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ACTION ON CENTRAL NERVOUS SYSTEM OF COMPOUNDS RP 3565 AND RP 3697 AND OF TETRAMETHYLAMMONIUM AND TETRAETHYLAMMONIUM

BY

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Continuing our previous studies (Salama and Wright, 1950, 1951) of the central action of " curariform " substances we have examined the action of the compounds RP 3565 and RP 3697 (Gallamine triethiodide, " Flaxedil ") and of tetramethylammonium and tetraethylammonium. RP 3565 (Bovet, Courvoisier, Ducrot, and Horclois, 1947) is the dimethiodide of bis-(dimethylaminophenoxy)-1 : 5-pentane. RP 3697 (Bovet, Depierre, and Lestrange, 1947) is the triethiodide of tris-(β-diethylaminoethoxy) benzene (see also Bovet and Bovet-Nitti, 1948). We did not examine the central action of RP 3381 (diethiodide of bis-(8-quinolyloxy)-1 : 5-pentane) (Bovet, Courvoisier, Ducrot, and Horclois, 1946) because of its low solubility in water and other solvents. The results to be described show that RP 3565 has a central excitatory action resembling that of *d*-tubocurarine but only 5–10 per cent as strong. RP 3697 has a still feebler and inconstant central excitatory action.

The main actions of tetraethylammonium (TEA) and tetramethylammonium (TMA) were first described by Burn and Dale (1914). The actions of the onium compounds have been reviewed by Ing (1936) and of TEA by Moe and Freyburger (1950). TEA has no peripheral muscarine-like action on the heart ; it paralyses autonomic ganglia without previous stimulation and has a weak peripheral neuromuscular blocking action. TMA has a peripheral muscarine-like action ; in small doses it stimulates and in large doses paralyses autonomic ganglia, and it is a potent neuromuscular blocking agent. It was of interest to determine how the actions of TEA and TMA on the central nervous system compared with their ganglionic action and their action at the neuromuscular junction (the " paradigm " of a synapse (Sherrington, 1947)). The results to be described show that TMA which is a ganglionic stimulant has a central depressant action (like nicotine), but is much weaker. The central action of TEA is complex, involving both excitation and inhibition. When injected intrathecally in large doses, however, TEA potentiates spinal reflexes by a direct action on the spinal neurones.

* The main results were reported by S. Salama to the Physiological Society (April, 1948) and were incorporated in a Ph.D. thesis which was accepted by the University of London.

METHODS

Cats were used in all the experiments, anaesthetized with chloralose (60–80 mg./kg. body weight) injected intravenously. The drugs investigated were injected by the intraventricular, intracisternal, intrathecal, or intravenous routes. Intraventricular and intracisternal injections were carried out as described by Salama and Wright (1950). Intrathecal injections were carried out by the method of Calma and Wright (1947) in intact and spinal animals. In the latter the spinal cord at the level of the proposed block was exposed ; a thread was passed round it enveloping the meninges, and very firmly tied around the dura and spinal cord. The block produced in this way was complete ; the cord inside the ligature appeared crushed. This type of block limits the local action of intrathecally injected drugs to the spinal cord caudal to the level of the ligature.

The knee-jerk was elicited at regular intervals (every 5 or 10 sec.) by means of an electromagnetically operated tapper (Schweitzer and Wright, 1937a) ; the flexor reflex by single break shocks applied at 5 or 10 sec. intervals to the central end of the cut tibial nerve.

The nerve-muscle preparation employed was the gastrocnemius, stimulated maximally through the sciatic nerve with break shocks once in 5 or 10 sec.

Respiration was recorded by connecting the tracheal cannula through suitable valves (obtained from discarded gas masks) to a Marey's tambour.

In order to differentiate between the central and peripheral action of the drugs the ischaemic hind-limb preparation (Schweitzer and Wright, 1937c, 1938a) was employed ; after the collateral vessels had been tied the aorta and inferior vena cava were clamped and the drug injected into the jugular vein. It could thus reach the central nervous system but not the hind-limb muscles. Changes in the hind-limb reflexes under these conditions must be due to a central action of the drug.

RESULTS

Action of RP 3565

Intravenous injection.—Injection of 0.15–0.25 mg./kg. intravenously produced a moderate fall of blood pressure. The respiration, the responses of the nerve-gastrocnemius preparation, and the knee-jerk were all abolished rapidly at about the same time. Owing to the powerful neuromuscular blocking action of the drug the central excitatory action (to be demonstrated below) was masked. Recovery gradually set in ; the knee-jerk and the responses of the gastrocnemius reappeared first, and finally respiration returned.

