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ACTION OF *d*-TUBOCURARINE CHLORIDE ON THE CENTRAL NERVOUS SYSTEM OF THE CAT*

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Though the method of grouping drugs into classes according to their most conspicuous pharmacological effects is of value it has the disadvantage that actions of a drug that do not fit conveniently into the system of classification adopted tend to be ignored. For example it is common to classify drugs into those acting peripherally and those acting centrally; but in more than one instance a drug which was initially classified as peripherally active was later found to be centrally active as well, with the result that the accepted system of classification tended to prevent acceptance of the discrepant observations for long periods. This has happened with curare. The earliest studies of the drug (Brodie, 1811–12; De La Condamine, 1813; Humboldt, 1821; all cited by McIntyre, 1947) indicated that the drug had a central action; but the work of Claude Bernard (1857) so emphasized the peripheral action of the drug that it was classified as a peripherally acting agent which paralysed neuromuscular transmission. The central actions were generally overlooked in spite of the work of many investigators, e.g., Vulpian (1881); Tillie (1890, 1891); Joseph and Meltzer (1911–12); McGuigan (1916); Amantea (1921); Santesson (1920); Blume (1934); Stern and Rothlin (1918); and West (1937), who showed that curare or its derivatives had an excitant action on the central nervous system in the frog and mammals. The relevant literature is fully reviewed by McIntyre (1947) and Boehm (1920). Recently Euler and Wahlund (1941) found that generalized convulsions occurred in cats as a result of injecting small doses of *d*-tubocurarine intrathecally. Cohnberg (1946) reported that Intocostrin or crystalline *d*-tubocurarine chloride injected in sufficient doses subcutaneously into rats, mice, guinea-pigs, rabbits, and cats produced hyper-excitability and clonic convulsions (in addition to peripheral partial curarization). The blocking action of curare on synaptic transmission in sympathetic ganglia induced Eccles (1946) to investigate its action on the frog's spinal cord, where he found that it had the reverse effect. Thus, soaking the spinal cord for 30 min. in a curare solution as weak as 6×10^{-6} molar increased the duration of the synaptic potential and the discharge of impulses set up by a single dorsal root volley. Larger concentrations of curare gave more striking effects, and finally a concentration of 150×10^{-6} molar set up sustained convulsant activity even

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in the absence of any stimulation. Eccles concluded that the central action of curare resembled that of strychnine.

In the experiments to be described the action of *d*-tubocurarine chloride on various levels of the central nervous system was examined.

METHODS

Cats were used in all experiments. The following three types of preparation were used:

(1) Animals anaesthetized with chloralose (0.06–0.08 g. per kg. of body weight): the drug was applied directly to the central nervous system by one of three routes: (*a*) intrathecal, (*b*) intracisternal, and (*c*) into the lateral ventricle.

(2) Decerebrate animals: a sharp sickle-shaped scalpel was introduced above the level of the tentorium cerebelli; the brain stem was cut across just above the level of the upper border of the pons. Intracisternal and intrathecal injections were carried out in these preparations.

(3) High spinal animal: the spinal cord was divided in the animal deeply anaesthetized with ether-chloroform, by introducing a sharp-pointed blunt-edged narrow instrument through the ligament between the occipital bone and the atlas vertebra. Respiration stopped and artificial respiration was immediately commenced. Immediately after the decapitation the blood pressure may rise to 200–220 mm. Hg; this is attributed to initial stimulation by the transection of the descending fibres in the spinal cord arising from the vasomotor centre. The blood pressure, however, very soon falls to a final level of about 60 mm. Hg. In such a preparation intrathecal injection was the only method available for applying the drug directly to the central nervous system.

Methods of injection

Intraventricular injections were made by introducing a 20-gauge needle via a trephine hole into the lateral ventricle through the parietal cortex. Control saline injections proved to be inert, i.e., they did not modify in any way the reflexes, blood pressure, or respiration.

Intracisternal injections were carried out by cisternal puncture with a 20-gauge needle. The volume of fluid injected was so small that it was sufficient to allow a few drops of cerebrospinal fluid to escape before each injection in order to prevent a rise of cerebrospinal fluid pressure. Control saline injections proved inert.

Intrathecal injections were carried out by the method of Calma and Wright (1947a).

