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EFFECTS OF *d*-TUBOCURARINE AND DECAMETHONIUM ON THE CENTRAL INTEGRATION OF SOMATIC REFLEXES

BY

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Ever since the demonstration of a neuromuscular action of curare by Bernard in 1856. most investigators have been preoccupied with the elucidation of the peripheral action of this drug. The central excitant action of *d*-tubocurarine has been generally overlooked, since the concomitant peripheral skeletal muscle paralysis produced by this agent would tend to mask any central action. However, Cohnberg (1946) reported that *d*-tubocurarine injected subcutaneously in rats, mice, guinea-pigs, rabbits and cats produced hyper-excitability and clonic convulsions, despite peripheral partial curarization. Baisset, Laporte & Grezes-Rueff (1949) and Næss (1950) denied an effect of intravenously administered *d*-tubocurarine on the monosynaptic and polysynaptic evoked potentials recorded from ventral root. However, when the drug was localized in the central nervous system, a facilitatory action of monosynaptic extensor reflex was observed by Salama & Wright (1950). Central effects of intravenous *d*-tubocurarine were observed by Bernhard & Taverner (1951) and Brooks & Koizumi (1953) on the electrophysiological correlates of spinal reflexes. A central depressant action of intravenously injected decamethonium has been reported on the knee jerk by Behrendt (1964).

d-Tubocurarine and decamethonium (C10) represent two major classes of peripheral neuromuscular blocking agents. The former acts by competition with acetylcholine (non-depolarizing) at the neuromuscular junction and the latter produces a neuromuscular block by depolarization of the muscle end-plates.

The present work was undertaken to study the effects of *d*-tubocurarine and decamethonium on the central integration of monosynaptic and polysynaptic reflexes, at the spinal and supraspinal levels, independent of their peripheral actions.

METHODS

Forty-six cats of either sex weighing between 2.8 and 4.0 kg were used. All the animals were bilaterally vagotomized and maintained on positive pressure ventilation. Spinal transections were done under ether anaesthesia. The spinal cord was clearly exposed by laminectomy, tied within the meninges by means of two ligatures and finally cut between the ligatures. Thus, the caudal

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spinal cord was severed of its central connexions and was still enclosed in the dural sac. In the case of high spinal transection at C_1, the anaesthetic was allowed to blow off and these preparations were considered unanaesthetized. After low spinal transection at C_7, light anaesthesia was maintained with pentobarbital sodium (25 mg/kg, I.P.) or chloralose (50 mg/kg, I.V.). The intact cats were anaesthetized with pentobarbital sodium (30 mg/kg, I.P.) or chloralose (80 mg/kg, I.V.). Blood pressure was recorded from a carotid artery by means of a mercury manometer on kymograph paper.

The drug solutions were localized in the spinal cord by intrathecal injection at the level of the lumbosacral articulation. Intracerebroventricular administration into a lateral ventricle was done according to the technique of Feldberg & Sherwood (1954). For topical application, a cotton pledget soaked in the drug solution was kept on the exposed brain stem.

The somatic reflexes were elicited 60 to 90 min after the administration of chloralose or pentobarbital. The procedures adopted for eliciting the somatic reflexes were similar to those employed in our earlier studies (Bhargava & Srivastava, 1964, 1965). The patellar extensor reflex (PR) was elicited by tapping the patellar tendon, with an electromagnetic hammer, and recorded through a system of pulleys (Calma & Wright, 1947). Facilitation of PR was induced by stimulation of the contralateral sciatic nerve and the brain stem reticular formation (Henneman, Kaplan & Unna, 1949). A concentric needle electrode was used to stimulate the medullary reticular formation. The coordinates for obtaining a facilitatory response were: anterior 12 to posterior 6 mm, lateral 4 to 5 mm and vertical -1 to 5 mm, and the coordinates for the inhibitory response were: posterior 8 to 10 mm, lateral 0 to 2 mm and vertical -5 to -8 mm. The inhibition of PR was induced by stimulating the ipsilateral sciatic nerve (Abdulian, Martin & Unna, 1960), the contralateral sciatic nerve and the brain stem reticular formation. The flexor reflex was recorded from the contractions of the tibialis anterior muscle produced by stimulation of the central cut end of the sciatic nerve, distal to the origin of the nerve to the tibialis muscle of the same side (Witkin, Spitalleta & Plummer, 1960). The polysynaptic linguomandibular reflex was obtained by stimulating the root of the tongue according to the method of King & Unna (1954). The sciatic nerve gastrocnemius preparation was employed in some experiments as an indicator of the peripheral neuromuscular blocking activity. All stimuli were derived from a Grass Model S4 electronic stimulator delivering rectangular pulses.

