Inhibitory Effect of Tetrodotoxin on the Contractile Activity of the Guinea-pig Ileum and Distal Colon

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INTRODUCTION

Auerbach's plexus is well known as the intrinsic nervous factors in the intestine and the contractile activity in the intestine is generally considered to be mediated by such intrinsic nervous factors. It is commonly accepted that three different types of neurones in Auerbach's plexus exsist. On the other hand, three different functional nerve types have been also demonstrated in the gastrointestinal tract, i.e., excitatory, inhibitory and non-adrenergic inhibitory nerve.

Recently the burst activity of neurones in the enteric plexus had reported[1)2)]. From the results on the electrical activity of neurones and effects of drugs on them, tonic inhibition and excitatory action of the neurones to cat intestinal smooth muscle had been estimated[1)2)]. When the neurone activity is inhibited or accelerated by drugs, changes in the contractile activity are expected. In this experiment, changes in the contractile activity of intestine on exposure to tetrodotoxin and other drugs which may influence the neurone activity were investigated.

METHODS

Guinea-pig of either sex, weighing between 200g and 500g, were used. The animals were stunned and bled. A suitable length, 2–2.5cm, of the distal colon and the ileum were removed. Since the terminal portion of the ileum has anomalous property[3)], the terminal 10cm of ileum was avoided. Taenia strip preparation, 2–2.5cm in length, as described by Burnstock et al[4)] was also dissected. This preparation may include ganglion neurones of Auerbach's plexus as pointed out by Burnstock et al[4)]. The tubular segment of the colon and the ileum were removed from adult cats and rabbits under alpha-chloralose anaesthesia. The tubular segment of the colon, the ileum or the taenia strip preparation was suspended in an organ bath containing 300ml of the modified Krebs solution bubbled with 95 % O_2 and 5 % CO_2. The temperature was maintained at between 36

and 37°C with a heated water-bath. The free end of the preparation was tied to an mechano-electronic transducer. The tension development was recorded by a conventional apparatus.

The composition of the modified Krebs solution was as follows (mM); NaCl, 120.7; KCl, 5.9; $CaCl_2$, 2.5; $MgCl_2$, 1.2; $NaHCO_3$, 15.5; NaH_2PO_4, 1.2 and glucose 11.5.

The following drugs were used; tetrodotoxin, three kinds of tetrodotoxin were used; crystalline tetrodotoxin which was dissolved in 0.5 % phenol (Sankyo), tetrodotoxin which includes citrate buffer (Sigma) and crystalline tetrodotoxin (Sankyo) which was indicated as RTE-2–3 in this paper. Ganglion chlocking durgs; dibucaine hydrochloride, hexamethonium bromide, lidocaine hydrochloride (Xylocaine) and pentolinium tartrate. Acetylcholine chloride, physostigmine sulfate and cholinergic blocking drugs; atropine sulfate, bevonium methylsulfate, hyoscine-N-butylbromide. Adrenaline chloride and adrenergic blocking drugs; guanethidine sulfate, phentolamine methansulfonate and phenoxybenzamine hydrochloride (Dibenzyline). Junction potential blocking drugs; hyoscine hydrobromide and procaine hydrochloride. All drug concentrations refer to the salts and are given in g/ml.

RESULTS

Effect of tetrodotoxin

Guinea-pig ileum and distal colon

The guinea-pig ileum and distal colon showed marked contractile activity but the activity was irregular in the magnitude as well as in the interval between the successive contractions. In the presence of very low concentration of tetrodotoxin (10^{-9}g/ml), the tone and the magnitude of phasic contraction were not changed. The addition of tetrodotoxin into the bath to give a concentration of 10^{-8}–10^{-6} g/ml was usually associated with a change in tone accompanied by change in magnitude and frequency of phasic contractile activity. By tetrodotoxin 10^{-7}–10^{-6}g/ml (Sigma and Sankyo), the tone of colon preparation was considerably reduced and the magnitude of phasic contraction was also reduced. The relaxation was continued for 30min or more and did not recover during exposure to tetrodotoxin. In some preparations of guinea-pig distal colon, the irregular contraction became more regular and rhythmical in tetrodotoxin solutions (10^{-7}–10^{-6} g/ml). However the frequency of this contraction was lower than that of normal activity. Fig. 1 shows the typical effect of tetrodotoxin on the contractile activity of guinea-pig distal colon.