Absorption of curare from the cerebrospinal fluid is so slow that even when large doses are injected intraventricularly, intracisternally, or intrathecally they do not produce any of the well-known peripheral actions of the drug—e.g., muscular paralysis.

The reflexes studied were: the knee jerk, flexor reflex, crossed extensor reflex, and jar reflex. The methods employed were similar to those described in earlier papers from this laboratory (Calma and Wright, 1947a).

RESULTS

In most of the experiments cats anaesthetized with chloralose were used. There are no qualitative differences between the results obtained in such animals and in decerebrate cats.

A solution of pure *d*-tubocurarine chloride has a *p*H of 7.3–7.4. When such a solution is applied, in doses of 0.1–0.2 mg./kg. to the central nervous system

of cats under chloralose anaesthesia, it produces a state of heightened reflex excitability, followed by tonic and clonic movements which are apparently "spontaneous" in character and will be so referred to, though they may, in fact, be produced reflexly by unrecognized afferent impulses which are constantly being set up. The central effects vary according to the route of administration and the region to which it has access. A description will first be given of the effects produced by *d*-tubocurarine chloride when injected intraventricularly and intracisternally. The somewhat different results of intrathecal injection are considered later.

Effects produced by intraventricular and intracisternal injections of d-*tubocurarine*

The results produced by intraventricular and intracisternal injections are indistinguishable except for certain eye changes.

Somatic reflexes.—*d*-Tubocurarine chloride introduced intraventricularly rapidly raises the excitability of the spinal centres. Fig. 1 shows that less than one minute after such an injection (0.4 mg.) there was an increase in the knee jerk and in the flexor reflex. In other experiments the crossed extensor reflex, which had

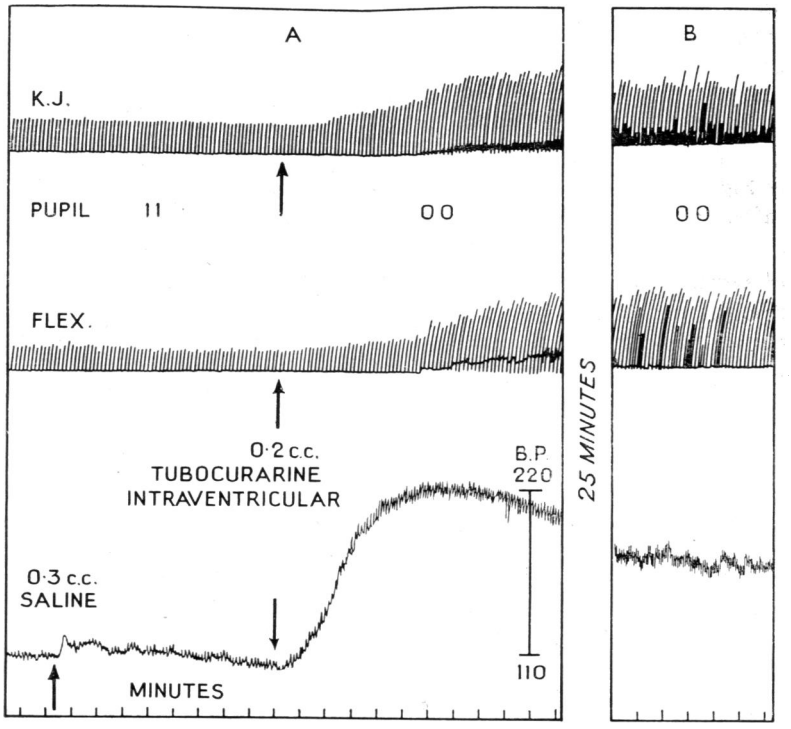

FIG. 1.—Cat, chloralose. Records from above downwards: knee jerk (right side); size of pupil; flexor reflex (left side); carotid blood pressure; signal line; time in min. First arrow, intraventricular injection of 0.3 c.c. saline. At the second arrow, intraventricular injection of 0.4 mg. *d*-tubocurarine chloride dissolved in 0.2 c.c. saline. The second part of record was taken after an interval of 25 min.

initially been absent, made its appearance. In experiments in which the crossed extensor reflex was initially present, it was greatly potentiated. In less than 4 minutes after the injection (Fig. 1) seemingly "spontaneous" movements and alterations in muscle tone took place. The "spontaneous" movements were usually preceded by quick "twitching" movements of the ears and of the facial muscles. Strong convulsive movements followed, first affecting the head, neck, and forelimbs, with subsequent spread to the hind limbs. The facial twitching generally appeared within one minute of the injection, and the spread of the "spontaneous" activity over the entire body usually occurred within 1–1.5 minutes. The "spontaneous" convulsive activities gradually gain in strength to such an extent that in many experiments the convulsive movements occurring in the quadriceps or tibialis anterior exceeded those reflexly elicited. The frequency of the convulsive movements varied a good deal and in marked cases they recurred every second.

