EXPERIMENTAL NEUROLOGY 95, 419–431 (1987)

On the Action of Intravenous Picrotoxin in the Sensorimotor Cortex of the Cat

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Received July 9, 1986; revision received September 15, 1986

The action of topical convulsants, such as strychnine, is not exerted equally on all sets of neurons in the sensorimotor cortex of cats. Small-field neurons near the surface are influenced whereas deeper, wide-field neurons are affected only indirectly. The agent, picrotoxin, was used to test whether or not the deeper neurons are spared the effects of topical convulsants simply because of their location. Picrotoxin, injected intravenously, produced enhancement of the corticofugal reflex discharge evoked by stimulation of any of the four paws and by auditory stimulation. The surface-recorded primary evoked response was also enhanced but only slightly, far less than with topical application. The evoked response in the medial lemniscus was not altered by picrotoxin, but that in the thalamic radiations was enhanced. The drug diazepam, injected intravenously, diminished the enhancements of both the corticofugal reflex discharge and the evoked potential, in some cases reducing the responses to amplitudes smaller than control values. Single-cell recordings in other laboratories have shown that intravenous picrotoxin converts small-field cells to wide-field cells, and that diazepam reverses this effect. The increase in the surface-recorded primary response and the size of the increase in the corticofugal reflex suggest that there is also a direct effect on wide-field neurons or on the pathway leading to them.

INTRODUCTION

Topical strychnine enhances the discharges of small-field or *s*a neurons in the sensorimotor cortex of the α-chloralose-anesthetized cat, but does not

Abbreviations: CF—contralateral forepaw; IF—ipsilateral forepaw; CH—contralateral hind paw; IH—ipsilateral hind paw; *s*a—neuron in forepaw cortex excited by CF stimulation only; *s*b—neuron excited by both CF and IF stimulation; *m*—neuron excited by stimulation of all four paws.

[1] The author thanks Francis J. Clark, Gregory Brandenberg, Arnold L. Towe, and C. Fred Tyner for reading an early draft of this manuscript.

0014-4886/87 $3.00

directly influence the discharges of wide-field or *m* neurons in the same tissue. Rather, the influence on *m* neurons is indirect via the facilitation exerted by local *sa* neurons (9, 16). These effects are exhibited as an enhancement of both the corticofugal reflex discharge and the primary evoked response when both *sa* and *m* neurons are active, i.e., when the contralateral forepaw is stimulated, and no change in either the cortical surface response or the corticofugal reflex when only *m* neurons are active, i.e., when any paw other than the contralateral forepaw is stimulated. Recordings from single *sa* and *m* neurons have confirmed these conclusions derived from the evoked potential recordings.

Based on these results and those of current source density analysis, Towe *et al.* (17) suggested that the effect of topical strychnine is actually on the terminal segments of thalamocortical afferent fibers, and that even the *sa* neurons are influenced indirectly. This hypothesis also explains why there is no change in the latency of the first spike evoked by stimulation of the contralateral forepaw when strychnine is applied to the surface of the cortex.

We wondered if this differential effect of strychnine on the *sa* neurons or their thalamocortical axons was simply due to the proximity of the neurons or the axons to the cortical surface or if there was some biochemical difference between the *sa* and *m* neurons or their respective afferent fibers. Attempts to influence *m* neurons by intravenous injection of strychnine were unsuccessful because, at low doses, it had no effect and could not be titrated because of tachyphylaxis and, at larger doses, it resulted in large and apparently unsystematic variations in potential, precluding clear analysis (unpublished observations).

Harris and Towe (6) found essentially the same effect of bicuculline in the same tissue. In fact, their figures are virtually indistinguishable from those of Towe and Mann (16), though strychnine, in many places within the central nervous system, is a glycine antagonist and bicuculline a GABA antagonist. However, because of its insolubility, bicuculline is not the substance of choice for intravenous studies. Another GABA antagonist and convulsant, picrotoxin, can be administered intravenously without the foregoing disadvantages. Picrotoxin was, therefore, used to determine whether *m* neurons or the pathway to *m* neurons could be influenced directly by convulsants. This paper reports some of the effects of intravenous picrotoxin.

