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The strychnine-like action of curare and related compounds on the somatosensory evoked response of the rat cortex

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1. Drugs were applied to the cerebral cortex of rats anaesthetized with pentobarbitone and changes measured in the somatosensory primary evoked response.

2. Computer-derived averages of thirty-two consecutive responses yielded stable and consistent measurements of the potential changes comprising the evoked response, and comparable records from the opposite (non-drug treated) cortex provided an essential control for systemic actions of the drug.

3. The modifications produced by curare and strychnine were indistinguishable. The first positive wave (peak latency 7 msec) was unaltered ; the second positive wave (peak latency 11·5 msec) was variably enhanced, and the first and second negative waves (peak latencies 16 and 40 msec) were replaced by a much larger negative wave (peak latency 22 msec).

4. The time of onset of the effect on the negative waves and the maximal amplitude attained by the abnormal negative wave were related to the log concentration of the drug used. Curare is approximately 10 times more potent than strychnine.

5. Toxiferine I, di-allylnortoxiferine and atropine also produced this effect but were less potent than strychnine.

6. Succinylcholine, dihydro-β-erythroidine and gallamine triethiodide did not produce this effect (in concentrations up to 10^{-3}M).

7. The observations are consistent with an action of curare and strychnine on an intracortical cholinergic inhibitory system, but other possibilities including a " non-specific excitatory action " cannot be excluded.

The similar effects of curare and strychnine when applied locally to the cortex were described by Chang (1953). Both substances induce spontaneous spike discharges and lead to similar modifications in topically evoked responses. Subsequently the convulsant action of intraventricularly administered D-tubocurarine was studied by Feldberg and colleagues (Feldberg, Malcolm, & Sherwood, 1956 ; Feldberg & Malcolm, 1959 ; Feldberg, 1963). The increase in the surface negative

component of responses evoked in the somatosensory cortex by peripheral stimulation was shown by Cairnie & Malcolm (1960) to follow a direct local action of D-tubocurarine on the cerebral cortex.

The intracortical site of action of strychnine or curare has yet to be defined in anatomical, physiological or pharmacological terms. In the spinal cord strychnine acts postsynaptically to block the inhibitory action of glycine, but this mechanism is apparently not important in the cortex (Curtis, Hösli, Johnston & Johnston, 1967). Curare does not influence the excitatory action of acetylcholine on Betz cells (Crawford & Curtis, 1966 ; Krnjević & Phillis, 1963). A cholinergic inhibitory system within layers II, III and IV of the cortex has been postulated by Phillis & York (1968a, b) but its properties and physiological role are not yet defined.

We are reporting a study of the strychnine-like action of curare and a variety of other cholinergic blocking agents, in order to provide pharmacological and physiological information about the intracortical synaptic mechanisms involved.

Methods

Male rats of CFE strain (Sprague-Dawley from Carworth Europe) weighing 250–300 g were anaesthetized with pentobarbitone (50 mg/kg initially, then 12 mg/kg half-hourly). The animals were prepared for the recording of cortical somatosensory evoked responses according to the method of Malcolm, Saraiva & Spear (1967), except that the cortex was exposed bilaterally. On both sides the potential changes at the primary receiving area were amplified, and then recorded on 35 mm film and, by means of frequency modulation, on magnetic tape. Stimuli were delivered alternately to each forepaw, and stimulus marker pulses were recorded on two tracks of the tape which were then available for triggering a digital computer (Biomac 500). This permitted the independent addition of the responses from each cortex to stimulation of either forepaw. Averages of thirty-two consecutive responses were written out on an X-Y plotter. Calibration pulses (100 μV) from a specially designed calibrator (G. W. Morris & B. S. Meldrum, to be published) were fed through the entire amplifying system, recorded on tape and added on the Biomac 500.

A continuous polygraphic record of cortical and rectal temperature was obtained from thermocouples.

