ON THE EFFECTS OF STRYCHNINE UPON THE MYELINATED NERVE FIBRES OF TOADS

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Strychnine has often been used as a useful instrument for analysing electrical activities of the central nervous system (Bremer and Bonnet, 1949; Brookes and Fuortes, 1952 and others). On the other hand, Tasaki (1949) reported that strychnine produced a change in the shape of the action current of a toad's nerve fibre by lengthening its duration. A similar phenomenon was observed in strychnized nerve trunks of the frog by Fromherz (1933) and Heinbecker and Bartley (1939). It seems probable that such a prolongation of the spike by strychnine is accompanied with changes in the excitability of nerve fibre, just as is observed in veratrine poisoning (Hodler, Stämpfli and Tasaki, 1950; Tasaki, 1949).

In the present experiment the effects of strychnine on various electrical characteristics of myelinated nerve fibres were investigated.

METHODS

Large motor nerve fibres cut off from sciatic-gastrocnemius (or -sartorius) preparations of the toad were used throughout the experiment. The fibre was mounted on two or three separate glass-plates, each brimmed with Ringer fluid (Tasaki, 1939, 1944, 1953). In each pool of Ringer fluid was immersed a non-polarizable electrode of Zn-ZnSO₄-Ringer Agar type, which was connected with the stimulating circuit or with the input of the amplifier, the grid of which was shorted to earth with a resistance of 200 K Ω . Both stimulating and recording were made through one and the same pair of non-polarizable electrodes each being dipped in the pool of Ringer fluid (diagram in fig. 2, 3).

Stimulation was effected by a brief shock from an induction coil, the strength of the shock being controlled by changes in the coil distance. The secondary coil was insulated from the ground, and a shock of about twice the threshold in strength was usually applied to the proximal stump of the nerve through a pair of platinum electrodes. In another series of experiments, rectangular current pulses of 50 msec. in duration were used as stimuli. The recovery curve

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was mapped out by applying two induction shocks, one at the proximal stump of the nerve as a conditioning and the other through a pair of non-polarizable electrodes immersed in pools of Ringer fluid as a test stimulus (diagram in fig. 6).

In order to obtain a "mononodal" action current, the fluid of the distal pool was replaced with a 3 per cent urethane-Ringer solution (Tasaki and Takeuchi, 1941; Tasaki, 1944). Strychnine was applied by replacing the fluid in either pool with strychnine-nitrate Ringer solution of various concentrations.

RESULTS

1) *The shape of the action current and strychnine concentration*

In accordance with Tasaki's finding, it was confirmed in this experiment that the action current was reduced in its spike height and augmented in its duration by strychnine (fig. 1). When the most distal node of nerve fibre in the central pool was within the stump, the effect of strychnine appeared gradually after the replacement of the solution, while, with the node exposed, the effect could be seen in two or three minutes after the administration of a dilute strychnine followed by little further changes. The former slow effect of strychnine may be interpreted as resulted by diffusion of the drug through the perior epineurium. When, however, a strychnine solution of high concentrations (more than 10^{-4} M) was applied to the node exposed to Ringer solution, the spike height decreased slowly, and it finally became very small; but, when, the test solution was washed out by a fresh Ringer solution, the action current recovered a little. Strychnine seems therefore to show two effects: (1) prolongation of spike duration, lasting for long time after washing out the test

solution, and (2) decrease of spike height, being restored partially by washing out the test solution. This pattern represents the direct effect of strychnine on the node of fibre. In the experiment shown in fig. 2 strychnine was applied either to the node of Ranvier or to the myelin sheath. It will be clear from this figure that strychnine acts on the node, but not on the myelin sheath, as was reported with various

FIG. 1. The effect of strychnine upon the shape of the action current in a nerve fibre.

- 1: Both node N_1 and N_2 in normal Ringer solution.
 - 2: N_1 normal, N_2 in a 3.5 per cent urethane-Ringer solution.
 - 3 to 5: N_2 in narcotics, N_1 in a 10^{-3} M strychnine-nitrate-Ringer, 5, 26 and 44 minutes after the replacement of the solution, respectively.
 - 6: 3 minutes after the replacement of N_1 in Ringer solution.
- Time marks: 1 msec. apart.
23° C.

drugs by other workers (Kato, 1934; Tasaki, 1944).