METHODS

Adult cats, anesthetized with α chloralose (50 to 60 mg/kg, i.p.) and paralyzed with decamethonium bromide or gallamine triethiodide (1 ml/40 min, i.v.), were ventilated artificially at 17 to 19 strokes/min, 25 to 38 ml/stroke, parameters selected to maintain end-expiratory CO_2 at a value of 3.5 to 4.0%.

Atelectasis was prevented by blocking the expiratory port of the respirator for two cycles every 5 min. The cat's body temperature was monitored using a rectal thermocouple and maintained at 37.5°C with a DC heating pad under servocontrol. The medullary pyramids were exposed by removing the basioccipital bone and reflecting the dura. One or both anterior cerebral hemispheres were exposed, and immediately covered with polyethylene film to prevent desiccation. The film was removed only during the times when recordings were made.

Bipolar needle stimulating electrodes were inserted into the central footpad of each limb. Stimulation consisted of 0.1-ms pulses of variable amplitude, frequently 25 mA, which is supramaximal for both the corticofugal reflex discharge and the surface primary response. A fire-polished silver wire electrode was used for recording the primary evoked response from the surface of the cerebral cortex in the postcruciate forepaw focus (16). A sharp, stainless-steel electrode, insulated except for the terminal 0.3-mm segment, was inserted into the medullary pyramid ipsilateral to the site of cerebral recording. This produced a good killed-end recording of the corticofugal reflex discharge.

In a few animals, concentric bipolar electrodes were placed stereotaxically into the medial lemniscus and the thalamic radiations in an attempt to "trap" the site of effect of intravenous picrotoxin. Electrodes were aimed at P 1, H −5.4 to −6.0, L 1.2 to 3.0 and at A 11.5, H 10.4, L 5.8 (12) and the final positions were adjusted to maximize the amplitudes of responses evoked by stimulation of the contralateral forepaw. Sites were later confirmed by histological examination to be within the medial lemniscus and thalamic radiations, respectively.

A 0.1% solution of picrotoxin in propylene glycol was used for intravenous administration. Dosages ranged from 150 to 200 μg/kg, values which produce enlargement of receptive fields of sensorimotor cortical neurons (C. F. Tyner, personal communication). Each injection was followed by a saline flush of the cannula to eliminate any drug remaining there. All times are referenced to the moment of completion of the injection. At least 2 h, usually more, were allowed between picrotoxin trials and subsequent control trials.

Recordings were made using two Grass P15B amplifiers, set at 1.5-Hz and 30-kHz half-amplitude frequency response. The output of the amplifiers was led in parallel to Tektronix 565 and 5111 oscilloscopes. A Grass C4 kymograph camera recorded the responses from the face of the 565 oscilloscope for later measurement. Film records were examined on a microfiche reader at approximately 7.5× magnification. For determination of the time integral of the evoked responses, the magnified images were traced and the area enclosed by the response trace and the zero baseline was measured using the HI-PAD digitizing tablet and Bioquant software. Each area was measured

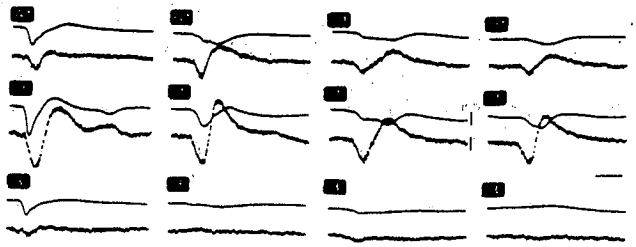

FIG. 1. Effect of intravenous picrotoxin on the cortical surface potential and corticofugal reflex discharge. Responses evoked at the cortical surface and the medullary pyramid are shown in the upper and lower traces, respectively, of each pair for stimulation of the contralateral forepaw (column A), ipsilateral forepaw (column B), contralateral hind paw (column C), and ipsilateral hind paw (column D). Records were made before (row 1) and 8 min after injection of 150 μg/kg picrotoxin (row 2) and 3 min after injection of 70 μg/kg diazepam (row 3). The diazepam was administered 10 min 50 s after treatment with picrotoxin. Paw stimuli consisted of 25-mA, 0.1-ms pulses delivered once per second. Calibrations: 1 mV for surface traces, 200 μV for corticofugal reflexes, and 20 ms for time. Positivity is down in all traces.

three times on each of the trials, usually 10 per condition, and the average was taken. Measurements were made on records from five animals, and they are reported as weighted means. Standard errors are reported as combined standard errors, the square root of the sum of squares of the individual standard errors.