Drugs were freshly dissolved in artificial cerebrospinal fluid (CSF) (Bradbury & Davson, 1964) at 37° C for each experiment. They were applied to the pial surface by injection through polythene tubing connected to the Perspex rings and removed by multiple washings with CSF. In most experiments the drug solution was applied to one cortex and CSF was applied to the contralateral cortex.

The drugs used were tubocurarine chloride (Burroughs Wellcome) ; diallylnortoxiferine dihydrochloride, Alloferin (Roche) ; Toxiferine I (RO 4-2906/2, Roche) ; gallamine triethiodide, Flaxedil (May & Baker) ; dihydro-β-erythroidine hydrobromide (Merck, Sharp & Dohme) ; strychnine sulphate (British Drug Houses) ; atropine sulphate (British Drug Houses) ; succinylcholine hydrochloride (Koch-Light Laboratories).

Results

Normal form of somatosensory evoked potentials under pentobarbitone

The moment to moment variability that is often prominent in the form of single evoked responses is largely removed by averaging thirty-two consecutive responses. The form of such evoked responses remains constant over several hours (see column D in Figs. 2 and 3). The potential changes in the primary sensory area in the first 50 msec after the contralateral stimulus are consistent between animals. They show an initial positive wave with a peak at $7{\cdot}0 \pm 1{\cdot}0$ msec ($N=65$) and a subsequent one at $11{\cdot}5 \pm 1{\cdot}8$ msec ($N=65$), followed by a longer-lasting negative wave, peak at $40{\cdot}0 \pm 6{\cdot}2$ msec ($N=65$). Some but not all records show a sharp early negative swing with a peak at $16{\cdot}3 \pm 2{\cdot}9$ msec ($N=27$). Figure 1 summarizes measurements of these successive peaks derived from averaged control records in ninety-two experiments.

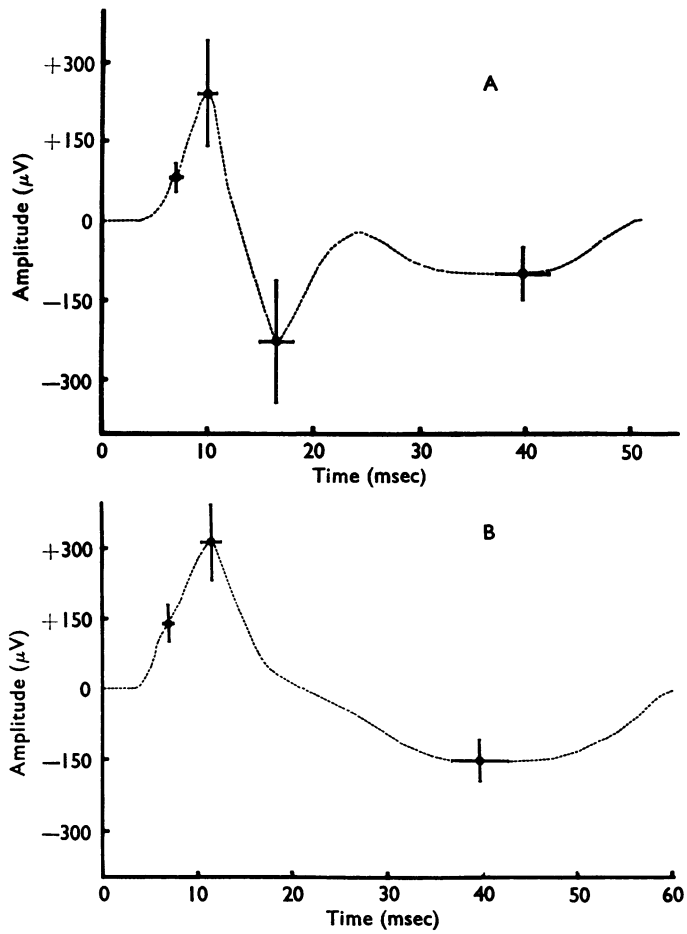

FIG. 1. Potentials evoked in the rat somatosensory cortex by stimulation of the contralateral forepaw under pentobarbitone anaesthesia. Averages of thirty-two consecutive responses during the initial control period in ninety-two experiments were used to derive the graphs. A, Means and standard deviations for the latency and amplitude of each of the main positive and negative peaks in those (twenty-seven) animals showing a prominent early negative wave. B, Corresponding values for the sixty-five animals not showing a sharp early negative wave.