The effect of tetrodotoxin on the guinea-pig ileum was similar to that on the distal colon, i.e., relaxation was produced and the magnitude and frequency of

the phasic contraction were reduced in high concentrations of tetrodotoxin (10^{-7} -10^{-6}g/ml, Sigma and Sankyo).

The relaxation and the inhibitory effect of RTE-2-3 (10^{-8}–10^{-7}g/ml) on the phasic contraction were also observed in the preparation of guinea-pig ileum and distal colon. The inhibitory action of RTE-2-3 in the distal colon was more weak than that of tetrodotoxin (Sigma and Sankyo).

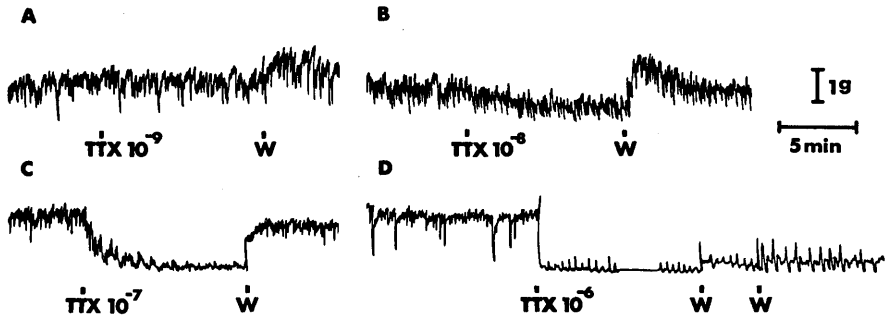

Fig. 1. Effect of teotrodotoxin on the contractile activity of guinea-pig distal colon. Low concentration of tetrodotoxin not produced the inhibitory effect while high concentrations produced the distinct relaxation and inhibitory action. Tetrodotoxin produced by Sigma was used.

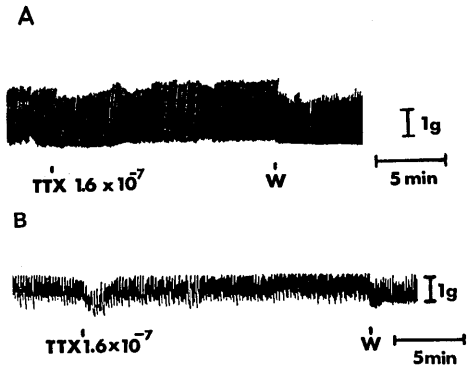

Fig. 2. Effect of tetrodotoxin on the contractile activity of rabbit (A) and cat ileum (B). Both magnitude and frequency of phasic contraction were increased in tetrodotoxin or not changed.

Guinea-pig taenia strip preparation

Effect of tetrodotoxin on the taenia strip preparation was also examined. As pointed out by Burnstock et al[4], this preparation may contain Auerbach's plexus with underlying connective tissue. Usually the taenia strip preparation was not showed rhythmic, phasic contraction but the tone was fluctuated slowly in some preparations. When low concentration of tetrodotoxin (1.6×10^{-8}g/ml) applied, the tone was not changed or slightly increased. In high concentration of tetrodotoxin

(1.6×10^{-7}g/ml), the tone was increased in some preparations. The increase in tone was maintained for 30 min or more during exposure to tetrodotoxin. In some preparations, the initial, temporary decrease in tone was observed but the tone was gradually increased more than the normal level. The effect of RTE-2-3 (10^{-7}g/ml) was also similar.

Cat and rabbit ileum

The spontaneous active contraction of cat and rabbit ileum preparation was observed in normal solution. The contractile activity of cat and rabbit ileum was regular. Most regularity in phasic contraction was observed in the rabbit ileum.

On the preparation of cat ileum, no relaxation or slight increase in tone was observed in the presence of tetrodotoxin 1.6×10^{-7}g/ml. After 10 min on exposure to tetrodotoxin, the frequency of phasic contraction was slightly increased. No relaxant effect of tetrodotoxin 1.6×10^{-7}g/ml was also observed in the preparation of rabbit ileum while the increase in tone was produced in some preparations. The magnitude and frequency of phasic contraction were slightly increased. The effects of tetrodotoxin on the contractile activity of rabbit and cat ileum were shown in Fig. 2.

