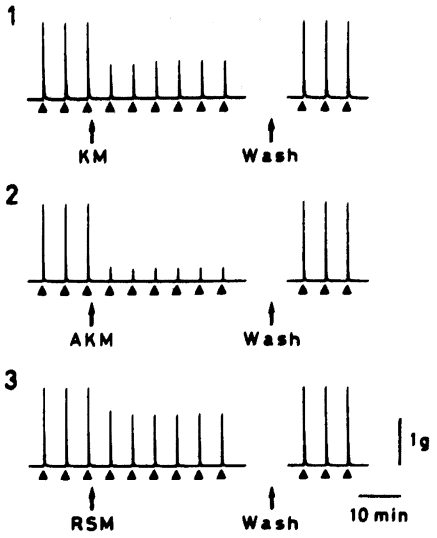


Fig. 2. Effects of kanamycin (KM), bekanamycin (AKM) and ribostamycin (RSM) on the contractile response induced by electrical stimulation.

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 KM, $5\times10^{-4}$ g/ml. 2: Effect of AKM, $5\times10^{-4}$ g/ml. 3: Effect of RSM, $5\times10^{-4}$ g/ml. Each agent (KM, AKM or RSM) was given at the arrow mark. The right side shows the contractile response observed 30—40 min after washing with normal Krebs solution.

g/ml—$1\times10^{-3}$ g/ml) and RSM ($5\times10^{-5}$ g/ml—$1\times10^{-3}$ g/ml) significantly reduced the amplitude of the contractile response in a concentration-dependent manner (Table 1). The reducing effects of these antibiotics were restored by washing with normal Krebs solution for approximately 30 min (Fig. 2). As shown in Table 1, the reducing effect on the amplitude of the contractile response was in the following order: AKM > KM > RSM.

**3. Effects of KM, AKM and RSM on the contractile response induced by electrical stimulation in the presence of tetrodotoxin**

First of all, the preparation, in the presence of tetrodotoxin ($3\times10^{-7}$ M), was electrically stimulated with rectangular pulses (50 volt, 5 Hz) of durations of 0.5 msec, 5 msec and 50 msec for a period of 5 sec. The preparation showed no response to the stimulation with rectangular pulses of 0.5 msec duration, while it showed a very weak contractile response to the stimulation with rectangular pulses of 5 msec duration (Fig. 3). The preparation, moreover, showed a remarkable contractile response to stimulation with rectangular pulses of 50 msec duration (Fig. 3). Then we observed the effects of KM, AKM and RSM at a concentration of $5\times10^{-4}$ g/ml on the contractile response induced by rectangular pulses (50 volt, 5 Hz) of 50 msec duration for a period of 5 sec in the presence of tetrodotoxin ($3\times10^{-7}$ M). At this concentration, each antibiotic

Table 1. Effect of kanamycin, bekanamycin and ribostamycin on the contractile response induced by electrical stimulation

| Agent | Concentration (g/ml) | N | Amplitude of contractile response (% of control) |
|---|---|---|---|
| Kanamycin | $5\times10^{-6}$ | 6 | 100±2 |
| | $1\times10^{-5}$ | 6 | 94±3** |
| | $5\times10^{-5}$ | 8 | 87±3*** |
| | $1\times10^{-4}$ | 8 | 80±4*** |
| | $5\times10^{-4}$ | 9 | 47±8*** |
| | $1\times10^{-3}$ | 6 | 15±3*** |
| Bekanamycin | $1\times10^{-6}$ | 6 | 100±2 |
| | $5\times10^{-6}$ | 6 | 96±2* |
| | $1\times10^{-5}$ | 6 | 87±3*** |
| | $5\times10^{-5}$ | 6 | 77±3*** |
| | $1\times10^{-4}$ | 9 | 65±8*** |
| | $5\times10^{-4}$ | 8 | 16±3*** |
| | $1\times10^{-3}$ | 5 | 0 |
| Ribostamycin | $1\times10^{-6}$ | 6 | 100±3 |
| | $5\times10^{-6}$ | 6 | 94±4* |
| | $1\times10^{-4}$ | 7 | 82±2*** |
| | $5\times10^{-4}$ | 7 | 61±5*** |
| | $1\times10^{-3}$ | 7 | 45±4*** |

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 contractile responses observed 14 min after the addition of an agent. *, **, and *** indicate significance differences from the value before the addition of an agent, namely, from the control, at $P<0.05$, $P<0.01$ and $P<0.001$, respectively.

reduced the amplitude of the contractile response (Fig. 3 and Table 2-A). The reducing effects of the antibiotics were restored by washing with Krebs solution containing tetrodotoxin ($3\times10^{-7}$ M) for approximately 30 min (Fig. 3). The reducing effect on the amplitude of the contractile response was in the following order: AKM>KM>RSM (Table 2-A).