Effect of strychnine

Cortical application of CSF containing 4×10^{-4}M strychnine consistently led to the appearance of an abnormally large early surface negative wave. The speed of onset of this effect was related to the concentration of strychnine; 2×10^{-3}M strychnine produced an effect in 1–3 min (Fig. 2) which reached a maximum at 5–8 min, often declining thereafter; 3×10^{-4}M strychnine produced an effect in 8–12 min and was maximal after 15 min. The averaged responses conceal a feature that was conspicuous in the early stages of strychnine's action, namely that normal responses were intermingled with those showing large negative waves (Fig. 4). When fully established the peak latency of the negative wave was $22{\cdot}7 \pm 2{\cdot}3$ msec ($N=7$). As this wave increased in amplitude the later negative wave (peak latency 40 msec $\pm$ 6 msec) became undetectable.

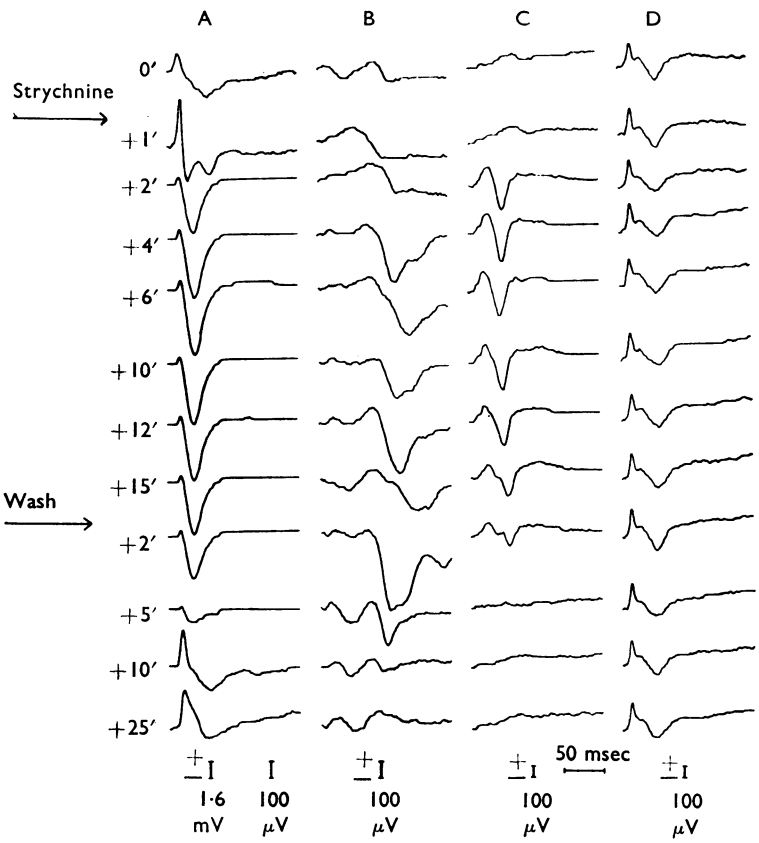

FIG 2. Each trace is the average of thirty-two consecutive responses recorded during a 165 msec epoch following forelimb stimulation. Positivity at the surface of the primary receiving area is shown upwards. Strychnine (2×10^{-3}M) was applied to the left cortex for 15 min. A, Response at the left cortex following stimulation of the right forepaw. The 1·6 mV calibration applies to the traces at times "strychnine + 2 min" to "5 min after washing"; the 100 μV calibration applies to the other traces. B, Response from the left cortex following stimulation of the left forepaw. C, Response from the right cortex following stimulation of the right forepaw. D, Response from the right cortex following stimulation of the left forepaw.

