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INFLUENCE OF VARIOUS DRUGS ON THE ACTION OF CURARE ON THE CENTRAL NERVOUS SYSTEM OF THE CAT

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In previous papers (Salama and Wright, 1950, 1951, 1952) the central effects of various curariform substances were described. In continuation of this work the effects of the following substances on the central action of *d*-tubocurarine and calabash curare were studied : (i) acetylcholine ; (ii) atropine ; (iii) neostigmine ; (iv) eserine (sulphate) ; (v) hexaethyltetraphosphate ; (vi) nicotine ; (vii) lobeline ; (viii) tetramethylammonium iodide ; (ix) potassium chloride. The drugs affected the central action of both curare preparations in a similar manner.

In addition, the effects of very large doses of *d*-tubocurarine were further examined.

METHODS

The methods employed were described in detail in the preceding paper (Salama and Wright, 1952).

RESULTS

Acetylcholine.—Acetylcholine injected by the intrathecal, intraventricular, or intravenous route inhibited convulsions set up by a previous injection of *d*-tubocurarine or calabash curare. The degree of inhibition produced depended on the amount of curare administered, the vigour of the convulsions, and the dose of acetylcholine employed. When the convulsions were very vigorous small doses of acetylcholine had little inhibitory effect, but larger doses of acetylcholine greatly depressed and sometimes completely abolished the convulsions.

Fig. 1 illustrates an experiment in an animal made spinal by tying a tight ligature round the meninges and spinal cord at the level of T 6. Previous intrathecal injection of 0.8 mg. (0.2 mg./kg.) calabash curare below the level of the block had produced violent rapid convulsions in the hind-limb muscles. Injection of 10 mg. (2.5 mg./kg.) acetylcholine intrathecally below the block produced an immediate slowing of the frequency of the convulsions with less change in their magnitude. There was a transient fall of blood pressure from 100 to 70 mm. Hg and little change in the respiratory record. The inhibitory effect was brief, and after 2.5 min. the convulsions returned to their initial frequency and then progressively increased

* The main results were reported by S. Salama to the Physiological Society (January, 1949) and were incorporated in a Ph.D. thesis which was accepted by the University of London.

in vigour. A second injection of 10 mg. acetylcholine was given intrathecally. There was the same transient fall of blood pressure and again the respiratory record was unaffected, but on this occasion the convulsions were completely abolished ; the quadriceps record showed only tiny knee-jerk responses which were far smaller than those obtained before the injection of the curare.

