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THE SITE OF ORIGIN OF THE TREMOR PRODUCED BY TUBOCURARINE ACTING FROM THE CEREBRAL VENTRICLES

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Tubocurarine when introduced into the cerebral ventricles of cats produces a diversity of phenomena: effects mediated via the autonomic nervous system, alterations in respiration, tremor, myoclonus, convulsions and, on the electroencephalogram (e.e.g.), a seizure discharge resembling that seen in epilepsy in man. To produce these effects the tubocurarine need not enter the fourth ventricle because they occur when tubocurarine is perfused from lateral ventricle to aqueduct. For one effect, the seizure discharge, a more precise localization has been obtained. This discharge arises from an action on structures lining the lateral ventricles, either the hippocampus or the amygdala, or both (for references see Feldberg & Fleischhauer 1962).

The present experiments establish localization for another effect: tremor. The structures on which the tubocurarine acts when eliciting this effect are different from those responsible for the abnormal discharge and are reached not from the lateral but from the third ventricle. Tremor is evoked from structures lining the ventral part of the third ventricle, the hypothalamus.

Further, a number of drugs have been perfused through the cerebral ventricles in order to study their effect on tubocurarine tremor. New observations have also been made on the changes in respiration, on the myoclonus, on the abnormal discharge and its relation to both myoclonus and tremor.

METHODS

In anaesthetized cats the cerebral ventricles were perfused with tubocurarine. Anaesthesia was either with intraperitoneal pentobarbitone sodium (36 mg/kg) or with intravenous chloralose (60 mg/kg) induced with ethyl chloride and ether to allow cannulation of the right femoral vein. Supplementary doses of pentobarbitone sodium or chloralose were given when required. After tracheotomy the right femoral artery was exposed for cannulation and recording of blood pressure at a later stage. With the cat lying on its belly the head was fixed to the ear bars and to the mouth piece of a head holder similar to that of the Horsley Clark stereotaxic instrument.

To perfuse the cerebral ventricles a collision cannula was implanted into each lateral ventricle and a polythene tube inserted through the exposed cisterna into the aqueduct by the method described elsewhere (Bhattacharya & Feldberg, 1957; Feldberg & Fleischhauer, 1962). The fluid used for perfusion was the artificial cerebrospinal fluid (c.s.f.) of Merlis (1940). Its composition was (g/l.): NaCl 8·1; KCl 0·25; $CaCl_2$ 0·14; $MgCl_2$ 0·11; $NaHCO_3$ 1·76; $Na_2HP^2O_4$ 0·07; glucose 0·61; $CO(NH_2)_2$ 0·13. The perfusion fluid shortly before entering the Collision cannula was warmed by passing through a water jacket; the water was usually kept near 39° C but variations of 2 to 3° C in either direction did not affect the result.

Perfusion was through both lateral ventricles with separate injectors each delivering fluid at a rate of 0·1 ml./min. One injector was filled with artificial c.s.f. and the other with tubocurarine dissolved in artificial c.s.f. It has been shown by Feldberg & Fleischhauer (1962) that with this method of simultaneous bilateral perfusion the tubocurarine is prevented from entering the lateral ventricle through which the artificial c.s.f. alone is perfused. Further, with this method the tubocurarine reaching the third ventricle is diluted 1/1 by the fluid entering from the opposite lateral ventricle.

Before perfusion with tubocurarine was begun the patency of the ventricular and aqueductal cannulae was tested by perfusion of artificial c.s.f. through each lateral ventricle in turn. Then for a control period lasting a variable time in each experiment only one lateral ventricle was perfused with artificial c.s.f.

At the end of the experiments the regions reached by the tubocurarine were ascertained by perfusing the dye bromophenol blue (0·2% solution) through the cannula by which the tubocurarine had been delivered. The brain was fixed by perfusing it with formalin through one carotid artery and dissected to reveal the regions stained by the dye.

In several experiments an attempt was made to limit perfusion of the tubocurarine to the third ventricle and rostral part of the aqueduct. For this purpose the cannula intended for the delivery of the tubocurarine was inserted in a more medial direction so as to bring the tip into the third ventricle. The tip had to be in the region of the foramen of Monro and with its opening directed medially and caudally, because in this position the cannula obstructed the foramen and prevented backflow into the lateral ventricle. When the tip of the cannula lay in the lumen of the third ventricle such backflow often occurred, as demonstrated by subsequent perfusion with bromophenol blue.

To examine their actions on the tubocurarine tremor drugs were dissolved in artificial c.s.f. and perfused through the lateral ventricle opposite to that being perfused with tubocurarine.

Tremor and jerks were recorded on a smoked drum from the left hind limb by means of a light tension lever attached to the paw by a thread. The hind quarters of the cat were rotated to the left, so that the left hind leg was free to move. Respiration was recorded by means of a stethograph placed across the chest or upper abdomen and connected to a piston recorder writing on the smoked drum. The e.e.g. was recorded monopolarly from frontal and occipital epidural electrodes on both sides, as described by Feldberg & Fleischhauer (1962).