The first positive wave (latency 6–8 msec) consistently showed no change. A moderate increase in amplitude of the second surface positive wave was sometimes observed during strychnine application but was often more prominent during subsequent washing (see Fig. 5). Commonly a decrease of 1–2 msec in the peak latency of the second positive wave was apparent when the negative wave was abnormally large.

In the control hemisphere the cortical responses to contralateral stimulation showed no change (column D, Fig. 2). When the strychnine-treated hemisphere showed an abnormal negative wave following contralateral stimulation the control (ipsilateral) cortex showed a biphasic wave positive at about 20 msec, negative at 35–50 msec (column C, Fig. 2). Recordings from subcortical electrodes (1–1·5 mm deep) showed that this surface positive wave inverted in the specific sensory cortex, and was therefore not simply a passive potential change resulting from the very large potential change on the opposite cortex (see Fig. 4).

On the strychnine-treated side large negative waves (" strychnine spikes ") were seen, sometimes bearing only an irregular relationship to stimulation of the ipsilateral forelimb, but sometimes occurring fairly regularly at 90–100 msec after such stimulation (column B, Fig. 2).

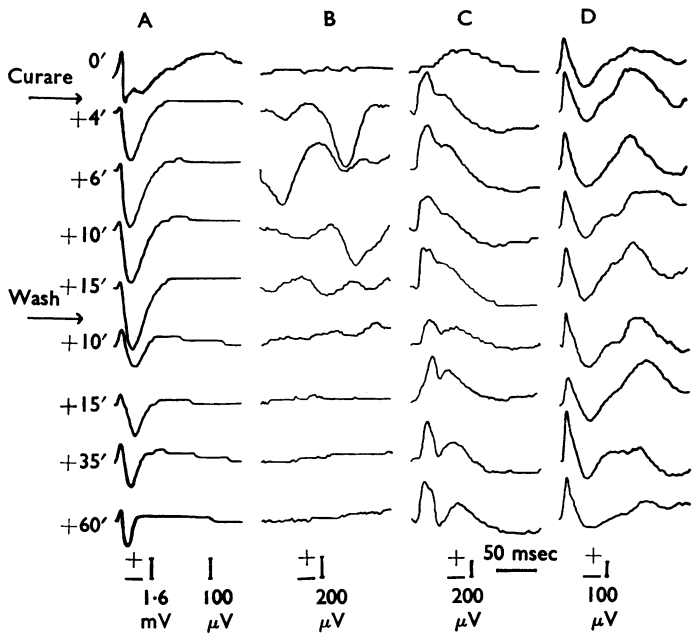

FIG. 3. Each trace is the average of thirty-two consecutive responses recorded during a 165 msec epoch following forelimb stimulation. Positivity at the surface of the primary receiving area is shown upwards. Curare (10^{-3}M) was applied to the right cortex for 15 min. A, Response at right cortex following stimulation of the left forepaw. The 100 μV calibration applies to the first trace, the 1·6 mV calibration applies to all the subsequent traces. B, Response from the right cortex following stimulation of the right forepaw. C, Response from the left cortex following stimulation of the left forepaw. D, Response from the left cortex following stimulation of the right forepaw.

Curare

The effects on the cortical evoked response of locally applied D-tubocurarine were indistinguishable from those produced by strychnine, except that curare was effective at lower concentrations (Figs. 3, 4, 5, and 6). Whereas 2×10^{-4}M strychnine was without effect in two experiments, 10^{-5}M curare produced an unequivocal effect in four out of six experiments. All the changes described above as following strychnine were also seen after concentrations of curare between 10^{-5}M and 10^{-3}M. For intermediate drug concentrations a direct linear relationship was observed