In some experiments the convulsions were not so marked, but there was a considerable sustained increase in the resting tone of the quadriceps. Under these conditions, reflex contraction of the contralateral quadriceps was sometimes observed occurring regularly in response to contralateral patellar stimulation. This is the "jar reflex" described by Sherrington (1898) and shown by him not to be a contralateral reflex; the tap on the patellar tendon by jarring the animal mechanically stimulates the contralateral quadriceps from which an ipsilateral reflex contraction is evoked.

The state of hyperreflexia described above, including the "convulsions," persists for long periods, sometimes for more than an hour. In the experiment illustrated by Fig. 1 the convulsions and increased reflexes were still at their peak 25 minutes after the injection. The convulsions finally die down partly as a result of fatigue.

Blood pressure.—Fig. 1 shows a typical response of the blood pressure to an intraventricular injection of *d*-tubocurarine chloride (0.4 mg.). There was an immediate, rapid, and large rise of blood pressure from 110 to 220 mm. Hg. There were considerable differences in the magnitude of the response in different experimental animals. The duration of the pressor response also varied in different cats and was usually longer with larger doses, up to a maximum dose of about 2 mg. The pressor effect always lasted for several minutes and not infrequently persisted for as long as 15 minutes, after which the blood pressure gradually declined to its initial level, which it usually attained within about an hour.

Sometimes after 1–1½ hours the blood pressure may decline by about 20 mm. Hg below the pre-injection level; when this happened a second injection of 0.4 mg. of *d*-tubocurarine generally failed to produce a pressor effect.

The changes in the blood pressure and in the spinal reflexes do not follow the same time course; thus in Fig. 1 the blood pressure had reached its peak level before the reflex effects had reached their maximum and when only slight "spontaneous" movement had appeared. After 25 minutes, when the spinal reflexes were still maximal and vigorous convulsions were still taking place, the blood pressure had fallen from the peak value of 220 mm. Hg to 185 mm. Hg.

The similarity of the effects of intraventricular and intracisternal injection of tubocurarine on the blood pressure and the knee jerk is well seen by comparing the relevant records in Fig. 1 and Fig. 2. In Fig. 2, however, more strikingly than in Fig. 1 there is at the peak of the blood pressure rise a considerable increase in the rate of the heart and the development of marked cardiac irregularities.

Respiration. — The effects on respiration produced by intracisternal injection of tubocurarine are well shown in Fig. 2. Within one minute of the injection, there was marked augmentation of respiration both in rate and depth. Sometimes the increase in rate preceded that in depth; in other experiments the reverse happened. The onset of stimulation of respiration and of blood pressure occurs at the same time; both precede the onset of the convulsions and therefore cannot be the result of the convulsions. The changes both in circulation and respiration are unaffected by bilateral denervation of the carotid sinuses and section of both vagi.