The drugs employed were *d*-tubocurarine chloride (Tubarine, Wellcome Foundation, London), decamethonium bromide (Syncurine, Burroughs Wellcome, N.Y.) and decamethonium iodide (Eulissin, Allen & Hanbury, London).

RESULTS

Effect of d-*tubocurarine and decamethonium on the extensor patellar reflex (PR)*

Spinal transected cats

The patellar reflex was elicited in three high spinal (C_1) and five low spinal (C_7) transected cats. Intrathecal injection of *d*-tubocurarine (20–50 μg), consistently enhanced the amplitude of PR in both preparations. The effect was observable within 10 min after drug administration. Recovery occurred in 70–110 min depending upon the dose employed. Under similar conditions, following intrathecal injection of decamethonium bromide (20–50 μg), there was initial transitory facilitation of PR which was followed by a more persistent depression of the PR. The transitory facilitation was not observable under barbiturate anaesthesia. Intrathecal injection of equal volume of normal saline (0.9%) and acidified saline (pH 3–4) had no effect on the PR. Figure 1 shows the effects of intrathecal injection of *d*-tubocurarine (30 μg) and decamethonium (50 μg) in a low spinal cat maintained on chloralose anaesthesia. Twenty minutes after injection of tubocurarine the amplitude of the PR was markedly increased. Subsequently, the effect

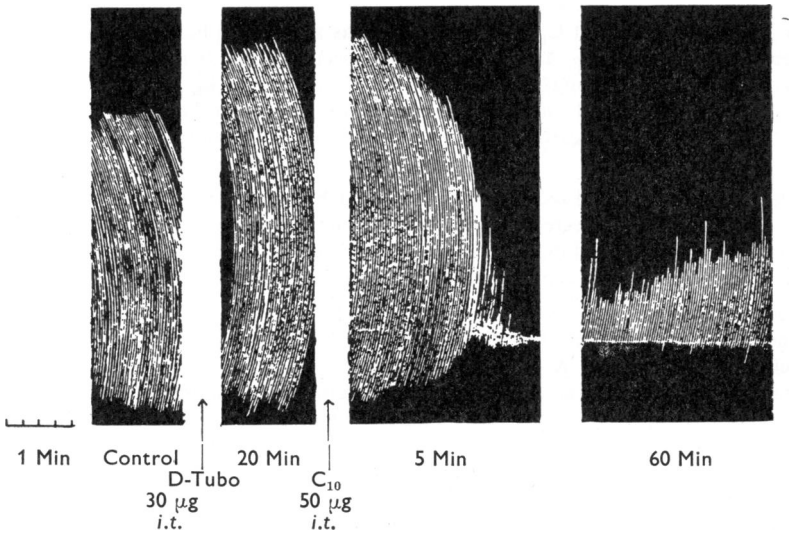

Fig. 1. Spinal (C_7) transected cat 2.2 kg, chloralose (50 mg/kg, I.V.). Record of patellar tap response (PR) elicited every 10 sec. Note, at 20 min, following intrathecal administration of *d*-tubocurarine (30 μg), the amplitude of the PR was markedly increased. Decamethonium (50 μg) injected intrathecally antagonized the *d*-tubocurarine potentiated PR after 5 min and also abolished the PR. Partial recovery was apparent at 60 min.

of decamethonium was observed on the facilitated PR. Decamethonium not only antagonized the *d*-tubocurarine induced facilitation of PR within 5 min, but also abolished the patellar tap response. Recovery was not complete at 60 min. No difference in the nature of actions of the bromide and the iodide salt of decamethonium was observed.