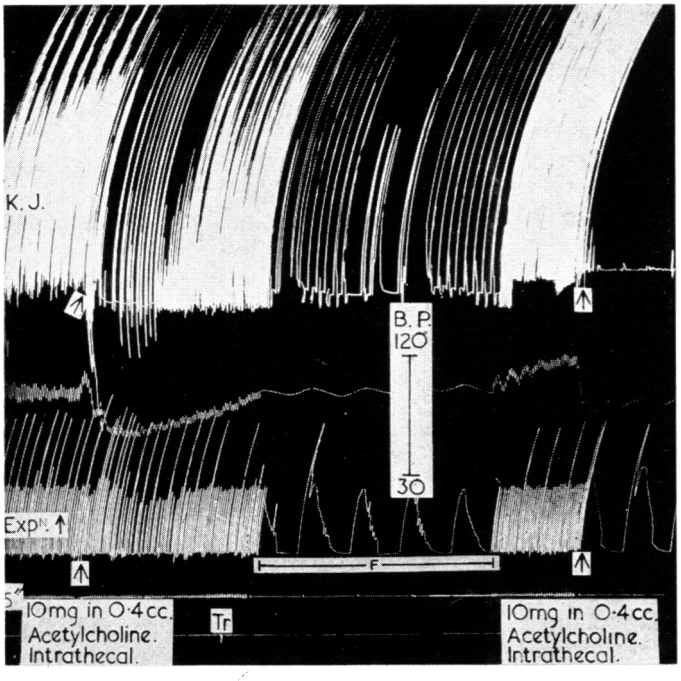

FIG. 1.—Cat, 4 kg., chloralose; spinal cord completely blocked by tight ligature at T 6. Records from above downwards are: knee-jerk; carotid blood pressure; respiration; time in 5 sec.; signal line. A previous injection of 0.8 mg. calabash curare made intrathecally below the spinal block had produced violent convulsions. At the first arrow, 10 mg. acetylcholine injected intrathecally below the spinal block. After 1.6 min. drum accelerated for 25 sec. (F). Return to slow drum. After 3 min., at the second arrow, 10 mg. acetylcholine injected intrathecally below the spinal block, and the drum immediately accelerated. At Tr, a few drops of c.s.f. were allowed to escape to restore its normal pressure.

There can be little doubt that the anticonvulsive action of acetylcholine described above is due to a direct action on the spinal neurones. It is independent of changes in the blood pressure or respiration. It is well known that large doses of acetylcholine injected intravenously produce peripheral neuromuscular block, but in the experiments just described it is most improbable that significant amounts of acetylcholine were absorbed from the cerebrospinal fluid into the circulation. As atropine was not administered a profound fall of blood pressure would have taken place if such absorption had occurred. Furthermore, the respiratory muscles would have been affected by the blocking action ; but Fig. 1 shows that when the convulsions were abolished the respiratory movements were almost unaltered. Lastly, it should again be emphasized that the decrease in frequency of the convulsions without

change in amplitude that may be produced by acetylcholine (Fig. 1) cannot be brought about by a peripheral blocking action.

Acetylcholine injected intraventricularly can also abolish curare convulsions. The anticonvulsive action of acetylcholine is partially annulled by atropine.

The central effect of injected acetylcholine may be excitatory or inhibitory according to the dose, the route of administration, and the exact experimental conditions (Feldberg, 1945, 1950). When injected intravenously into the cat under chloralose it generally depresses the reflexes and inhibits strychnine convulsions. Occasionally with small doses under these conditions there is an initial stimulating effect (Schweitzer and Wright, 1937b, c). Kremer (1942) injected acetylcholine in man intrathecally in doses of 2–500 mg. without result; but when the drug was administered together with subliminal doses of neostigmine it depressed muscle tone and reflexes by a central action.

Bülbring and Burn (1941), working on the isolated perfused spinal cord, obtained with acetylcholine a motor discharge from the resting spinal cord; the knee-jerk showed a transient depression followed by stimulation, but the flexor reflex was potentiated. Calma and Wright (1944), using the decerebrate cat, injected acetylcholine intra-arterially into the central end of the subclavian artery and found that it produced a discharge from the spinal motor neurones.

Atropine.—Atropine has a mild inhibitory effect on spinal cord excitability, and partially or wholly annuls both the central excitatory and the central depressant action of acetylcholine (Schweitzer and Wright, 1937b; Calma and Wright, 1944). We found that atropine diminishes the central excitatory action of tubocurarine.

In a representative experiment in which 0.4 mg. (0.16 mg./kg.) *d*-tubocurarine was intraventricularly injected the usual effects appeared; the knee-jerk and the previously very weak flexor reflex were immediately enhanced; the tone of both flexors and extensors increased; the crossed extensor reflex appeared; the flexor reflex and the knee-jerk showed considerable after-discharge; and " spontaneous " movements set in. Previous experience indicated that violent convulsions were about to develop. Injection of 1 mg. (0.37 mg./kg.) atropine intraventricularly at this stage depressed, after a delay of about 3 min., the mounting state of hyperexcitability and finally abolished the " spontaneous " movements as well as the increase in tone and the after-discharge. The enhanced knee-jerk and flexor reflex, however, were only slightly depressed.

Six minutes later the hyperexcitability induced by tubocurarine began to return; the depressant effect of the atropine was thus transient. Moreover, the anticonvulsive effects of acetylcholine are smaller in the atropinized than in the unatropinized preparation.

Neostigmine.—Neostigmine inhibited curare convulsions when injected intrathecally or intraventricularly; this antagonistic action is indistinguishable from that produced by acetylcholine. The minimum dose of prostigmine which inhibited the convulsions was usually about 0.5 mg. (0.15 mg./kg.).

