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CENTRAL RESPIRATORY AND CIRCULATORY DEPRESSION CAUSED BY INTRAVASCULAR SAXITOXIN

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1 In cats anaesthetized with pentobarbitone and vagotomized, observations were made on the phrenic nerve action potential and the diaphragm electromyogram (EMG) at constant end-tidal P_{CO_2}. Arterial blood pressure was stabilized by intravenous infusions of noradrenaline.

2 Intravenous administration of saxitoxin (STX) initially abolished respiratory activity in the EMG and caused a slowing of oscillation in the central phrenic neurogram. Additional STX produced apneustic phrenic discharges followed by a progressive loss of nerve action potentials.

3 The inspiratory centre in the medulla oblongata was stimulated electrically to evoke a sustained phrenic nerve discharge. STX, given intravenously, resulted in the elimination of spontaneous nerve activity without interfering with the evoked response.

4 The cephalic intravascular infusion of STX into a carotid or vertebral artery depressed spontaneous respiratory activity while sparing EMG activity evoked by electrical stimulation of the intact phrenic nerve.

5 Spontaneous respiratory discharge in the phrenic nerve was eliminated by smaller doses of STX administered intra-arterially than were required intravenously. In addition, onset of and recovery from neural silence occurred faster following intra-arterial injection of STX.

6 Depressant effects on arterial blood pressure coincided with those on respiration when STX was given intra-arterially.

7 An electrophysiological assay on frog sartorius muscle was used to measure STX in the cerebrospinal fluid. Levels of STX detected were proportional to amounts of the toxin infused intra-arterially.

8 It is concluded that STX exchanges rapidly between blood and brain to bring about central depression and this adds to its peripheral paralytic actions.

Introduction

As late as 1960, it was the general consensus that the paralytic shellfish poison, saxitoxin (STX), acted centrally as well as peripherally to cause respiratory and circulatory failure after systemic injection (Murtha, 1960). Since then, the authors of two major reviews on saxitoxin have vigorously contested the arguments for a central component of toxic action (Kao, 1966; Evans, 1972). Indeed, Evans (1975) concluded that 'The poisons seem unable to pass through the blood brain barrier, so the respiratory centers in the CNS are not affected.' 'Poisons' refers to tetrodotoxin (puffer fish poison) and STX which, despite their molecular dissimilarity, behave alike on excitable membranes to inhibit sodium conductance.

The present study was undertaken to reassess a central component of action in the syndrome of systemic intoxication by STX under optimal experimental conditions permitting spontaneous reversal of effects. We anticipated the possibility of nerve root conduction block simulating a depressant effect of the toxin within the neuraxis. No such block occurred. Our results demonstrated instead that STX exercises a direct central action as a contributing cause of respiratory paralysis and circulatory hypotension. Furthermore, it became evident that STX moves rapidly into and out of the central nervous system along its concentration gradient.

Methods

Experiments were performed on 15 cats of either sex. All the cats were initially anaesthetized with 40 mg/kg pentobarbitone sodium injected intraperitoneally. Three kinds of experiments were undertaken to evaluate functionally a central action of STX.

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(1) Spontaneous electrical discharge in the phrenic nerve was compared with activity in the diaphragm electromyogram (EMG) for the effect of STX administered intravenously. Artificial ventilation was given following the onset of neuromuscular paralysis, and phrenic nerve activity was further observed under constant end-tidal P_{CO_2}. The phrenic nerve on one side was exposed and sectioned low in the neck. The central stump of the nerve was desheathed and laid over a pair of stainless steel electrodes. Phrenic nerve potentials were amplified and integrated with standard signal conditioners and recorded on a Gould rectilinear polygraph. The EMG was recorded without integration from the innervated hemidiaphragm approached through an abdominal incision. End-tidal CO_2 concentration was measured by continuous sampling of tracheal gas through a Beckman infra-red CO_2 analyzer. During artificial ventilation, CO_2 was administered through the respirator in order to maintain the isocapnic condition. The vagus nerves were severed bilaterally at the mid-cervical level in most experiments in order to circumvent a possible blocking action of STX on this reflex pathway that could affect the frequency of breathing. Noradrenaline bitartrate (NA), up to 10 μg/ml in physiological saline, was infused intravenously at the rate needed to keep mean arterial blood pressure at about 100 mmHg. Control of P_{CO_2} and support of the blood pressure were exercised in all of the present experiments. Body temperature was maintained routinely within normal limits by use of a heating lamp.