An example of experiment showing the relation of changes in the spike height and its duration at different concentrations of strychnine is given in fig.

3. With increase in the concentration of drug the spike height fell markedly but the duration did not change appreciably.

FIG. 2. Records showing the effect of various concentrations of strychnine upon a node exposed in Ringer solution (A) and upon the myelin sheath (B).

The record G_1 (left column) was obtained with the middle electrode connected to the grid of an amplifier with low input resistance, the two lateral electrodes being grounded. The record G_2 (right column) was secured with the proximal and middle electrodes earthed, leading the remaining electrode to the amplifier. The picture shows a continuous series of experiment.

A. 1: Node N_1 , N_2 , N_3 in normal Ringer solution.

2: N_1 and N_2 normal, N_3 in a 3.5 per cent urethane-Ringer solution.

3 to 6: N_1 normal, N_3 in narcotic, N_2 in strychnine-Ringer solution in the concentration of $2 \cdot 10^{-6}$ M, 10^{-5} M and $2 \cdot 10^{-5}$ M and $2 \cdot 10^{-4}$ M.

7: 3 minutes after the test solution in the middle pool being washed out by fresh Ringer solution.

Time marks: 1 msec. apart. 17° C.

B. The length of the fibre in the middle pool was 0.4 mm. and no node of Ranvier was present.

1: Each pool filled with Ringer.

2: 40 minutes after replacement of Ringer solution in the middle pool with a $2 \cdot 10^{-3}$ M of strychnine.

Time marks: 1 msec. apart. 15° C.

2) Changes in the excitability by various strychnine concentrations

The rheobasic voltage or the threshold of induction shock was found to fall below the normal value when the nerve fibre was treated with low strychnine concentrations (from about 10^{-17} M to 10^{-5} M) and rose when treated with strychnine solutions of high concentrations (10^{-6} M to 10^{-3} M). The results of one experiment are shown in fig. 3 and fig. 4. It is interesting to note that the rheobasic voltage (n) of the node (node N_2 in fig. 3) in Ringer solution was also raised in proportion to the increase in the strychnine concentration of the neighbouring pool (N_1). This effect by strychnine was not modified by the addition of urethane (3%) to the strychnine solution in the neighbouring pool.

FIG. 3. The relation between the concentration of strychnine and the spike height (*h*), spike duration (*d*) and the rheobasic voltage (*s*).

N_1 in the test solution, N_2 in a 3 per cent of urethane-Ringer solution. 16°C .

FIG. 4. The relation of the strychnine concentration to rheobasic voltage of the strychnized node (*s*) and to the neighbouring node (*n*).

The arrow shows the point where the repetitive responses by a single shock stimulation at the stump was obtained. 19°C .

3) Tolerance of the nerve to strychnine

The effect of strychnine on nerve fibres was less marked when its concentration was increased gradually than when it was increased suddenly to the same concentration. This relation can be seen from table 1.

TABLE 1. Changes of the Rheobasic Voltage by Increase in Strychnine Concentration

No. of experiments	Temperature (°C.)	Concentration of strychnine before application of test solution (in M)	Concentration of test solution (in M)	Rheobasic voltage (per cent of normal)
1	16	$2 \cdot 10^{-11}$	$2 \cdot 10^{-9}$	108
2	15	$2 \cdot 10^{-12}$, $2 \cdot 10^{-11}$, $2 \cdot 10^{-10}$	$2 \cdot 10^{-9}$	87
3	16.5	$2 \cdot 10^{-15}$	$2 \cdot 10^{-8}$	92.5
4	17	—	$2 \cdot 10^{-8}$	111
5	18	$2 \cdot 10^{-7}$, $2 \cdot 10^{-5}$	$2 \cdot 10^{-4}$	135(165)
6	18	$2 \cdot 10^{-8}$	$2 \cdot 10^{-4}$	175(230)

Determinations were made 20 minutes after application of the test solution. The values in brackets were obtained after 30 minutes, indicating further increases.

