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PHARMACOLOGICAL STUDIES ON SURUGATOXIN, THE TOXIC PRINCIPLE FROM JAPANESE IVORY MOLLUSC *(Babylonia japonica)*

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1 Some pharmacological properties of surugatoxin (SGTX), a purified toxic substance from the Japanese ivory mollusc (*Babylonia japonica*), have been investigated. SGTX (50 nmol/kg i.v.) produced a prolonged fall of blood pressure in anaesthetized cats. This hypotensive effect was neither blocked by atropine and propranolol nor by spinal cord transection.

2 SGTX (37-50 nmol/kg i.v.) inhibited the hypertensive and hypotensive response to 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP) and to electrical stimulation of the splanchnic and vagal nerve, whereas it usually augmented the hypertensive response to adrenaline and to 4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride (McN-A-343) in anaesthetized cats.

3 Close intra-arterial injection of SGTX (6.2-12.3 nmol/kg) to the superior cervical ganglion blocked the contractile response of the nictitating membrane to preganglionic stimulation of cervical sympathetic nerve or injected DMPP, but not to postganglionic stimulation or to injected adrenaline and McN-A-343.

4 SGTX affected neither the indirectly nor the directly stimulated response of the rat isolated phrenic nerve-diaphragm at concentrations less than 12.3 μM.

5 The effect of SGTX on the contractile response to some agonists and on the twitch response to transmural stimulation in the guinea-pig isolated ileum was investigated. At <12.3 μM SGTX did not depress responses to acetylcholine or histamine. The curves for nicotine- and DMPP-induced contractions were shifted to the right and depressed gradually as the concentration of SGTX was increased (12.3 nM-1.23 μM). SGTX partially inhibited the contraction induced by 5-hydroxytryptamine and the transmurally-stimulated twitch response.

6 These results suggest that SGTX has a ganglion-blocking action. The mode of anti-nicotinic action of SGTX in the guinea-pig isolated ileum seems to differ from that of hexamethonium and tetraethylammonium and to resemble more closely that of mecamylamine.

Introduction

In September 1965, food poisoning occurred from ingestion of a carnivorous gastropod, the Japanese ivory mollusc (*Babylonia japonica*), captured in the Shizuoka district of Suruga Bay. The patients complained of visual disorders, mydriasis abdominal distention, dryness of mouth, constipation and vomiting. The poisoning was apparently due to toxins, which were later demonstrated in the mid-gut gland of the mollusc (Kimura & Sugiyama, 1967).

In 1972, Kosuge, Zenda & Ochiai (1972) isolated a toxic principle in crystalline form and determined its chemical structure (molecular formula: $C_{25}H_{26}N_5O_{13}Br \cdot 7H_2O$; mol. wt: 810.53) (Figure 1). The toxin was named surugatoxin (SGTX), after Suruga Bay. SGTX causes a mydriasis with an effective minimum subcutaneous dose of 0.05 μg/g of body weight (in mice), approximately equivalent to that of atropine sulphate.

Hirayama & Gohgi (1970) have previously reported a ganglion-blocking action on the cat superior cervical ganglion of a crude extract (IS-toxin) isolated from the same species of mollusc. The action of pure SGTX has been studied further in the present experiments. We have found that SGTX produced a prolonged hypotension in anaesthetized cats and have obtained evidence that this effect might result from a ganglion-blocking action. In addition, an anti-nicotinic action of SGTX in the guinea-pig isolated ileum has been studied.

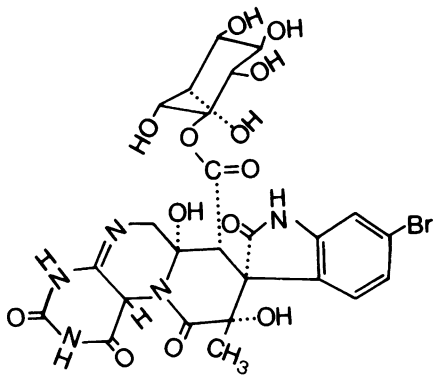

Figure 1 The chemical structure of surugatoxin.

Some accounts of this work have been given to the Japanese Pharmacological Society (Yamada & Hayashi, 1973; Yamada, Mori, Takamura & Hayashi, 1973).