(2) The inspiratory centre in the medulla oblongata was stimulated electrically as a means of testing the efferent pathway to the phrenic recording electrodes following alteration of spontaneous central respiratory activity by intravenous STX. A bipolar stimulating electrode, approximately 1 mm in diameter and insulated except for its tip, was oriented stereotaxically in the medial reticular formation. A sustained inspiratory discharge was evoked by stimulation with a square-wave pulse of 1 ms duration at 50 Hz delivered by a Grass stimulator through a stimulus isolation unit at current strengths between 50 and 100 μA (4 to 8 V).

(3) STX was infused intra-arterially into the cranial circulation in order selectively to depress the respiratory centre. Differentiation between peripheral and central effects of STX was accomplished by comparing evoked discharge in the diaphragm EMG, obtained by periodic stimulation of the intact phrenic nerve, with the spontaneous respiratory EMG of central origin. STX was infused either into a carotid artery by retrograde catheterization of the lingual branch, or into a vertebral artery by retrograde catheterization of the subclavian artery plus ligation of all other branches. Regardless of the arterial route employed, the occipital-vertebral anastomosis was ligated and the three remaining arteries to the head were clamped in advance. A McDowell vertebral artery clamp was applied below the wings of the atlas when STX was given via the carotid artery. In the case of intravertebral infusion, the thorax was opened and artificial ventilation was administered from the outset. Dependence of the respiratory centre on the single isolated arterial blood supply was demonstrated by brief occlusion of the vessel. This resulted in prompt reversible respiratory failure. The cats were heparinized before receiving the arterial infusions to forestall the formation of obstructive emboli.

Another set of experiments was performed *in vitro* to identify STX in the cerebrospinal fluid (CSF). In each of three cats to which STX was administered intra-arterially and in two cats that received no STX, 1.5 to 2.0 ml of clear CSF was removed from the cisterna magna by direct puncture of the exposed atlanto-occipital membrane. Intracellular recording from frog sartorius muscle fibres *in vitro* was employed for the assay of STX in the CSF samples. STX activity was measured by the reduction in the first derivative with respect to time (dV/dt) of the depolarizing phase of the muscle action potential. This technique has been described previously as a sensitive bioassay for tetrodotoxin (Jaimovich, Venosa, Shrager & Horowicz, 1976). A standard dose-response curve relating the decrease in maximum dV/dt to the bath concentration of STX was initially established with known amounts of STX added to artificial CSF of the following composition (mM): KCl 2.98, NaCl 158, $NaHCO_3$ 24.6, $CaCl_2$ 3.0, $MgCl_2$ 1.33, glucose 0.64 plus albumin at 25 mg/ml. CSF samples drawn from the experimental and control animals were then examined as unknowns to obtain estimates of STX concentration.

STX was kindly supplied by Dr E.J. Schantz. The toxin was dissolved in 0.001 N HCl to an original stock concentration of 500 μg/ml. This stock solution was stored at a temperature below freezing and was thawed occasionally to make diluted secondary stock solutions.

Results

Spontaneous phrenic nerve activity

The effect of intravenous STX on the spontaneous breathing pattern was assessed in vagotomized cats maintained at constant end-tidal P_{CO_2}. The vagotomy served to uncouple frequency control from pulmonary stretch receptor feedback, and the constant P_{CO_2} served to uncouple tidal volume control from chemoreceptor feedback. Figure 1 illustrates the course of events resulting from the cumulative influence of STX. The first dose of STX (3.3 μg/kg) caused motor para-