Intraventricular injection.—Fig. 1 illustrates a representative experiment in which 5 mg. (1.5 mg./kg.) RP 3565 was injected intraventricularly. The responses of the nerve-gastrocnemius preparation began to decrease in 1 min. and disappeared in 11 min. This effect shows that in this dosage enough of the drug is rapidly absorbed from the cerebrospinal fluid into the general circulation to produce neuromuscular block. There was no initial stimulation of breathing. Respiration declined about the same time as the peripheral paralysis set in and finally ceased ; artificial respiration, therefore, had to be started. In spite of the coincidental development of neuromuscular block, the knee-jerk was initially doubled in height ; resting quadriceps tone was increased and seemingly spontaneous movements (convulsions) appeared. The hyper-reflexia and the spontaneous movements reached their peak in 3 min. These observations prove that RP 3565 has an excitant action on the central nervous system. Asphyxia played little part in the production of the convulsions,

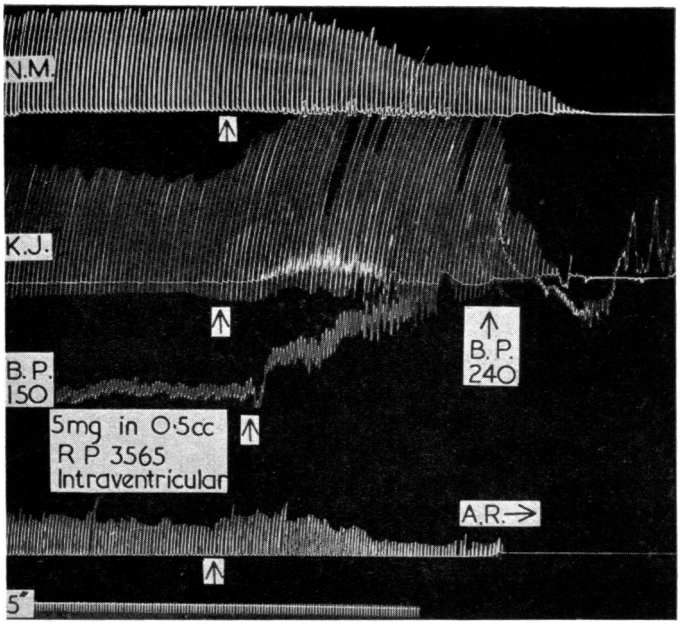

FIG. 1.—Cat, 3.2 kg.; chloralose. Records from above downwards are: (N.M.) contractions of gastrocnemius (left side) stimulated through motor nerve; (K.J.) knee-jerk (right side); (B.P.) carotid blood pressure; respiration; time in 5 sec. At arrow, 5 mg. RP 3565 injected intraventricularly. Level of blood pressure at second arrow is 240 mm. Hg. At AR: artificial respiration started.

as they were equally intense in experiments carried out under artificial respiration. Finally, however, the peripheral paralytic action became dominant; the increase in the reflex responses and in tone and the convulsions passed off; the knee-jerk became progressively weaker and finally disappeared after 10 min.

After the injection the blood pressure showed an immediate but gradual rise from 150 to 240 mm. Hg, accompanied by an intense bradycardia; these changes were not due to asphyxia. Since *intravenous* injection of similar (or smaller) doses of the drug lowered the blood pressure, the hypertension must have been due to increased activity of the vasomotor centre.

Intrathecal injection.—The following were the effects of intrathecal injection of 8 mg. (2 mg./kg.) RP 3565 into the lumbar theca below a spinal block produced at the level of T 6 (to prevent upward flow of the drug) in an animal under artificial respiration. The knee-jerk was immediately enhanced. This increase attained its peak in 1.3 min., but was soon followed by a rapid decline and disappearance of the knee-jerk in 3.3 min. While the knee-jerk was enhanced, the responses of the gastrocnemius muscle rapidly failed, indicating speedy absorption of the drug from the spinal subarachnoid space into the general circulation. The increase in the knee-jerk which occurred in spite of neuromuscular block indicates that the drug directly increased the excitability of the spinal cord.

After 45 min. the nerve-muscle responses partially recovered (to less than half their initial height), but the knee-jerk recovered completely. Subsequently, some spontaneous movements appeared, indicating persistent spinal cord hyper-excitability.

Interaction of central and peripheral effects.—In order to determine the extent to which the peripheral paralysing action of the drug was masking its central excitatory effects the ischaemic hind-limb technique (Schweitzer and Wright, 1937c, 1938a) was employed. These experiments also demonstrated that the drug was fixed or destroyed by the tissues generally and especially by the elements of the central nervous system.

(i) The abdominal aorta and inferior vena cava were clamped and then 10 mg. (2.5 mg./kg.) RP 3565 were injected *intravenously* (Fig. 2). The blood pressure