Methods

Measurements of blood pressure and contractile response of nictitating membrane in cats

Cats of either sex weighing between 2.5 and 4.5 kg were anaesthetized with an intraperitoneal injection of a mixture of urethane (500 mg/kg) and chloralose (40 mg/kg). The blood pressure was recorded from the right femoral artery with a pressure transducer and the contractile response of the nictitating membrane was recorded with a force-displacement transducer connected to a multipurpose polygraph (Nihon Kohden RM-150). A force of 6 g was placed on the resting nictitating membrane in each experiment.

Drugs were administered intra-arterially close to the superior cervical ganglion or to the nictitating membrane through a polyethylene cannula inserted into the lingual artery (Trendelenburg, 1956), or intravenously into the femoral vein. Less than 0.2 ml of drug was injected through the cannula, which was flushed immediately with 0.2 ml of 0.9% w/v NaCl solution (saline). All experiments were repeated in 5-9 different animals.

Autonomic nerve stimulation

The nerves (splanchnic, vagal, or superior cervical) were placed on a pair of platinum electrodes kept moist and electrically insulated from the surrounding tissues by warm liquid paraffin. Stimulation was applied with an electrical stimulator (Nihon Kohden MSE-3R) delivering rectangular pulses of submaximal or supramaximal voltage, 1 ms duration, 5 to 30 Hz frequencies for 10 s at 2-3 min intervals. The responses recorded were: an increased and decreased blood pressure during splanchnic and vagal nerve stimulation respectively, and a contraction of the nictitating membrane during pre- and postganglionic cervical sympathetic nerve stimulation. Cats sectioned at C1 of the spinal cord were artificially ventilated and the decrease of blood pressure was prevented with an intravenous injection of $BaCl_2$.

Rat phrenic nerve-diaphragm preparation

The rat phrenic nerve-diaphragm was prepared as described by Bülbring (1946). The preparation was suspended in Tyrode solution in a 30 ml organ bath at 37°C and gassed with oxygen. The responses to electrical stimulation (duration 1 ms, frequency 0.1 Hz, submaximal voltage) were isometrically recorded with a force-displacement transducer connected to a multipurpose polygraph (RM-150).

Construction of the dose-response curves for agonists in the guinea-pig isolated ileum

Male guinea-pigs weighing 300-500 g were killed by a blow on the head and a segment of the ileum was dissected at least 8 cm from the ileocaecal junction. A preparation (2-3 cm, unstretched) was suspended in Tyrode solution in a thermostatically controlled organ bath (10 ml capacity) at 37°C and gassed with oxygen. Responses of the ileum to drugs were recorded on a smoked drum with an isotonic frontal writing lever producing an approximately six-fold magnification and exerting a tension of 1 gram. The preparation was allowed to stabilize for 40 to 50 min before addition of drugs. The composition of Tyrode solution (pH: 7.6-7.8) was (g/l): NaCl, 8.0; KCl, 0.2; $CaCl_2$, 0.2; $MgCl_2$, 0.1; NaH_2PO_4, 0.05; $NaHCO_3$, 1.0; glucose, 1.0. Acetylcholine and histamine were added by means of the cumulative dose method described by van Rossum & Ariëns (1962) and van Rossum (1963) and nicotine, 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP) and 5-hydroxytryptamine by the single dose method. In each experiment the control dose-response curves were constructed for the agonist with five to six doses before and after the construction of the dose-response curves in the presence of SGTX or other antagonists, the second control curve being obtained 20 min after washing out the antagonists. The time of contact with agonist was 30 s and the interval between doses was 10 minutes. SGTX and some other antagonists were added to the organ bath 3-5 min before an addition of the agonist at