4) The effect of polarization on the threshold and spike height of the strychnized fibre

Both the decreased spike height and the reduced threshold of the weakly strychnized nerve fibre could be restored to the normal value by anodal polarization. On the other hand, when the threshold was raised by a strong strychnization, it could be reduced to the normal value by cathodal polarization, but the decreased spike height was restored to the normal value by anodal polarization. The results of an experiment are summarized in table 2.

TABLE 2. The Strength of the Polarizing Voltage Just Restoring the Decreased Spike Height and Increased Threshold Due to Strychnization to the Normal Value

Stage	Action currents (in monodal)		Thresholds by induction shock	
	Spike height (in %)	Polarizing strengths to compensate to spike height normal (in mV)	Threshold (in %)	Polarizing strengths to compensate thresholds to the normal value (in mV)
Normal	100	0	100	0
After strychnization				
Strychnine concentrations				
$2 \cdot 10^{-8}$ M	89	35	126	-21
$2 \cdot 10^{-7}$ M	89	35	149	-25
$2 \cdot 10^{-6}$ M	84	47	167	-47

The values were obtained in the same fibre. The values after strychnization were obtained 20 minutes after the application of the test solutions.

FIG. 5. The time-course of the strychnine effect on both the rheobasic voltage and spike height of a single nerve fibre. Repetitive responses after a single shock stimulation were obtained at the bar. The curves (s) and (n) indicate the rheobasic change of the strychnized and the neighbouring node and (h) shows the change in spike height. 19° C.

FIG. 6. The effect of strychnine on the recovery curve of nerve fibre. (1): normal Ringer solution; (2): $2 \cdot 10^{-15}$ M, (3): $2 \cdot 10^{-8}$ M. 16.5° C. Inset: another preparation, (1'): normal, (4): $2 \cdot 10^{-5}$ M. 16.5° C. The curves were obtained one after another in numerical order in the figure.

5) The recovery process in the strychnized nerve fibre

The recovery curve in strychnized fibre showed that the relative recovery period in the strychnized nerve fibre was shorter, and the supernormality was greater and longer than the normal, which amounted to 120-130% and persisted for more than 120 msec. (16.5° C.). The effect of strychnine of higher concentration (10^{-8} M) was not so marked as that of lower one (10^{-15} M), and a more concentrated strychnine solution (10^{-5} M) depressed the recovery process to sub-normal. These measurements are summarized in fig. 6.

The recovery curve in the normal nerve fibre, which was mapped out by taking the relative spike height as an index, has no supernormal phase regardless room temperatures (Adrian, 1928). This recovery curve was also obtained in our experiment, but it was hardly influenced by strychnization of the fibre (fig. 7).

FIG. 7. The effect of strychnine on the recovery curve of action currents of nerve fibre.

Abcissae: Response intervals of two nerve responses in msec, Ordinates: Recovery of spike heights in per cents, Full line: the recovery curve in normal at 19.5° C., Dotted line: in normal at 16° C.

The experiment was done as the following: 19.5°, 17° C. in normal, and 24.5°, 16° C. in the test solution. Room temp. 19.5° C.

6) Threshold of constant current evoking repetitive responses in the strychnized fibre and the effect of polarization on them

It is well known that strychnine produces a rhythmic activity in the central

nerve cells (Bremer and others). Considering that the same effect might be obtained in peripheral nerve fibres, experiments were made and it was found that a series of repetitive impulses really occurred by the application of a constant current, two or three times stronger than the rheobase, to strychnized nerves (table 3).