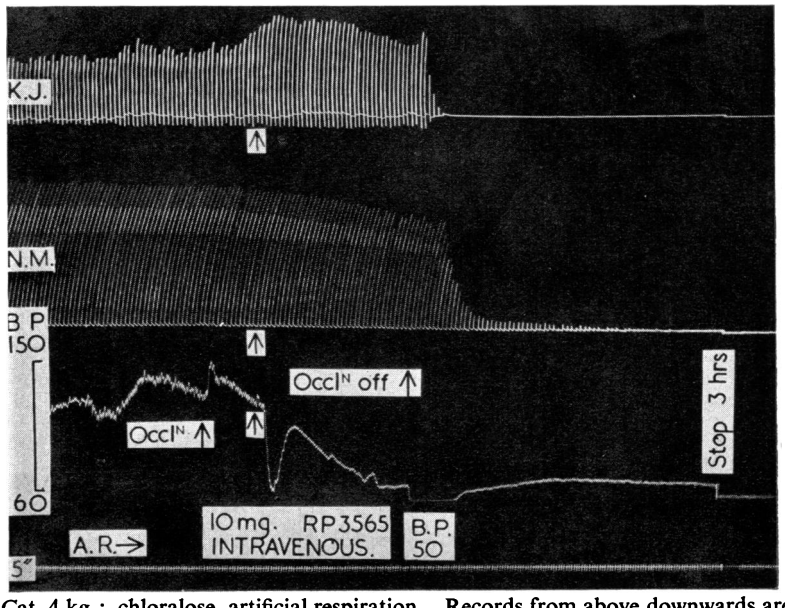

FIG. 2.—Cat, 4 kg.; chloralose, artificial respiration. Records from above downwards are: (K.J.) knee-jerk (right side); (N.M.) contraction of gastrocnemius (left side) stimulated through motor nerve; (B.P.) carotid blood pressure; time in 5 sec. At the first arrow, abdominal aorta and inferior vena cava clamped to produce hind-limb ischaemia. At the second arrow, 10 mg. RP 3565 injected *intravenously*. At the third arrow, clamps on the blood vessels released. The drum was stopped for 3 hr. at the point indicated. No recovery of the knee-jerk, the nerve-muscle response, or the blood pressure occurred.

showed an initial profound but temporary fall followed by a secondary more profound and sustained fall. Immediately after the injection, the knee-jerk was enhanced, although the responses of the nerve-gastrocnemius preparation were simultaneously declining very slightly, possibly owing to some small leakage of the drug into the hind-limb circulation. The drug thus has a central excitatory action on spinal reflexes even when injected intravenously ; but if the drug is allowed access to the muscles the peripheral blocking action masks this effect. On release of the aorta and the inferior vena cava both the knee-jerk and the nerve-muscle response

disappeared owing to the drug reaching the hind-limb muscles in sufficient concentration to produce peripheral paralysis.

(ii) In another experiment, after clamping the aorta and inferior vena cava, 5.0 mg. (1.3 mg./kg.) RP 3565 were injected *intraventricularly* (Fig. 3). The blood

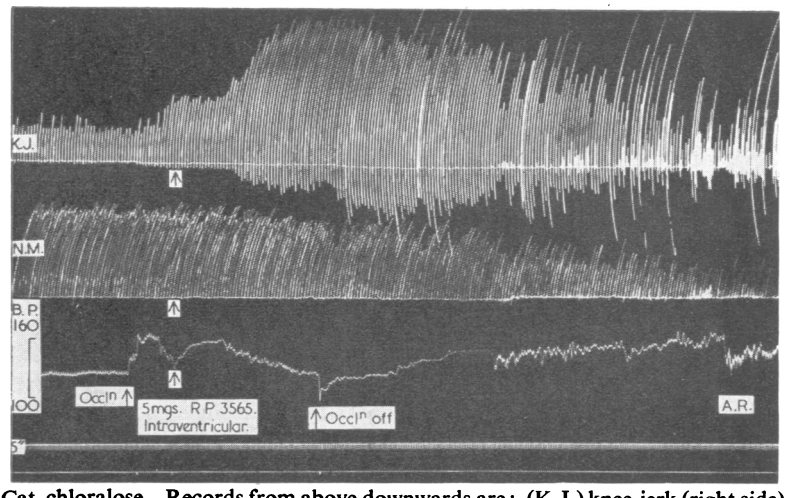

FIG. 3.—Cat, chloralose. Records from above downwards are: (K.J.) knee-jerk (right side); (N.M. contraction of gastrocnemius (left side) stimulated through its motor nerve; (B.P.) carotid blood pressure; time in 5 sec.; signal line. At the first arrow, abdominal aorta and inferior vena cava clamped to produce hind-limb ischaemia. At the second arrow, 5 mg. RP 3565 injected *intraventricularly*. At the third arrow, the clamps on the blood vessels released. At AR: artificial respiration started.

pressure rose at first (from 130 to 160 mm. Hg) owing to stimulation of the vasomotor centre and then returned to about the initial level. The knee-jerk rapidly increased first to twice, and then further to four and a half times, the initial value, but there were no spontaneous movements at this stage. The responses of the gastrocnemius decreased only slightly during the period of occlusion. When the circulation was released the knee-jerk remained enhanced ; in addition, at about this time spontaneous movements set in which became rapid and violent and persisted for about 20 min. This experiment demonstrates that the central excitation produced by supraspinal injection is of considerable duration, but that it is annulled, in the absence of hind-limb ischaemia, by the rapid onset of neuromuscular paralysis.

On releasing the hind-limb circulation, depression of the nerve-muscle responses developed gradually and progressively.