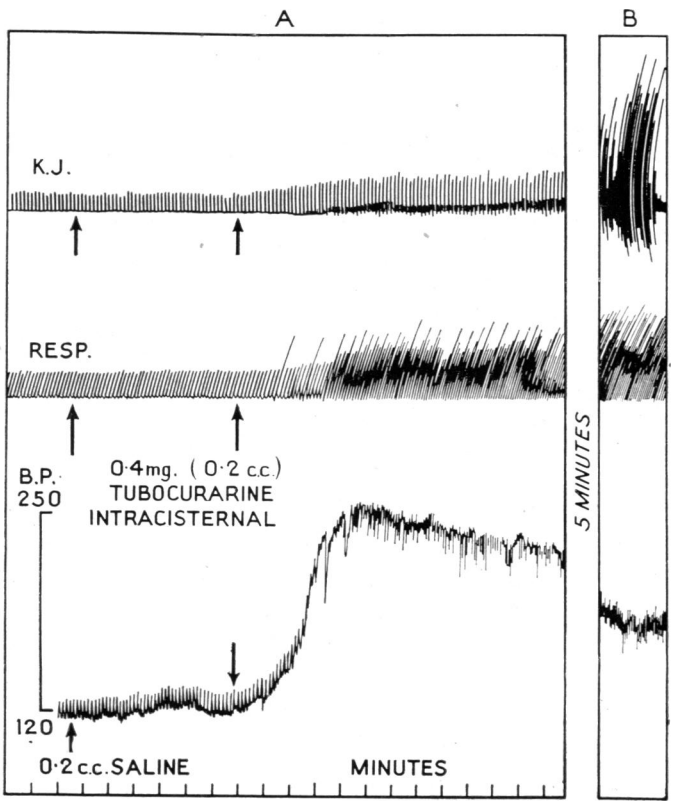

FIG. 2.—Cat, chloralose. Records from above downwards: knee jerk (right side); respiration (inspiration upwards); carotid blood pressure; signal line; time in min. First arrow, intracisternal injection of 0.2 c.c. saline. At the second arrow, intracisternal injection of 0.4 mg. *d*-tubocurarine chloride, dissolved in 0.2 c.c. saline. There was an interval of five minutes between the first and second half of the record.

As the convulsions become more widespread and more violent, the respiratory muscles also become involved, with the result that breathing movements become shallow, rapid, incoordinated, and therefore less effective. Breathing, however, generally remains adequate as shown by the normal bright red colour of the blood in the arterial cannula. Furthermore, the blood pressure returns to normal while the respiratory muscles are still convulsed. If asphyxia had been present, the resulting stimulation of the vasomotor centres would presumably have produced a sustained rise of blood pressure.

In some experiments, however, the breathing was more severely disturbed. Because of tonic contractions due to a central discharge, respiratory movements may cease for some time, with the chest wall fixed in the expiratory position. If this expiratory spasm is unduly prolonged asphyxia develops, and, unless artificial respiration is employed, the animal may die. Considerable positive pressure has to be used to inflate the lungs against the resistance imposed by the powerful contractions of the expiratory muscles. As the chest was not opened, no observations were made on the state of the diaphragm. There have, however, been clinical reports of sustained expiratory spasm of the diaphragm in operations during which curare was used; such spasm was presumably of central origin, overcoming the peripheral neuromuscular paralysis.

Eye changes.—As a rule, immediately after the intraventricular injection of tubocurarine, the pupils begin to increase gradually in size until maximal dilatation occurs. The lids are powerfully retracted and the eyeballs are fixed. The widely open staring eyes and fully dilated pupils resemble those of an animal in a state of rage. In some experiments, the initial dilatation of the pupil was not steadily maintained, but the pupils alternately contracted and dilated about once a minute. Finally, however, full steady pupil dilatation occurred and persisted (together with the other eye changes described) throughout the experiment—e.g., for periods of 2–3 hours.

Sometimes initial rapid blinking movements accompany the rapid twitching of the ears, but they cease when the sustained lid retraction develops. No convulsive movements of the eyeballs were ever noted and no squint developed. The eyeballs were always fixed in the central position, the gaze being directed straight ahead.

The eye changes just described are, as stated, those which follow intraventricular injections. When the tubocurarine is injected intracisternally the eye changes may not appear at all or develop very slowly—e.g., after a latent period of 15 minutes—and may not involve all the eye structures. The lid retraction occurred more commonly than did pupil dilatation. (On intrathecal injection, no eye changes take place.)

Salivary, lacrimal, and bronchial secretions.—Salivation and excessive lacrimal secretion almost always followed intraventricular injections of *d*-tubocurarine. Moreover, bronchial secretion usually showed a considerable increase in volume, and in some of the early experiments animals died from blocking of the trachea with large quantities of mucus. It therefore became a routine procedure to clear the trachea every five minutes during the convulsions.

Effects produced by intrathecal injection of d-*tubocurarine*

The results of intrathecal injection, though in general similar to those of intraventricular and intracisternal injection, differ in important details.