The following drugs were used: tubocurarine chloride, adrenaline bitartrate, noradrenaline bitartrate, dopamine hydrochloride, atropine sulphate, and hyoscine hydrobromide. The concentrations refer to the weight of the salts. The bromophenol blue solution was prepared as described by Feldberg & Fleischhauer (1960*a*).

RESULTS

Tremor

Perfusion of tubocurarine in a concentration of 1/20,000 from one lateral ventricle to aqueduct produces tremor. This concentration is too weak to produce a rise in arterial blood pressure as seen on perfusion with

stronger concentrations (Feldberg & Fleischhauer, 1962). Under chloralose anaesthesia the tremor continues for hours without or with only a small reduction in amplitude and often uninterrupted by muscle jerks. With stronger concentrations of tubocurarine (1/5000 or 1/1000) muscle jerks interrupt tremor at an early stage of perfusion, later the amplitude of the tremor decreases, and finally tremor may cease. Under pentobarbitone sodium anaesthesia, perfusion with tubocurarine 1/20,000 also produces tremor but of shorter duration than under chloralose. Sometimes the tremor ceases after a few minutes, sometimes after an hour, even though perfusion with tubocurarine is continued. Subsequent increase in the concentration of tubocurarine in the perfusion fluid does not restore tremor, or at most produces tremor of low amplitude and short duration. Most of the experiments have therefore been carried out with perfusion of tubocurarine 1/20,000, under chloralose anaesthesia.

Onset of tremor occurs in the flanks and hind limbs a few minutes after the beginning of the perfusion with tubocurarine. Often fasciculation precedes tremor which later increases in amplitude and spreads to the shoulder girdle and forelimbs.

When recorded from a hind limb, tremor is shown as beginning in small bursts related to respiration and increasing in amplitude at the end of each expiration. In some experiments the bursts remain small in amplitude throughout the perfusion, in others they become greater within a minute or two, or over a period of 10–30 min and tremor becomes continuous between the bursts. The bursts are then no longer closely associated with respiration and vary both in strength and duration.

Figures 1 and 5 illustrate experiments in which tremor begins 2–3 min after commencing perfusion with tubocurarine and reaches its maximum within a further 2 min. From the recordings on a fast-moving drum, tremor is seen to occur in irregular bursts. In the experiment illustrated in Fig. 1 some of the bursts are associated with the respiratory movements.

Onset of tremor is associated with an increase in muscle tension. In the hind leg this often results in increased flexion which produces a rise in the record. With the method used for recording respiration the increase in tension of the trunk muscles causes a fall in the respiratory records. These muscular effects are illustrated in Fig. 1*A*.

The site where the tubocurarine acts when eliciting tremor has been determined by experiments in which parts of the ventricular system have been excluded from the perfusion with tubocurarine. The results of these experiments are described with the help of Fig. 2. The shaded areas indicate the regions reached by the tubocurarine as verified at the end of each experiment by perfusion with bromophenol blue through the same cannula.

Figure 2*A* illustrates experiments in which the tip of the cannula delivering

tubocurarine has been resting in the third ventricle. The tubocurarine has not entered the lateral ventricle, but has passed through the third both ventral and dorsal to the massa intermedia and through the rostral part of the aqueduct. Tremor has occurred.

Figure 2*B* illustrates experiments in which the tip of the inflow cannula has again been resting in the third ventricle, but the tubocurarine has not entered that part of the third ventricle lying ventral to the massa intermedia. No tremor has occurred.