Action of RP 3697

This drug has only a slight central excitant action which is shown mainly by the appearance of spontaneous movements in the upper part of the body.

Intravenous injection.—Injection of 0.5 mg. (0.2 mg./kg.) RP 3697 had no effect on the response of the gastrocnemius muscle to motor nerve stimulation, on the knee-jerk, or on respiration. There was slight bradycardia and irregular fluctuations of blood pressure. Six minutes later, a further 0.5 mg. was injected. The responses

of the gastrocnemius and the breathing were still unaffected; the knee-jerk, however, was slightly depressed. After an initial transient rise, the blood pressure fell from 110 mm. Hg to a sustained level of 70 mm. Hg. Eight minutes later, a further dose of 1.0 mg. was injected. The responses of the gastrocnemius muscle were unchanged. The knee-jerk diminished further; the blood pressure fell to about 50–60 mm. Respiration, however, failed rapidly (in about 1 min.), and artificial respiration had to be started. Fifteen minutes later the responses of the gastrocnemius were still unchanged, the knee-jerk was hardly detectable, and the blood pressure was only 40 mm. Hg. Natural respiration was still absent. After an injection of a further dose of 1.0 mg. (making 3.0 mg. in all, or 1.2 mg./kg.), the knee-jerk was abolished completely. At the same time the responses of the gastrocnemius rapidly declined to about one-third of their initial height, but after 1 min. recovery gradually set in, the responses returning to their initial height in about 12 min. The knee-jerk, however, remained absent; neither the breathing nor the blood pressure showed any signs of recovery.

In other experiments, a *single* 3 mg. dose of RP 3697 (1.3 mg./kg., equal to the total dose given in four injections in the previous experiment) produced the same sequence of events as described above; first, paralysis of respiration; then disappearance of the knee-jerk; lastly the responses of the gastrocnemius were depressed and finally disappeared after 15 min.; they remained absent for one hour or longer, when recovery set in. The blood pressure fell immediately after the injection to a persistently low level.

The effects of RP 3697 on blood pressure were variable. In the experiments described above in which artificial respiration was begun only after natural breathing had failed, considerable and sustained falls of blood pressure occurred. In other experiments, however, which were carried out under artificial respiration from the start, even larger and repeated injections of the drug (3.3 mg./kg.) produced no change in the blood pressure (Fig. 4).

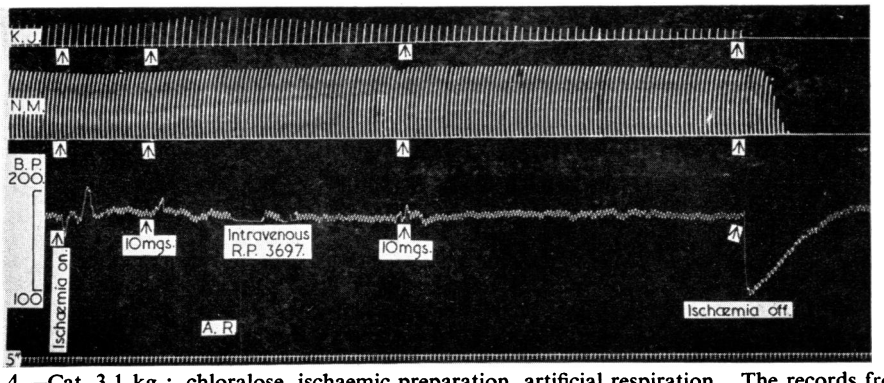

FIG. 4.—Cat, 3.1 kg.; chloralose, ischaemic preparation, artificial respiration. The records from above downwards are: (K.J.) knee-jerk (right side); (N.M.) contraction of gastrocnemius (left side) stimulated through its motor nerve; (B.P.) carotid blood pressure; time in 5 sec. At the first arrow, the abdominal aorta and inferior vena cava clamped. At the second arrow, 10 mg. RP 3697 injected intravenously. At the third arrow, 10 mg. RP 3697 injected intravenously. At the fourth arrow clamps on the blood vessels released. Immediately, the knee-jerk and the nerve-muscle response were depressed and finally abolished. The blood pressure fell sharply, but recovered its initial level very rapidly.

In order to elucidate further the cause of the alterations in the knee-jerk, experiments were carried out using the ischaemic hind-limb technique. The abdominal aorta and inferior vena cava were clamped, and then two successive injections of 10 mg. (3.3 mg./kg.) RP 3697 were carried out intravenously (Fig. 4). The drug did not reach the hind limbs in significant amounts, as shown by the fact that the responses of the nerve-muscle preparation remained unaltered during the period of the ischaemia. The knee-jerk, however, was slightly stimulated after the first intravenous injection of the drug ; later it declined slightly, but not to a greater extent than may occur solely from the effects of ischaemia. On releasing the clamps the knee-jerk disappeared at once, while the nerve-muscle response remained unchanged for some 30 sec. and then rapidly and progressively failed. The depression of the knee-jerk which was produced by injection of much smaller doses of the drug in the intact (non-ischaemic) preparation must, therefore, have been due to a peripheral and not to a central action. The results obtained in the intact animal also showed that the peripheral blocking action of the drug was not exerted equally on all muscles or on all forms of muscular activity. The maximal twitch of the gastrocnemius resulting from stimulation of its motor nerve every 5 or 10 sec. was more resistant than the knee-jerk and the movements of respiration ; the two latter are due to short subtetanic bursts of impulses from the motor neurones. Experiments described below showed that RP 3697 stimulated somatic reflex arcs by a central action.