RESULTS

Effect on the Corticofugal Reflex and Primary Response. Intravenous injection of 150 to 200 μg/kg of picrotoxin enhanced the corticofugal reflex discharge evoked by stimulation of each paw. The effect began usually within 3 min and always within 8 min after the end of the injection, gradually increased over the first 8 to 15 min, and then remained fairly constant for about 1 h. Finally, the effect diminished to control levels 1.5 to 2.5 h after injection. Figure 1 shows the records of responses from the postcruciate cortical surface and the ipsilateral medullary pyramid to stimulation of the contralateral forepaw (CF, column A), ipsilateral forepaw (IF, column B), contralateral hind paw (CH, column C), and ipsilateral hind paw (IH, column D). These records were made before (row 1) and 8 min after (row 2) injection of 150 μg/kg. In this case, the CF-evoked corticofugal reflex (positive deflection only) doubled as a result of treatment with picrotoxin, and the same doubling was seen for the corticofugal reflexes evoked by stimulation of the IF, CH, and IH.

The responses recorded at the cortical surface also increased in amplitude as a result of treatment with picrotoxin, but usually the increases were

TABLE I

Time Integrals (Areas) and Amplitudes of Evoked Responses

Response	Surface response				Pyramidal tract response	
	+area[a]	−area[a]	T area[a]	P–p amp[b]	+area[a]	+amp[b]
Contralateral forepaw						
Control	4.75 ± 0.63	2.41 ± 1.14	6.56 ± 0.91	3.23 ± 0.16	4.56 ± 0.48	2.62 ± 0.15
Picrotoxin	4.51 ± 0.20	3.15 ± 0.74	7.66 ± 0.70	4.87 ± 0.21	10.58 ± 0.41	5.78 ± 0.28
Difference	−0.24	0.74	1.10	1.64	6.02	3.16
% Difference	−5.0	30.7	16.8	50.6	131.8	120.5
Contralateral hind paw						
Control	2.56 ± 0.69	0.25 ± 0.23	1.96 ± 0.68	0.47 ± 0.10	3.45 ± 0.82	1.12 ± 0.21
Picrotoxin	2.66 ± 0.99	0.16 ± 0.14	2.82 ± 0.91	0.78 ± 0.17	6.00 ± 1.34	2.08 ± 0.37
Difference	0.10	−0.09	0.86	0.31	2.55	0.96
% Difference	3.8	−34.0	43.5	65.6	74.1	84.7

[a] +area = area under positive-going potential, −area = area under negative-going potential, T area = the sum of +area and −area.

[b] P–p amp = peak-to-peak amplitude, +amp = amplitude of the positive-going potential.

smaller than those for the corticofugal reflex, at least for the CF-evoked response. In Fig. 1, the CF-evoked primary response increased in amplitude by about 60%, the surface response to IF stimulation increased in amplitude by about 75%, and the surface responses to stimulation of CH and IH doubled.

A dosage of 150 to 200 μg/kg picrotoxin usually gave results like those illustrated in Fig. 1. An occasional animal had no corticofugal reflex discharge in response to stimulation off-focus, i.e., in response to stimulation of the IF, CH, or IH (16). In these animals, a corticofugal reflex appeared after picrotoxin administration, and, once present, remained as long as the observations were continued, often for more than 10 h. In addition, corticofugal reflex discharges in response to audible clicks were enhanced by intravenous picrotoxin. In a few animals there was little or no change in the CF-evoked surface primary response, while the corticofugal reflex discharge was enhanced for all inputs.

A dosage smaller than 150 μg/kg usually did not influence either the primary response or the corticofugal reflex discharge. With doses larger than 150 to 200 μg/kg, the corticofugal reflex and the surface primary response were both enhanced to a greater extent than shown in Fig. 1.