Cat and rabbit colon

The rabbit colon also showed active phasic conractile activity. When tetrodotoxin 1.6×10^{-7}g/ml applied, both frequency and magnitude of phasic contraction were reduced, that is, the inhibitory effect was seen in contrast with the result of the rabbit ileum. The frequency of phasic contraction of cat colon was low in normal solution. Tetrodotoxin 1.6×10^{-7}g/ml produced the slight increase in the contractile activity, i.e., the frequency of the phasic contraction was increased slightly but the maximum magnitude of phasic contraction was nearly not changed.

Effects of ganglion blocking drugs

Guinea-pig distal colon

When hexamethonium 10^{-8}g/ml applied on the guinea-pig distal colon, the tone was slightly decreased or not changed. Further decrease in tone was observed by addition of hexamethonium 10^{-6}–10^{-5}g/ml. The magnitude and frequency of the phasic contraction were not changed or slightly decreased by high concentrations of hexamethonium. After 10–15 min exposure to hexamethonium 10^{-6} or 10^{-5} g/ml, addition of tetrodotoxin 10^{-7}g/ml produced further large decrease in tone. The magnitude and frequency of phasic contraction were also reduced. After 10–15 min on exposure to tetrodotoxin 10^{-7}g/ml, no further relaxation was observed by addition of hexamethonium 10^{-5}g/ml. Since the magnitude of phasic contraction was already reduced by tetrodotoxin, no further reduction in magnitude of contraction was observed by addition of hexamethonium.

The effect of lidocaine (10^{-5}g/ml) was similar to that of hexamethonium (10^{-5} g/ml). Dibucaine (3×10^{-5}g/ml) produced clear relaxation and the frequency of

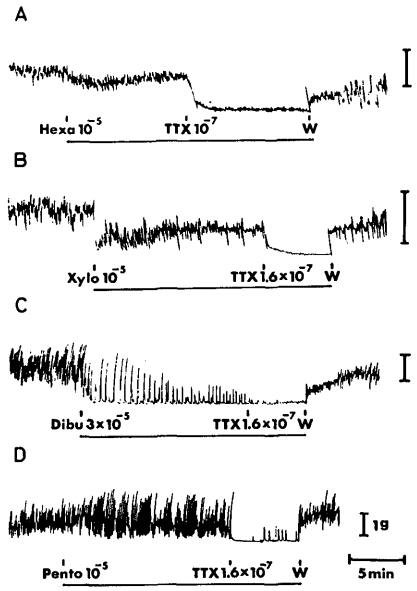

Fig. 3. Effects of ganglion blocking drugs on the contractile activity of guinea-pig distal colon. A, hexamethonium; B, lidocaine (xylocaine); C, dibucaine and D, pentolinium. Underbar in each column indicates the exposure period in each drug. Tetrodotoxin was added into the bath.

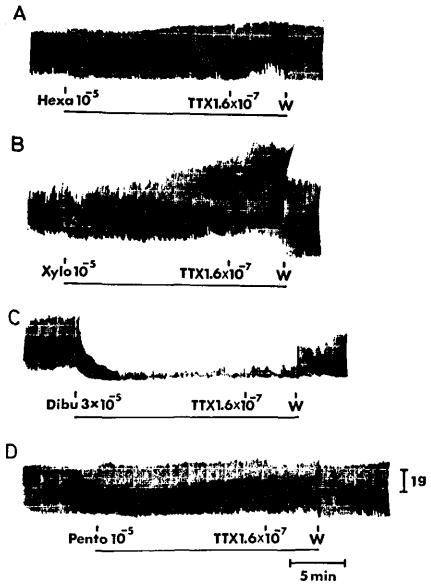

Fig. 4. Effects of ganglion blocking drugs on the contractile activity of rabbit ileum. A, hexamethonium; B, lidocaine (xylocaine); C, dibucaine and D, pentolinium. Underbar in each column indicates the exposure period in each drug. Tetrod otoxin was added into the bath.

phasic contraction was reduced strongly, the magnitude was also reduced considerably. The inhibitory effect of dibucaine on the contractile activity was most distinctly. Pentolinium (10^{-5}g/ml) did not show the inhibitory effect. After the incubation to lidocaine, dibucaine or pentolinium, the further relaxation and inhibitory effect on the contractile activity was observed by tetrodotoxin 1.6×10^{-7} g/ml. Fig. 3 shows the effects of various ganglion blocking drugs on the contractile activity of guinea-pig distal colon.