Intact cats

Intracerebroventricular injection of *d*-tubocurarine (20–30 μg) consistently enhanced the PR. The effect appeared within 10 min. On the other hand, decamethonium in the same doses depressed the PR. It was, therefore, essential to include a peripheral control for a possible neuromuscular blocking action of decamethonium. The records in Fig. 2 were obtained from a cat under sodium pentobarbital anaesthesia. The upper record is the gastrocnemius response to peripheral sciatic nerve stimulation (SGR), and the lower record is the patellar tap response (PR) of the other leg. Within 3 min of intracerebroventricular injection of decamethonium (20 μg) the PR was abolished and partial recovery occurred at 100 min. The SGR remained unaltered throughout the study.

Effect of d-*tubocurarine and C10 on the facilitation of PR induced by stimulation of contralateral sciatic nerve in spinal (C_7) transected cats*

In Fig. 3 the facilitation of PR was induced by stimulation of contralateral sciatic nerve (3 V, 120 shocks/sec for 10 sec). Intrathecal injection of *d*-tubocurarine (10 μg)

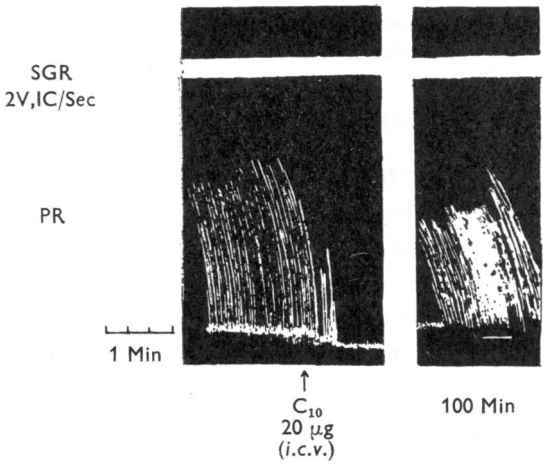

Fig. 2. Cat 3.6 kg pentobarbital anaesthesia (35 mg/kg, I.P.). Effect of decamethonium on the gastrocnemius contractions (SGR, upper trace) induced by peripheral sciatic nerve stimulation (2 V, 1 shock/sec) and the patellar tap reflex (PR, lower trace) induced by patellar tap once every 10 sec. Intracerebroventricular decamethonium (20 μg, at arrow), abolished the PR within 3 min, whereas the SGR was not affected throughout. Recovery of the PR is observable at 100 min. The white signal in panel 2 shows the record at slow speed of the drum.

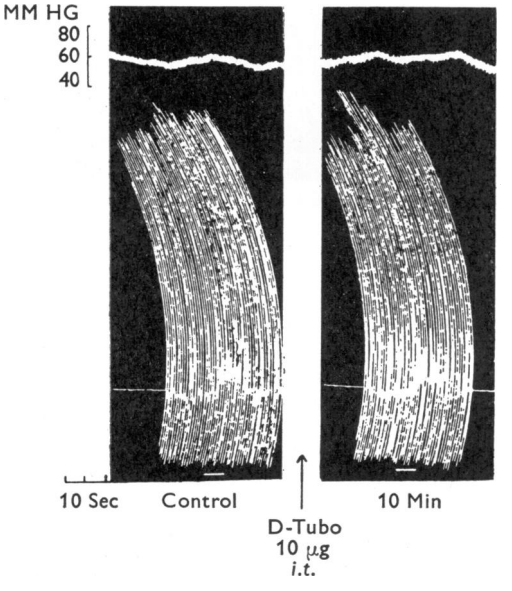

Fig. 3. Spinal (C_7) transected cat 3.6 kg, chloralose (50 mg/kg, I.V.). Record of patellar tap response (PR) 1/sec and facilitation of the PR to contralateral sciatic nerve stimulation (3 V, 120 shocks/sec, for 10 sec at signal marks). Note that intrathecal *d*-tubocurarine (10 μg, at arrow) increased the facilitation of the PR to nerve stimulation without affecting the amplitude of the patellar response. The blood pressure (upper tracing) remained unaffected.

effectively enhanced the facilitation of PR and there was no appreciable effect on the blood pressure level. Doses higher than 10 μg concomitantly increased the amplitude of the PR. Decamethonium (10–20 μg) under similar experimental conditions antagonized the facilitation of PR induced by nerve stimulation.