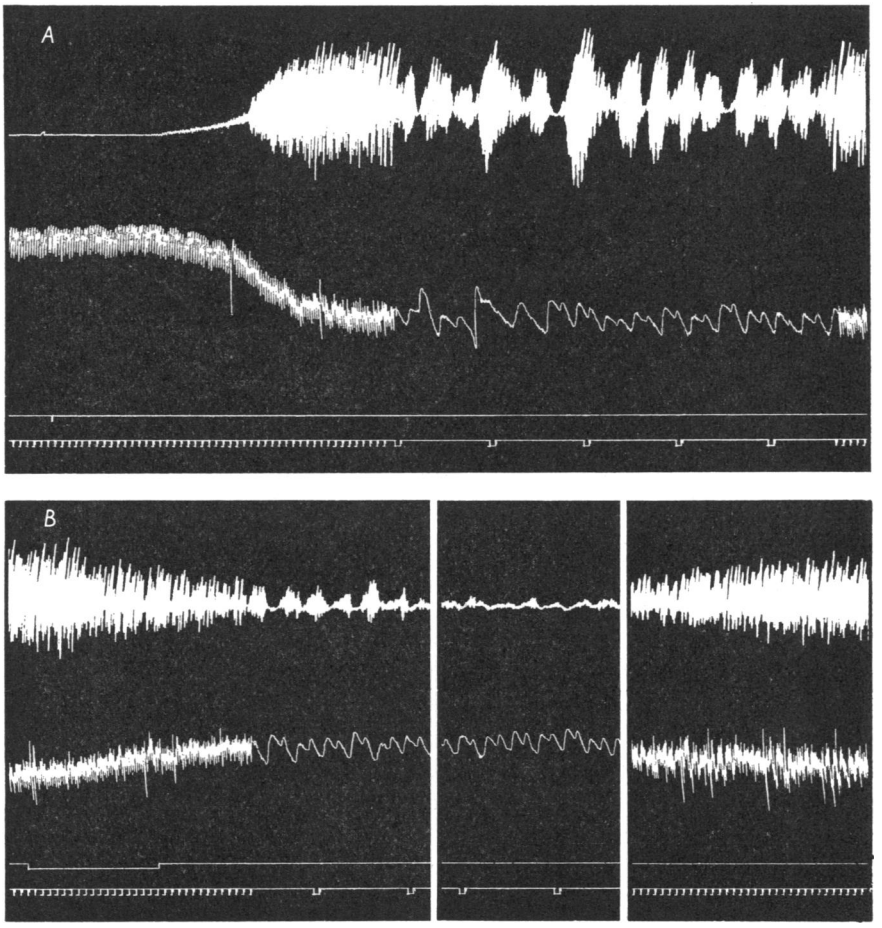

Fig. 1. Tremor of left hind leg (upper record) and respiration (lower record) in a cat under chloralose anaesthesia during perfusion from both lateral ventricles to aqueduct. (*A*) perfusion with tubocurarine 1/20,000 from left lateral ventricle beginning at the signal and continuing throughout the experiment. (*B*) at the signal 3 min perfusion of atropine 1/5000 from right lateral ventricle. The interval between first and second section is 5, between second and third 15 min. Time marker 10 sec.

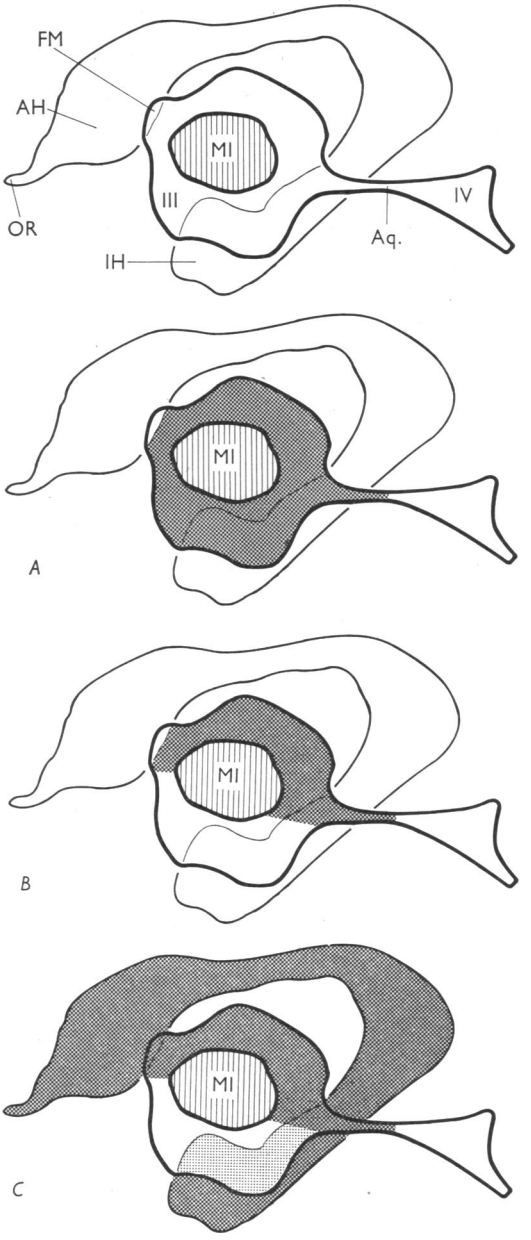

Fig. 2. Diagrams of the ventricular system of the cat's brain. Only one lateral ventricle shown. AH, anterior horn of lateral ventricle; FM, foramen of Monro; IH, inferior horn of lateral ventricle; MI, massa intermedia; OR, olfactory recess of lateral ventricle; III, third ventricle; IV, fourth ventricle. Aq, indicates tip of outflowing cannula in aqueduct. In *A* to *C* the shaded areas represent the regions of the ventricular system reached by tubocurarine under different conditions of perfusion. For details see text.

Figure 2*C* illustrates experiments in which the tubocurarine has reached the lateral ventricle, has passed through the third ventricle dorsal to the massa intermedia and through the rostral end of the aqueduct but has failed to enter that part of the third ventricle lying ventral to the massa. Again no tremor has occurred.

From the results of these three sets of experiments it is clear that the only region from which tubocurarine evokes tremor when passing through the lateral and third ventricle and through the rostral end of the aqueduct is the hypothalamus.