Magnitude of the Effects. Table I summarizes measurements of amplitudes and areas of the components of the surface responses and corticofugal

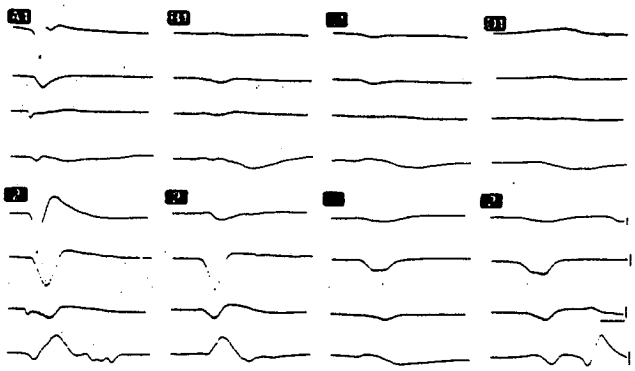

FIG. 2. Effect of intravenous picrotoxin on responses recorded at the cortical surface, medullary pyramid, medial lemniscus, and thalamic radiations. Each set of four traces shows responses in the order above starting with the top trace. Conventions for rows and columns and stimulus parameters are the same as in Fig. 1. Responses in row 2 were observed 20 min after picrotoxin administration. Calibrations: 1.5 mV for surface traces, 500 μV for all others, and 20 ms for time.

reflex discharges for stimulation of the CF and CH. Values shown are the average values (expressed in arbitrary units) plus one standard error for five animals. Picrotoxin increased the area and amplitude of the CF corticofugal reflex by 132% and 120%, respectively. By contrast, the CF primary response increased in area by only 17% and in peak-to-peak amplitude by only 51%. Most of the change in the primary response was due to an increase in the surface negativity; the surface positivity was virtually unchanged.

The surface response to CH stimulation increased in area by 44% and in peak-to-peak amplitude by 66%, whereas the corticofugal reflex discharge increased in area by 74% and in amplitude by 85%. Care must be exercised in comparing the percentage changes for different inputs because the magnitudes of the changes can be quite different. For example, the change in the area of the CF corticofugal reflex was about twice that for the CH corticofugal reflex, but the change in the magnitude of the CF reflex was nearly three times that for the CH reflex. Similarly, the change in the amplitude of the CH corticofugal reflex was two-thirds that for the CF reflex, whereas the percentage change in the CH reflex was less than one-third that for the CF reflex.

Site of Action of Intravenous Picrotoxin. Figure 2 shows records similar to those in Fig. 1 except that responses from the medial lemniscus and thalamic radiations are shown in the third and fourth traces of each set of four. As in Fig. 1, the two upper traces represent the responses from the cortical surface and the medullary pyramids to stimulation of each of the four paws (A to D). Comparison of the third traces in Fig. 2A1 and 2A2 illustrates that the

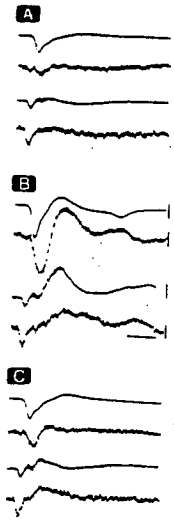

FIG. 3. Effect of intravenous picrotoxin on response recorded at the cortical surface, medullary pyramid, thalamic radiations, and medial lemniscus and evoked by contralateral forepaw stimulation. Each set of four traces shows responses in the order above starting with the top trace. Row A contains control records, row B records 8 min after 150 μg/kg picrotoxin and row C records 3 min after 70 μg/kg diazepam. Diazepam was administered 10 min 50 s after picrotoxin. Stimulus parameters are as in Fig. 1. Calibrations: 500 μV for surface traces, 200 μV for all others, and 20 ms for time.

effect of picrotoxin on the medial lemniscus response was primarily upon the later components. The only deflection in the third trace of Fig. 2A1 and the first deflection in the third trace of Fig. 2A2 reflect the discharge of axons in the medial lemniscus. The later discharge in Fig. 2A2 perhaps reflects postsynaptic effects due to the corticofugal reflex in nearby brain stem structures, including reticular nuclei (16) or more slowly conducting afferent fibers in the lemniscal pathway or some other pathway, whose activity is recruited by the picrotoxin. However, if this component reflects afferent activity, it is unlikely that it accounts for the increase in the corticofugal reflex, because the peak of this discharge followed the peak of that recorded further caudally in the pyramids. The early response, that due to cuneothalamic discharges, was virtually unchanged by picrotoxin.