Effect of d-*tubocurarine and C10 on the facilitation of PR induced by stereotaxic stimulation of brain stem reticular formation*

Facilitation of PR was induced by stereotaxic stimulation of the brain stem reticular formation (4–8 V, 100 shocks/sec for 5 sec) in three cats. The results of one such study are shown in Fig. 4, where the facilitation of PR was markedly exaggerated following

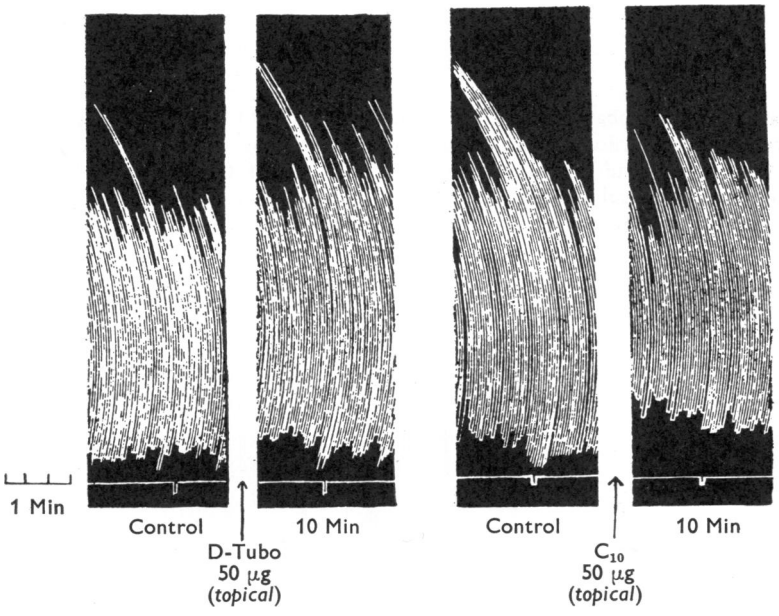

Fig. 4. Cat 3.7 kg, chloralose (80 mg/kg, I.V.). Record of polysynaptic facilitation of patellar reflex induced by stereotaxic stimulation (4 V, 120 shocks/sec for 10 sec at signal marks) of the brain stem reticular formation. *d*-Tubocurarine (50 μg, at arrow) was applied for 5 min in a cotton pledget on calamus scriptorius. Time interval between panels was 10 min. Note the enhancement of the facilitatory response (second panel), which was more marked at 20 min, and this served as the control for observing the effect of decamethonium (C10). After 10 min of application of C10 the facilitation of PR was reduced considerably.

topical application, at electrode site, of *d*-tubocurarine (50 μg) soaked in cotton pledget. The PR remained markedly exaggerated even after an interval of 30 min. The exaggerated response of PR produced by *d*-tubocurarine served as control for observing the effects of C10. Topical application of C10 (50 μg) reduced the facilitation of the PR within 10 min. With higher dose of the drug even the amplitude of PR was found to be depressed.

Effect of d-*tubocurarine and C10 on the inhibition of the PR*

Inhibition of the PR was induced by stimulation of the ipsilateral and contralateral sciatic nerves in eight spinal (C_1 and C_7) transected cats. Inhibition of PR due to brain stem reticular formation was obtained in three intact cats.

In Fig. 5 are shown the effects of *d*-tubocurarine and C10 on the (monosynaptic) inhibition of PR induced by ipsilateral asciatic nerve stimulation (0.3 V, 120 shocks/sec