**4. Effects of KM, AKM and RSM on the contractile response induced by exogenously added noradrenaline**

As shown in Fig. 4, the preparation showed a contractile response to exogenously added noradrenaline ($1\times10^{-5}$ M). KM, AKM and RSM, each at a concentration of $5\times10^{-4}$ g/ml, reduced its amplitude (Fig. 4 and Table 2-B). The reducing effects of these antibiotics were restored by washing with normal Krebs solution for approximately 30 min (Fig. 4). The reducing effect on the amplitude of the contractile response was in the following order: AKM>KM>RSM (Table 2-B).

**5. Effects of KM, AKM and RSM on the contractile response induced by exogenously added adenosine triphosphate**

As shown in Fig. 5, the preparation showed a contractile response to exogenously added adenosine triphosphate ($5\times10^{-5}$ M). KM, AKM and RSM, each at a concentration of $5\times10^{-4}$ g/ml, reduced its amplitude (Fig. 5 and Table 2-C). The reducing effects of these antibiotics were restored by washing with normal Krebs solution for approximately 30 min (Fig. 5). The reducing effect on the

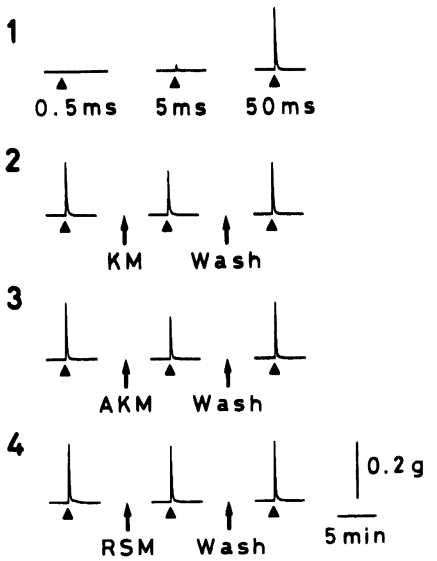


Fig. 3. Effects of kanamycin (KM), bekanamycin (AKM) and ribostamycin (RSM) on the contractile response induced by electrical stimulation in the presence of tetrodotoxin.

1: The preparation, in the presence of tetrodotoxin ($3\times10^{-7}$ M), was stimulated with rectangular pulses (50 volt, 5 Hz) of durations of 0.5, 5, and 50 msec (ms) at the triangular dot, as indicated, for a period of 5 sec. 2—4: The preparation, in the presence of tetrodotoxin ($3\times10^{-7}$ M), was stimulated with rectangular pulses (50 volt, 5 Hz) of 50 msec duration at the triangular dots for a period of 5 sec. 2: Effect of KM, $5\times10^{-4}$ g/ml. 3: Effect of AKM, $5\times10^{-4}$ g/ml. 4: Effect of RSM, $5\times10^{-4}$ g/ml. The left side in 2—4 shows the contractile response in the absence of an agent (KM, AKM or RSM), namely, the control. The middle in 2—4 shows the contractile response in the presence of an agent. Each agent was given 14 min before electrical stimulation (at the arrow mark). The right side in 2—4 shows the contractile response observed 30—40 min after washing with Krebs solution containing tetrodotoxin ($3\times10^{-7}$ M).

amplitude of the contractile response was in the following order: AKM>KM>RSM (Table 2-C).

## DISCUSSION

Electrical stimulation with rectangular pulses of 0.5 msec duration evoked a contractile response.

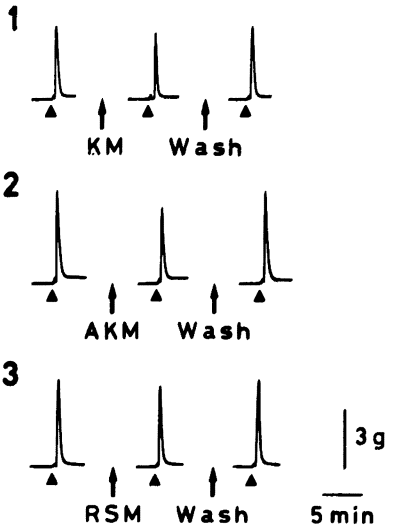


Fig. 4. Effects of kanamycin (KM), bekanamycin (AKM) and ribostamycin (RSM) on the contractile response induced by exogenously added noradrenaline.

1: Effect of KM, $5\times10^{-4}$ g/ml. 2: Effect of AKM, $5\times10^{-4}$ g/ml. 3: Effect of RSM, $5\times10^{-4}$ g/ml. In all experiments, noradrenaline ($1\times10^{-5}$ M) was given at the triangular dot. Each agent (KM, AKM or RSM) was given 14 min before the addition of noradrenaline (at the arrow mark). The left side in 1—3 shows the contractile response in the absence of an agent, namely, the control. The middle in 1—3 shows the contractile response in the presence of an agent. The right side in 1—3 shows the contractile response observed 30 min after washing with normal Krebs solution.