There was an increase in the corticopetal response recorded from the thalamic radiation (compare the fourth traces in the same sets). The size of this increase varied from animal to animal. In Fig. 2, the increase had a magnitude of about 16%, whereas in the records of Fig. 3, the increase amounted to about 50%. There was also an increase in the later responses recorded from

the electrode in the thalamic radiations, but the origin of these responses is unknown.

Effect of Diazepam on the Picrotoxin-Enhanced Responses. Tyner *et al.* (21) observed that the effects of intravenous picrotoxin could be reversed by administration of diazepam. In Fig. 3, the responses in the cortex, the medullary pyramid, the thalamic radiation, and the medial lemniscus are shown for the control condition (A), 8 min after 150 μg/kg picrotoxin (B), and 3 min after administration of 70 μg/kg diazepam (C), the administration of which was begun 10 min 50 s after the picrotoxin injection. Diazepam reduced the magnitude of the enhanced primary evoked response (compare upper traces in Fig. 3A to C) toward the control condition. The amplitude of the enhanced corticofugal reflex discharge was reduced (compare second traces), but the earlier, small lemniscal discharge was unchanged (see also first deflection in lower traces). In the third traces of Fig. 3A, the first deflection represented thalamocortical activity, whereas the second, because of its timing, probably reflected the corticofugal reflex discharge. Picrotoxin enhanced the second deflection (Fig. 3B), and diazepam reduced it nearly to control values (Fig. 3C). In the lower traces, it is seen that picrotoxin enhanced primarily the late responses in the medial lemniscus recording (those representing postsynaptic responses from nearby brain stem structures), and diazepam reduced them again toward control values.

More often, this dose of diazepam obliterated or nearly obliterated all responses from the cortex or medullary pyramid. Figure 1 shows an example of records in which the administration of the same dose of diazepam reduced the responses in the cortex and pyramids for all inputs to nearly flat traces. Whether or not this represents a simple difference in sensitivity to diazepam of different animals is not clear.

DISCUSSION

In this study, intravenous picrotoxin increased the amplitude and time integral of the corticofugal reflex discharge evoked by stimulation of each of the four paws and by clicks in the ear. The same dose of picrotoxin usually enhanced the surface-recorded primary evoked potential, as reported for much larger doses (2, 8). The response evoked by CF stimulation in the thalamic radiations was enhanced by picrotoxin, whereas that evoked in the medial lemniscus was essentially unchanged.

Sets of Neurons in Postcruciate Cortex. In the cat, the corticofugal reflex discharge reflects the discharge of pyramidal tract neurons, the majority of which are *m* neurons (18, 20). In observing the corticofugal reflex, we are observing the behavior of about half of the *m*-neuron population, with little *s*a contamination. *m* neurons respond to stimulation of all four paws, to

light, sound, and visceral nerve stimulation, explaining the existence of the corticofugal reflex for such a wide range of inputs.

The primary evoked response, on the other hand, reflects the discharges of both *sa* and *m* neurons, each type making a contribution weighted by its average distance from the recording electrode at the cortical surface (14). Stimulation of the CF excites both *sa* and *m* neurons, but *sa* neurons contribute most to the response at the surface because they lie closer to the recording electrode and they exist in large numbers (15, 18, 20). In contrast, stimulation of the IF, CH, or IH excites only *m* neurons, producing a surface-recorded response which is smaller than that for CF stimulation.

The *m* neurons receive a thalamocortical input separate from that projecting to *sa* neurons. All inputs except that from the CF produce the same number of spikes per discharge in *m* neurons, a property Towe has termed coadunate behavior (20). The CF input produces either equal, more, or fewer spikes per discharge, depending on whether the particular neuron receives no effect, facilitation, or inhibition from local *sa* neurons.