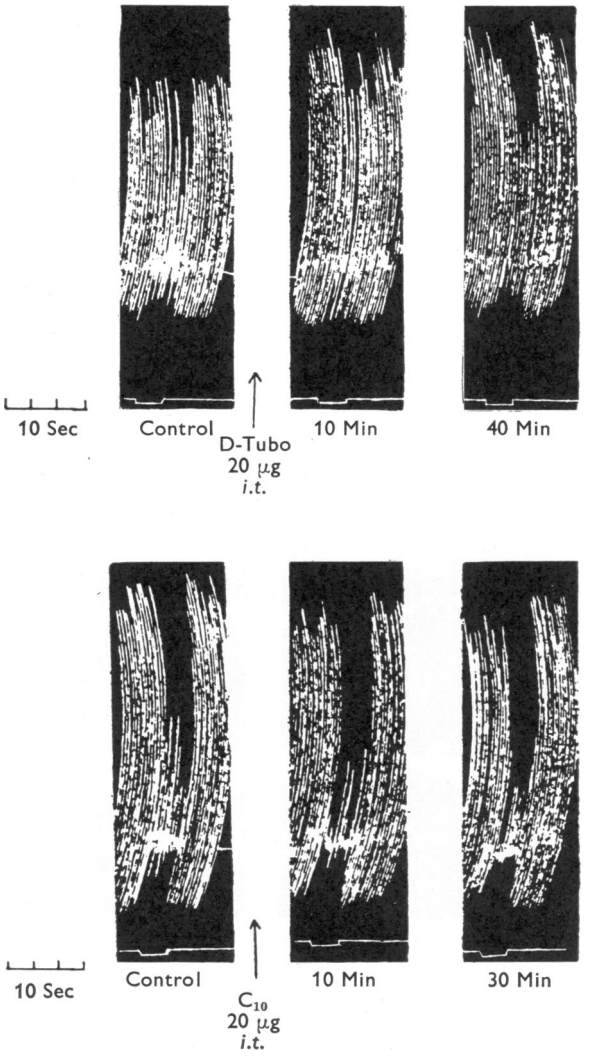

Fig. 5. Spinal (C_1) transected cat 3.2 kg. Record of patellar tap response (PR) elicited 1/sec. The inhibition of the PR was induced by electrical stimulation of the ipsilateral sciatic nerve (0.3 V, 120 shocks/sec for 10 sec at signal marks). Note that intrathecal *d*-tubocurarine (20 μg, at arrow) markedly antagonized the inhibition of PR induced by nerve stimulation (upper panels). C10 (20 μg, lower panels) intensified the inhibition. Recovery was observable in 40 min with *d*-tubocurarine, whereas with C10 only partial recovery occurred in 30 min.

for 10 sec) in a spinal (C_7) transected cat. Upper panels show the effects of *d*-tubocurarine (20 μg) injected into the spinal theca. At 10 min, the inhibition of the PR to nerve stimulation was reduced considerably and the amplitude of the PR was slightly increased. Recovery of the inhibitory response to nerve stimulation was seen at 40 min. In the lower panels are shown the effects of intrathecal injection of C10 (20 μg); the inhibition of PR to nerve stimulation was more marked and partial recovery was seen at 30 min. Similar results were obtained with these drugs when tested on the inhibition of the PR to contralateral (polysynaptic) sciatic nerve stimulation (3–5 V, 120 shocks/sec for 10 sec) and stimulation of brain stem reticular formation (0.4–0.8 V, 100 shocks/sec for 5–10 sec).

Effect of d-*tubocurarine and C10 on the tibialis anterior flexor reflex*

Contractions of the tibialis anterior muscle elicited by stimulation of the central cut end of the posterior tibial nerve were recorded in three low spinal cats. The results of a typical experiment are shown in Fig. 6. The upper tracing shows the carotid blood pressure and in the lower record are the contractions of tibialis anterior muscle to nerve stimulation. In the first panel, intrathecal injection of *d*-tubocurarine (20 μg) gradually reduced the reflex contractions, which were abolished in about 15 min. Partial recovery was seen at 30 min (panel 2). The interval between panel 2 and 3 was 10 min. Subsequently, intrathecal injection of C10 (20 μg) reversed the effects of *d*-tubocurarine. Complete recovery of the depressed PR was seen at 30 min following C10 administration. In other experiments in low spinal cats the period required for recovery of the inhibited flexor reflex following intrathecal *d*-tubocurarine was never less than 120 min.