Rabbit ileum

The effects of hexamethonium and pentolinium on the contractile activity of rabbit ileum were similar. When hexamethonium (10^{-5}g/ml) or pentolinium (10^{-5}g/ml) applied, the magnitude of phasic contraction was increased slightly while no significant change was observed in the frequency of phasic contraction. After 15 min in hexamethonium (10^{-5}g/ml) or pentolinium (10^{-5}g/ml), no considerable change in the contractile activity was recorded by further addition of tetrodotoxin (1.6×10^{-7}g/ml) into these solutions. Slight increase in tone by addition of tetrodotoxin was recorded in hexamethonium on some preparations.

The small excitatory effect of lidocaine (10^{-5}g/ml) was observed on the magnitude of phasic contraction. By additional treatment of tetrodotoxin 1.6×10^{-7}g/ml after 15 min in lidocaine, the continuous increase in the magnitude of contraction was produced. Only dibucaine showed the inhibitory effect, i.e., clear relaxation was produced and both magnitude and frequency of phasic contraction were reduced by dibucaine 3×10^{-5}g/ml. Further treatment of tetrodotoxin 1.6×10^{-7} g/ml in dibucaine, no observal change was recorded. The effects of various ganglion blocking drugs on the contractile activity were shown in Fig. 4.

Acetylcholine and physostigmine

Guinea-pig distal colon

Acetylcholine produced contracture of guinea-pig distal colon. No distinct excitatory effect on the contractile activity was observed by low concentration of acetylcholine (10^{-9}g/ml). Large doses of acetylcholine more than 10^{-9}g/ml increased the tone. In tetrodotoxin 10^{-7}g/ml, contractures were still recorded with application of acetylcholine 10^{-8}–10^{-6}g/ml. The magnitudes of the contractures were not significantly different from those in normal solution.

When physostigmine (10^{-8} and 2×10^{-8}g/ml) successively applied, the tone was gradually increased. In high concentration of physostigmine 10^{-7}g/ml, the contracture was produced. After increasing the tone by physostigmine 2×10^{-8}g/ml, the addition of tetrodotoxin 10^{-7}g/ml produced distinct relaxation and both magnitude and frequency of phasic contraction were also reduced. After exposure 10 min to tetrodotoxin 10^{-7}g/ml, physostigmine 2×10^{-8}g/ml still produced the increase in tone but slightly.

Cholinergic blocking drugs

Guinea-pig distal colon

Three kinds of cholinergic blocking drugs have been employed: atropine sulfate, hyoscine-N-butylbromide and methylsalfate bevonium. All the drugs might modify cholinergic transmission at the ganglionic synapse and/or the neuroeffector junction.

The effects of these drugs on the contractile activity on guinea-pig distal colon were similar, i.e., the decrease in tone, magnitude and frequency of phasic contraction were produced in the concentration 10^{-5}g/ml of atropine, bevonium and 2×10^{-5}g/ml of hyoscine-N. After 15 min incubation in above solutions, the effects of tetrodotoxin 1.6×10^{-7}g/ml were similar, i.e., the supressed contractile activity was more inhibited. Fig. 5 shows the effects of various cholinergic blocking drugs on the contractile activity.

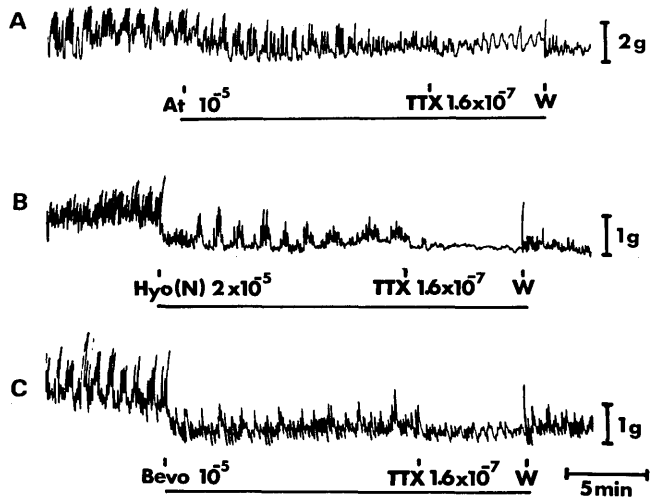

Fig. 5. Effects of cholinergic blocking drugs on the contractile activity of guinea-pig distal colon. A, atropine; B, hyoscine-N and C, bevonium. Underbar in each column indicates the exposure period in each drug. Tetrodotoxin was added into the bath.