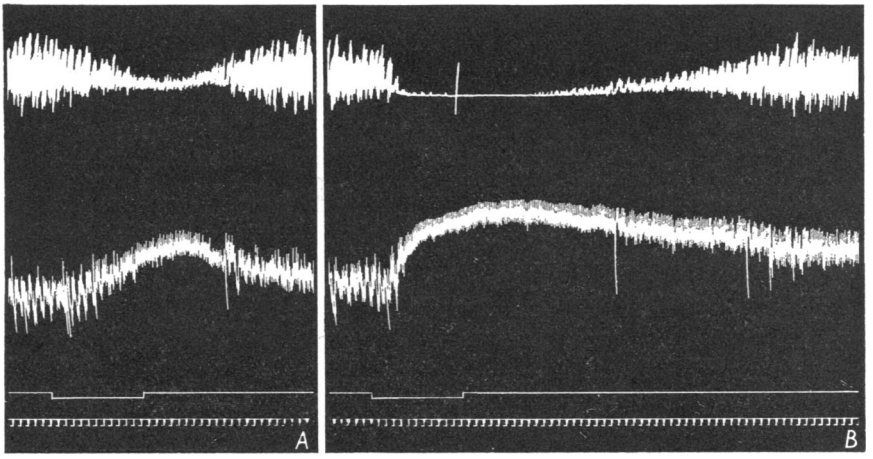

Fig. 3. Continuation of experiment illustrated in Fig. 1. At the signals 2 min perfusion from the right lateral ventricle of 1/100,000 noradrenaline (at *A*) and adrenaline (at *B*).

The finding that under chloralose the perfusion with tubocurarine 1/20,000 results in long-lasting tremor uninterrupted by jerks, allowed the study of the effects on this tremor of substances perfused for short periods through the cannula opposite to that delivering tubocurarine.

Adrenaline and noradrenaline reduce or abolish tremor. The effect begins within seconds. Adrenaline is 2–4 times more potent than noradrenaline and exerts some anti-tremor effect when perfused in a concentration of 1/1 million and sometimes of 1/5 million. With these threshold concentrations the effect still begins within a minute. Since the rate of infusion is 0·1 ml./min this means that with a concentration of 1/5 million the effect appears before 20 ng has entered the cerebral ventricles.

The experiment illustrated in Fig. 3 illustrates the results of 2 min perfusion with noradrenaline (at *A*) and with adrenaline (at *B*) each in a concentration of 1/100,000. With noradrenaline tremor decreases in amplitude and returns to its previous level within 3 min after the end of perfusion,

while with adrenaline it ceases and returns to its previous level 7 min after the end of perfusion. Coincident with the decrease in tremor there is relaxation of muscle tension, reflected both on the tension record of the hind limb and on the respiratory record; and as tremor returns tension increases again.

Dopamine acts similarly but only in stronger concentrations. In the experiment shown in Fig. 4 the effect of different concentrations is shown.

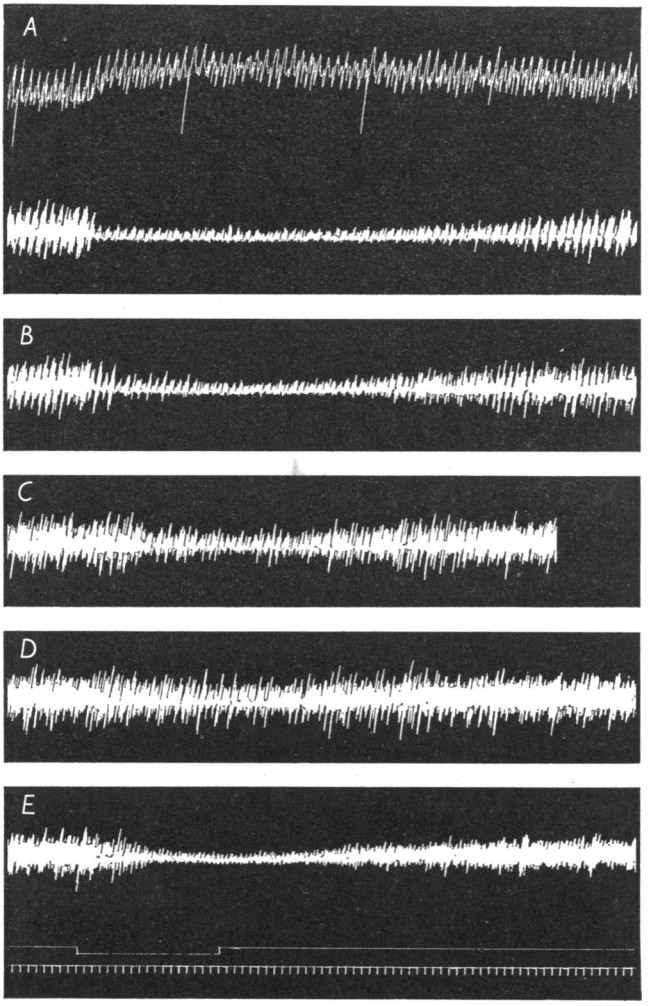

Fig. 4. Respiration (upper record at *A*) and tremor of left hind leg (lower record at *A*, and records *B* to *E*) in a cat under chloralose anaesthesia during perfusion with tubocurarine 1/20,000 from one lateral ventricle to aqueduct and the effects of 3 min perfusion from the other lateral ventricle of dopamine 1/2500 (at *A*), 1/10,000 (at *B*), 1/20,000 (at *C*), 1/50,000 (at *D*) and of adrenaline 1/1 million (at *E*). Time marker 10 sec.