Sets of Neurons Influenced by Intravenous Picrotoxin. Intravenous picrotoxin could influence either *sa* or *m* neurons directly, or it could change their interactions with each other, or it could influence subcortical pathways leading to them. Both picrotoxin and naloxone, administered intravenously, produce a shift in the receptive fields of neurons in sensorimotor cortex from *sa* responsiveness to *m* responsiveness, i.e., neurons formerly responsive only to stimulation of the CF begin to respond to stimulation of all four paws [(13, C. F. Tyner, personal communication]. On the other hand, *m* neurons suffer no change in the latency of the first spike in responses to stimulation of any paw, but there was a decrease in the threshold and an increase in spikes per discharge for off-focus inputs (C. F. Tyner, personal communication). Batuev *et al.* (1) examined the effect of electrophoretically administered picrotoxin on receptive fields of neurons in this same area of cortex and found substantial increases in receptive field sizes. They did not employ the *sa* and *m* classification scheme, but it is likely that they studied only *sa* neurons, because they used barbiturate-anesthetized animals (5). Apparently, only the CF was stimulated in their experiments, making *sa* to *m* conversions unobservable.

Picrotoxin could convert *sa* to *m* neurons by changing an inhibitory influence from *m* neurons onto *sa* neurons (19) to an excitatory influence. Then, if connectivity remained the same, any input to *m* neurons would excite *sa* neurons, which would, in turn, reexcite *m* neurons. If this is the mechanism of the conversion, then a similar large picrotoxin-induced increase in the amplitude of the corticofugal reflex discharge would be expected for any input. Likewise, the primary evoked response should be enhanced equally for all inputs. On the other hand, if *sa* neurons are converted to *m* neurons by

the action of picrotoxin on the *s*a neuron or on a subcortical neuron, increasing the effectiveness of normally subthreshold off-focus inputs (11), then only a small change in the corticofugal reflex discharge would be expected for any input because the number of *s*a neurons that contribute an axon to the pyramidal tract is negligible, and the only source of enhancement of the corticofugal reflex would be from *s*a facilitation of *m* neurons.

The amount of this facilitation can be judged by comparing the amplitudes of the corticofugal discharges evoked by the CF and CH. In some animals, the facilitatory effect can be quite large (e.g., Fig. 2) and, in others, quite small (e.g., Fig. 1), yet the picrotoxin effect is roughly the same. Judging from the figures presented by Batuev *et al.* (1), picrotoxin does not increase the number of spikes per discharge for CF stimulation, at least for the first application. Therefore, no change in the corticofugal discharge evoked by the CF would be expected, and the only change expected would be in the off-focus reflex discharges. Similarly, no change in the CF-evoked primary response is expected, but the surface-recorded responses to off-focus stimulation should be enhanced. An enhancement by as much as 25% of the control CF-evoked primary response might be expected because 25% of *s*a neurons in this tissue receive facilitation from off-focus, and the degree of facilitation is equal for all off-focus inputs (11). Clearly, neither of these expectations is congruent with the data obtained here. The slightly larger effect on IF-evoked responses than on CH- or IH-evoked responses suggests an effect of picrotoxin on the few *s*b neurons in this tissue. The observed enhancement of the corticofugal reflex discharge evoked by stimulation of any paw suggests that intravenous picrotoxin acts on *m* neurons or on the pathway leading to them.

Because both *s*a and *m* neurons contribute to the CF-evoked primary response, an enhancement of the primary response would be expected whether or not *s*a neurons are influenced. In an attempt to detect an effect on *s*a neurons, I measured the amplitudes and areas of the responses evoked by stimulation of the CF, representing both *s*a and *m* activity, and the CH, representing only *m* activity (Table 1). If intravenous picrotoxin affects only *m* neurons, then the magnitudes of the changes in the time integral of the surface-recorded responses evoked by the CF and CH should be the same. This prediction can be made because of the coadunate behavior of *m* neurons, i.e., the tendency to fire the same number of spikes for each input. This tendency is not disrupted by picrotoxin, as indicated by the similar changes in the corticofugal reflex for all off-focus inputs (e.g., Fig. 1). Therefore, the same amount of change in the surface potential is expected for both CF and CH inputs if only *m* neurons are affected. On the other hand, if both *s*a and *m* neurons are affected, the change in the CF-evoked surface potential should be larger. From Table 1, it is clear that the change in the CF-surface primary response area and amplitude is larger, though percentage increases are smaller.