Guinea-pig taenia strip preparation

When atropine (10^{-5}g/ml), hyoscine-N (2×10^{-5}g/ml) or bevonium (10^{-5}g/ml) applied, no clear change in tone was recorded. After 15–25 min exposure to above cholinergic blocking drugs, no distinct change in tone was observed by further addition of tetrodotoxin 1.6×10^{-7}g/ml. Tension was still increased fluctuately in tetrodotoxin.

Adrenaline

Guinea-pig distal colon

Adrenaline (10^{-9}–10^{-7}g/ml) produced relaxation in the guinea-pig distal colon.

Small phasic contraction was still presented on the decreased tone level produced by adrenaline 10^{-8}g/ml. In adrenaline 10^{-7}g/ml, the tone decreased steeply and phasic contraction was completely blocked. After the incubation in tetrodotoxin 10^{-7}g/ml during 10–15 min, no observal change in contractile activity was recorded by addition of adrenaline 10^{-9}–10^{-8}g/ml. However small phasic contraction which remained in tetrodotoxin 10^{-7}g/ml was completely abolished by addition of adrenaline 10^{-7}g/ml.

Adrenergic blocking drugs

Guinea-pig distal colon and ileum

Three kinds of adrenergic blocking drugs, guanethidine, phentolamine and phenoxybezamine, were used. The tone was nearly no change or was slightly decreased temporary at inital stage of application of guanethidine 10^{-5}g/ml. In some preparations, the magnitude of phasic contraction was slightly increased. Phentolamine 10^{-5}g/ml produced the increase in the magnitude of phasic contraction but the frequency was slightly reduced. In contrast on the results of guanethidine or phentolamine, distinct relaxation in tone was observed by phenoxybenzamine 10^{-5}g/ml, the inhibitory effect on the phasic contraction was also produced. Tetrodotoxin 1.6×10^{-7}g/ml in the above solutions of the adrenergic blocking drugs induced the inhibitory effect on phasic contraction and tone. In guinea-pig ileum, the magnitude of phasic contraction was increased by guanethidine 10^{-5}g/ml and phentolamine 10^{-5}g/ml. Only phenoxybenzamine 10^{-5}g/ml produced the inhibitory effect on the tone and phasic contraction. Fig. 6 shows the effects of various adrenergic blocking drugs on the contractile activity of guinea-pig distal colon.

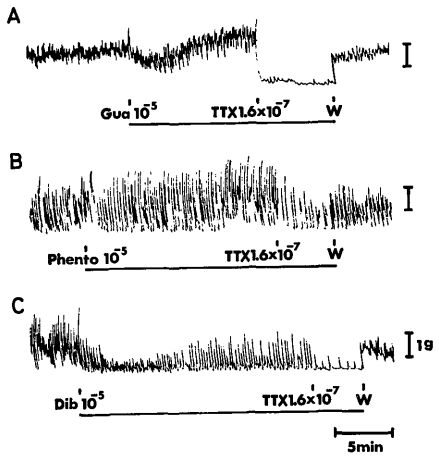

Fig. 6. Effects of adrenergic blocking drugs on the contractile activity of guinea-pig distal colon. A, guanethidine; B, phentolamine and C, phenoxybenzamine (dibenzyline). Underbar in each column indicates the exposure period in each drug. Tetrodotoxin was added into the bath.

Guinea-pig taenia strip preparation

Guanethidine 10^{-5}g/ml or phentolamine 10^{-5}g/ml gave rise the tone. The tone was reduced in the presence of phenoxybenzamine 10^{-5}g/ml, slow fluctuation in tone was also diminished.

Rabbit ileum

In rabbit ileum preparations, guanethidine 10^{-5}g/ml and phentolamine 10^{-5}g/ml increased the magnitude of phasic contraction while the frequency was unchanged. When tetrodotoxin 1.6×10^{-7}g/ml applied after 15 min in guanethidine, slight decrease in the frequency of phasic contraction was produced. Phasic contraction which was potentiated by phentolamine was inhibited strongly by addition of tetrodotoxin in the solution. The effect of phenoxybenzamine 10^{-5}g/ml was different from above results of the drugs, i.e., the slight decrease in tone and the frequency of phasic contraction were observed. No observable change was recorded by addition of tetrodotoxin 1.6×10^{-7}g/ml in phenoxybenzamine.