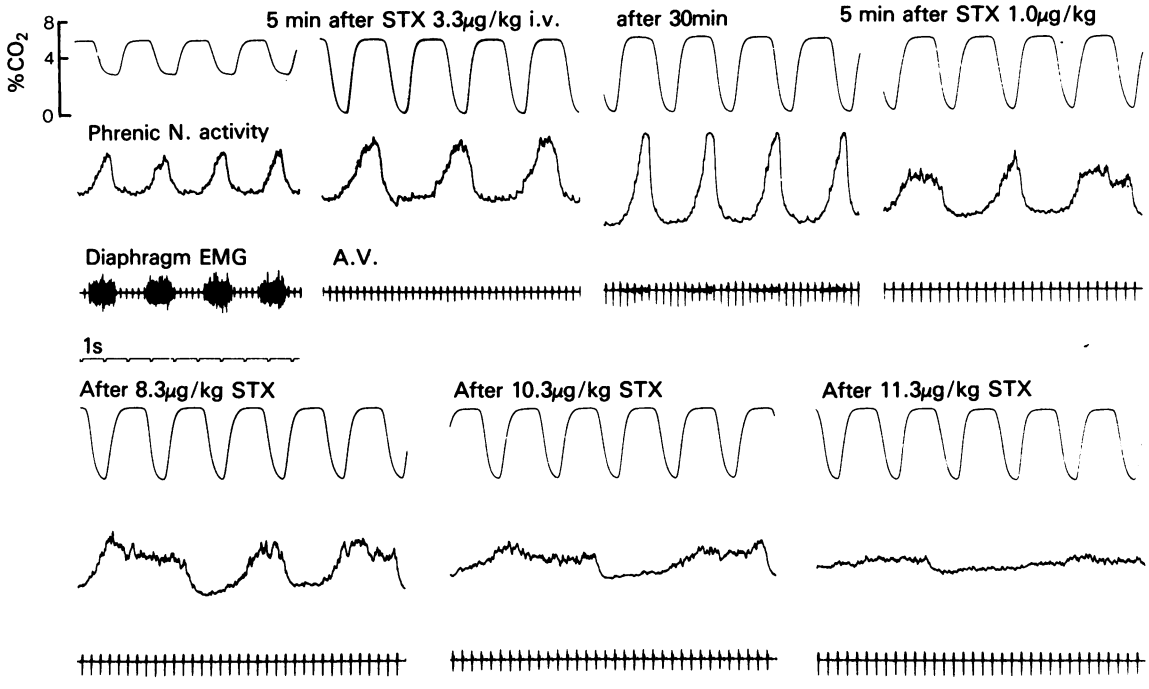

Figure 1 Cumulative effect of intravenous saxitoxin (STX) on the integrated action potential recorded from the central end of the phrenic nerve and on the diaphragm EMG in a vagotomized cat. The uppermost trace shows end-tidal P_{CO_2} (peak level) maintained at about 6% before and during the delivery of artificial ventilation (A.V.). Apneustic cycles are characterized by a prolonged phase of inspiration. Note the electrocardiogram in the EMG trace. Time marker: 1 s.

lysis of respiration, evident as the loss of activity in the diaphragm EMG and making artificial ventilation necessary; rhythmic phrenic discharge persisted but at a slower rate than control. Partial recovery of the EMG with improvement in central activity resulted in the next half hour. Further administration of STX then quickly reinstituted neuromuscular paralysis and converted the central breathing train into a slow, ataxic and apneustic pattern which flattened progressively. A regular cardiac beat was visible throughout as an ECG contaminant in the EMG trace.

Thus, after intravenous administration of STX, central respiratory activity persisted after complete peripheral motor paralysis had been established. However, a slowing of respiration attributable to a central action of the toxin became evident coincidentally with the motor failure. Peripheral inactivation was observed consistently at a dose level of 2 to 4 μg/kg. Doubling the dose of STX was sufficient to disrupt the normal cyclic pattern of respiration, with further dose increments leading ultimately to phrenic nerve silence. Recovery of muscle function was observed regularly on stopping the administration of STX following doses that did not impair phrenic nerve discharge. However, recovery from central respiratory arrest produced by larger intravenous doses of STX occurred less readily despite controlled ventilatory P_{CO_2} and a well maintained cardiovascular status.

Centrally-evoked phrenic nerve discharge

The influence of intravenous STX upon the evoked response to electrical stimulation of the respiratory center in a vagotomized cat is shown in Figure 2. Prior to the administration of the toxin, it was established that a stimulus strength of 4 V was subthreshold and that 6 V was sufficient to elicit a sustained efferent discharge. This response was reproducible upon repeated stimulation. Injection of 2 μg/kg STX intravenously abolished respiratory muscle function and even produced apneustic phrenic nerve activity, yet the centrally evoked response remained essentially unaffected. A total dose of 8 μg/kg STX was required to eliminate spontaneous respiratory discharge. Nonetheless, the stimulus strength of 6 V was still maximally effective while 5 V continued to evoke a submaximal response. End-tidal P_{CO_2} and blood pressure were controlled in routine fashion. In this