The effect of polarization upon the threshold of constant current evoking repetitive responses (V_r') of a strychnized nerve fibre was compared with that on the same threshold (V_r) of a normal nerve fibre. In the normal fibre the ratio V_r/V_0 (V_0 denotes the rheobase) became smaller by anodal polarization and larger by cathodal one (fig. 9 curve n). The shape of this curve was very similar to that representing the effect of electrotonus on the minimal gradient of a nerve fibre obtained by Tasaki (1950). In the strychnized nerve fibre the anodal polarization had also the same effect (curve s), but under catelectrotonus the value V_r'/V_0 (the threshold for repetitive responses/rheobase) fluctuated between the curve s_1 and s_2 in fig. 8 and 9. The curve s_1 in fig. 9 has almost the same feature as that in the normal fibre. The threshold represented by curve s_2 was very unstable and it may be of some interest to note that the sum of the polarizing voltage and V_r' of the curve s_2 was nearly constant (fig. 8). Since it was difficult to increase the minimal gradient of the strychnized fibre by such weak depolarizations, it seems to suggest that the accommodation of nerve fibres became small by strychnization and they tended merely to respond to the applied current.

It is not surprising that the curve representing V_r/V_0 -polarizing voltage is similar to the effect of the polarization upon the minimal gradient, because V_r/V_0 is inversely proportional to the logarithm of Hill's time-constant of accommodation (Sato, 1952), which means that V_r/V_0 is nearly proportional to the minimal gradient. The results obtained in strychnized nerve fibres are consistent with the fact that a nerve fibre is apt to respond repetitively to constant currents, when its minimal gradient is small (Katz, 1938; Tasaki, 1950; Sato, 1952 and others).

TABLE 3. The Decrease of the Threshold for Repetitive Response by Constant Currents in Strychnized Nerve Fibre

No. of experiments	Stage	Rheobase (V_0) (mV)	Threshold for repetition (V_r) (mV)	V_r/V_0
1	normal $2 \cdot 10^{-6}$ M	31.8-32.4 39.6-40.2	— 120-132	over 10 3.2
2	normal $2 \cdot 10^{-7}$ M	15.2-17.4 25.8-26.4	— 84- 87	over 20 3.25
3	normal $2 \cdot 10^{-8}$ M	31.2-31.6 28 -30	— 78	over 10 2.7
4	normal $2 \cdot 10^{-7}$ M	33 -33.6 64.2-64.8	— 120	over 10 1.85

Nerve fibres under normal condition did not respond repetitively even to constant currents as strong as 300 mV.

FIG. 8

FIG. 8. The effects of polarization on the threshold for repetitive responses by constant currents in strychnized nerve fibre.

Abscisae: Polarizing strengths in mV.

Ordinates: The thresholds for repetitive responses in mV.

Curve (s), (s₁) and (s₂): Strychnized nerve fibre. Dotted squares show fluctuated values.

Curve (n): Normal fibre.

Curve (r) shows the relation between the rheobase and the polarizing strengths in normal fibre. Strychnine concentration $2 \cdot 10^{-5}$ M. 19.5° C.

FIG. 9

FIG. 9. The relation between the ratio V_r'/V_0' and the polarizing strengths in the strychnized nerve fibre. The curves were drawn from the results in fig. 8. The marks in the figure are the same as in fig. 8.

7) Repetitive response of the strychnized nerve fibre to single shock stimulation

As above mentioned, the excitable property of the nerve was so modified by strychnization that it tended to respond repetitively to a stimulation with constant current. At high temperatures (over 20° C.) repetitive responses were often observed at a single shock or even spontaneously, but never at lower temperatures except that the constant current was used.

In fig. 10 A a $2 \cdot 10^{-5}$ M strychnine solution was applied to the node N₂ in the distal pool. The rheobase decreased gradually during the next several

FIG. 10. The repetitive responses after single shock stimulation of the strychnized nerve fibre at the stump.

(A) Strychnine concentration: 10^{-4} M. Strychnization of the fibre at the distal pool. Time marks: 5 msec. apart. 19° C.

(B) $2 \cdot 10^{-4}$ M. 1: normal, 2: distal pool in a 3% urethane-Ringer fluid, 3: proximal pool in $2 \cdot 10^{-4}$ M strychnine. Time marks: 1 msec. apart. 22° C.