The fluid injected may mechanically stimulate the posterior nerve roots and produce various reflex effects as described by Calma and Wright (1947b). The drug primarily has access to the spinal cord centres only, but secondarily it flows upwards in the subarachnoid space and ultimately reaches supraspinal levels where

it will produce the same type of effect as that which results from intracisternal or intraventricular injection, though to a less extent because smaller concentrations of the drug reach these higher levels. As is explained later the results of intrathecal injection are modified in the high spinal preparations or after blocking the subarachnoid space at the level at Th. 6. In both of these experimental conditions the upward spread of the drug to the supraspinal levels is prevented. The main results of intrathecal injections are as follows:—

Somatic reflexes.—A slight enhancement of the knee jerk sets in after about the same short latent period as by the other routes, but it is generally smaller in magnitude; this enhancement may perhaps be partly produced reflexly as a result of mechanical stimulation of the posterior nerve roots. The "spontaneous movements," however, do not appear until after a latent period of about 10 minutes (Fig. 3 B). Marked "convulsions" like those resulting from intraventricular and intracisternal injections do not occur until about 20 minutes after the injection (Fig. 3 C).

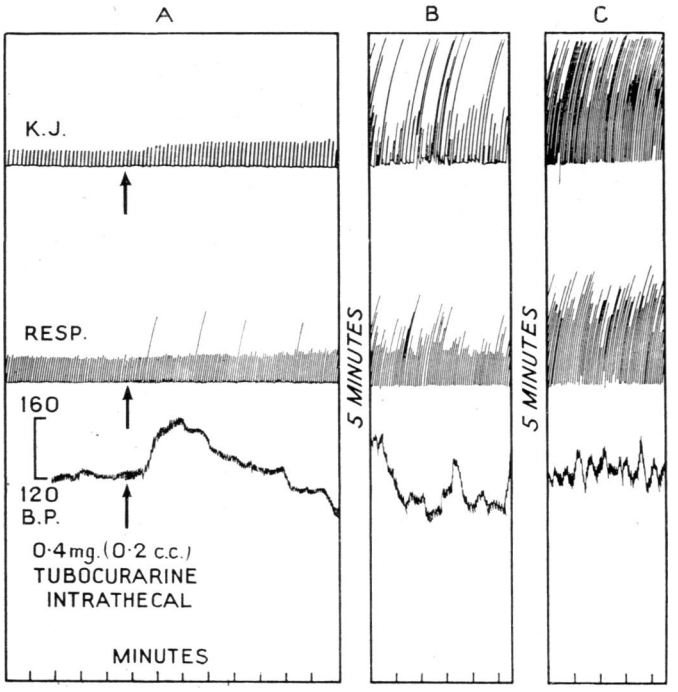

FIG. 3.—Cat, chloralose. Records from above downwards: knee jerk (right side); respiration (up-stroke equals inspiration); carotid blood pressure; signal line; time in min. First arrow, intrathecal injection of 0.4 mg. *d*-tubocurarine chloride, dissolved in 0.2 c.c. saline. There was an interval of five minutes between the first and second records, and another interval of five minutes between the second and third records.

Respiration.—A slight increase in depth develops during the first 5 minutes; occasionally very deep breaths occur. After 10 minutes, the breathing is further increased in rate and also becomes deeper (Fig. 3 B); the respiratory movements are modified by the concurrent convulsive movements of the respiratory muscles. After 20 minutes, when the convulsions had become severe and general, breathing was very deep and rapid (Fig. 3 C).

Blood pressure.—The immediate response of the blood pressure was a very slight rise, which was not maintained (Fig. 3 A). In view of the work of Calma and Wright (1947b), this small pressor effect might be the result of mechanical stimulation of the posterior nerve roots. Later, the blood pressure showed swinging

variations above and below its original level (Fig. 3 B). It is worthy of notice that during the convulsions that occurred later in the experiment the blood pressure was at about its original level (Fig. 3 C).

Site of action of d-*tubocurarine on central nervous system*

The differences between the results of intrathecal and intraventricular injections of tubocurarine are thus considerable. The time course of the events when tubocurarine is injected intrathecally suggests that the drug produces most of its effects by an action on supraspinal centres. This view is supported by the following experiments.

(1) When the effects of tubocurarine applied directly to the spinal cord by intrathecal injection are compared with those of intracisternal and intraventricular injection, it is found that with the former procedure equal doses produce smaller reflex effects after a somewhat longer latent period.