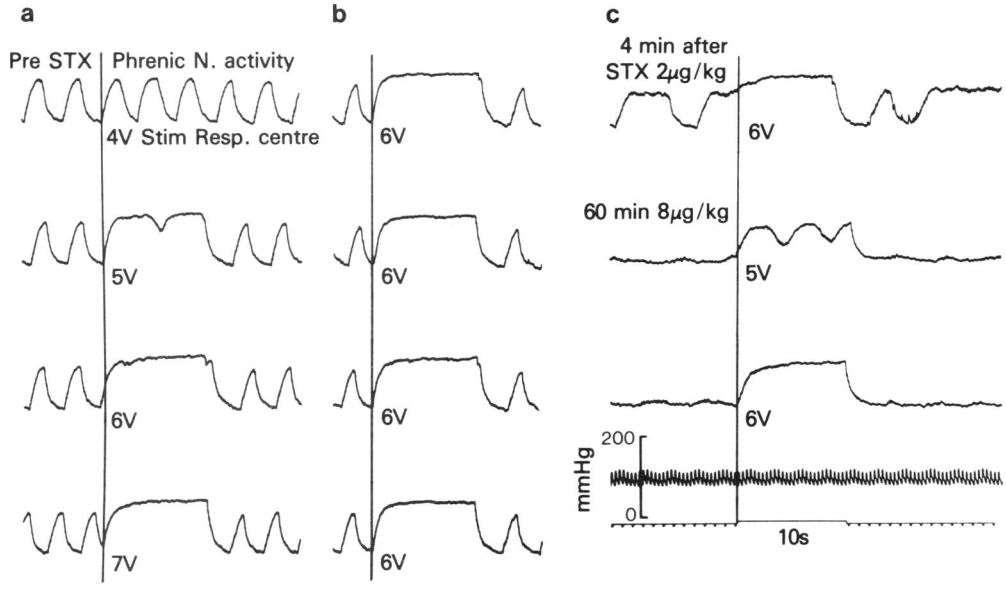

Figure 2 Effect of intravenous saxitoxin (STX) on the phrenic nerve discharge evoked by electrical stimulation (50 Hz) of the respiratory centre in a vagotomized cat at a constant end-tidal P_{CO_2}. (a) Comparison of responses to stimuli of increasing strength (4 to 7 V); (b) repeated tests with 6 V before administration of STX; (c) intravenous STX initially produced apneustic activity which was later suppressed by additional STX while the evoked discharge remained unaffected. Final blood pressure was sustained at 100 mmHg by infusion of noradrenaline. Artificial ventilation was given in the presence of STX. Time marker: 1 s.

animal, considerable recuperation of spontaneous respiratory discharge occurred over the next hour, although the renewed rhythmicity was not entirely regular. STX was then reinstituted at 1 μg/kg intravenously injected at approx. 1 min intervals. The resulting dose-response sequence is shown in Figure 3 at a slow chart speed. Once again, the first prominent effect was a severe depression of spontaneous activity with sparing of evoked activity. Continuing injections of STX finally brought about an attenuation of the evoked response as well. Each injection of STX, at the arrowhead, elicited a prompt fall in arterial blood pressure. Fluctuation of the blood pressure baseline is due to adjustments made in the rate of noradrenaline infusion.

This experiment demonstrates that the rhythm generator of spontaneous respiration is more vulnerable to the depressant action of systemic STX than is the final common pathway for central integration of respiratory output.

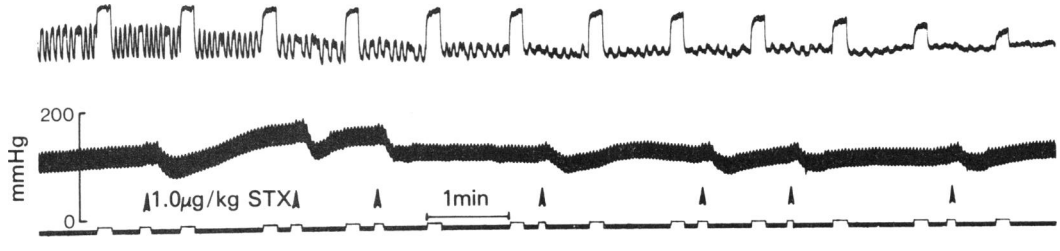

Figure 3 Same cat as in Figure 2, approx. 1 h later, showing recovery of spontaneous respiration with intermittent apneustic breaths in the phrenic neurogram recorded at a slow chart speed. The respiratory centre was stimulated for 10 s at 1 min intervals. Saxitoxin (STX) 1.0 μg/kg i.v., was injected periodically at the arrowheads. Note the early depression of spontaneous phrenic activity followed by an attenuation of the evoked response. Each injection of STX produced a prompt fall in blood pressure; slower fluctuations are due to compensatory adjustments made in the rate of noradrenaline infusion.