(C) Spontaneous discharges by strychnization of the fibre. $2 \cdot 10^{-6}$ M. Time marks: 20 msec. apart. 26° C.

minutes, which finally reached the value of 90% of the initial value, and the same value was maintained for about twenty minutes. At this stage the solution was replaced with a 10^{-4} M strychnine solution. The rheobase began to rise slowly, attaining about 105% of the initial value in the first 15 minutes, 130% in the next 15 minutes and showing no further change (fig. 5). When the rheobase was increasing slowly (see the bar in fig. 5), repetitive responses were obtained from the strychnized node following the stimulation of the stump by a single shock (fig. 10 A). Washing out the test solution by fresh Ringer solution was a more successful means to obtain repetitive responses for a long time. The result in B of fig. 10 was obtained by this procedure.

8) Influence of temperature upon the effect of strychnine on nerve fibres

A. The effect on rheobase

Two kinds of experiments on the temperature effect were performed. First, under different room temperatures the strychnine concentration which caused a fall of rheobase (or threshold) was determined. At temperatures lower than about 17° C. it ranged from 10^{-18} to 10^{-9} M, while at temperatures over 20° C. it was higher than 10^{-7} M, *i.e.* at lower temperatures the curve in fig. 4 shifted towards left and at higher temperatures it did to the right hand side. In table 4 the results of these experiments are summarised.

Secondly, after the strychnine solution was applied to the fibre, the temperature was changed and the change of rheobase was measured. One experiment of this kind is shown in fig. 11 and table 5, in which the temperature was first high and lowered. The rheobase was lower under higher temperatures and became higher under lower temperatures. This is very interesting, because Tasaki found in the normal fibre that the rheobase was raised with increase in temperature. On the other hand, when the temperature was raised from a low degree, the rheobase was difficult to be lowered and maintained at a high level.

B. The effect on recovery process

The recovery process was enhanced at higher temperatures and depressed at lower temperatures. An example of experiments is shown in fig. 12. In this figure the normal recovery curve of the same fibre was also plotted before

No. of experiments	Room temperature (°C)	Concentrations of strychnine solutions (M)	Shifts of rheobase (% of the value before application of test solutions)
1	14.5	$2 \cdot 10^{-18}$ $2 \cdot 10^{-17}$	93% (31') 117% (10')
2	15	$2 \cdot 15^{-15}$	121% (9')
3	16	$2 \cdot 10^{-13}$ $2 \cdot 10^{-11}$	94 % (8') 107 % (16')
4	18	$2 \cdot 10^{-10}$	92.5% (10')
5	18	$2 \cdot 10^{-7}$ $2 \cdot 10^{-5}$	88 % (19') 107 % (23')
6	19	$2 \cdot 10^{-6}$ $2 \cdot 10^{-5}$	87 % (24') 135 % (23')
7	24	$2 \cdot 10^{-7}$	88 % (10')

FIG. 11. The influence of temperature upon the strychnine effect on nerve fibre. The room temperature was lowered during 12 minutes from 24° C. to 17° C. The concentration of strychnine used was about $2 \cdot 10^{-7}$ M. "ON" in the figure means the start of strychnization. Strychnine solution was substituted by normal Ringer solution at "OFF." 16.5° C.

TABLE 5. The Influence of the Lowering of the Room Temperature upon the Strychnine Effects on Nerve Fibres

No. of experiments	Stage	Temperature (°C.)	Rheobasic voltage (mV)
1	Normal	26	37.2-37.8
		18	28.2-28.8
	After strychnization ($2 \cdot 10^{-9}$ M)	26	33-33.6
		16.5	72-73.2
2	Normal	24	34.8-35.4
		16.5	33.6-34.2
	After strychnization ($2 \cdot 10^{-7}$ M)	24	31.2-31.8
		17	37.8-39

The values were obtained about 20 minutes after the modification of the room temperature.

strychnization. This is consistent with the results of Adrian (1928) and Tasaki (1948). The supernormality of the strychnized fibre at a high temperature (26° C.) lasted about 70 msec. Comparing fig. 12 with fig. 6 showing changes in the recovery due to various concentrations of strychnine, we find an interesting coincidence between the result with a low strychnine concentration and that at

FIG. 12. The influence of temperature upon the recovery curve of the strychnized nerve fibre; Strychnine concentration: $2.5 \cdot 10^{-9}$ M.