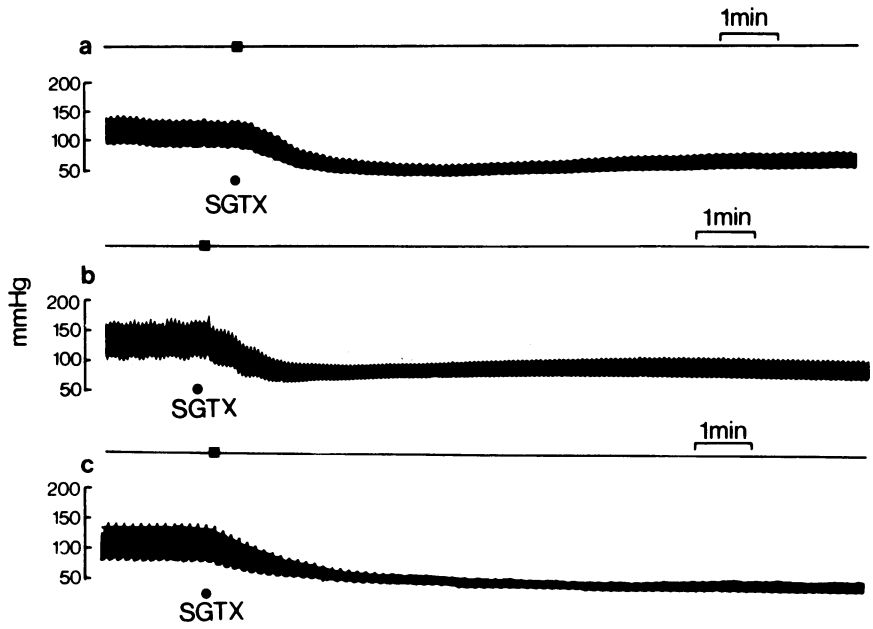

Figure 2 Absence of effect of atropine and propranolol on the hypotensive response to surugatoxin (SGTX, 50 nmol/kg i.v.) in anaesthetized cats. (a) Control, (b) after atropine (2.9 μmol/kg i.v.), (c) after propranolol (3.4 μmol/kg i.v.).

3-5 dose levels. The dose-response curves for the agonists were obtained by plotting the log concentration of agonist used against the contraction expressed as a percentage of the control maximal contraction.

Transmural stimulation

Transmural stimulation was carried out by a technique essentially similar to that described by Paton (1955, 1957). The electrodes were made of platinum and the intraluminal electrode was the anode. Rectangular pulses were used of 0.4 ms duration at a frequency of 0.1 Hz and strength sufficient to give a maximal response. The responses were recorded isometrically.

Measurement of the activity of acetylcholinesterase

The activity of the acetylcholinesterase of the guinea-pig isolated ileum was determined by the method of Guenther & Klaus (1970).

Drugs

The drugs used were obtained from the following sources: acetylcholine chloride (Daiichi), histamine diphosphate (Wako), nicotine tartrate (Wako), 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP) (Aldrich), 5-hydroxytryptamine (Wako), adrenaline hydrochloride (Daiichi), 4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride (McN-A-343) (McNeil Labs., Inc.), hexamethonium chloride (Wako), tetraethylammonium chloride (Wako), mecamylamine hydrochloride (Sigma), atropine sulphate (Merck), propranolol hydrochloride (Sumitomo), morphine hydrochloride (Takeda), cocaine hydrochloride (Sankyo), phenoxybenzamine hydrochloride (Tokyo Kasei), tetrodotoxin (Sankyo), physostigmine sulphate (Merck), urethane (Merck), α-chloralose (Wako). Crystalline SGTX was provided by Prof. Takuo Kosuge of this college. Drugs were dissolved in saline and the injected doses refer to the weights of the salts.

Results

Effects on blood pressure

Intravenous injection of SGTX (37-50 nmol/kg) produced a hypotension of 1-2 h duration in both anaesthetized and spinal cats. The hypotension was not prevented by atropine (2.9 μmol/kg i.v.) or propranolol (3.4 μmol/kg i.v.) (Figure 2).