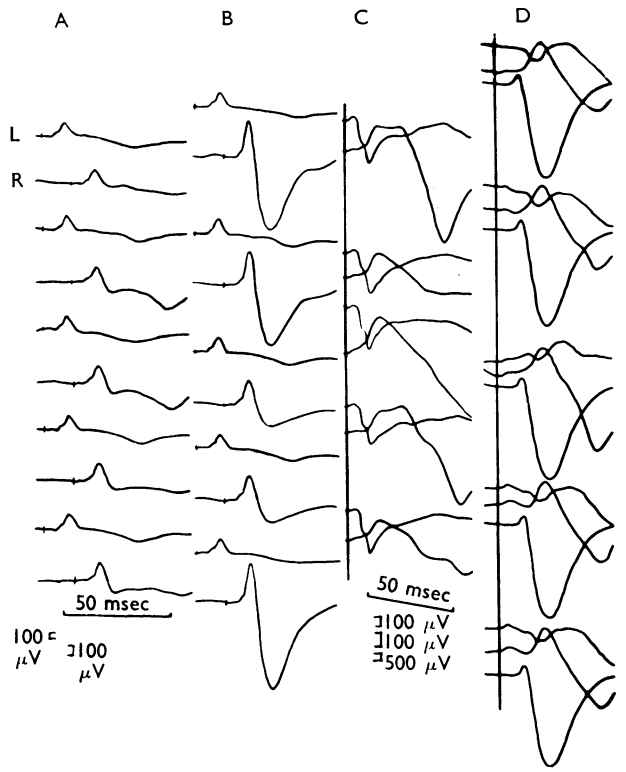

FIG. 4. Tracings from film of consecutive single evoked responses recorded in a rat treated with strychnine (A and B) and one treated with alloferin (C and D). A, Consecutive responses from the left and right somatosensory cortex following contralateral stimulation. One minute before strychnine application. B, Consecutive responses from left and right somatosensory cortex beginning 1 min 50 sec after the application of 2×10^{-3}M strychnine to the right cortex. C, Responses to stimulation of the right forepaw recorded from the left somatosensory cortex simultaneously at the cortical surface and at approximately 1 mm below the surface (upper trace of each pair). Pairs of traces are consecutive at 2·013 sec intervals beginning 12 min after 2×10^{-3}M alloferin was applied to the right cortex. D, Recordings over the same 10 sec period as in column C in response to stimulation of left forepaw. Each triplet shows responses occurring at the depth and surface of the left cortex and the surface of the right cortex (from above down). Note that whereas the deep negative wave of the normal contralateral response (column C) has latencies of onset (5·0 msec) and peak (8·0 msec) less than those of the corresponding surface positive wave (8·5 and 9·5 msec), the ipsilateral responses (column D) show an onset latency that is the same (13·5 msec) for the deep negative wave and the surface positive wave. The voltage calibrations for the deep and surface records on the left cortex are the same as under column C, and the 500 μV calibration applies to the lowest record (surface of right cortex).

between the logarithm of the concentration used and the amplitude of the effect produced (see Fig. 6). The onset of action was within 1–3 min for the highest concentrations used. The peak latency of the abnormal negative wave when fully established was $21{\cdot}9 \pm 3{\cdot}6$ msec ($N = 13$).

The time course of recovery after 15 min exposure to a drug concentration having a submaximal effect was closely similar. Recovery occurred within 15–25 min of washing off 4×10^{-4}M strychnine and after washing off 5×10^{-5}M curare (which produced a similar amplitude change in the negative wave) (see Figs. 2, 3, 5, and 6). Recovery following higher concentrations of curare (10^{-4}–10^{-3}M) was very much prolonged (40–90 min).

Alkaloids resembling curare

The effects of various concentrations of toxiferine, diallylnortoxiferine and of dihydro-β-erythroidine were also assessed. Toxiferine at low concentration (10^{-4}M) was without effect, but 10^{-3}M toxiferine in eight out of ten experiments caused death of the animal from respiratory failure in 4–14 min. Two animals showed a typical strychnine-like effect, starting after 8–10 min, and recovering within 10–25 min of washing.