The experiment was done in the following orders: 18°, 26° C. in the normal Ringer's solution, 26°, 16.5° C. in the test solution.

high temperature. High temperature seems therefore to increase the supernormal phase and shorten the relative refractory period.

DISCUSSION

The present research on the effects of strychnine upon nerve fibres has confirmed the results obtained by Heinbecker and Bartley in nerve trunks (1939). The results of experiments on the effect of strychnine are summarized in table 6, together with the results of the polarization on nerve fibres for comparison. As is shown in table 6 *A*, the threshold of nerve fibres is decreased and the spike height is depressed by low strychnine concentrations, similar by to the effects of the weak depolarization (table 6 *B*). On the other hand, the effects of strychnine on the recovery process, minimal gradient and threshold for repetitive response in the constant current are the same as those of hyperpolarization. It is therefore probable that the effects of strychnine on nerve fibres cannot simply be explained either by its depolarizing or by its hyperpolarizing action. This conclusion is also applicable to the effects of strychnine of higher concentrations, as shown from the comparison of the results in table 6 *A* and *B*.

The remarkable influence of temperature upon the strychnine effects seems to suggest that strychnine has an appreciable effect on the metabolic activity of the nerve.

TABLE 6
(A) The Summarized Strychnine Effects upon the Excitable
Properties of Myelinated Nerve Fibres

1 Strychnine concentrations		2 Threshold	3 Spike height	4 Recovery process	5 Repetition	6 Temperature effect
low	from 10^{-15} M to 10^{-5} M	decrease	depress	accelerate and super- normality increase	occur	accelerate the strychnine effect by low temp.
high	from 10^{-7} M to 10^{-2} M	increase	depress	inhibit	occur	inhibit the strychnine effect by high temp.

(B) The Effect of Polarization upon the Excitable Properties
of Myelinated Nerve Fibres

1 Polarization		2 Threshold	3 Spike height	4 Recovery process	5 Minimal gradient	6 Threshold for repetition
Depolarization	stronger than about 100 mV	increase	depress	inhibit	increase	increase
	lower about 100 mV	decreased	depress	inhibit	increase	increase
Hyperpolarization		increase	increase	accelerate	decrease	decrease

The columns in 2, 3 and 5 are adopted by Tasaki (1944, 1948, 1950), the column in 4 by Maruhashi and Kobayashi and the column 6 by Maruhashi (1955).

As stated above, the enhanced supernormality and the decreased minimal gradient may account for the aptness of the strychnized nerve fibre to repetitive responses, but the problems concerning the under-lying mechanisms are left for future research. It may be pointed out, however, that these effects of strychnine on peripheral nerve fibres may give some clue to the phenomena observed in the strychnized central nervous system.

SUMMARY

1. The effects of strychnine upon the nerve fibres of toads were investigated.
2. Strychnine had little effect on the myelinated portion, while it had marked effects on the node of Ranvier.
3. The rheobasic voltage of the node was decreased by the application of strychnine solutions of lower concentration (from about 10^{-17} M to 10^{-5} M), but was increased by higher strychnine concentrations (more than 10^{-4} M).
4. The rheobase of the node in Ringer solution rose by strychnization of the neighbouring node.
5. Thresholds for repetitive response to constant current was decreased by strychnization of the fibre. The decreased threshold for repetitive response produced by strychnization of the fibre was hardly possible to be restored to the initial value by washing the fibre with fresh Ringer solution.
6. The relative refractory phase of nerve fibres became shorter than in the normal, and the supernormality of the fibre was increased and prolonged by weak strychnization, but the recovery process was depressed by strong strychnization.
7. The strychnine concentration, which was necessary to decrease the rheobase of the fibre, became high by raising the room temperature over 20° C.
8. Repetitive responses due to single shock stimulation were observed in strychnine-treated nerve fibres (from about 10^{-7} M to 10^{-4} M) at temperatures higher than about 20° C.

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