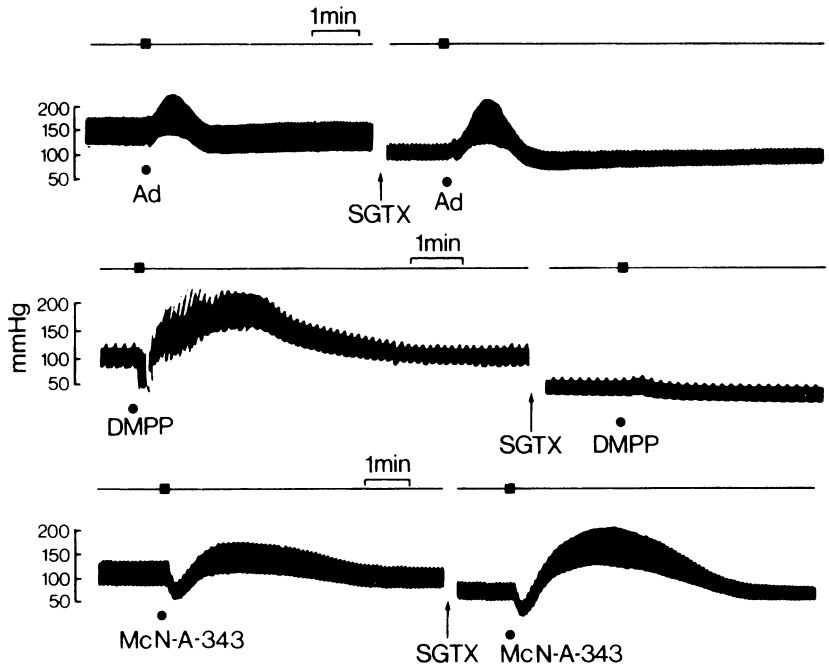

Figure 3 The effects of surugatoxin (SGTX, 50 nmol/kg i.v.) on the hypertensive response in anaesthetized cat to (a) adrenaline (Ad, 22.8 nmol/kg i.v.), (b) 1,1-dimethyl-4-phenylpiperazinium (DMPP, 94.2 nmol/kg i.v.) and (c) McN-A-343 (94.8 nmol/kg i.v.). SGTX was given 5 min before injection of agonists.

SGTX blocked the pressor response to the nicotinic ganglion-stimulant DMPP but usually enhanced the pressor response to adrenaline and the secondary pressor response to the muscarinic ganglion-stimulant McN-A-343 (Figure 3).

SGTX reduced the pressor or depressor response to both splanchnic and vagal nerve stimulation (Figure 4).

Effects on ganglionic transmission

Intravenously-injected SGTX (50 nmol/kg) inhibited the contraction of the nictitating membrane produced by preganglionic stimulation of the cervical sympathetic nerve without affecting the response to postganglionic stimulation of the nerve or to intravenously injected adrenaline (Figure 5). Close-arterial injection of SGTX (6.2-12.3 nmol/kg) to the superior cervical ganglion blocked the response of the nictitating membrane to preganglionic stimulation and to close-arterial injection of DMPP (6.3 nmol/kg), but not that to McN-A-343 (31.6 nmol/kg). Close-arterial injection of SGTX (12.3 nmol/kg) did not affect the response to postganglionic stimulation or adrenaline (injected into the external carotid artery). The effect of SGTX on ganglionic transmission was compared quantitatively with that of hexamethonium and mecamylamine in nine experiments (Figure 6). The molar potency of SGTX was 20 to 30 times greater than that of mecamylamine and approximately 50 times greater than that of hexamethonium.

Neuromuscular transmission

SGTX did not reduce the amplitude of the contractions of the rat isolated diaphragm preparation to the direct (muscle) or indirect (phrenic nerve) stimulation at a concentration of 12.3 μM.

Effects on the guinea-pig isolated ileum

SGTX itself had very little effect on the tone of the ileum at concentrations less than 12.3 μM.

The dose-response curves for acetylcholine and histamine were not affected by SGTX at concentrations below 12.3 μM. Bell-shaped dose-response curves were obtained for nicotine (2.0 μM-2.0 mM) and DMPP (0.94 μM-0.94 mM) as previously described by Trendelenburg (1961)