With the strong concentration of 1/2500 tremor is nearly abolished while with 1/50,000 a just-perceptible effect is present. Usually in comparison with adrenaline, dopamine 1/10,000 is more, and 1/20,000 less effective than adrenaline 1/1 million. As these concentrations refer to adrenaline bitartrate and to dopamine chloride, dopamine is about 200 times less active than adrenaline. The diminution in tremor is again associated with a general reduction in muscle tension as seen on the respiratory record in *A*.

Atropine in strong concentration is required to abolish or reduce tremor. The effect differs from that of the catechol amines in that it develops more slowly and lasts longer. With a concentration of atropine 1/2000 tremor is abolished sometimes for as long as 30 min. With concentrations of 1/5000 or 1/10,000 it is reduced for 20–40 min; with 1/20,000 some reduction is occasionally obtained. Figure 1 illustrates the effect of 3 min perfusion of atropine 1/5000. Maximal reduction of tremor is delayed until the 7th min following the end of perfusion (at *B*); record *C* begins 15 min later and shows that full recovery takes more than 20 min. There is again a reduction in muscle tension discernible in the respiratory record.

Hyoscine has an action and a potency similar to that of atropine. Figure 5 illustrates the effect of perfusion for 3 min with hyoscine 1/5000. Reduction of tremor begins during perfusion (*B*) and becomes maximal some 15 min after the end of perfusion (*E*). Seventy-five minutes later, recovery is still incomplete. There is an associated reduction in muscle tension.

Chloralose abolishes tremor when perfused in a concentration 1/5000 for 3 min. The effect develops within a few minutes and recovery is complete within 15 min. A reduction in tremor is obtained with a concentration as weak as 1/50,000. The effect is associated with reduction in muscle tension.

Bromophenol blue. Feldberg & Fleischhauer (1962) have shown that bromophenol blue perfused from one lateral ventricle to the aqueduct in a concentration of 1/500 produces an abnormal seizure discharge in the e.e.g. similar to that produced by tubocurarine. But as far as tremor is concerned bromophenol blue is an antagonist. Perfused in a concentration 1/500 it abolishes the tubocurarine-evoked tremor. The effect is associated with relaxation of muscle tension.

Changes in respiration

Although the fourth ventricle is excluded from the perfusion in all experiments, tubocurarine has produced pronounced changes in respiration. The first effect is an increase in depth and in frequency of the respiratory movements at the time tremor begins and general muscle tension increases. Inspiratory gasps, which before perfusion with tubocurarine occur at long intervals, become frequent and increase in depth;

there are also small, abrupt, irregular inspiratory movements commencing sometimes early, sometimes late, which interrupt the smooth rhythm. The initial effects, increase in depth and frequency of respiration, are illustrated in Fig. 6. *A* shows the respiration before, and *B* during the first minutes of perfusion with tubocurarine 1/20,000 from one lateral ventricle to aqueduct. The small irregular inspiratory movements are seen in Fig. 1.

The substances which on perfusion through the ventricles abolish tremor also reduce some of the respiratory changes produced by tubocurarine. This is illustrated for noradrenaline and adrenaline in Fig. 3.

Myoclonus

Muscular jerks which begin with short contractions in the region of the shoulder girdle and neck often result in abrupt synchronous movements of