Junction potential blocking drugs

Guniea-pig distal colon

In guinea-pig distal colon, the excitatory and inhibitory junction potential in the smooth muscle cell membrane had reported[5]. Furness[5] and Bennett[6][7] had reported that the excitatory junction potential was blocked by hyoscine. The blocking action of procaine on the inhibitory junction potential in intestinal smooth muscle cell membrane had also reported[5]. The relationship between the excitatory or inhibitory junction potential and the burst activity of neurones in the intrinsic plexus is unknown. However, it is interesting that junction potential in intestinal smooth muscle was not oberved in Auerbach's plexus-free preparation[6]. This result suggests some relationship between the junction potential and the burst activity of ganglion neurones.

From above reason, junction potential blocking drugs such as hyoscine and procaine were used. When hyoscine 10^{-5}g/ml, excitatory junction potential blocking drug, applied, the tone was slightly decreased. The magnitude of phasic contraction was increased during inital 5–10 min then ıeduced gradually. The inhibitory junction potential blocking drug, procaine 10^{-5}–10^{-4}g/ml, produced the increase in tone then gradually slowed down. The magnitude of phasic contraction was gradually increased.

DISCUSSION

In Auerbach's plexus, at least two functional neuıones are estimated from the result of drugs on them, i.e., excitatory and inhibitory neurone to intestinal smooth muscle[8]. The burst activity from neurones in enteric plexus and some relationship

between activities of neurones and intestinal smooth muscles had also reported[1)2)]. Kosterlitz and Lydon[9)] had emphasized the impulse transmission in the Auerbach's plexus-longitudinal muscle of the guinea-pig ileum. It had also reported that tetrodotoxin blocked the neurone activity of enteric plexus of cat small intestine[8)]. The quantitive distribution of both functional neurones in various parts of the gastrointestinal tract is unknown. However, the contractile activity may increase by the activity of the excitatory neurone and decrease by the inhibitory neurone. When the preparation was exposured to tetrodotoxin, all the activity of both functional neurones might be blocked and changes in the contractile activity might be expected.

In the present experiment, the inhibitory effect of tetrodotoxin on the contractile and spike activity of guinea-pig ileum and distal colon was obtained. In contrast, the contractile activity of the taenia strip preparation of guinea-pig, cat and rabbit ileum were not affected or slightly increased by treatment with tetrodotoxin.

On visceral smooth muscles, the action of tetrodotoxin are somewhat more complex. Some were not affected[9)10)] and some were inhibited[11)]. In taenia coli and vas deferens, it had reported that no effect of tetrodotoxin was observed on spike activity[12)13)]. The membrane potential of the longitudinal muscle cell of guinea-pig jejunum was also not affected by tetrodotoxin[14)]. From above results, it seems that tetrodotoxin has no direct inhibitory action on the electrical activity of intestinal smooth muscle. When the excitation-contraction coupling in smooth muscle cell is normally maintained in tetrodotoxin, the contractile activity might be similar before and after tetrodotoxin.

As above mentioned, in the present experiment, the contractile activity of guinea-pig ileum and distal colon were inhibited by tetrodotoxin. This result might be due to a blocking action on the activity of intrinsic neurone by tetrodotoxin without the effect on intestinal smooth muscle. Furthermore, since the relaxation and the inhibitory effect were produced as total result of blocking the activity of both functional neurones, it suggests that the excitatory neurone in intrinsic plexus are more dominant functionally and/or quantitively.

In contrast, no inhibitory effect was observed in the preparation of guinea-pig taenia strip, cat and rabbit ileum. Even slight increase in tone and the frequency of phasic contraction were seen. As mentioned in the methods and above, the taenia strip preparation may include the ganglion cells in Auerbach's plexus and tetrodotoxin had no direct action on spike activity of taenia coli smooth muscle. The excitatory effect of tetrodotoxin on the phasic contraction of cat and rabbit small intestine had also reported[15)16)]. Therefore the increase in the contractile activity of these preparations may be due to block the intrinsic neurone activity. Since the direction of the effect of tetrodotoxin was opposite, the inhibitory neurones might be dominant in these segments functionally and/or quantitively.

However, changes in the contractile activity were not distinctly as those in guinea-pig ileum and distal colon. The contribution of intrinsic neurones to the contractile activity of these intestinal smooth muscles may be smaller than those of guinea-pig ileum and distal colon.

Ganglion blocking drugs such as hexamethonium, lidocaine and dibucaine had the inhibitory action on the contractile activity of guinea-pig distal colon. However the excitatory effect on the rabbit ileum was observed by these drugs.