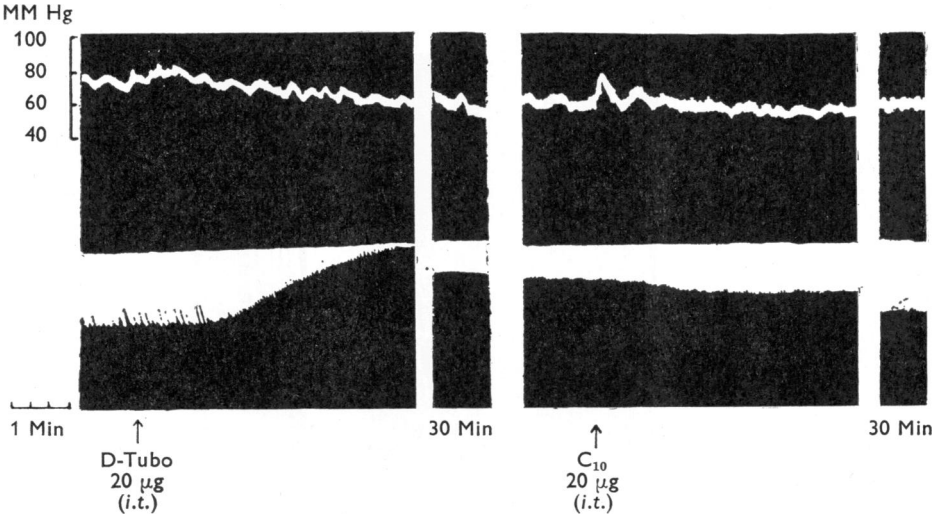

Fig. 6. Spinal (C_7) transected cat 3.4 kg, chloralose (50 mg/kg, I.V.). Record of blood pressure (upper tracing) and contractions of tibialis anterior muscle induced by electrical stimulation (8 V, 1 shock/sec) of the central cut end of the posterior tibial nerve (flexor reflex). Note intrathecal *d*-tubocurarine (20 μg, at arrow) abolished the reflex in 10 min. Partial recovery occurred at 30 min. C10 (20 μg at arrow in panel 3) enhanced the amplitude of the reflex. Complete recovery was observable at 30 min. Normally this degree of recovery following *d*-tubocurarine injection would have occurred in 120 to 180 min.

Effect of d-*tubocurarine and decamethonium on the linguomandibular reflex integrated at the brain stem level*

Linguomandibular reflex (LMR) was elicited in four cats by stimulation (2–4 V, 1 shock/sec) of the root of the tongue by means of two needle electrodes. The drug solutions were injected by the intracerebroventricular route. Decamethonium (10–40 μg) consistently reduced the amplitude of LMR in 5 min, and recovery occurred in 40 to 60 min. On the other hand, *d*-tubocurarine (10–30 μg) regularly enhanced the amplitude of LMR. Recovery was observable in about 60 to 70 min. Figure 7 shows the results of one such study. The LMR elicited by the stimulation of the root of the tongue (2 V, 1 shock/sec) was depressed by C10 (20 μg) at 5 min (panel 2) and recovery occurred at 40 min (panel 3). At this stage *d*-tubocurarine (20 μg) potentiated the reflex within 5 min.

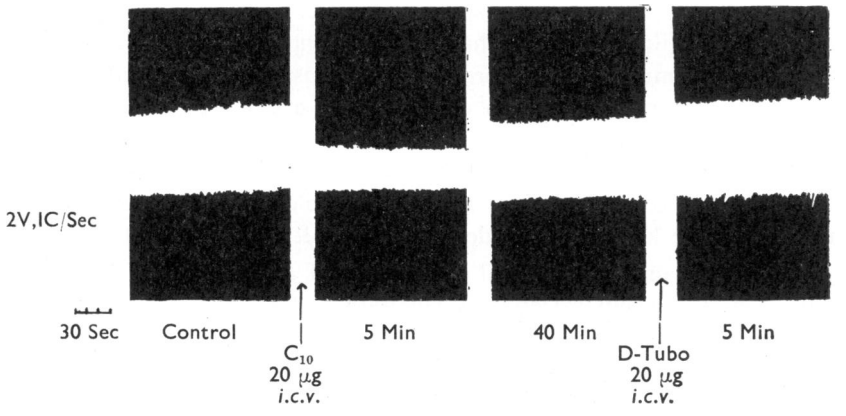

Fig. 7. Cat 3.4 kg, chloralose (80 mg/kg, I.V.). Record of the lower jaw movements induced by electrical stimulation (2 V, 1 shock/sec) of the root of tongue (linguomandibular reflex). Intracerebroventricular administration of C10 (20 μg, at arrow between panels 1 and 2), significantly reduced the reflex at 5 min. Partial recovery was observable at 40 min. *d*-Tubocurarine (20 μg, at arrow between panel 3 and 4) injected intracerebroventricularly increased the amplitude of the reflex at 5 min.