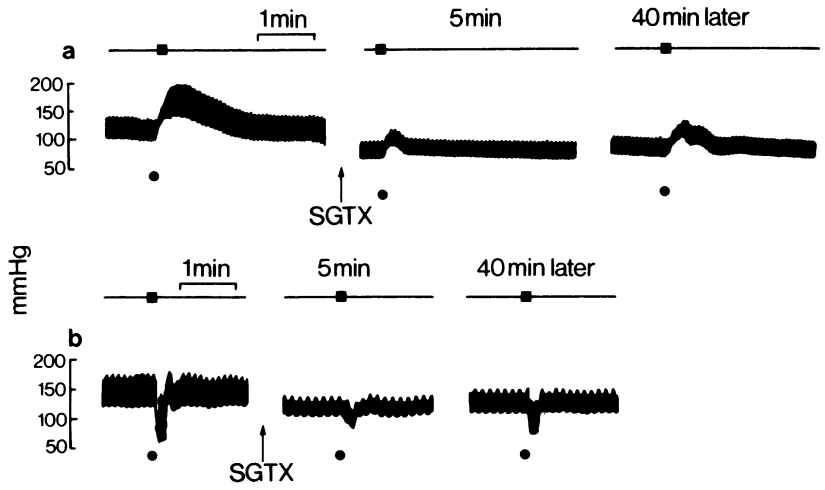

Figure 4 The effects of surugatoxin (SGTX, 50 nmol/kg i.v.) on (a) the hypertensive and (b) hypotensive responses to electrical stimulation of splanchnic and vagal nerves respectively in anaesthetized cats. Dots: supramaximal stimulation for 10 seconds. (a) The response to splanchnic nerve stimulation, (b) the response to vagal nerve stimulation.

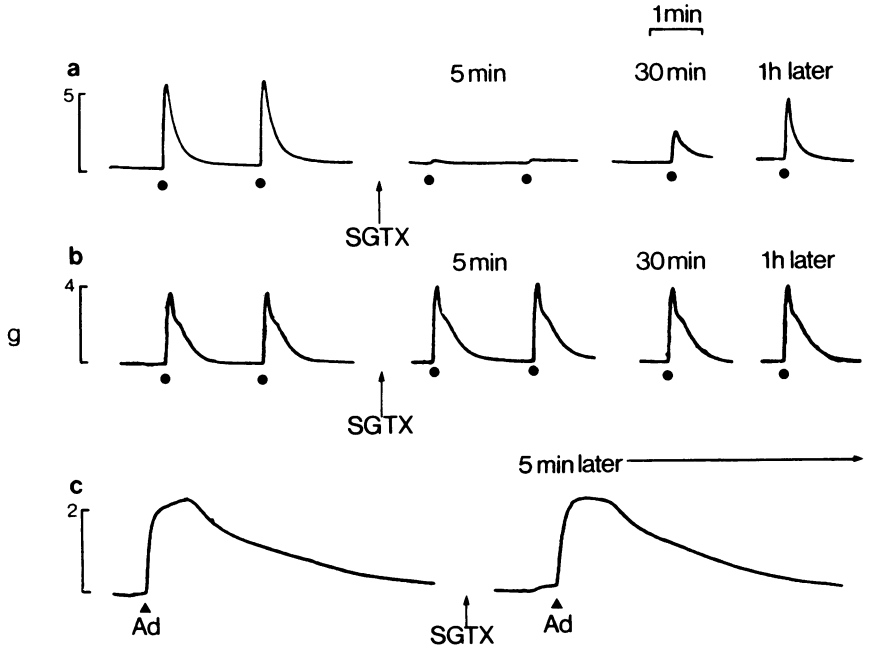

Figure 5 The effects of surugatoxin (SGTX, 50 nmol/kg i.v.) on the contractile responses of the nictitating membrane to (a) preganglionic and (b) postganglionic stimulation of the cervical sympathethic nerve and to (c) injected adrenaline (Ad, 45.5 nmol/kg i.v.). Dots: (a) supramaximal preganglionic and (b) submaximal postganglionic stimulation (30 and 15 Hz) for 10 s at 2 min intervals.

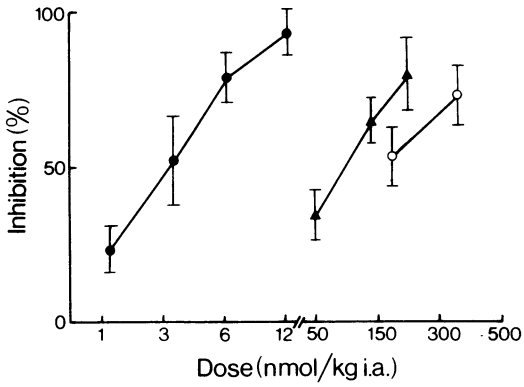

Figure 6 The effects of close-arterial surugatoxin (●), mecamylamine (▲) and hexamethonium (○) on the contractile response of the nictitating membrane to supramaximal preganglionic stimulation of the cervical sympathetic nerve. Ordinates: average % of inhibition (n = 6-9). Abscissae: doses of surugatoxin, hexamethonium and mecamylamine (injected close-arterially to the superior cervical ganglion). Vertical bars indicate s.e. mean.