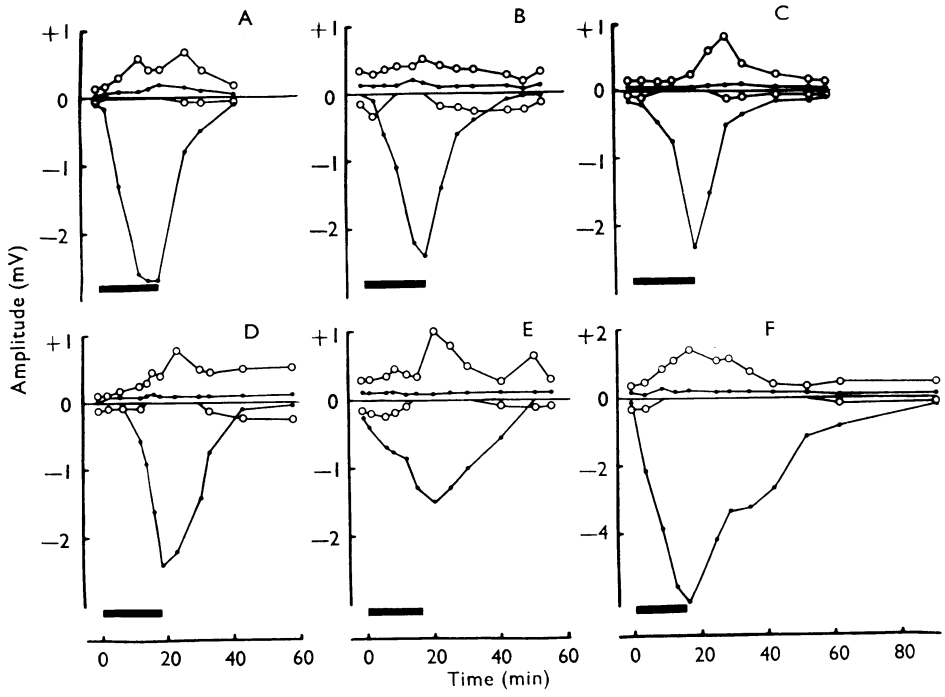

FIG. 5. Graphs showing the time course of the effects of drugs on the amplitude of the positive and negative waves of the contralateral somatosensory evoked potentials in rats anaesthetized with pentobarbitone. ●——●, Amplitude of the first positive (7 msec) and first negative (16 msec) waves. ○——○, Amplitude of the second positive (11 msec) and second negative (40 msec) waves. The bar represents the duration of the application of drug in each case. A, Curare 5×10^{-5}M; B, strychnine 4×10^{-4}M; C, toxiferine 10^{-3}M; D, Alloferin 10^{-3}M; E, atropine 10^{-3}M; F, curare 10^{-3}M.

Alloferin was identical in its effects to curare and strychnine. The threshold concentration was 3×10^{-4}M, which produced an effect beginning after 15–20 min. Alloferin was rather less effective than the same concentration of strychnine (see Fig. 6). The apparent difference in the slope of the regression line compared with strychnine is not statistically significant ($P>0{\cdot}1$).

Dihydro-β-erythroidine applied at a concentration of 10^{-3}M for 40–50 min was without effect on either the positive or negative waves of the somatosensory evoked response.

Other neuromuscular blocking drugs

Succinylcholine (10^{-3}M and 4×10^{-3}M applied respectively for 30 and 15 min) was without effect on the primary evoked response.

Gallamine triethiodide (10^{-3}M applied to the cortex for 10, 20 or 40 min) was without effect on the negative waves of the evoked response but diminished slightly the amplitude of the second positive wave.

Atropine

The effect of 10^{-4}M was equivocal, but 10^{-3}M atropine produced an effect on the negative wave comparable with that produced by 10^{-5}M curare. Higher concentrations (2 and 5×10^{-3}M and 10^{-2}M) usually lead to depression of all the cortical evoked response and sometimes to the death of the animal, but strychnine-like effects were sometimes seen, often after washing off the atropine.