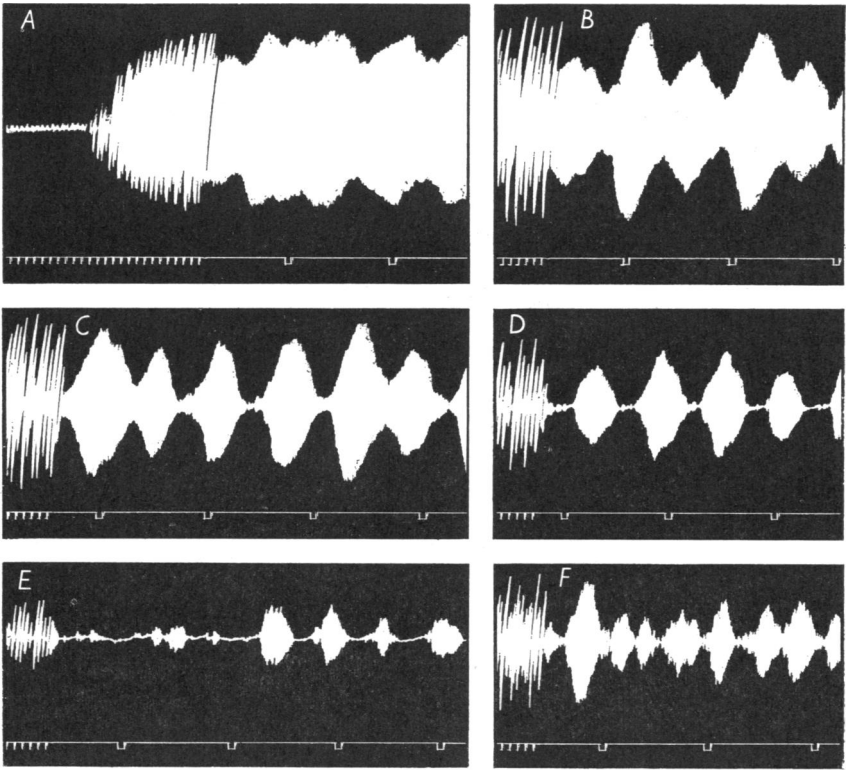

Fig. 5. Tremor of left hind leg in a cat under chloralose anaesthesia during perfusion with tubocurarine 1/20,000 from the right lateral ventricle to aqueduct, starting 8 min before *A* and continued throughout the experiment. Effect of 3 min perfusion of hyoscine 1/5000 from left lateral ventricle starting 30 sec before *B*. Records *C*, *D*, *E* and *F*, taken 1, 5, 15 and 90 min after end of hyoscine perfusion. Time marker 10 sec.

the two forelegs. These jerks increase in strength and frequency and gradually spread to the muscles of the trunk and hind legs where the jerks consist of flexion of the limbs. Once the hind legs are involved the jerks are synchronous in all four limbs. Latency and time course of this developing myoclonus depend both on the concentration of tubocurarine and on the anaesthetic.

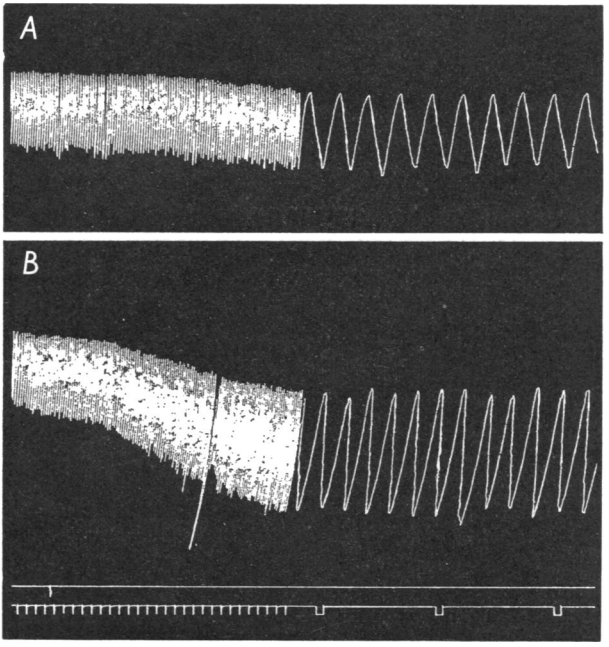

Fig. 6. Respiration in a cat under pentobarbitone sodium anaesthesia during perfusion from both lateral ventricles to aqueduct. *A*, before, *B*, during perfusion with tubocurarine 1/20,000 from left lateral ventricle starting at the arrow. Rate of respiration at the end of *A*, 22½/min, of *B*, 30/min. Time marker 10 sec.

Under pentobarbitone sodium, jerks do not occur during perfusion with tubocurarine 1/20,000 even when perfusion continues for up to 2 hr. However, under chloralose, they may occur after 30–60 min perfusion and gradually increase in strength and frequency. If stronger concentrations of tubocurarine are used, muscular jerks also occur under pentobarbitone sodium, while under chloralose they occur earlier and increase more rapidly in strength.

Though one lateral ventricle is excluded from the perfusion with tubocurarine, myoclonus is never one-sided. It begins simultaneously, and is of equal intensity, on both sides of the body.

To obtain these muscular jerks the tubocurarine must reach the walls of at least one lateral ventricle. No myoclonus is encountered in those experi-

ments in which the tip of the cannula delivering the tubocurarine is resting in the third ventricle and the tubocurarine does not enter either lateral ventricle. The site where tubocurarine acts appears to be structures reached from the posterior half of the lateral ventricle. In one experiment this part of the lateral ventricle was excluded from the perfusion and the tubocurarine had only passed through the anterior half of the lateral ventricle, as revealed by subsequent perfusion with bromophenol blue. In this experiment no myoclonus occurred, although the concentration of tubocurarine was 1/1000.

Effects on the electroencephalogram

In previous experiments on cats anaesthetized with pentobarbitone sodium a characteristic pattern of changes in the e.e.g. has been observed during perfusion of the cerebral ventricles with tubocurarine 1/500 to 1/5000. It consists of continuous rhythmic discharges of surface-negative spikes of high voltage which become multiple as the perfusion progresses and are interrupted from time to time by bursts of fast activity, termed episodes. The abnormal discharge appears first in the occipital and then in the frontal leads but at a lower voltage. When the perfusion with tubocurarine is through one lateral ventricle the changes begin, and are later recorded predominantly, in the ipsilateral leads.