(2) *Experiments with spinal fluid block.*—A ligature was tied tightly round the dura in the mid-thoracic region so as to occlude the subarachnoid space, but without impairing nerve conduction in the spinal cord. When tubocurarine was injected intrathecally below the block, its action was limited to the distal part of the spinal cord. The latent period before the onset of increased reflex excitability was markedly longer (e.g., 1 hour instead of 15 minutes) and the minimal effective dose was about three times greater than when the injection was given with the subarachnoid space unobstructed (thus permitting the ascent of the drug to the supraspinal levels). Intraventricular injection of tubocurarine in this preparation produced the same heightening of reflex excitability in the *distal* cord as in animals with a subarachnoid space unoccluded. The time relations of the responses were also unaffected. It follows that the changes occurring in the hind limbs with intraventricular injections in preparations with a spinal fluid block must be due to impulses passing down from higher levels and cannot be due to a direct action of the drug on the hind limb centres of the spinal cord. These experiments were controlled by injecting methylene blue intraventricularly, and the experiment was regarded as satisfactory when no methylene blue was found in the lumbar theca.

(3) *Experiments with complete spinal block.*—The ligature round the cord was tied very tightly so as to abolish transmission of all nervous impulses up and down the spinal cord as well as to block the flow of cerebrospinal fluid. The tubocurarine solution was injected *intrathecally below* the level of the block. Under these conditions, the knee jerk (and other somatic reflexes) showed no change during the first hour, during which period three doses (3 × 0.4 mg.) were injected intrathecally; 0.4 mg. would have produced marked and immediate changes had it been injected intraventricularly. During this period also, there were no changes in the circulation, respiration, or the eyes. Subsequently the knee jerk increased and "convulsive" movements (limited to the hind limbs) became vigorous. It is noteworthy that such convulsions produced no changes in respiration or blood pressure.

(4) In some experiments after complete spinal transection had been carried out at the level of T.6, as described in (2), intraventricular injections of tubocurarine were made repeatedly; typical changes were produced above the level of the transection, but no changes whatsoever occurred in the somatic reflexes below the level of the section. These results show that intraventricularly injected tubocurarine is not absorbed into the circulation in sufficient amounts to affect the reflex excitability of the isolated region of the spinal cord.

Action of commercial solutions

In preliminary experiments a commercial solution of *d*-tubocurarine chloride (Burroughs Wellcome) was used. This solution contained, in addition to the tubocurarine, chlorocresol (as a preservative) and potassium metabisulphite; the *p*H was about 3.5. Some experiments were carried out to determine the central actions of these constituents of the commercial solution.

Action of chlorocresol.—The commercial tubocurarine solution used contained 0.1 per cent of chlorocresol; the effects of an intrathecal injection of 0.1 c.c. of such a solution were studied. The knee jerk showed, after a latent period of 4.5 minutes, a brief enhancement followed by a gradual decline; after 10 minutes the knee jerk was one-fifth of the original value. The flexor reflex was unchanged. The blood pressure (initial level 70 mm. Hg) showed an initial brief sharp rise which was followed by a slower decline to the pre-injection level and then by a secondary more gradual but prolonged rise of blood pressure which reached a maximum of 220 mm. Hg in 10 minutes. The pressure then fell very slowly, regaining its original level after more than 40 minutes. Respiration was unchanged.

Action of potassium metabisulphite and p*H of the solution.*—The commercial solution used contained potassium metabisulphite in a concentration which has not been disclosed by the manufacturers. However, a 1.0% solution of potassium metabisulphite has a *p*H value of about 3.5, which is approximately the *p*H of the commercial solution employed. In doses of 1 mg. intrathecally injected potassium metabisulphite raises the blood pressure but depresses the reflex excitability of the spinal cord.

Discussion

The experiments recorded above prove that *d*-tubocurarine chloride has a direct and striking excitatory action on the central nervous system. The changes in the reflex responses described and the "convulsions" that supervene are not due to associated alterations in the circulation or respiration. The peripheral action of curare on skeletal muscle is to produce paralysis; therefore, any changes in the peripheral responses of the muscles, if they took place at all, would tend to mask any central stimulating action that occurred. But as was mentioned on page 50 in none of the experiments in which tubocurarine was injected intraventricularly, intracisternally, or intrathecally was the response of the nerve muscle preparation depressed, indicating that the amount of tubocurarine absorbed into the circulation was negligibly small.