Intraventricular injection.—Intraventricular injection of less than 2 mg. (0.5 mg./kg.) had no effect. After injection of 2.0 mg. spontaneous movements appeared in the head and forelimbs, resembling in their mode of onset and development those observed after intraventricular injection of tubocurarine, but much feebler and more restricted in distribution. They affected the trunk and the respiratory muscles, but not the muscles of the lower limbs. They did not occur in all experiments and were never generalized. They did not occur after intrathecal injection of the drug. Asphyxia was not a factor, since artificial respiration did not abolish them. A second dose of 2.0 mg. did not usually intensify the effects. The blood pressure was usually unaltered.

Injection of 5 mg. (1.4 mg./kg.) intraventricularly produced a slight gradual enhancement of the knee-jerk ; the spontaneous movements which were well marked in the forepart of the animal did not involve the hind limbs. Injection of 10 mg. (2.7 mg./kg.) produced an exceptionally striking but temporary enhancement of the knee-jerk ; this phase was followed by depression and finally by disappearance of the response.

These experiments show that RP 3697 has a significant but not very intense stimulating action on the central nervous system ; it exerts its effects more readily at the supraspinal than at the spinal level.

The drug is readily absorbed from the cerebrospinal fluid. Thus after injection of 20 mg. (5 mg./kg.) RP 3697 intraventricularly the nerve-muscle response began to decrease after 2 min. and almost completely disappeared in about 8 min. The disappearance of the knee-jerk was due to the peripheral blocking action of the drug overcoming the central stimulating action. The failure of respiration which often occurred was also presumably due to the peripheral blocking action.

The effects of intraventricular injection of RP 3697 on blood pressure were variable. In the absence of asphyxia little if any change generally occurred.

Action of tetramethylammonium

Injections of TMA in divided doses totalling less than 10 mg. (about 3 mg./kg.), either by the intraventricular or the intrathecal route, had no effect on the reflexes, the blood pressure, or the respiration. In doses of 10 mg. or more, injected intraventricularly or intrathecally, TMA depresses the reflexes by a central action. No initial central stimulating action was ever noted.

Intraventricular injection (Fig. 5).—When 10 mg. was injected in a single dose intraventricularly, the knee-jerk and the flexor reflex were gradually depressed ; the

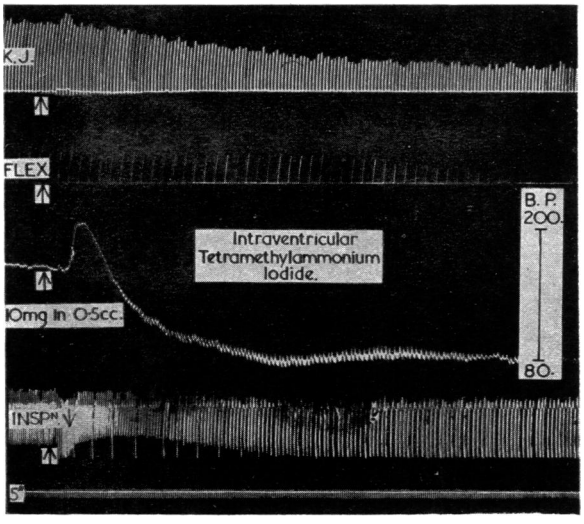

FIG. 5.—Cat, chloralose. Records from above downwards are: (K.J.) knee-jerk (right side); (Flex) flexor reflex (left side); carotid blood pressure; respiration; time in 5 sec. At the arrow, 10 mg. tetramethylammonium iodide injected intraventricularly.

blood pressure showed an initial rise (from 150 to 200 mm. Hg) followed immediately by a fairly rapid fall to 80 mm. Hg ; it remained at this low level for the rest of the experiment. Respiration showed a " triple response " : an initial phase of increase in rate and amplitude, followed immediately (during the period of decline of the blood pressure) by a second phase of increased rate but of diminished amplitude ; in the third phase, which coincided with the period of maintained low blood pressure, breathing was slow in rate but increased in amplitude.

Intrathecal injection.—Fig. 6 illustrates an experiment in which TMA was injected intrathecally. When a dose of 10 mg. was injected (Fig. 6A) the knee-jerk was unaffected for about 2.5 min. and then rapidly declined. The responses of the gastrocnemius muscle to stimulation of its motor nerve were hardly affected, indicating that the decline of the knee-jerk was due to direct depression by the drug of spinal neurones. After a second 10 mg. dose of TMA (not shown in the Fig.) the

blood pressure tended to fall further very gradually, and the respiration showed the "triple" response previously described, but to a less extent. Stimulation of the sciatic nerve and patellar tendon was resumed and a third dose of 10 mg. TMA was injected (Fig. 6B). The responses of the gastrocnemius muscle were not affected, but the knee-jerk remained absent.