The contractile response is adrenergic in nature, since it is abolished by guanethidine, an adrenergic neuron blocking agent, and tetrodotoxin, a neuron blocker. Hexamethonium, a ganglionic blocker, did not affect the amplitude of the contractile response induced by the electrical stimulation (Fig. 1). Therefore, the contractile response may be due to the release of transmitter from intramural postganglionic sympathetic nerve endings of the preparation as a result of a stimulus effect of the electrical current on the intramural nerves of the preparation (electrical nerve stimulation). On the other hand, electrical stimulation with rectangular pulses of 50

Table 2. Effects of kanamycin, bekanamycin and ribostamycin on the contractile response induced by electrical stimulation, exogenously added noradrenaline and exogenously added adenosine triphosphate

| | Agent | Concentration (g/ml) | N | Amplitude of Contractile response (% of control) |
|---|---|---|---|---|
| A | kanamycin | $5\times10^{-4}$ | 7 | 85± 4*** |
| | bekanamycin | $5\times10^{-4}$ | 7 | 71±10** |
| | ribostamycin | $5\times10^{-4}$ | 7 | 95± 6 |
| B | kanamycin | $5\times10^{-4}$ | 8 | 85± 5*** |
| | bekanamycin | $5\times10^{-4}$ | 8 | 81±12*** |
| | ribostamycin | $5\times10^{-4}$ | 8 | 89± 4** |
| C | kanamycin | $5\times10^{-4}$ | 6 | 73± 5*** |
| | bekanamycin | $5\times10^{-4}$ | 6 | 71± 3*** |
| | ribostamycin | $5\times10^{-4}$ | 6 | 85± 5** |

A: Effect of each agent on the amplitude of contractile response induced by electrical stimulation. The preparation, in the presence of tetrodotoxin ($3\times10^{-7}$ M), was stimulated with rectangular pulses (50 volt, 5 Hz) of 50 msec duration for a period of 5 sec. B: Effect of each agent on the amplitude of contractile response induced by exogenously added noradrenaline ($1\times10^{-5}$ M). C: Effect of each agent on the amplitude of contractile response induced by exogenously added adenosine triphosphate ($5\times10^{-5}$ M). N indicates the number of preparations used. Each value represents the mean ±SD of the amplitudes of contractile responses observed 14 min after the addition of an agent. ** and *** indicate significance differences from the value before the addition of an agent, namely, from the control, at $P<0.01$ and $P<0.001$, respectively.

msec duration in the presence of tetrodotoxin, a neuron blocker, evoked a contractile response (Fig. 3). This result suggests that 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 adenosine triphosphate are simultaneously released from sympathetic nerves in the tissue, and act as co-transmitters[7~9]. Exogenously added noradrenaline and adenoshine triphosphate have been shown to act, respectively, at $\alpha_1$-adrenoceptor and $P_2$-purinoceptor of the muscle in the vas deferens wall, and to mediate the contractile response of the muscle[7~9]. That is to say, they act directly on the muscle in the vas deferens wall.

We then observed the effects of KM, AKM and RSM on the contractile response of the preparation induced by electrical nerve stimulation, electrical muscle stimulation, exogenously added noradrenaline and exogenously added adenosine triphosphate. The highest concentration of KM, AKM and RSM in the blood is in the range of about $1.9\times10^{-5}$ g/ml to $8\times10^{-5}$ g/ml, as already known, when these antibiotics are intramuscularly administrated to a man at the clinical dose[10~18]. However, we have not found any report from clinical point of view concerning the effects of these antibiotics on organs with smooth muscle under the control of the sympathetic nerves. KM ($1\times10^{-5}$ g/ml—$1\times10^{-3}$ g/ml), AKM ($5\times10^{-6}$ g/ml —$1\times10^{-3}$ g/ml) and RSM ($5\times10^{-5}$ g/ml —$1\times10^{-3}$ g/ml) each reduced the amplitude of the contractile response induced by electrical nerve stimulation in a concentration-dependent manner (Table 1). KM, AKM and RSM, each at a concentration of $5\times10^{-4}$ g/ml, reduced,

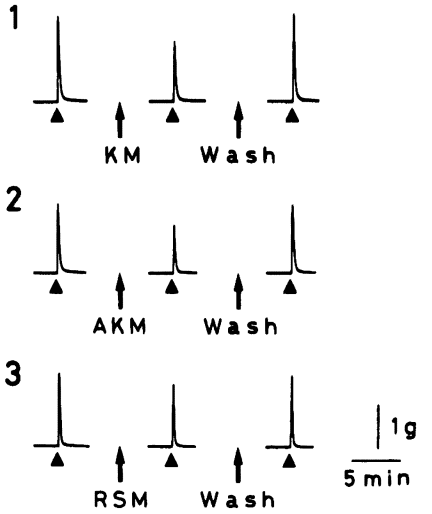


Fig. 5. Effects of kanamycin (KM), bekanamycin (AKM) and ribostamycin (RSM) on the contractile response induced by exogenously added adenosine triphosphate.