Fig. 2 illustrates an experiment in which *d*-tubocurarine had been injected intracisternally in an unatropinized animal and had produced violent convulsions. Injection of 0.5 mg. neostigmine intracisternally immediately produced marked inhibition which was, however, very brief, the convulsions soon reappearing with their full previous violence.

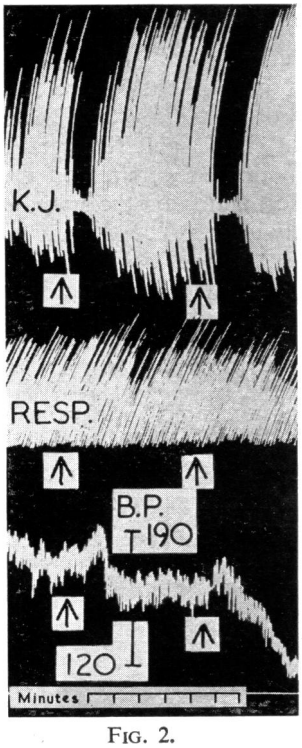

FIG. 2.

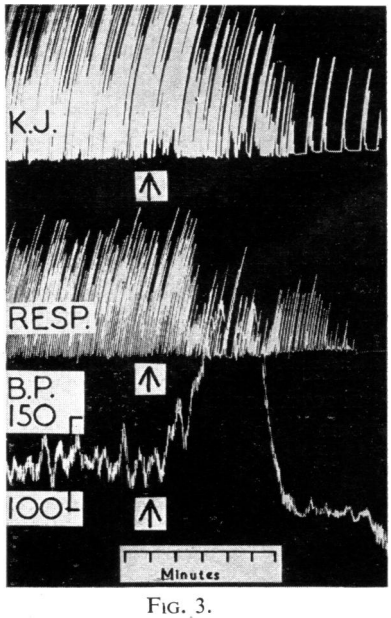

FIG. 3.

FIG. 2.—Cat, 3.5 kg., chloralose. Records from above downwards are: knee-jerk (right side); respiration; carotid blood pressure; signal line; time in min. Seventeen minutes before the start of the record, 0.4 mg. *d*-tubocurarine had been injected intracisternally and violent convulsions had been set up. At first and second arrows 0.5 mg. neostigmine in 0.5 c.c. saline injected intracisternally.

FIG. 3.—Cat, chloralose. Records from above downwards are: knee-jerk (right side); respiration; carotid blood pressure; time in min. Eighteen minutes before the start of the record, 0.4 mg. *d*-tubocurarine had been injected intrathecally. At arrow, 0.5 mg. neostigmine injected intrathecally.

Fig. 3 illustrates an experiment in which an *intrathecal* injection of 0.4 mg. *d*-tubocurarine in the unatropinized animal had produced violent rapid convulsions. Injection of 0.5 mg. neostigmine intrathecally rapidly abolished the convulsions; the knee-jerk, however, remained enhanced and showed an appended shortening reaction.

The anticonvulsive action of neostigmine was partially annulled by atropine. There was no relationship between the blood pressure changes produced by neostigmine and its action on spinal cord excitability. Thus Fig. 2 shows that both the first transient inhibition of the curare convulsions by neostigmine and their subsequent rapid return occurred while only minor alterations in the blood pressure were taking place. In Fig. 3 the inhibition of the convulsions began during the rapid rise of blood pressure produced by neostigmine; it became complete when the pressure had almost returned to its initial value.

When neostigmine was injected intraventricularly in the atropinized animal under artificial respiration it likewise inhibited curare convulsions and reflex spinal excitability, but no change in the blood pressure occurred.

Schweitzer and Wright (1937c) demonstrated that intravenously injected neostigmine in cats under chloralose depressed spinal cord excitability and abolished strychnine convulsions. Kremer, Pearson, and Wright (1937) and Kremer (1942) found that intrathecally injected neostigmine in man likewise diminished muscle tone and the strength of voluntary movements by a direct action on the spinal cord. Calma (1949), however, found that in the cat intrathecally injected neostigmine stimulated spinal cord excitability.