In the present experiments it has been found that with the unilateral perfusion of tubocurarine a concentration as weak as 1/20,000 may still produce an abnormal discharge on the e.e.g. Under pentobarbitone sodium the abnormal discharge does not occur invariably and if it occurs it begins after a latency of 20–75 min and does not develop to its full pattern. It appears as a rhythmic discharge of single spikes in the occipital lead on the side perfused with tubocurarine. This pattern does not change; neither multiple spikes nor episodes occur. Under chloralose, on the other hand, a tubocurarine concentration of 1/20,000 invariably produces a rhythmic discharge of single spikes which occurs after a latency of 15–60 min, and in many experiments multiple spikes and episodes are recorded on continued perfusion. The development of these changes is similar to that found with a concentration of 1/5000 under pentobarbitone sodium. Therefore, as far as the e.e.g. changes produced by intraventricular tubocurarine are concerned, cats are more sensitive under chloralose than under pentobarbitone sodium.

Correlation between e.e.g. changes and muscular effects

There is some correlation between myoclonus and the abnormal discharge on the e.e.g. Muscle jerks may or may not be present during the period when single spikes are recorded. The jerks are then small, involving the muscles of the neck and shoulder girdle, and often synchronize with the spikes although

spikes are more frequent than jerks. Violent jerks only occur after the spikes have become multiple and there are then long periods during which each multiple spike is followed by a jerk. Yet multiple spikes may occur without muscle jerks and violent jerks without spikes. In the one experiment in which the posterior half of the lateral ventricle was excluded from the perfusion and no muscle jerks occurred, the abnormal discharge was also absent, although the concentration of tubocurarine perfused was as strong as 1/1000.

Tremor is independent of the changes in the e.e.g. It may occur long before the onset of the abnormal discharge and even with concentrations of tubocurarine too low to affect the e.e.g. When the abnormal discharge appears tremor continues. As long as no jerks occur there is no correlation between the abnormal discharge and tremor, regardless of whether the discharge consists of single spikes, multiple spikes, or of episodes. A jerk, however, interrupts tremor, and when myoclonus becomes violent tremor ceases for a short time after each jerk.

DISCUSSION

The tubocurarine tremor resembles shivering. The finding that it originates from that part of the brain, the hypothalamus, in which the centre for temperature control is situated suggests that the mechanisms activated in the two phenomena are the same.

On electrical stimulation tremor-like movements are produced in cats not only from the hypothalamus but also from structures in the mesencephalon surrounding the aqueduct (Birzis & Hemingway, 1957). But tubocurarine appears to be unable to elicit tremor by an action on these structures, since in the present perfusion experiments tremor only occurs when the structures lining the ventral part of the third ventricle, i.e. the hypothalamus, have been reached by the tubocurarine. This difference between the effects of electrical stimulation and of tubocurarine is readily understood on the assumption that tubocurarine acts on synapses, whereas electrical stimulation of the mesencephalic regions produces tremor by acting on nerve fibres which form the efferent pathway from the centre in the hypothalamus. Otherwise one would have to assume differences in sensitivity to tubocurarine between the synapses in the hypothalamus and those in the mesencephalon.

The finding that tremor is produced by an action of tubocurarine on the hypothalamus is at variance with the statement by Feldberg & Malcolm (1959) that the most sensitive regions where tubocurarine produces muscular effects including tremor are those surrounding the aqueduct. In some of their experiments they found that the aqueduct was excluded

from perfusion because the tip of the outflowing cannula was lying at the opening into the third ventricle. Under these circumstances, a stronger concentration of tubocurarine was needed to produce the muscular effects than if the aqueduct had been included. These results may be explained on the assumption that the tubocurarine has a facilitatory effect on tremor by penetrating the structures surrounding the aqueduct.

The production by tubocurarine of long-lasting tremor uninterrupted by myoclonus provides a method for studying the effects on tremor of a number of substances given by the intraventricular route. A striking difference is found in the potency and time course of action between the sympathomimetic amines, adrenaline and noradrenaline on the one hand, and atropine and hyoscine on the other. For atropine and hyoscine to act strong concentrations are required. The effect occurs after a latency of about 1 min; it takes several minutes to reach its maximum and recovery is slow. In contrast the two amines act in weak concentrations, and onset, development and recovery are more rapid. With adrenaline, the more potent of the two, a concentration as weak as 1/5 million perfused through one of the two cannulated ventricles is sometimes found to be effective which, in the third ventricle, would correspond to a concentration of 1/10 million as a result of dilution from the fluid entering from the opposite lateral ventricle. In addition the latency is so short that considering the time required for the perfusion fluid to reach the third ventricle the effect often appears to be immediate. The amines must therefore act on superficial structures of the ventricular wall. Penetration into the brain tissue may not be necessary, for the action may be on intra-ependymal nerve endings which have been described in several species of mammals including man (Agduhr, 1932; Pesonen, 1940*a*, *b*; Blanc, 1955), or on chemoreceptors within specialized regions of hitherto unknown function, such as the intercolumnar tubercle. The action of atropine and hyoscine, on the other hand, is readily explicable by penetration of the brain tissue.