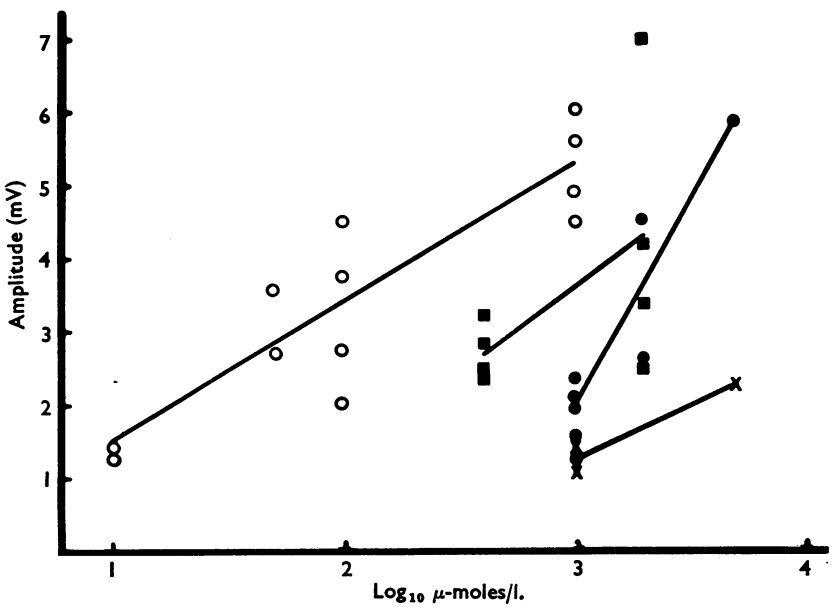

FIG. 6. Scatter diagram illustrating the effect of drugs (applied for 15–18 min) on the negative wave of the contralateral somatosensory evoked potentials in rats anaesthetized with pentobarbitone. The maximum amplitude of the negative wave (21 msec) is plotted against the logarithm of the dose of the drug. Each point in the diagram represents the result of a single experiment. The solid lines are calculated regression lines. ○, Curare ; ■, strychnine ; ●, alloferin ; ×, atropine.

Discussion

Application of drugs to the cortex

Because of the blood brain barrier comparison of the action of different drugs on the cerebral cortex requires local application. This means choosing between two extremes, either studying whole tissue responses following whole tissue drug application or studying changes in the responses of single cells following microiontophoretic application of the drug. Presently available microiontophoretic procedures are not favourable for the study of the action of drugs at sites remote from the soma of cortical neurones. However, neurones can display regional specialization in their pharmacological properties (Diamond, 1968), so that some drugs will act mainly on the finer dendritic branches. Thus the application of drugs via cortical cups is the preferred procedure for studying certain drug actions.

Two possible sources of error are systemic reflexes induced by a local action of the drug (for example, application of noradrenaline to the cortex can modify the blood pressure, Walaszek, 1960) and remote effects of the drug following its systemic absorption (when applying eserine or carbachol to the cortex we have observed marked parasympathomimetic effects). These factors are well controlled by recording from the opposite (non-drug treated) cortex throughout the experimental period and this also monitors any " spontaneous " variations in the general condition of the animal.

All the direct effects of drugs on the primary somatosensory evoked response that we have reported are seen in the absence of any change in the primary evoked response of the opposite cortex. However, changed responses are sometimes seen in the control cortex following ipsilateral stimulation. As the contralateral responses are unaltered these changes presumably result from abnormal efferent activity in the drug-treated cortex. Histological evidence shows that callosal fibres end directly on pyramidal cells (Globus & Scheibel, 1967). This pathway could give ipsilateral evoked responses with the short latency and the pattern of depth inversion observed (Fig. 4).