Action on reflex excitability.—The experiments described above indicate that tubocurarine enhances reflex excitability and produces "convulsions" in the cat mainly by an action on supraspinal centres and only to a less extent by an action on the spinal cord itself.

The reason for the greater sensitivity to curare of the supraspinal levels must be considered. As tubocurarine has no action on nerve fibres, its central effects must be due to an action on the grey matter. When intrathecal, intracisternal, or intraventricular injections are used, the drug can only begin to produce its effects after it has penetrated any intervening white fibres to reach the deeper nerve cells. The white columns of the spinal cord might constitute a considerable barrier between the drug present in the theca and the grey horns. When the drug is injected intracisternally, it doubtless rapidly enters the fourth ventricle. As will be explained later, the centres in the brain stem which are acted on by the drug are probably the cells of the reticular formation of the midbrain, pons, and medulla ; these, too, are situated fairly deeply, and the drug might be expected to encounter the same difficulty as in the spinal cord in penetrating to them. When the drug is injected intraventricularly, it might be expected to reach the grey matter of the thalamus and hypothalamus more readily. But there is no significant difference in the latent period and sensitivity of the response when the effects of intracisternal and intraventricular injections are compared in the whole animal or when the results of intracisternal injection are compared in the whole animal and in the decerebrate animal. The conclusion may be tentatively drawn that the supraspinal levels have a higher sensitivity to the action of tubocurarine.

The intimate nature of the central excitatory action of tubocurarine must now be considered. The known peripheral actions of tubocurarine are predominantly of an inhibitory or paralysing character: thus tubocurarine blocks both neuromuscular and ganglionic transmission. The excitatory action of tubocurarine on the spinal centres might therefore be attributed to depression of supraspinal inhibitory centres. It is known that a mid-collicular transection cuts off both facilitatory and inhibitory fibres arising from higher levels ; as decerebrate rigidity results from such a transection higher inhibitory influences must have been cut off to a greater extent than excitatory. One must suppose that the supraspinal centres which are left intact in the decerebrate animal are predominantly excitatory in action. If tubocurarine acted by depressing inhibitory centres, one would expect its excitatory action in the decerebrate animal to be less marked than in the intact animal because in the former fewer inhibitory centres are present to be depressed ; this is not the case, however. On the whole, it seems more probable that tubocurarine either stimulates the supraspinal centres indiscriminately, with the action of facilitatory centres predominating, or that it stimulates selectively the facilitatory centres. The fact that tubocurarine enhances the reflex excitability of the distal part of the transected cord and stimulates respiration and circulation points strongly in favour of a direct stimulating action of tubocurarine on cells in the central nervous system. The problem, however, could only be solved by introducing tubocurarine directly into different regions of the grey matter and studying the effects which are produced.

Action on respiration.—The stimulation of respiration produced by tubocurarine is probably due to direct stimulation of the respiratory centre. The effect is absent after intrathecal injection if the subarachnoid space is blocked; it is thus not reflexly produced by stimulation of dorsal nerve roots. It is not due to the increased muscular activity or blood pressure changes, as the effects on respiration are unrelated to alterations in these other systems. It is not reflexly produced from the chemoreceptors, as it occurs after denervation of the carotid sinus areas and section of the two vagi. It is not due solely to stimulation of the respiratory centre from higher centres, as the effects are also observed in the decerebrate preparation.

As already mentioned, tonic spasm of the respiratory muscles may occur, usually in the phase of expiration. This disturbance may possibly be due to the drug acting unequally on different parts of the respiratory centre, perhaps stimulating the expiratory centre more markedly than the inspiratory.

When large doses of tubocurarine were injected, respiration ceased. There are reasons for supposing that this effect is also probably of central origin; thus neuromuscular excitability is unaffected. Generally when respiration stopped the generalized convulsions (and the high blood pressure) persisted for a long period if artificial respiration was employed. Thus with increasing dosage tubocurarine first stimulates, then disorganizes, and finally paralyses the respiratory centre.