DISCUSSION

In order to demonstrate the central action of a neuromuscular blocking agent, it is imperative to exclude the peripheral actions of the drug. Because of the difficulty in avoiding the peripheral actions of *d*-tubocurarine, most investigators have been content with recordings of spinal monosynaptic and polysynaptic potentials or electrocortiogram upon intravenous injection of the drug (McCawley, 1949; Baisset *et al.*, 1949; Næss, 1950; Bernhard & Taverner, 1951; Taverner, 1953; Brooks & Koizumi, 1953). Such studies provide evidence for passage of *d*-tubocurarine into the C.N.S., but they do not suffice for a proper evaluation of the drug effect on the specific reflexes concerned. Furthermore, the studies on the late and prolonged discharge of electrophysiological potentials may not truly represent the polysynaptic nature of the reflex (Lloyd, 1944; Bremer, 1953). Intravenous administration of *d*-tubocurarine is associated with a fall

in the blood pressure level and asphyxia ; these effects have been shown to modify the electrophysiological potential record (Bernhard & Taverner, 1951 ; Brooks & Koizumi, 1953).

The negative results of Næss (1950) with *d*-tubocurarine in electrophysiological studies were apparently due to the use of barbiturate anaesthesia. In a previous report from this laboratory an action of pentobarbital sodium antagonistic to *d*-tubocurarine has been shown on spinal vasomotor neurones (Bhargava & Kulsreshtha, 1960). However, the depth of anaesthesia is of crucial importance for eliciting the facilitatory effect of *d*-tubocurarine on central responses.

In the present study, the controversial factor of blood-brain barrier to *d*-tubocurarine has been eliminated by introducing the drug into the C.N.S. by suitable routes of administration (see Methods). That the drug did not leak out from the cerebrospinal fluid to the periphery is evident from the facilitatory rather than inhibitory action of *d*-tubocurarine on the somatic reflex responses and lack of action on the blood pressure. In the case of decamethonium, which had a depressant effect on the central integration of somatic reflexes, simultaneous recording of the gastrocnemius contractions induced by peripheral sciatic nerve stimulation did not show a peripheral leakage of the drug. All the animals were vagotomized and maintained on artificial ventilation to exclude the influence of asphyxia on the central nervous system. The effects of *d*-tubocurarine could not be due to the *p*H of the solution, and the possible action of preservatives used in the commercial sample has been excluded by Salama & Wright (1950).

It is now generally agreed that local application of *d*-tubocurarine has an excitatory action on the central nervous system. A facilitation of PR could be obtained in intact cats upon intracerebroventricular or topical application of *d*-tubocurarine, as well as in spinal transected cats upon intrathecal administration. It is emphasized that, in animals with complete spinal transection, injection of the drug in the spinal theca could not have reached the supraspinal structures. Thus, it may be stated that *d*-tubocurarine has facilitatory actions at supraspinal as well as spinal levels of integration. Salama & Wright (1950), however, were not convinced of a spinal locus of action of *d*-tubocurarine and they concluded that the augmentation of spinal reflexes was due to stimulation of facilitatory neurones in the brain. An independent spinal locus of *d*-tubocurarine, however, has also been demonstrated by Bernhard & Taverner (1951).

There is no dispute regarding the facilitatory action of *d*-tubocurarine on the monosynaptic extensor reflex. The electrophysiological studies of Bernhard & Taverner (1951) and of Brooks & Koizumi (1953) differ regarding the action of *d*-tubocurarine on polysynaptic reflexes. Salama & Wright (1950) have shown a facilitation of the polysynaptic reflexes in their myographic studies. Our results are in accordance with these authors. The augmentation by *d*-tubocurarine of the facilitation of PR induced by sciatic nerve stimulation must be due to a spinal locus of action, since it was observed in low spinal transected cats. We have further shown an augmentation by *d*-tubocurarine of the facilitation of PR induced by reticular stimulation when the drug was applied topically at the electrode site. A similar action of *d*-tubocurarine at the brain stem level must be responsible for the facilitation of the LMR.