Comparative potencies of drugs used

Chang (1953), applying curare and strychnine on filter paper, found that the minimally effective concentration of both was 10^{-7}M. With our procedure rather higher concentrations were required. Also, we found that curare is slightly more potent than strychnine. At the neuromuscular junction diallylnortoxiferine and toxiferine are as potent as D-tubocurare (Lund & Stovner, 1962) ; the much lower potency we observe at the cortex argues against an action on receptors pharmacologically similar to those in skeletal muscle, as does the total lack of effect of dihydro-β-erythroidine, succinylcholine and gallamine. Atropine has several effects on cortical electrical activity. It blocks the excitatory action of acetylcholine on Betz cells (Crawford & Curtis, 1966) and the e.e.g. activating effect of stimulation of the brain stem reticular formation (Longo, 1966). Its variable effects are probably the outcome of action at several sites, one of which is presumably the same mechanism as that influenced by curare and strychnine.

Physiological and pharmacological site of action

Curare and strychnine applied by microiontophoresis have been shown (Biscoe & Curtis, 1967 ; Crawford & Curtis, 1966 ; Krnjević, Randić & Straughan, 1966c) to

possess a " non-specific excitatory action " on neuronal membranes (which may be a consequence of their detergent properties). However, gallamine triethiodide possesses a similar excitatory action on Betz cells (Crawford & Curtis, 1966), so that its lack of effect in our system has to be accounted for separately if this non-specific excitatory action of curare is producing the effect.

Several authors (Pollen & Ajmone Marsan, 1965 ; Pollen & Lux, 1966 ; Stefanis & Jasper, 1965) after applying high concentrations of strychnine (about 10^{-2}M) to the cortical surface have observed a conversion of the hyperpolarizing inhibitory postsynaptic potentials that follow antidromic stimulation of the pyramidal tract, into depolarizing potentials with similar time courses. Biscoe and Curtis (1967), however, suggest that this is not due to an action on synapses on pyramidal cells but is probably due to an action on interneurones elsewhere.

Curare or strychnine do not influence the intracortical inhibitory system (Krnjević, Randić & Straughan, 1966a, b) which can be activated by superficial or deep cortical stimulation and which produces relatively short (100–300 msec) inhibition in pyramidal neurones. A small proportion of neurones (in layers II and III), however, are inhibited by acetylcholine (Randić, Siminoff & Straughan, 1964). Phillis & York (1968b) have described an inhibitory mechanism acting on cells in layers II, III and IV. Pyramidal tract or lateral hypothalamic stimulation produces inhibition with a long time course (up to 1 sec). These cells are also inhibited by cholinomimetic agents and anticholinesterases, and this inhibition is blocked by atropine, curare and strychnine but not by gallamine triethiodide. Thus this inhibitory mechanism and enhancement of the negative wave show the same drug sensitivity. If the cells receiving a cholinergic inhibitory input are excitatory to pyramidal neurones, the final outcome of blocking their inhibitory input could be excessive depolarization of apical dendrites of pyramidal cells. Recently superficially located (250–600 μ down) neurones which are excitatory to pyramidal tract neurones have been described by Biscoe & Curtis (1967).

Several curious features of the response to curare and strychnine can be accounted for by the hypothesis that both block cholinergic inhibitory mechanisms in layers II, III and IV of the cortex and secondarily permit the occurrence of excessive depolarization of superficial dendritic branches of pyramidal neurones (seen as abnormal negatives waves in the evoked response, Bishop & Clare, 1952). These features include the long latency occasionally seen with low doses of strychnine (Bishop & Clare, 1952 ; Cobb, Cowan, Powell & Wright, 1955a), the slow transmission of strychnine spikes from point to point in the cortex (Cobb, Cowan, Powell & Wright, 1955b) and the lack of effect of curare and strychnine on directly evoked dendritic responses (Chang, 1953).

To suggest that curare and strychnine are acting on the same synaptic mechanism does not necessarily mean that they are acting on the same receptor. Molecules of strychnine and curare have several structural features in common, however, including a positively charged nitrogen atom together with oxygen and unsaturated carbon atoms similarly spaced from the nitrogen atom. Toxiferine and Alloferin resemble strychnine in possessing a substituted indole nucleus in a polycyclic structure with charged nitrogen atoms similarly disposed with respect to the indole ring.

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