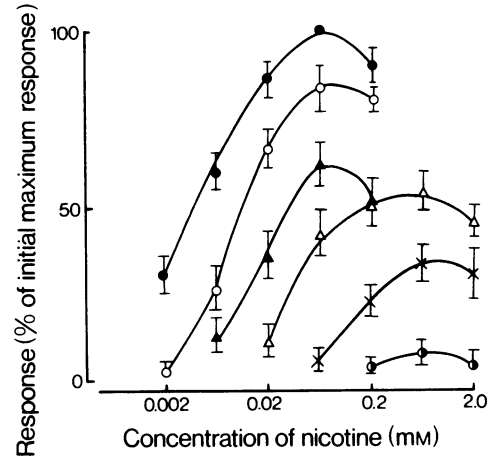

Figure 7 The effects of surugatoxin (SGTX) on the dose-response curves for nicotine in the guinea-pig isolated ileum. (●) Control, in the presence of SGTX, (○) 12.3 nM, (▲) 36.9 nM, (△) 123 nM, (x) 369 nM, (○) 1.23 μM. Each point represents the mean of at least six experiments and vertical bars indicate s.e. mean.

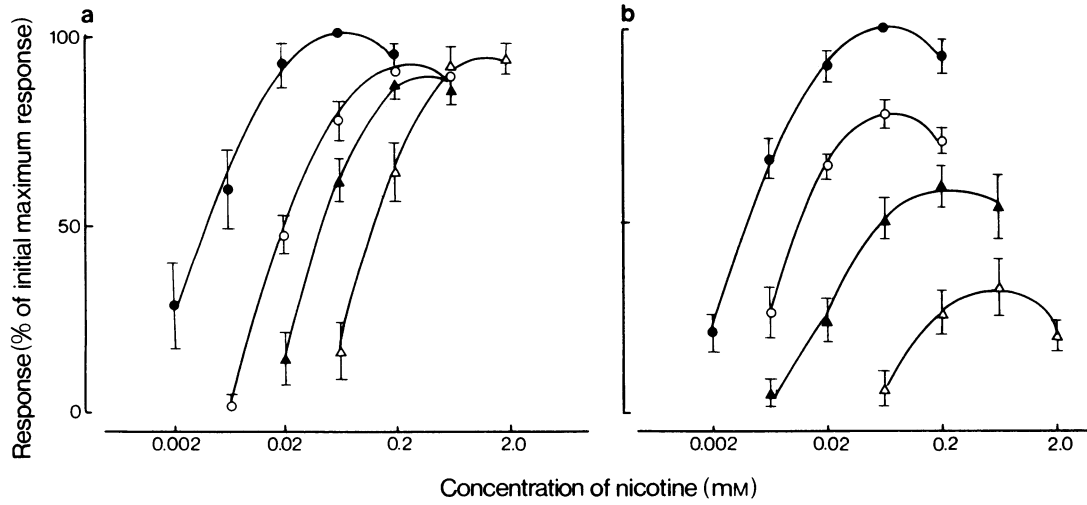

Figure 8 The effects of (a) hexamethonium and (b) mecamylamine on the dose-response curves for nicotine in the guinea-pig isolated ileum. (●) Control; in the presence of (a) hexamethonium (○) 3.66 μM, (▲) 10.98 μM, (△) 36.6 μM and (b) mecamylamine (○) 0.49 μM, (▲) 1.47 μM, (△) 4.9 μM. Each point represents the mean of at least five experiments and vertical bars indicate s.e. mean.

and van Rossum (1962). The dose-response curves for nicotine and DMPP were shifted to the right and depressed gradually as the concentration of SGTX was increased from 12.3 nM to 1.23 μM (Figure 7). The contraction produced by either nicotine or DMPP was reduced to less than 10% of the maximal contraction with a concentration of SGTX of 1.23 μM.