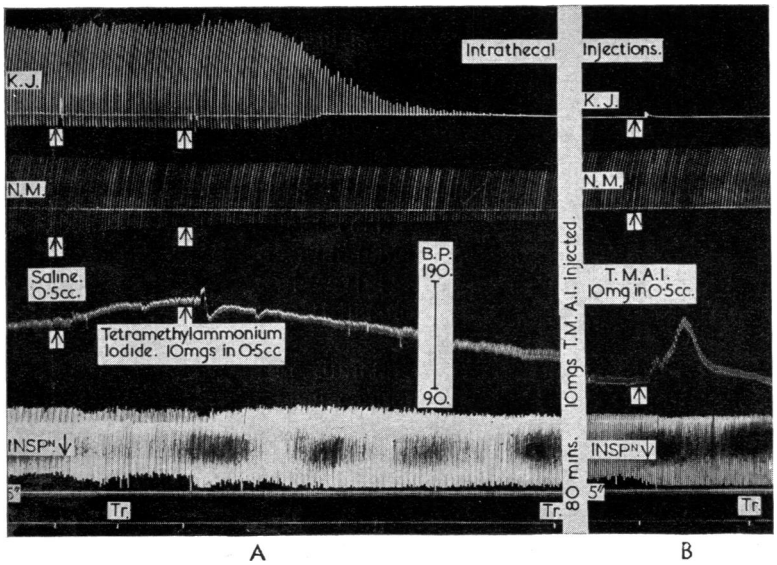

FIG. 6.—Cat, chloralose. Records from above downwards are: (K.J.) knee-jerk (right side); (N.M.) contraction of gastrocnemius (left side) stimulated through its motor nerve; carotid blood pressure; respiration; time in 5 sec.; signal line. (A) At the first arrow, 0.5 c.c. saline injected intrathecally. At the second arrow, 10 mg. tetramethylammonium iodide injected intrathecally. (B) Recorded after an interval of 80 min. rest (no stimulation), during which a dose of 10 mg. tetramethylammonium iodide was injected intrathecally. At arrow, 10 mg. tetramethylammonium iodide injected intrathecally. At Tr a few drops of c.s.f. allowed to escape to restore its normal pressure.

The limited number of experiments performed suggested that the central depression of the spinal reflexes occurred more readily after intrathecal than after supraspinal injection of the drug.

Action of tetraethylammonium

Intravenous injection.—Repeated intravenous injections of tetraethylammonium iodide (TEA) in doses of 10 mg. had no effect on the reflexes until the total dose was 100 mg. (about 30 mg./kg.).

Fig. 7 illustrates an experiment in which 100 mg. TEA was intravenously injected in a single dose; within 70 sec. the knee-jerk was abolished, but at the same time the flexor reflex was potentiated. In view of this result and the feeble neuromuscular blocking action of TEA the abolition of the knee-jerk must be attributed to a central and not to a peripheral effect of the drug. The blood pressure fell gradually and remained at a low level.

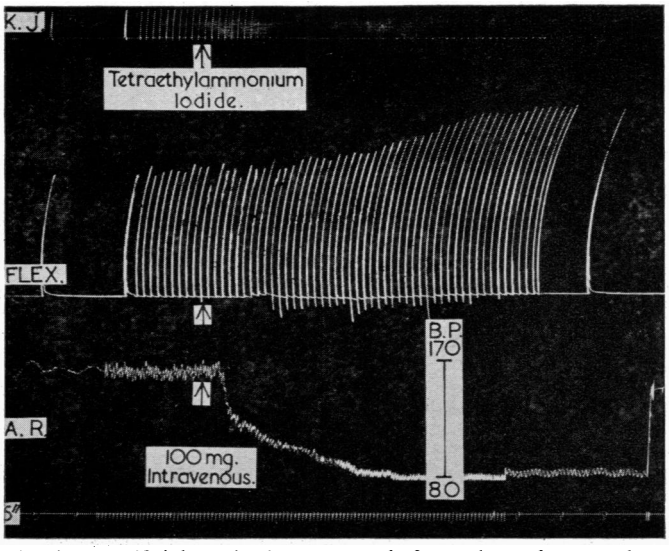

FIG. 7.—Cat, chloralose, artificial respiration. Records from above downwards are: (K.J.) knee-jerk (right side); (Flex) flexor reflex (left side); carotid blood pressure; time in 5 sec. The drum accelerated and two reflex responses of the quadriceps and tibialis anticus muscles recorded; slow speed of drum restored. At the arrow, 100 mg. tetraethylammonium iodide injected *intravenously*. Drum accelerated and one response of the tibialis anticus muscle recorded.

Intrathecal injection.—Repeated injections of 10 mg. TEA up to a total of 100 mg. had no effect on any system.