In the present study intrathecal *d*-tubocurarine was found to inhibit the flexor reflex (tibialis anterior muscle) in spinal transected animals. Such an action could be explained

on the basis of reciprocal inhibition. Facilitation of the extensor motoneurone by *d*-tubocurarine should be expected to inhibit the flexor reflex.

Inhibition of the PR induced by sciatic nerve or reticular stimulation was decreased by *d*-tubocurarine. The patellar reflex inhibition obtained by sciatic nerve stimulation is attributed to the influence of a flexor motor unit within the spinal cord (Fuortes & Hubel, 1956; De Salva & Oester, 1959). When the extensor motor unit is activated by *d*-tubocurarine it is natural to expect a decreased inhibitory influence of the flexor mechanism.

The effects of decamethonium on the central loci concerned with the integration of somatic reflexes were antagonistic to the effects of *d*-tubocurarine. This may suggest a common site of drug action at the central synapses.

The intimate nature of the central excitatory action of *d*-tubocurarine can now be considered. The well-known peripheral action of *d*-tubocurarine is a block of cholinergic transmission at neuromuscular junctions and autonomic ganglia. The excitatory action of *d*-tubocurarine on the central nervous system could be attributed to the inhibition of the inhibitory influence which subserves the motoneurone. One such inhibitory influence on the spinal α-motoneurone is known to arise from a recurrent collateral axon acting *via* an interneurone, the Renshaw cell (Renshaw, 1941). The Renshaw cell "feed back system" has been extensively studied by Eccles, Eccles & Fatt (1956). The transmission at the synapse formed between motor axon and the Renshaw cell is mediated by acetylcholine, and *d*-tubocurarine can block this (Eccles, 1962). It is our contention that the central excitatory effect of *d*-tubocurarine may result from a block of the cholinergic synapse in the inhibitory feed back mechanism. Such an explanation should be adequate to explain the excitatory effect of *d*-tubocurarine on the PR and its facilitation or inhibition observed in the spinal transected animals. Similarly, decamethonium, which is a powerful depolarizer of the muscle end-plate, may produce a persistent depolarization of the central cholinergic synapse. This in turn may lead to continuous activation of the inhibitory feed back mechanism. Such an action would result in the inhibition of the spinal motoneurone.

Direct evidence for the participation of cholinergic synapse in the inhibitory mechanism of the supraspinal structures is, however, lacking. It appears that *d*-tubocurarine may have inhibitory action on several inhibitory synaptic complexes existing at the brain stem level and even more rostrally.

SUMMARY

1. Injection of *d*-tubocurarine, intrathecally in spinal transected cats and intracerebroventricularly in intact cats, facilitated the patellar reflex (PR). Decamethonium (C10) depressed the PR.

2. Facilitation of PR induced by stimulation of contralateral sciatic nerve (spinal transected cats) or brain stem reticular formation (intact cats) was augmented by *d*-tubocurarine. C10 antagonized the facilitation.

3. Intrathecal *d*-tubocurarine decreased the inhibition of PR induced by the stimulation of the ipsilateral (monosynaptic) and contralateral (polysynaptic) sciatic nerves in spinal transected cats. Topical application of *d*-tubocurarine at the electrode site

decreased the inhibition of PR induced by stimulation of the brain stem reticular formation. C10 intensified the inhibition of PR.

4. *d*-Tubocurarine introduced into the spinal theca in spinal transected cats inhibited the tibialis anterior flexor reflex, whereas C10 enhanced the reflex.

5. Intracerebroventricular injection of *d*-tubocurarine augmented the linguomandibular reflex (LMR). C10 depressed the LMR.

6. A clear cut antagonism between the action of *d*-tubocurarine and C10 was observed on the central integration of the somatic reflexes studied, suggestive of a common site of action.

7. The excitatory action of *d*-tubocurarine on the C.N.S. has been attributed to the inhibition of the cholinergic synapse concerned in the inhibitory " feed back " mechanism, which subserves the motoneurone.

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