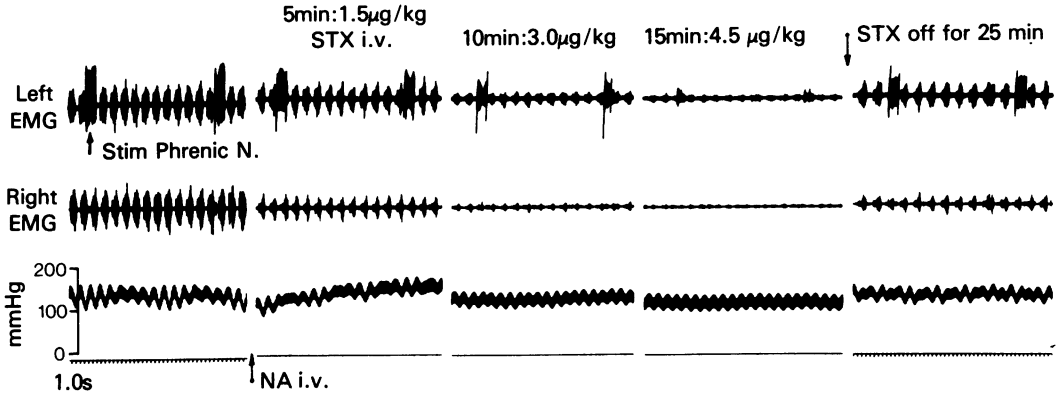

Figure 4 Effect of intravenous infusion of saxitoxin (STX) on the diaphragm EMG recorded bilaterally while the intact left phrenic nerve was stimulated electrically at 50 Hz for 2 s every 30 s in a vagotomized cat on artificial ventilation at constant end-tidal P_{CO_2}. Depression of all EMG components was detectable at 5 min (STX, 1.5 μg/kg) and was essentially complete at 15 min (4.5 μg/kg). Moderate recovery of both spontaneous and evoked activities was evident at 25 min following the end of STX infusion. NA = noradrenaline. Time marker: 1 s.

Cephalic intra-arterial infusion of saxitoxin

STX was delivered preferentially to the brain by infusion into a carotid artery or into a vertebral artery as the only sustaining blood supply to the cranium. Two physiological indicators were employed to reveal a selective central action of STX by the cephalic intra-arterial route of administration. First, the diaphragm EMG was used to monitor both central (spontaneous) respiratory activity and peripheral neuromuscular competence as tested by periodic stimulation of the intact phrenic nerve. It is plain that primary failure of peripheral motor function in response to STX infusion also defeats the expression of a central action;

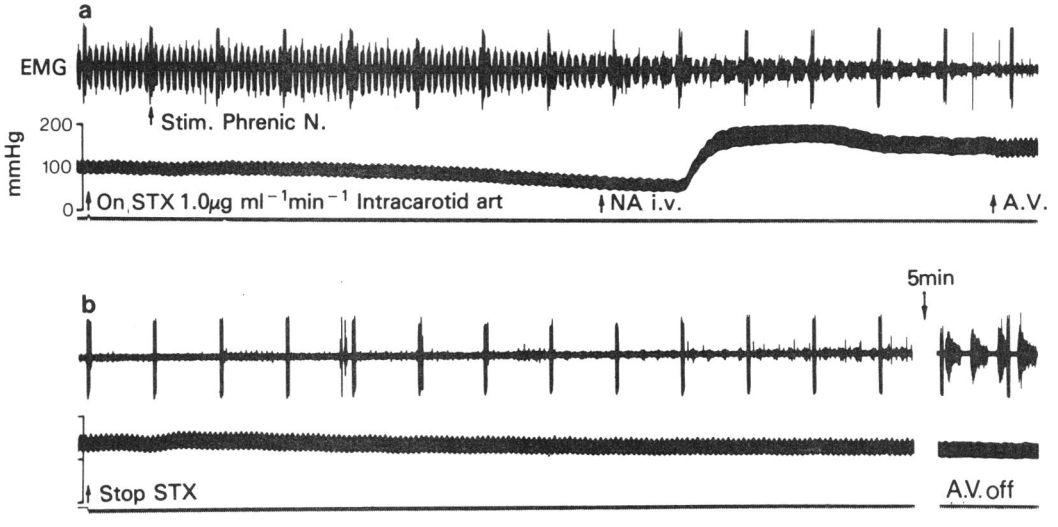

Figure 5 Effect of intracarotid arterial infusion of saxitoxin (STX, 1.0 μg ml^{-1} min^{-1}) upon the diaphragm EMG and the blood pressure in a non-vagotomized cat at constant end-tidal P_{CO_2}. The intact phrenic nerve was stimulated electrically at 50 Hz for 1 s every 30 s. In (a) noradrenaline (NA) infusion was withheld until a decided hypotensive effect was produced by the STX. Artificial ventilation (A.V.) was instituted at the arrow after pronounced respiratory slowing and apneustic activity had developed. STX infusion was stopped when A.V. was started; (b) is the continuation of panel (a). Note the complete loss of spontaneous respiratory activity while the phrenic-evoked response is fully retained. Central recovery began within the next few minutes but the spontaneous EMG still showed an abnormal pattern after a break of 5 min. Time marker: 1 s.