Action on vasomotor centre.—The rise of blood pressure produced by intraventricular and intracisternal injections of tubocurarine is probably due to a direct action on the vasomotor centre. This rise of blood pressure is not affected by double vagotomy and denervation of both carotid sinuses; it is not related to changes in respiration, and in fact it often sets in before respiration is affected at all. It occurs before the onset of "convulsions," indicating that it is not due to increased muscular activity. The marked rise of blood pressure does not occur after intrathecal injection with the spinal cord blocked at T.6, even if "convulsions" take place.

Intrathecal injections produce an initial small rise of blood pressure, which may partly be produced reflexly by mechanical stimulation of the dorsal nerve roots by the injected fluid (Calma and Wright, 1947b).

Occasionally, towards the end of an experiment, a fall of blood pressure sets in, or the blood pressure fails to rise on giving further injections of curare. This phenomenon might be due to the effects of hyperventilation or to a paralysis of the vasoconstrictor centre or to both factors.

Action on heart rate.—The rise of blood pressure is accompanied by increased heart rate and the development of cardiac irregularities (Fig. 2). The tachycardia is not abolished by double vagotomy or carotid sinus denervation, indicating that tubocurarine directly stimulates the cardio-accelerator centre.

Action on the eye.—The changes in the eye described on page 54 are probably due to stimulation of appropriate centres by tubocurarine. The pupils begin to dilate immediately after intraventricular injection of small doses of tubocurarine which have no peripheral action on the eye. This mydriasis is thus not due to peripheral "oculomotor weakening" as suggested by Zelenski (1862), or to

asphyxia. There is no evidence that the mydriasis is due to changes in the tension of the blood gases or in the blood pressure or respiration. It does not occur at all after intrathecal injection with the subarachnoid space blocked; it does occur if the subarachnoid space is free but then only after a very long latent period (about 20 min.), during which time the drug presumably has travelled up to the brain, as evidenced by the onset of violent convulsions. These last observations also prove that the mydriasis is not reflexly produced by mechanical stimulation of the posterior nerve roots. The centre in the brain which is acted on by tubocurarine is probably the pupillodilator centre in the superior colliculus. In support of this localization is the fact that, when tubocurarine is intracisternally injected in preparations with the brain stem transected at the mid-collicular level, pupillary dilatation is rarely seen, presumably owing to the ablation of the superior colliculus.

Reference was made on page 54 to the fact that after a tubocurarine injection the pupil may alternately constrict and dilate; such changes may be attributed to simultaneous stimulation of the pupilloconstrictor and pupillodilator centres in the superior colliculus, one or other centre being prepotent at any moment, and not to a peripheral action as suggested by McIntyre (1947).

In the decerebrate preparation, however, intracisternal tubocurarine still produces blinking, accompanied by twitching of the facial muscles and ultimately retraction of the eye-lids as described on page 54. These changes may be due to stimulation of the facial nucleus which lies below the level of the transection.

Action on salivary, lacrimal, and bronchial glands and bronchial muscle.—McIntyre (1947) concluded that the salivation which follows rapid intravenous injections of tubocurarine into anaesthetized dogs is central in origin. The results in the experiments described above support this deduction. Moreover, centrally injected tubocurarine also stimulates the lacrimal and the bronchial secretions.

West (1937) reported that curarine, before inducing generalized paralysis in dogs, sometimes caused an initial phase of slow stertorous breathing with inspiratory difficulty which he attributed to bronchial spasm. He did not consider whether the effects were produced centrally or peripherally. The evidence recorded above, however, shows that this bronchial spasm is central in origin.

SUMMARY

1. The action of *d*-tubocurarine chloride on the central nervous system was studied by intraventricular, intracisternal, and intrathecal injections in cats under chloralose anaesthesia and in the decerebrate preparation.

2. *d*-Tubocurarine chloride, directly applied to the central nervous system of cat under chloralose anaesthesia or decerebrated, has an excitatory action. Small doses introduced intraventricularly or intracisternally directly excite the vasomotor, the respiratory, the cardiac, and the other autonomic centres, especially those innervating the salivary glands and the bronchi. They produce heightened reflex excitability of the spinal cord and later generalized convulsions. The effects on the spinal cord are due only to a minor extent to a direct action on the spinal centres; they are mainly the result of stimulation of the cells of origin of the facilitatory pathways in the brain.

3. *d*-Tubocurarine chloride injected intracisternally or intraventricularly produces complex changes in the eyes and muscles of the head owing to an action on centres in the midbrain and pons.

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