1: Effect of KM, $5\times10^{-4}$ g/ml. 2: Effect of AKM, $5\times10^{-4}$ g/ml. 3: Effect of RSM, $5\times10^{-4}$ g/ml. In all experiments, adenosine triphosphate ($5\times10^{-5}$ M) was given at the triangular dot. Each agent (KM, AKM or RSM) was given 14 min before the addition of adenosine triphosphate (at the arrow mark). The left side in 1—3 shows the contractile response in the absence of an agent, namely, the control. The middle in 1—3 shows the contractile response in the presence of each agent. The right side in 1—3 shows the contractile response observed 30 min after washing with normal Krebs solution.

with much approximation, the amplitudes of contractile responses induced by the three treatments, that is, electrical muscle stimulation, exogenously added noradrenaline and exogenously added adenosine triphosphate (Figs. 3~5 and Table 2). However, each of these antibiotics at a concentration of $5\times10^{-4}$ g/ml was exceedingly potent in reducing the amplitude of the contractile response induced by electrical nerve stimulation (Table 1).

From the above-described results, two possible mechanisms might explain the effects of KM, AKM and RSM in reducing the contractile response. One of the two possible mechanisms is supposed to be that these antibiotics directly act on the muscle and reduce its contractile response, since each one of these antibiotics reduced the amplitude of the contractile responses induced by the above three treatments with much approximation. This mechanism is the same as that reported previously concerning the effect of such antibiotics on the organs with smooth muscle[2~5]. The other possibility is that KM, AKM and RSM act on the intramural sympathetic nerves of the vas deferens and reduce the contractile response of the tissue mediated by the release of transmitter from its nerve endings, since all of these antibiotics were exceedingly potent in reducing the amplitude of the contractile response induced by electrical nerve stimulation, even at the lower concentration than $5\times10^{-4}$g/ml, reduced such amplitude significantly (Table 1). It also seems possible that the effects of these antibiotics are greater on the intramural sympathetic nerves than they are on the muscle of the vas deferens. In addition, as shown in Tables 1 and 2, the reduction in the amplitude of the contractile response was in the following order: AKM>KM>RSM.

All these findings may bring about a conclusion that KM, AKM and RSM affect both intramural sympathetic nerves and muscle of the vas deferens. It also seems possible that the effects of these antibiotics are greater on the former than they are on the latter.

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# モルモット輸精管の収縮反応におよぼすaminoglycoside antibioticsの影響

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Aminoglycoside antibioticsに属するkanamycin (KM), bekanamycin (AKM) およびrebostamycin (RSM) 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。電気刺激 (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は，guanethidineやtetrodotoxinにより阻止されたが，hexamethoniumの影響を受けなかった。したがって，輸精管に分布している壁内神経は交感神経の節後線維であることは確かであり，上記の収縮反応は，その神経に対する電流の刺激効果（電気的神経刺激）に基因している。また，tetrodotoxin存在下で，電気刺激 (50 volt, 50 msecの矩形波にて，5 Hzの頻度で5 sec間刺激) により惹起される収縮反応は，電流の輸精管筋に対する直接刺激効果（電気的筋刺激）に基因している。さらに，noradrenalineとadenosine triphosphate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adenosine triphosphateを加えても，輸精管標本は収縮反応を示した。KM ($1\times10^{-5}$ g/ml～$1\times10^{-3}$ g/ml)，AKM ($5\times10^{-6}$ g/ml～$1\times10^{-3}$ g/ml) およびRSM ($5\times10^{-5}$ g/ml～$1\times10^{-3}$ g/ml) は，各々，濃度依存的に電気的神経刺激により惹起される収縮反応の収縮高を減弱させた。$5\times10^{-4}$ g/mlの濃度のKM，AKMおよびRSMは，各々，電気的筋刺激，外来性に与えたnoradrenalineおよび外来性に与えたadenosine triphosphateの3つの処置により惹起される収縮反応の収縮高をほぼ同程度に減弱させた。しかし，同濃度の各抗生剤，KM，AKMおよびRSMは，各々，電気的神経刺激により惹起される収縮反応の収縮高に対して，より明らかな減弱効果を示した。上記の事実より，KM，AKMおよびRSMは，輸精管の壁内交感神経と筋の両者に抑制的影響をおよぼすことが示唆された。その抑制的影響は，後者よりも前者に対して大であった。

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