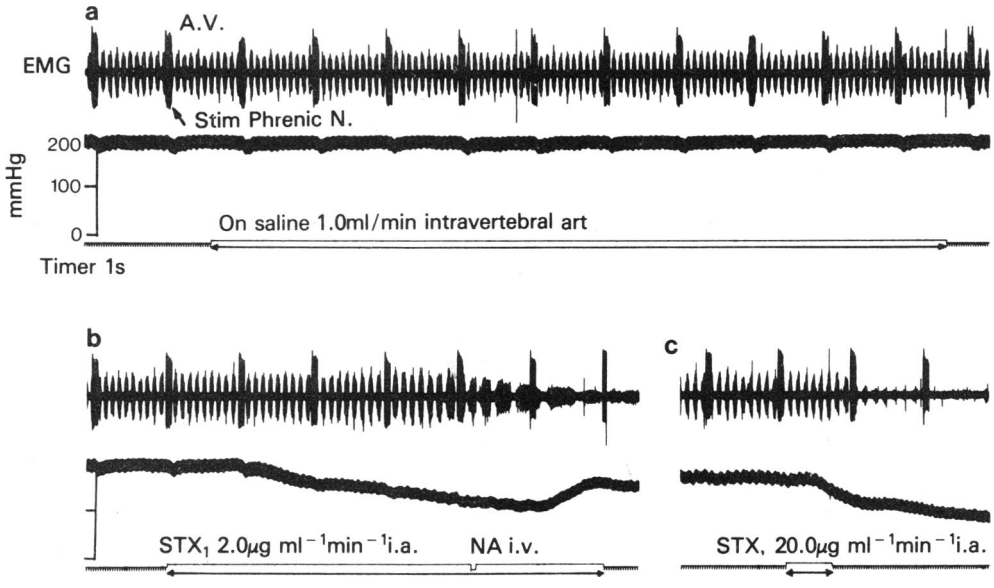

Figure 6 Effect of intravertebral arterial infusion of saxitoxin (STX) upon the diaphragm EMG and blood pressure in a cat with vagus and carotid sinus nerves sectioned. The intact phrenic nerve was stimulated electrically at 50 Hz for 2 s every 30 s. Artificial ventilation (A.V.) was given continuously at a constant end-tidal P_{CO_2}. In (a) physiological saline was infused for control purposes. In (b) intra-arterial infusion of STX (2 μg/ml at 1 ml/min) produced hypotension and central respiratory failure in rapid sequence. Note the circulation time delay in onset of the cardiovascular response to noradrenaline (NA) infusion. In (c), following central recovery with noradrenaline off, the brief infusion of STX at 20 μg/ml at 1 ml/min resulted in a precipitous hypotensive effect and central respiratory failure occurring within seconds thereafter. Note later reduction in the phrenic evoked EMG response following the entry of STX into the general blood circulation. Time marker: 1 s.

however, a restricted change in spontaneous activity while leaving evoked activity unchanged, proves a selective central depressant action. Second, the hypotensive effect of STX was a valuable indicator of central action. Circulation time from the point of infusion to the peripheral resistance vessels is approx. 0.5 min longer than the transport delay to the vasomotor centre. Thus, a shorter latency of onset argues for a central vasodepressor action.

The experiment presented in Figure 4 was designed to show (1) that the EMG response to phrenic nerve stimulation is as vulnerable to intravenous STX as the spontaneous respiratory EMG, and (2) that periodic phrenic nerve stimulation does not modify the susceptibility of spontaneous EMG activity to the peripheral blocking action of STX. Indeed, except for a slight slowing of the spontaneous oscillation indicative of a weak contributing central action, the spontaneous and evoked EMG components were depressed *paripassu* by the STX in the left hemidiaphragm. Recovery also occurred simultaneously in all the EMG components. Thus, it may be concluded that the peripheral depressant influence of STX is non-selective for spontaneous and evoked EMG activities thereby validating the method to prove a selective central action by the intra-arterial administration of STX.

A central depressant effect of intracarotid STX according to the above mentioned criteria is shown in Figure 5. Four features of the test infusion are noteworthy: (1) About one-third the dose normally required by intravenous injection sufficed to depress both respiration and blood pressure. (2) An apneustic pattern appeared as the initial disturbance in the respiration even though the cat was not vagotomized. (3) Spontaneous respiratory activity was abolished selectively. (4) Signs of central recovery were manifested within minutes after the arrest of STX infusion.