Eserine.—Eserine (sulphate) antagonizes the central excitatory action of curare. Fig. 4A illustrates an experiment in which the usual violent convulsions had appeared after the intrathecal injection of 0.8 mg. (0.2 mg./kg.) *d*-tubocurarine ; 0.4 mg. (0.1 mg./kg.) of eserine (sulphate) was then injected and inhibited the convulsions. The effect was transient ; after one minute the convulsions reappeared. A further dose of 0.4 mg. eserine (sulphate) frequently produced a " triple effect " (Fig. 4B). There was an initial depression of the convulsions followed by a brief excitation and then the convulsions and the other reflexes were abolished. The hyperexcitable state of the spinal cord, however, could be restored by a further injection of curare, and could again be inhibited by a further dose of eserine. The inhibitory effect of eserine was independent of the changes in the blood pressure or respiration.

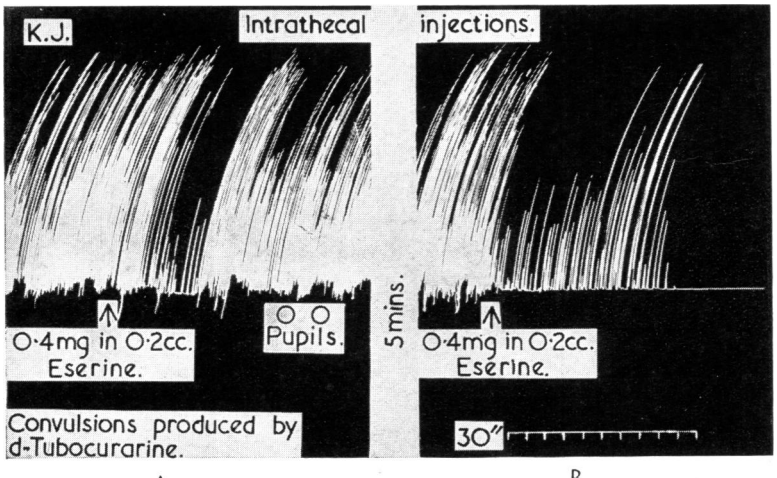

FIG. 4.—Cat, 4 kg., chloralose. Records from above downwards are: knee-jerk; pupillary size; time in 30 sec. Before the start of the record 0.8 mg. *d*-tubocurarine had been injected intrathecally. When the usual violent convulsions had appeared recording was begun. (A) At the arrow, 0.4 mg. eserine (sulphate) injected intrathecally. The pupils were widely dilated during the convulsions. (B) Taken after an interval of 5 min. At the arrow, 0.4 mg. eserine (sulphate) injected intrathecally.

The results described above were unexpected, because eserine (sulphate) excites the central nervous system in the intact cat under chloralose anaesthesia, and may itself produce violent convulsions (Schweitzer and Wright, 1937b, c).

Hexaethyltetraphosphate (HETP).—Chennells, Floyd, and Wright (1949) found that HETP (which is an anticholinesterase) produces, when injected intrathecally in the cat, hyper-reflexia and violent convulsions. The main action of HETP on curare convulsions is to abolish them temporarily, but subsequently the convulsions may return with greater vigour.

In a representative experiment convulsions were first induced by the injection of 0.4 mg. *d*-tubocurarine intraventricularly; they were almost unaffected by a subsequent intravenous injection of 1 mg. atropine; 0.25 mg. HETP was then injected intraventricularly. There was an immediate decrease in the frequency and vigour of the convulsive movements. There was only a small coincident rise of blood pressure, indicating once more the independence of reflex spinal excitability of the changes in blood pressure. This effect lasted only for about 2 min.; the convulsions then rapidly increased in frequency and vigour to the pre-injection level. An injection of 0.5 mg. (0.15 mg./kg.) HETP was now made intraventricularly; the convulsions were immediately arrested for 2 min., during which time only weak responses of the knee-jerk and the flexor reflex were recorded. A marked rise of blood pressure, i.e., from 80 to 210 mm. Hg, was produced by this larger dose of HETP. The convulsions then progressively returned and gained in strength and frequency; ultimately they became much more frequent and more violent than before the injection of HETP. This experiment also illustrates that HETP can produce its anticonvulsive effect in the atropinized animal.