Because it is known that lidocaine have been reported to have direct excitatory effect on smooth muscle[17], it could not be neglect to affect directly to smooth muscle. However, in the previous paper[8], it was observed that the burst activity of the intrinsic neurone in the cat small intestine was blocked while the spike activity of longitudinal and circular smooth muscles were increased by lidocaine. The contractile activity of cat circular muscle preparation including the intrinsic plexus was accerelated by lidocaine[15]. As shown in the present result, the responses of rabbit ileum and cat ileum to tetrodotoxin were similar. So lidocaine may block the intrinsic neurone activity of rabbit ileum. If so, the excitatory effect of lidocaine on the contractile activity of rabbit ileum may due to block the neurone activity and partly the direct action.

On the other hand, the inhibitory action of lidocaine on the contractile activity of guinea-pig distal colon was obtained, neverthless lidocaine is considered to have a direct excitatory effect on smooth muscle. This result also suggests that the excitatory neurones are more dominant functionally and/or quantitively. Hexamethonium and dibucaine may have similar effect on the activity of the intrinsic neurones. The excitatory or inhibitory actions by these drugs on the contractile activity of different type intestine might be produced by inverse process.

As discussed in the effect of tetrodotoxin, it seems that the excitatory neurone is dominant in guinea-pig ileum and distal colon. The inhibitory action by tetrodotoxin may be mainly due to block the excitatory neurone. Cholinergic blocking drugs showed also the inhibitory effect on guinea-pig distal colon as same as ganglion blocking drugs. The explanation on this action could be lead from above consideration in which the excitatory neurones are assumed to be cholinergic. As described above, the less contribution and the inhibitory dominant in the intrinsic neurones in taenia strip preparation was discussed. Therefore cholinergic blocking drugs may produce no distinct effect on the contractile activity. In fact, no obvious change in tone of the taenia strip preparation was recorded.

When adrenergic blocking drugs applied, the excitatory effect on the contractile activity of guinea-pig ileum and distal colon are expected from the assumption that inhibitory neurone in the intrinsic plexus is adrenergic. However, it seems that this excitatory action may be small because the excitatory neurone is rather dominant and the inhibitory neurone is minor functionally and/or quantitively. In fact, no distinct effects or slight increase on the contractile activity were observed

by adrenergic blocking drugs such as guanethidine and phentolamine. In rabbit ileum which was assumed to be the inhibitory dominant but less contribution, the contractile activity was potentiated by guanethidine and phentolamine.

Only phenoxybenzamine exhibited the inhibitory action in guinea-pig ileum, distal colon, taenia strip preparation and rabbit ileum. The effect of phenoxybenzamine was not depended the type of the assumed dominant neurones. This results suggests that phenoxydenzamine had both actions, i.e., adrenergic blocking and direct inhibitory effect to smooth muscle.

Finally, the effects of procaine and hyoscine were investigated. As described above, the blocking action of the drugs on the excitatory or inhibitory junction potential in smooth muscle cells had reported[5)6)7)]. In the present experiment, hyoscine decreased the contractile activity and procaine reduced it.

From the present experiment, it is possible to conclude that the excitatory neurone in the intrinsic plexus of guinea-pig ileum and distal colon are more dominant functionally and/or quantitively.

SUMMARY

1. Effects of tetrodotoxin, ganglion blocking drugs, cholinergic blocking drugs, adrenergic blocking drugs and junction potential blocking drugs on the contractile activity of intestine were investigated.
2. Tetrodotoxin produced the distinct relaxation and inhibited the contractile activity of the guinea-pig ileum and distal colon while no inhibition or slight increase in the contractile activity of the guinea-pig taenia strip preparation, cat and rabbit ileum were observed.
3. Ganglion blocking drugs, hexamethonium, lidocaine and dibucaine, showed the inhibitory action on the guinea-pig distal colon. In contrast, potentiation in the contractile activity of the rabbit ileum was observed except dibucaine.
4. All cholinergic blocking drugs produced the inhibitory effect on the guinea-pig distal colon.
5. No distinct change or slight increase effect of adrenergic blocking drugs were observed on the guinea-pig distal colon, except phenoxybenzamine. In rabbit ileum, the potentiation on the contractile activity was observed by adrenergic blocking drugs except phenoxybenzamine.
6. The possibility which excitatory dominant in the intrinsic neurones of guinea-pig ileum and distal colon was discussed.

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