Figure 6 illustrates the effect of infusing STX into a vertebral artery in a vagotomized cat. Neurogenic hypertension was present because the carotid sinus nerve had been severed in the procedure of ligating the vertebral-occipital arterial anastomosis. Panel (a) shows that the infusion of saline into the blood stream produced no change. In panel (b), the infusion of 2 μg/ml STX at 1 ml/min rapidly depressed spontaneous breathing and caused a fall in blood pressure. Following complete recovery, in panel (c), 20 μg/ml STX was infused at 1 ml/min for only 18 s. Spon-

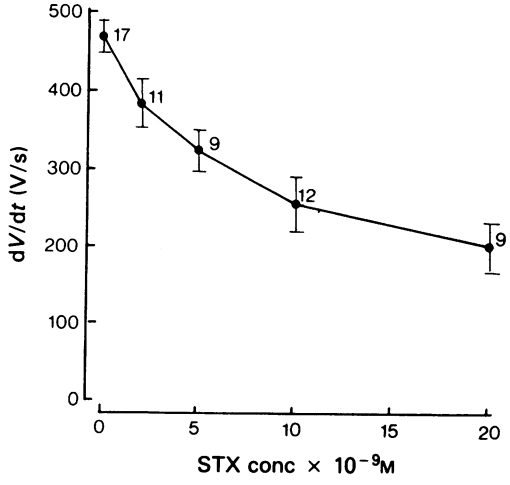

Figure 7 Depression by saxitoxin (STX) of the maximum rate of rise of the depolarizing phase of the action potential in frog sartorius muscle. Intracellular recordings were obtained before and again after exposure for 20 min to known concentrations of STX in a bathing medium of artificial cat CSF. Data points are the means for the number of measurements indicated (vertical lines show s.d.) at the different concentrations of STX.

taneous respiration was largely eliminated within 30 s but the phrenic-evoked response was only slightly attenuated after a minute. It is particularly significant that the onset of vascular hypotension was evident before the end of infusion. A delay of at least 0.5 min preceded the pressor response to intravenous infusion of noradrenaline (see panel b). This means that the elapsed time for the entry of STX into the general circulation includes the additional interval for transport through the cranial vascular circuit. Hence, because of its very short latency, the vasodepressor effect of STX must have originated centrally.

Saxitoxin passage into the cerebrospinal fluid

Electrophysiological behaviour of frog sartorius muscle was first determined in artificial cat CSF. Measurements of dV/dt during depolarization were considered acceptable only from clean microelectrode penetrations that yielded stable resting membrane potentials more negative than −85 mV. A second determination of the excited depolarization rate was made 20 min after replacing the bathing medium with solutions of known STX content. Figure 7 shows the relationship between STX concentration and maximum dV/dt for the depolarizing phase of the action potential. Unequivocal dose-related depression of dV/dt was evident at STX concentrations above 2.0×10^{-9} M.

Samples of CSF from five cats of which two received no STX were assayed for their effect on the frog muscle action potential. Results are presented in Table 1. Muscle fibres exposed to the CSF samples from STX-free animals (numbers 1 and 3) showed no measurable change in the action potential kinetics. By contrast, definite depression in the rate of depolarization was produced by the CSF samples from the cats in which STX was infused intra-arterially. The STX concentrations in these samples, as estimated from the standard dose-response curve shown in Figure 7, were consistent with the amounts of toxin administered.

Table 1 Assay of saxitoxin (STX) in cerebrospinal fluid: depression of rate of membrane depolarization in frog sartorius muscle action potential

	Control		*Experimental*			
Cat No.	*Resting potential* ($-mV$)	*Maximum depolarization* dV/dt (V/s)	*Resting potential* ($-mV$)	*Maximum depolarization* dV/dt (V/s)	*[STX] in CSF*[1] (M)	*Comments*[2]
1	89 ± 2	480 ± 20	89 ± 2	490 ± 21	0	No STX given
2	87 ± 3	490 ± 25	88 ± 5	119 ± 68	2×10^{-8}	12 μg/kg STX. intracarotid artery
3	90 ± 4	490 ± 25	90 ± 3	470 ± 33	5×10^{-10}	No STX given
4	90 ± 4	485 ± 26	88 ± 4	330 ± 57	4×10^{-9}	8 μg/kg STX, intravertebral artery
5	90 ± 2	470 ± 16	89 ± 4	367 ± 51	2.5×10^{-9}	3 μg/kg STX, intravertebral artery

[1] Concentrations of STX estimated from dose-response curve shown in Figure 7.
[2] CSF samples taken while STX being infused terminally in cats 2, 4 and 5. STX determinations made under single blind conditions.

Discussion

Interpretation of the results in favour of a central component of depression caused by systemic STX is based on three decisive functional criteria, namely: (1) change in the character of respiratory output occurring independently of neural and chemical feedback to the control centre, (2) vulnerability of the respiratory rhythm generator while conduction was retained in the efferent neural pathway, (3) differential influence upon central and peripheral functions obtained by intra-arterial STX from the standpoints of dose requirement and response dynamics.