These results were unexpected because as already mentioned when HETP is injected intrathecally it produces hyper-reflexia and violent convulsions.

Nicotine.—Schweitzer and Wright (1938) found that intravenously injected nicotine even in doses of 5 μg. (about 1.5 μg. per kg.) exerted a depressant action on the spinal reflexes in the cat, without any initial central excitation. They also found that nicotine exerted an antistrychnine action.

In the experiments to be described the central effects produced by intraventricular injection of nicotine were investigated as well as the possible central antagonism between nicotine and curare.

Spinal reflexes.—Intraventricular injection of 0.25 and 0.5 mg. nicotine produced no significant diminution of the knee-jerk or the flexor reflex.

Blood pressure.—Injection of 0.25 mg. of nicotine produced a slight transient fall of blood pressure similar to that produced by an equal volume of saline. When 0.5 mg. was injected there was in addition a second gradual and considerable fall of blood pressure (e.g., from 160 to 110 mm. Hg), accompanied by bradycardia. The blood pressure gradually recovered to its initial level.

Pupils.—Complex effects were produced on injection of 0.25 mg. The pupils gradually constricted and the nictitating membrane relaxed; ultimately the pupils were slit-like and the nictitating membrane covered the sclera up to the margin of the iris. After a subsequent injection of 0.5 mg. nicotine, the pupils first dilated and then gradually constricted once more.

Central nicotine-curare antagonism.—A dose of nicotine injected intraventricularly which itself produced negligible effects on the spinal reflexes delayed for a long time, and partially annulled, the central excitatory effects of subsequently injected *d*-tubocurarine, both on the motor neurones and on the vasomotor centre. Thus in

one experiment 0.5 mg. nicotine was injected intraventricularly ; 5 min. later 0.6 mg. *d*-tubocurarine was injected intraventricularly. After 6 min. there was only a slight increase in the knee-jerk ; after 15 min. only mild convulsions had appeared. The flexor reflex was unaltered. The rise of blood pressure was delayed in onset and small in extent.

In another experiment the drugs were injected in the reverse order : 0.6 mg. *d*-tubocurarine was first injected intraventricularly ; convulsions appeared after 3 min. and there was a considerable rise of blood pressure ; 6.5 min. later 1 mg. (0.4 mg./kg.) nicotine hydrochloride was injected intraventricularly ; there was a temporary fall of the blood pressure from 260 to 200 mm. Hg, but it soon returned to its previous high level. The convulsions were not depressed but progressively increased in violence.

It thus seems that the anticonvulsant action of nicotine can only be demonstrated when its injection *precedes* that of curare. One may suppose that once the nicotine has become fixed to the nerve cells it can only be replaced with difficulty by curare ; but if curare is injected first, subsequently administered nicotine can neither replace nor neutralize it.

Lobeline.—Intraventricular injection of 0.2 mg. (0.07 mg./kg.) lobeline hydrochloride produced a gradual but considerable fall of blood pressure from 160 to 70 mm. Hg, associated with a slight depression of the spinal reflexes examined (flexor reflex, crossed extensor reflex, jar reflex, and knee-jerk).

The depression of the reflexes cannot be attributed to the circulatory changes. Schweitzer and Wright (1937a) found that a fall of blood pressure depressed the knee-jerk only when it was acute and very severe ; a fall of blood pressure even down to 40–50 mm. Hg did not usually modify the knee-jerk, or, if it did, it enhanced it. The depression of the reflexes produced by lobeline is, therefore, due to a direct action on the central nervous system.

Lobeline, like nicotine, delays and diminishes the central excitatory effects of subsequently injected curare. Unlike nicotine, however, lobeline can also annul the convulsions induced by a preceding injection of curare.