Fig. 8A illustrates a representative experiment in which 100 mg. TEA was intrathecally injected in a single dose. The flexor reflex showed no change; the knee-jerk, however, was profoundly modified. There was a momentary enhancement of the knee-jerk immediately followed by a marked increase in quadriceps extensor tone. Moreover, the crossed extensor reflex which had previously been absent made its appearance. The phase of relaxation of the knee-jerk was prolonged, indicating increased after-discharge. The changes in the knee-jerk and the appearance of the crossed extensor reflex must be attributed to stimulation of the spinal nerve centres by the drug.

In the experiment illustrated by Fig. 8B, immediately after the intrathecal injection of 100 mg. TEA, there was an initial transient tonic spasm of central origin, followed by a second more gradually developing central tonic spasm which reached its maximum in about 2 min.; it then gradually and irregularly declined to a lower level at which minor undulations of tone were observed. The flexor reflex showed no change. These experiments demonstrate that TEA directly enhances the excitability of the spinal cord, affecting mainly the monosynaptic reflexes responsible for the knee-jerk and muscle tone.

The effects produced by intrathecal injections of TEA were compared with those of intravenous injections. At the beginning of the experiment, the knee-jerk was almost absent and the flexor reflex was present, but feeble. After an *intrathecal* injection of 100 mg. TEA the knee-jerk gradually increased in amplitude and was

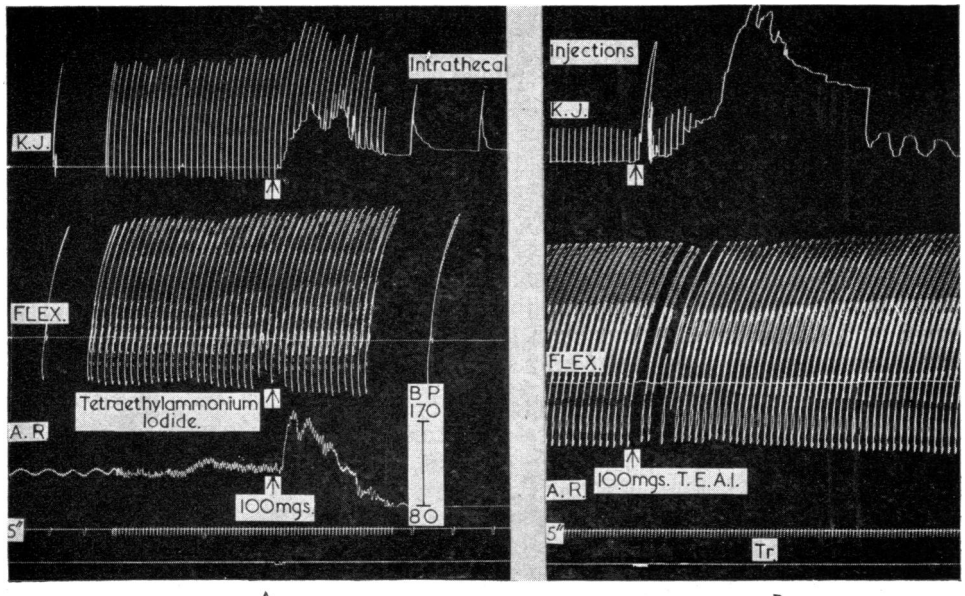

FIG. 8.—Cat, chloralose, artificial respiration. Records from above downwards are: (K.J.) knee-jerk (right side); (Flex) flexor reflex (left side); carotid blood pressure; time in 5 sec.; signal line. (A) Drum accelerated and one response of the quadriceps and tibialis anticus muscles recorded. Slow speed of drum recorded. At arrow, 100 mg. tetraethylammonium iodide injected intrathecally. (B) Another similar preparation. At the arrow, 100 mg. tetraethylammonium iodide injected intrathecally. At Tr a few drops of c.s.f. allowed to escape to restore its normal pressure.

accompanied by vigorous and very rapidly repeated clonic spasm of central origin. The flexor reflex, on the contrary, gradually weakened and finally disappeared. On *intravenous* injection of a similar 100 mg. dose of TEA the spontaneous movements were markedly depressed, but, strangely enough, the flexor reflex reappeared.

DISCUSSION

RP 3565.—The central excitatory action of RP 3565 resembles that of *d*-tubocurarine in several respects. The spinal reflexes are more effectively stimulated by supraspinal than by intrathecal injection of the drug, suggesting that like tubocurarine it acts preferentially on supraspinal facilitatory neurones ; there is, however, a direct excitatory action on spinal neurones also. The drug (like tubocurarine) directly stimulates the vasomotor centre, but (unlike tubocurarine) it does not stimulate the respiratory centre. Quantitatively the central action (using intraventricular injections) is about one-tenth that of tubocurarine. Unlike tubocurarine, RP 3565 is rapidly absorbed from the cerebrospinal fluid (both spinal and cerebral), so that when it is injected into this fluid peripheral paralysis occurs which tends to mask the central excitatory action.