The control of breathing

No mechanism is known to exist by which the rate and/or rhythm of central respiratory discharge can be modified by a peripheral paralytic chemical action in the vagotomized animal maintained at a constant arterial blood CO_2 tension and a normal arterial blood pressure. Hence the conclusion is inescapable that the slowing of phrenic respiratory discharge frequency and the appearance of apneusis (breathholding) resulted from a central action of the STX given intravenously. It is true that phrenic activity persisted after the diaphragm EMG had been eliminated, as emphasized by Evans (1972), but the slowing effect became evident before the EMG was eradicated and only a fractional addition of STX was generally required to produce apneustic respiratory behaviour. The central phenomena cannot be attributed to functional deterioration since the changes in activity were dose-related and reversible. Respiratory slowing associated with the paralytic effect of 'mussel poison' was observed in vagotomized dogs and rabbits many years ago (Prinzmetal, Sommer & Leake, 1932; Kellaway, 1935). The development of apneustic activity has not, however, been described previously following the intravascular administration of STX. Apparently, this manifestation requires greater stability in blood gas and blood pressure levels than were previously available.

Order of central vulnerability to saxitoxin

We have demonstrated in previous work (Borison & McCarthy, 1977) that minute amounts of STX introduced directly into the CSF surrounding the brain stem produced the following sequence of events in the respiration: slowing, apneustic activity, loss of spontaneous function and finally a depression of responsiveness to electrical stimulation of the respiratory centre. If the premise were correct that the blood-brain barrier is impermeable to STX, then these past findings would have little bearing on the mechanisms involved in the systemic effects of STX. However, it was by no means proved that STX does not enter the brain from the blood. Moreover, the present results with intravascular STX bear a remarkable similarity to the effects of STX placed in the CSF. Indeed, the meaningful conclusion to be reached from the two sets of experiments is that regardless of the route by which it is administered, STX is able to depress the neural circuits in the brain stem responsible for respiratory oscillation while sparing the efferent conduction pathways through the spinal cord to the periphery.

Central versus peripheral saxitoxin response dynamics

It was possible to achieve three effects of STX by cephalic intra-arterial infusion not attainable through the intravenous route: (1) selective disruption of respiratory rhythmicity with doses that were ineffective in producing motor paralysis; (2) onset of brainstem depression in a fraction of the whole body circulation time; (3) early recovery of spontaneous respiratory behaviour. These results strongly support the contention that STX readily moves in and out of the central nervous system from and to the blood. It soon became evident to us that slow intra-arterial infusions of STX offered no advantage over intravenous infusions, possibly because the brain does not store the toxin. The best preferential effect on the brain was obtained with a high concentration of STX infused intra-arterially for a short period so as not to reach the systemic paralytic dose. Coupled with fast recovery from the central depression thus induced, it follows that brain tissue comes into rapid equilibrium with its capillary blood concentration of STX. When a sufficiently high level of STX is attained systemically to produce central failure, recovery can only proceed at the pace determined by metabolism and excretion of the toxin because distribution equilibrium has been reached in all compartments and washout from the brain is no longer possible.

Saxitoxin entry into the CSF from the blood

The presence of STX in CSF samples drawn during intra-arterial infusion of the toxin reinforces two of the foregoing contentions, namely that STX is able to cross the blood-brain barrier and that STX moves rapidly in the direction of its concentration gradient. We have no way of knowing whether the intravascular toxin moves into the CSF via the choroid plexus or whether it passes through the brain extracellular fluid on its way to the CSF. Nevertheless, as can be judged from the associated alterations in physiological behaviour, the implication seems strong that the concentration of STX in brain tissue at the time of CSF sampling is at least as high as that found in the CSF.

Saxitoxin on vasomotor control

Although the primary objective of this study was to examine the depressant effects of STX on breathing at a sustained blood pressure level, parallel effects of STX on the vasomotor system became self-evident. For example, the prompt hypotensive response to a subparalytic dose of STX infused into a cranial artery is best explained by a depressant action on the brain-stem vasomotor centre. It is pertinent that STX placed in the CSF caused a rise in blood pressure associated with apneustic breathing followed by a fall in blood pressure associated with respiratory attenuation. However, when STX was infused intra-arterially, this rostral influence was superseded by lower brain stem depression which yielded an arrest of breathing and a precipitous hypotension.

The present experiments indicate that actions of intravascular STX in the brain keep close step with those in the periphery. However, under distribution equilibrium conditions, interference with the motor execution of breathing takes precedence over depression of the respiratory centre. Similarly, central vasomotor depression adds to the more direct influence of STX on peripheral vascular resistance.

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