The anti-nicotinic action of SGTX on the guinea-pig isolated ileum was compared with that of hexamethonium, tetraethylammonium and mecamylamine. Hexamethonium (3.66-36.6 μM) and tetraethylammonium (6.0-60.0 μM) shifted the curve for nicotine to the right without depression (Figure 8a), whereas mecamylamine (0.49-4.9 μM) caused a shift to the right with

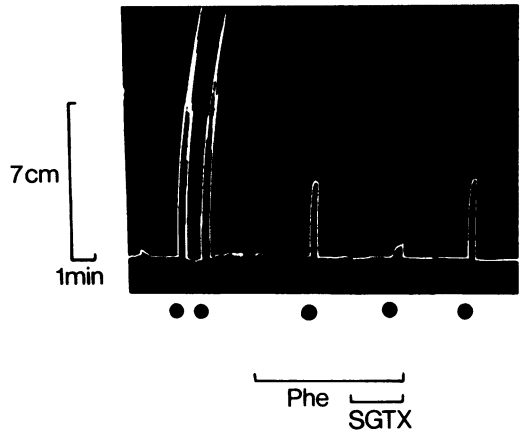

Figure 9 The effect of phenoxybenzamine (Phe) and surugatoxin (SGTX) on the contraction induced by 5-hydroxytryptamine in the guinea-pig isolated ileum. Dots indicate an addition of 5-hydroxytryptamine (1.7 μM) and the bars indicate the presence of phenoxybenzamine (0.31 μM for 30 min) and SGTX (1.23 μM). Time marker: 1 min, vertical calibration: 7 cm on kymograph tracing.

gradual depression resembling SGTX (Figure 8b). These results obtained with hexamethonium and mecamylamine are consistent with those in the guinea-pig isolated jejunum reported by Ariëns (1964). In order to quantify the results pA_2 and pD_2' values for these ganglion-blocking agents were calculated as described by previous workers (Schild, 1949; Ariëns & van Rossum, 1957). pA_2 values for hexamethonium, tetraethylammonium, mecamylamine and SGTX against nicotine were 5.95 ± 0.04 (n = 4), 5.34 ± 0.09 (n = 3), 6.68 (n = 2) and 8.10 (n = 2) respectively. pD_2' values for mecamylamine and SGTX were 5.70 ± 0.05 (n = 4) and 7.00 ± 0.11 (n = 5) (mean ± s.e. mean). The pA_2 value for hexamethonium in the present experiment was reasonably close to that (5.8) obtained by van Rossum (1962). These data indicate that the anti-nicotinic action of SGTX in the guinea-pig isolated ileum is approximately 100 times greater than that of hexamethonium or tetraethylammonium, and 20 to 30 times greater than that of mecamylamine.

SGTX (0.12-1.24 μM) partially (40-50%) inhibited the contraction due to 5-hydroxytryptamine. An attempt was made to find out which of the 5-hydroxytryptamine receptors (D- or M-receptors, Gaddum & Picarelli, 1957) was inhibited by SGTX. As shown in Figure 9, the contraction of the ileum to 5-hydroxytryptamine was almost completely inhibited on the addition of SGTX in the presence of phenoxybenzamine. After washing the preparation, only the inhibition due to SGTX disappeared and that due to phenoxybenzamine still remained. In contrast, after morphine-inhibition, SGTX (1.23 μM) produced little or no further depression of the response to 5-hydroxytryptamine.