A careful comparison of the effects of intraventricular injection with and without hind-limb ischaemia and of intravenous injection has shown that the drug is

readily fixed or destroyed by the tissues and more especially by the elements of the central nervous system.

The fall of blood pressure and failure of respiration observed when the drug is administered intravenously are probably due to a peripheral action.

Both RP 3565 and tubocurarine are bis-onium compounds in which the quaternary ammonium groups are separated by 10–11 C atoms. As RP 3565 is so much weaker in its central excitant action than tubocurarine it may be concluded that in contrast to the peripheral blocking action the central excitatory action is not directly related to the number of atoms which separate the quaternary ammonium groups. Neither RP 3565 nor tubocurarine has any significant anticholinesterase action ; their central actions cannot, therefore, be attributed to the preservation of naturally formed acetylcholine. Both RP 3565 and tubocurarine release histamine, but histamine depresses spinal cord reflexes (Schweitzer and Wright, 1937a).

RP 3697.—Injected intraventricularly, this substance has only a slight central excitatory action. RP 3697 is a tris-onium compound, unlike RP 3565 and tubocurarine, which are bis-onium compounds. RP 3697, however, resembles tubocurarine very closely in the way it produces its peripheral blocking action. It has no anticholinesterase action.

RP 3565 and RP 3697, like tubocurarine, calabash curare, and curine dimethyl ether dimethiodide, are drugs that produce neuromuscular block but have a central excitant action. These findings suggest that, though the motor endplate may be the " paradigm " of a central synapse, transmission at the motor endplate and excitatory transmission at central synapses must differ in important respects.

Tetramethylammonium (TMA).—TMA, like nicotine, has an initial stimulating action on autonomic ganglia. Its central action is to produce a weak depression of spinal reflexes without preliminary stimulation, whatever the route of administration. Qualitatively, this action resembles that of nicotine, but is much weaker. A dose of 10 mg. TMA intraventricularly produces a degree of central depression, judged by the decline of the knee-jerk, equivalent to that of 0.1 mg. nicotine intravenously (Schweitzer and Wright, 1938b). The action of a drug on autonomic ganglia is clearly no guide even to the direction of its action on central neurones.

Tetraethylammonium (TEA).—TEA resembles tubocurarine in producing ganglionic block, but differs from it in having a feeble peripheral neuromuscular blocking action. The central action of TEA is likewise feeble and is only shown by doses of 100 mg. or more (tubocurarine has striking central actions in doses of 0.4 mg. when applied directly to the neuraxis). When 100 mg. TEA is injected intrathecally, the main effect is to increase the excitability of the spinal extensor neurones. TEA, however (unlike tubocurarine), is not a pure central excitant ; it also displays a central inhibitory action. There are significant differences between the central effects of intravenous and intrathecal injection. When the drug is injected intrathecally the extensor reflexes are potentiated by a central action ; the flexor reflex is unaffected. When the drug is injected intravenously the flexor reflex is potentiated by a central action, while the knee-jerk is depressed. Similar differences have been noted with eserine (Calma and Wright, 1947 ; Wikler, 1945 ; Bülbring and Burn, 1941). With TEA there is the further complication that it may also directly stimulate nerve fibres (Cowan and Walter, 1937).

Summary

1. The actions on the central nervous system of the cat under chloralose anaesthesia of the neuromuscular blocking agents RP 3565 and RP 3697 (Flaxedil) and of tetramethylammonium and tetraethylammonium are described. The drugs were administered by the intraventricular, intracisternal, intrathecal, and intravenous routes.

2. RP 3565 when injected intraventricularly in doses of 1.5 mg./kg. or over has a central excitant action on somatic neurones resembling qualitatively that of *d*-tubocurarine, but about 10–20 times as weak. The drug stimulates both the supraspinal and spinal neurones. It directly stimulates the vasomotor centre, but not the respiratory centre.

3. RP 3697 has only a weak central excitant action ; its main effect when injected intraventricularly in doses of 0.5 mg./kg. or over is to produce spontaneous movements in the forepart of the animal.

4. Both RP 3565 and RP 3697 are rapidly absorbed from the cerebrospinal fluid, both cerebral and spinal, into the circulation. The peripheral paralysing action thus produced partially or wholly masks the central excitant action.

5. RP 3565 and RP 3697, like tubocurarine, calabash curare, and curine dimethyl ether dimethiodide, are drugs that produce neuromuscular block but have a central excitant action. These findings suggest that, though the motor endplate may be the " paradigm " of a synapse, transmission at the motor endplate and excitatory transmission at central synapses must differ in significant respects.

6. Tetramethylammonium has a central depressant action qualitatively similar to that of nicotine but about 100 times as weak. Tetramethylammonium and tubocurarine show that the direction of the action of a drug on autonomic ganglia may be the reverse of that on central synapses.

7. Tetraethylammonium in doses of 30 mg./kg. is predominantly a central excitant, though its action on autonomic ganglia is depressant. The central actions of tetraethylammonium are complex, the detailed findings depending on the route of administration and on the reflex under examination.

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