When 0.5 mg. *d*-tubocurarine was injected intraventricularly after two previous injections of 0.2 mg. (0.07 mg./kg.) lobeline, it produced its usual effects, but they appeared after a longer latent period. Thus the rise of blood pressure and the convulsive movements were delayed both in onset and in rate of development. Ultimately, however, the convulsions became violent and rapid.

When a further 0.5 mg. (0.17 mg./kg.) lobeline was injected (Fig. 5A) the curare convulsions were at once markedly diminished in frequency and amplitude ; this inhibition set in before the blood pressure had significantly altered. The blood pressure gradually fell from 130 mm. to a minimum level of 30 mm.; at this stage the convulsions completely ceased and only a reduced knee-jerk persisted. Probably this secondary phase of inhibition was only partly attributable to the fall of blood pressure, as the flexor reflex was not affected. Moreover, the convulsions began to return while the blood pressure was still at a low level (Fig. 5B, C).

Tetramethylammonium (TMA).—We have shown (Salama and Wright, 1952) that intraventricularly injected TMA has a central depressant action. The experiments to be described show that it also antagonizes the convulsant action of curare.

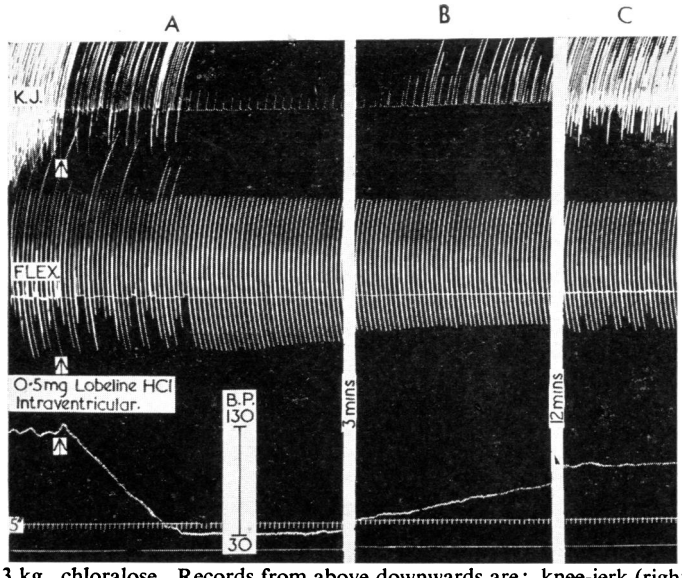

FIG. 5.—Cat, 3 kg., chloralose. Records from above downwards are: knee-jerk (right side) ; flexor reflex (left side); carotid blood pressure; time in 5 sec. (A) Before the record began the animal had received two intraventricular injections of 0.2 mg. lobeline HCl. Subsequent injection of 0.5 mg. *d*-tubocurarine intraventricularly had ultimately produced violent convulsions. At the arrow, 0.5 mg. lobeline hydrochloride injected intraventricularly. (B) Taken 3 min. after A. (C) Taken 12 min. after B.

Fig. 6 illustrates an experiment in which the usual convulsive state was produced by an intraventricular injection of 0.4 mg. *d*-tubocurarine. Injection of 10 mg. (4.1 mg./kg.) of TMA intraventricularly immediately inhibited the spontaneous movements of both flexors and extensors ; a little later the knee-jerk and flexor reflex were depressed and finally abolished for a long time (up to 45 min.). During this period of inhibition intraventricular injection of small doses of *d*-tubocurarine failed