Contraction of the ileum induced by transmural

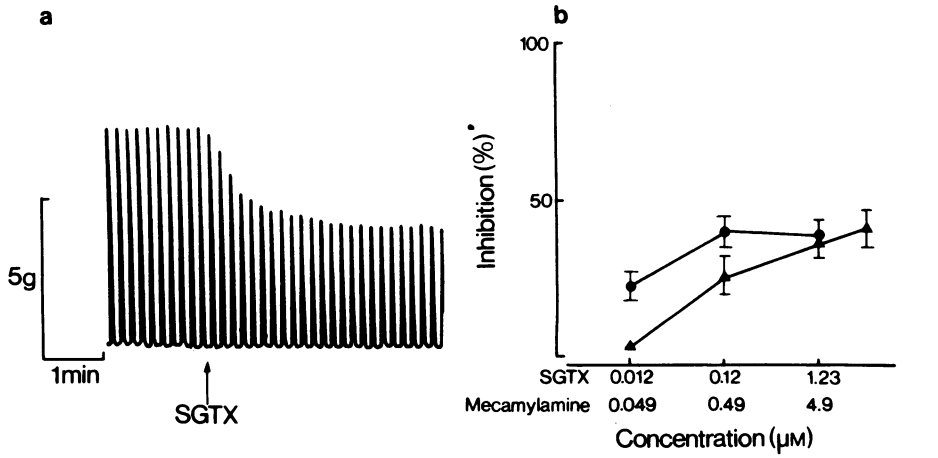

Figure 10 The effect of surugatoxin (SGTX) and mecamylamine on the twitch response to transmural stimulation in the guinea-pig isolated ileum. (a) The inhibitory action of SGTX (123 nM) on the twitch response. Time marker: 1 min, vertical calibration: 5 g. (b) The dose-inhibition curves for SGTX (●) and mecamylamine (▲) on the twitch response. Each point represents the mean of at least five experiments and vertical bars indicate s.e. mean.

electrical stimulation was blocked by morphine (8.0 μM), adenosine (0.15 μM), tetrodotoxin (0.31 μM) and atropine (0.14 μM) and potentiated by physostigmine (0.15 μM). Hexamethonium and tetraethylammonium had very little effect on the response at concentrations less than 36.6 μM. These results accord with previous findings (Paton, 1955, 1957; Scriabine & Peklak, 1970) that contractions of the guinea-pig isolated ileum in response to transmural stimulation involved the excitation of postganglionic cholinergic nerves and the consequent release of acetylcholine. SGTX partially inhibited, by approximately 20-40%, the transmurally induced contractions of the ileum at concentrations of 12.3 nM-1.23 μM. Mecamylamine (0.49-14.7 μM) exerted a similar effect (Figure 10).

SGTX and mecamylamine had no effect on the acetylcholinesterase activity of the ileum at concentrations less than 1.23 μM and 49.0 μM respectively.

Discussion

The experiments with anaesthetized cats indicate that SGTX exerts a ganglion-blocking action. The mechanism of block appears to be similar to that of hexamethonium in that (a) only nicotinic receptors are blocked and (b) blockade is not preceded by ganglionic stimulation. We have not established whether SGTX exerts any prejunctional effect, but this seems unlikely because neuromuscular transmission was not impaired.

In the guinea-pig ileum, SGTX appears to act preferentially upon the intrinsic nerve supply of the ileum rather than on the smooth muscle, since it antagonized the effects of nicotine and DMPP without affecting direct muscle responses to acetylcholine and histamine. Antagonism to nicotine and DMPP may largely result from ganglion-blockade. However, this antagonism did not appear to be strictly competitive in that the maximum responses to nicotine and DMPP were depressed, perhaps resulting from an additional component of activity upon the postganglionic nerves *per se* rather than the nicotinic receptors alone. This is further indicated by (a) partial depression of the response to transmural stimulation and (b) inhibition of the phenoxybenzamine-resistant component of the response to 5-hydroxytryptamine, which has been attributed to stimulation of intramural nerves (Gaddum & Picarelli, 1957). In these respects SGTX differs from hexamethonium and more closely resembles mecamylamine.

Most of the clinical symptoms resulting from ingestion of the mollusc appear to be mediated by ganglion-blockade at various sites; visual disorder and mydriasis, due to ciliary ganglion blockade, dryness of mouth, due to submaxillary and otic ganglion blockade, and constipation and abdominal distention due to blockade of the intrinsic nerve in the intestine.

A ganglion-blocking action of a crude extract from this species has been reported previously by Hirayama & Gohgi (1970). However, the active principle which they used (IS-toxin) appears to be different from SGTX in terms of elemental composition and molecular weight. SGTX has the formula $C_{25}H_{26}N_5O_{13}Br \cdot 7H_2O$ (mol. wt 810.53), whereas the IS-toxin has a formula $C_{22}H_{36}N_4O_{14}Br$. (mol. wt 660) and the chemical structure is unknown. Further, the two toxins are eluted in different fractions from a CM-Sephadex C-25 column. Consequently, there appear to be two separate toxins in this species with similar pharmacological properties.

Structurally, SGTX differs appreciably from other known ganglion-blocking agents. Its potency is 50 to 100 times greater than that of hexamethonium. In these respects, SGTX appears to be of some pharmacological interest as a new type of ganglion-blocking agent.

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