The tubocurarine tremor has the same appearance as that produced by intraperitoneal pentobarbitone sodium, which is also abolished by weak concentrations of either adrenaline or noradrenaline perfused through the cerebral ventricle; but unlike the tubocurarine tremor that produced by pentobarbitone is not affected by perfusion with strong concentrations of atropine or hyoscine (Domer & Feldberg, 1960). The cause of this difference has not been investigated.

Whereas the tremor produced both by intraventricular tubocurarine and intraperitoneal pentobarbitone closely resembles shivering, the tremor seen in man suffering from paralysis agitans is of a different character. It has a slow rhythm, affects the more distal joints and is associated with lesions involving the substantia nigra. A drug which affects the tubocura-

rine or pentobarbitone tremor therefore need not be effective on tremor in Parkinson's disease and accordingly the possibility of producing tremor by an action of tubocurarine on the hypothalamus will not necessarily provide a method for assessing the action of drugs for the treatment of Parkinsonism.

Whereas the tubocurarine tremor arises from an action on structures in the hypothalamus, myoclonus occurs only if the tubocurarine reaches the walls of the posterior half of the lateral ventricle. As the abnormal discharge on the e.e.g. has also been shown to result from an action of tubocurarine on structures lining this part of the lateral ventricle, namely the hippocampus and amygdala, the question arises as to whether there is an association between myoclonus and abnormal discharge. Such an association has been found to exist. Unlike tremor, myoclonic jerks are often associated with spikes. The association, however, is not close, because jerks also occur without spikes, and spikes without jerks. Further, the myoclonus begins bilaterally and remains of equal strength on both sides although the perfusion with tubocurarine is one-sided and the spike discharge recorded predominantly from the ipsilateral hemisphere. These findings may be explained on the assumption that myoclonus and seizure discharge result from an activation of the same regions, the hippocampus and/or the amygdala, and that these structures are connected with the ipsilateral cortex as well as with lower centres on either side of the mid line in the diencephalon and mesencephalon. Activation of such mid-line structures by impulses originating unilaterally in the hippocampus or amygdala could account for the fact that the jerks occur bilaterally. Direct as well as indirect fibre connexions to such mid-line structures from the hippocampus and amygdala have been described in the cat by Nauta (1958).

The present experiments do not exclude the possibility that for the production of myoclonic jerks tubocurarine has not only to activate the hippocampus and/or amygdala, but has also to exert a facilitatory effect by acting also on other structures which lie close to either the lateral or third ventricles, or particularly to the rostral part of the aqueduct. The possibility of such a facilitatory effect has been discussed in relation to the production of tremor.

From the findings that under chloralose myoclonus is obtained with weaker concentrations of tubocurarine and that the tremor is of longer duration than under pentobarbitone sodium anaesthesia, the pentobarbitone sodium appears to have a stronger depressant influence on the motor effects of tubocurarine than chloralose. However, this is not so for all the motor effects, because when tubocurarine is applied to the dorsal surface of the upper cervical cord, scratching movements are produced

only under pentobarbitone sodium and not under chloralose anaesthesia (Feldberg & Fleischhauer, 1960*b*). These two anaesthetics also influence differently the effects of tubocurarine applied to the cerebral cortex (Feldberg, Malcolm & Darian Smith, 1957).

SUMMARY

1. Tremor, myoclonus and an abnormal discharge on the e.e.g. are produced in cats anaesthetized with either chloralose or pentobarbitone sodium on perfusion of tubocurarine from one lateral ventricle to aqueduct.

2. Tremor results from an action of tubocurarine on the hypothalamus. This conclusion is based on the results of experiments in which different parts of the ventricular system are excluded from the perfusion with tubocurarine. Tremor occurs only when the part of the third ventricle which lies ventral to the massa intermedia is reached by the tubocurarine.

3. Tremor resembles shivering and is different in character from the tremor of Parkinsonism.

4. Tremor is reduced or abolished when adrenaline, noradrenaline, dopamine, atropine or hyoscine are perfused from the other lateral ventricle to aqueduct. Adrenaline acts in weak concentrations; it is 2–4 times more potent than noradrenaline and 200 times more potent than dopamine. Atropine and hyoscine act only in strong concentrations and their effect develops more slowly and is more prolonged than that of the amines.

5. Myoclonus results from an action on structures lining the lateral ventricle, probably its posterior half.

6. Myoclonus is bilateral although one lateral ventricle is excluded from the perfusion.

7. Abnormal discharge on the e.e.g. has no association with the tremor but there is a correlation, though not absolute, between the discharge and myoclonus.

8. In producing tremor, myoclonus and the abnormal discharge, tubocurarine is more effective under chloralose than pentobarbitone sodium anaesthesia.

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