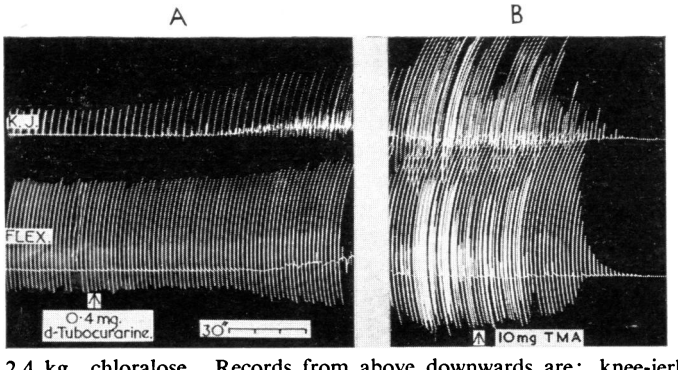

FIG. 6.—Cat, 2.4 kg., chloralose. Records from above downwards are: knee-jerk (right side); flexor reflex (left side); time in 30 sec. (A) At the arrow, 0.4 mg. of *d*-tubocurarine intraventricularly. (B) At the arrow, 10 mg. of tetramethylammonium iodide (TMA) injected intraventricularly.

to restore normal spinal excitability. The inhibitory action of TMA on the convulsions and reflexes is due to a central effect, since the responses of the gastrocnemius muscle stimulated through its motor nerve were not affected.

Potassium chloride.—Intraventricularly injected potassium chloride annuls by a central action the central excitatory action of *d*-tubocurarine.

Fig. 7A illustrates an experiment in which 0.4 mg. *d*-tubocurarine had been injected intraventricularly; when marked hyperexcitability had developed 0.4 mg. KCl (0.16 mg./kg.) was injected intraventricularly. It immediately decreased and then almost abolished the "spontaneous" movements in the extensor and flexor

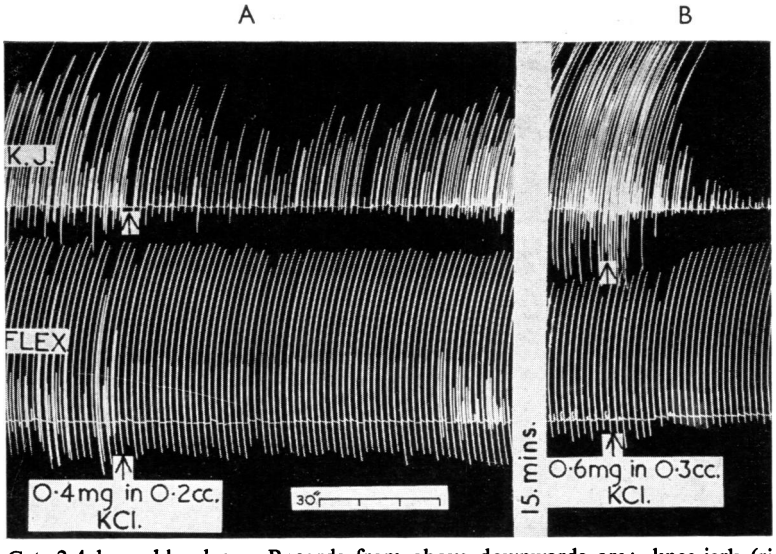

FIG. 7.—Cat, 2.4 kg., chloralose. Records from above downwards are: knee-jerk (right side); flexor reflex (left side); time in 30 sec. Before the start of the record 0.4 mg. *d*-tubocurarine had been injected intraventricularly and had produced central hyperexcitability. (A) At the arrow, 0.4 mg. KCl injected intraventricularly. Interval of 15 min. between A and B. (B) At the arrow, 0.6 mg. KCl injected intraventricularly.

muscles. Later the knee-jerk was slightly inhibited, but the flexor reflex remained unaffected. The central depression lasted only 4 min., after which spinal hyperexcitability gradually returned. When a larger dose, i.e., 0.6 mg. (0.25 mg./kg.) KCl was injected against a background of more violent curare convulsions (Fig. 7B), the "spontaneous" movements soon disappeared, and the knee-jerk was also very much diminished. The flexor reflex was slightly increased. The abolition of the convulsions lasted 15 min. In other experiments intraventricular injection of KCl also abolished curare convulsions affecting the flexor muscles.