Similarly, if only the *m* neurons are influenced by picrotoxin, then the change in the corticofugal reflex should be the same, whether evoked by stimulation of the CF or the CH. The facilitation of *m* neurons by *s*a neurons should remain constant if the *s*a neurons are not affected. The increases in the area and amplitude of the CF-evoked corticofugal reflex are greater both in value and percentage than for the equivalent CH-evoked response. On the other hand, the enhancement of the surface response by intravenous picrotoxin is small compared with the enhancement by topical picrotoxin (unpublished observations), which by analogy to the effects of topical strychnine, probably affects primarily *s*a neurons (16). At least tentatively, I conclude that the major effect of intravenous picrotoxin is exerted preferentially upon the pathway to cortical *m* neurons or on the neurons themselves—a lesser effect is exerted on *s*a neurons or upon the pathway to cortical *s*a neurons. The results of Pockberger *et al.* (10) suggest that local application of penicillin also can excite *m* neurons or *s*a neurons, depending on the site of application.

Site of Action. The enhancement of the responses in the thalamic radiations indicates that picrotoxin may be acting outside the cerebral cortex, and that part of the enhancement of *m* neuron activity is due to increased thalamocortical input. Picrotoxin has apparently not been used to examine thalamic transmission. Bicuculline, a drug with actions similar to those of picrotoxin, blocks collateral inhibition in the thalamic n. ventralis posterolateralis, initiated by either ortho- or antidromic impulses (3, 4) and blocks the collateral inhibition in the lateral geniculate nucleus due to antidromic impulses (3). These inhibitions are presumed to be mediated by GABA, but the caution expressed by Johnston (7) regarding the association of picrotoxin with GABA may apply here. No one has studied the influence of picrotoxin or bicuculline in the thalamic n. ventralis lateralis, but presumably the effects there may be similar. The absence of a significant effect on the medial lemniscus discharge suggests that the enhancement of the thalamocortical discharge may reflect increases in other inputs to cortex, among them reticulothalamocortical inputs, but this problem was not addressed in these studies. The extraordinarily long latency (3 to 8 min) in the action of picrotoxin may be due, in part, to the use of propylene glycol as a solvent, perhaps slowing the rate of absorption into the extracellular space. However, the long latency gives no clue about the site of action, because 3 to 8 min is long enough to reach any site in the central nervous system.

The increase in the thalamocortical volley after picrotoxin treatment does not preclude a direct effect of the drug on cortical neurons. It is possible that those thalamocortical afferent fibers that increase their activity in response to picrotoxin are not the fibers responsible for excitation of the *m* neurons. On the other hand, an effect confined to the cortex requires that the picrotoxin not circulate to the *s*a neurons or other neurons that inhibit them, or that these neurons be insensitive to picrotoxin. Enhancement of the primary

evoked response and, therefore, the discharges of *sa* neurons by topical picrotoxin (unpublished observations) rules out the latter possibility. No differential circulation to the different sets of neurons is known.

Action of Diazepam. Diazepam causes conversion of *m* responsiveness to *sa* responsiveness in sensorimotor cortex (21). When administered following picrotoxin or naloxone, it can also reverse their action, i.e., convert *m* to *sa*. In my experiment, diazepam reduced the action of intravenous picrotoxin on both the surface primary evoked response and the corticofugal reflex, and, in some cases, reduced these responses to below control values. Presumably, diazepam works on the same cortical elements affected by picrotoxin, and the same lines of reasoning can be applied to which sets of elements are affected by diazepam. It is doubtful that diazepam simply blocks the action of picrotoxin because it converts *m* responsiveness to *sa* responsiveness in animals not treated with picrotoxin and because simply blocking picrotoxin should not reduce responses to less than control values.

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