Potassium ions annul the blocking action of curare at the motor endplates (Wilson and Wright, 1936); they stimulate autonomic ganglion cells after transmission at the synapses has been blocked by curarine (Brown and Feldberg, 1936). The experiments described above show that potassium ions annul the curare-induced hyperexcitability of the central nervous system. The effects of potassium ions on the nervous system have been described by Mullins *et al.* (1938), Resnik *et al.* (1936),

Downman and Mackenzie (1943), and Walker *et al.* (1945). Calma and Wright (1947) found that intrathecally injected KCl regularly depressed the flexor reflex, had variable effects on the knee-jerk, and regularly produced dilatation of the pupils, a rise of blood pressure, changes in the rate and rhythm of the heart, and alterations in breathing. Application of an isotonic KCl solution to the " isolated posterior nerve root preparation " reproduced all the above-mentioned changes except for the modification of the spinal reflexes. They concluded that externally applied potassium ions specifically stimulated the afferent fibres in the posterior roots concerned with visceral reflexes, but affected less, if at all, the afferents concerned with somatic reflexes. They suggested that when KCl is injected intracisternally, in addition to its direct action on the medullary centres, it stimulated nerves which may contribute to the production of the modifications in the visceral, but not the somatic reflexes.

Large doses of curare.—Large doses of curare *depress* somatic nervous reflexes. In a representative experiment, 0.4 mg. *d*-tubocurarine (0.13 mg./kg.) injected intraventricularly produced the usual hyper-reflexia. A large dose (4 mg.) of *d*-tubocurarine (1.3 mg./kg.) was then injected. Within 2 min. both the convulsions and the knee-jerk were markedly depressed. The response of the nerve-muscle preparation was entirely unaffected, showing that none of the drug was absorbed into the circulation. Later in the experiment, after an interval of 40 min., small doses of *d*-tubocurarine produced no central excitation. (Previous experiments have shown that an initial dose of 0.4 mg. produced convulsions which maintain their vigour and frequency for periods of up to 90 min. or longer.) Similar depressant effects were obtained with large doses of calabash curare.

It is a common experience that drugs which are convulsant in small doses are depressant in much larger doses. Such is the case, for example, with the convulsions induced by eserine (sulphate) in the cat under chloralose anaesthesia.

Discussion

Little need be added to the comments which were appended to the description of the action of each drug studied.

Acetylcholine and neostigmine, which antagonize strychnine convulsions, likewise antagonize curare convulsions. The central inhibitory action of both these drugs is partially annulled by atropine. Eserine (sulphate) and HETP, which are themselves convulsants, also annul curare convulsions; with HETP the initial inhibition is followed by a secondary stimulation. Tetramethylammonium iodide, which is a central depressant, also annuls curare convulsions. Nicotine and lobeline, which are weak central depressants, annul curare convulsions, nicotine only acting if it is injected before administering curare. Potassium chloride annuls curare convulsions when it is injected intraventricularly, although it produces convulsions in the normal animal when it is injected intracisternally.

Summary

1. The effects of intraventricular, intrathecal, and occasionally intravenous injection of certain drugs on the central excitant action of curare (*d*-tubocurarine and calabash curare) in the cat under chloralose anaesthesia were examined.

2. Atropine, which is a weak central depressant, diminishes the central excitatory action of curare.

3. Acetylcholine and neostigmine, which inhibit strychnine convulsions in the cat under chloralose, likewise antagonize curare convulsions. The central inhibitory action of both drugs is partially annulled by atropine.

4. Eserine and HETP, both of which produce convulsions in the cat under chloralose, also annul curare convulsions. With HETP the initial inhibition is followed by a secondary stimulation.

5. Tetramethylammonium, which is a central depressant, also annuls curare convulsions.

6. Nicotine, which annuls strychnine convulsions, can delay or diminish the central excitatory effect of subsequently injected *d*-tubocurarine ; it is comparatively ineffective in annulling curare convulsions that have already been set up.

7. The central actions of lobeline are described. It is a central depressant like nicotine or atropine. It not only delays or diminishes the central excitatory effect of subsequently injected curare but also annuls the convulsions induced by a preceding injection of curare.

8. Intraventricularly injected potassium chloride annuls curare convulsions.

9. Large doses of curare injected intraventricularly depress somatic nervous reflexes by a central action.

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