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Some studies on peripheral actions of mephenesin, methocarbamol and diazepam

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1. Mephenesin, methocarbamol and diazepam abolished polysynaptic reflex contractions of the cat tibialis anterior muscle elicited by stimulation of the homolateral femoral nerve.

2. Mephenesin and methocarbamol caused a prolongation of the mean refractory period of directly or indirectly stimulated skeletal muscle. These effects were due to a direct action on the muscle fibres. There was no effect on responses to single stimuli.

3. The increase in refractory period produced by mephenesin was greater in indirectly than in directly stimulated rat diaphragms. Experiments using the isolated phrenic nerve suggest that this difference is due to the local anaesthetic action of mephenesin.

4. In the indirectly stimulated cat tibialis anterior muscle high frequency stimulation resulted in a non-maintained tetanus in the presence of mephenesin and methocarbamol.

5. Diazepam was without peripheral effects on the responses of skeletal muscle.

6. The results with mephenesin and methocarbamol are discussed in relation to their mode of action in reducing muscle spasm.

A common property of virtually all drugs which have been classified as centrally acting skeletal muscle relaxants is their ability to abolish polysynaptic reflex contractions at dose levels which have no effect on monosynaptic reflex contractions (see Domino, 1956, and Smith, 1967 for references). This property, which distinguishes these drugs from other central nervous system depressants such as the barbiturates (Berger, 1949), has led to the suggestion that the locus of action of the centrally acting muscle relaxants is the spinal interneurone. This has been proposed for mephenesin (Berger, 1947), methocarbamol (Truitt & Little, 1958) and diazepam (Randall, Heise, Schallek, Bagdon, Banziger, Boris, Moe & Abrams, 1961), which were used in the present experiments.

Longo (1961), using microelectrode techniques, investigated the effects of mephenesin on firing rate of interneurones in the spinal cord of the cat. Afferent input, provided either by skin stimulation or by stimulation of a sensory nerve, caused discharges in interneurones. Mephenesin (20 mg/kg, intravenously) depressed only six of the nine cells studied, suggesting that additional sites of action may be involved in its effect on spinal reflexes.

Rosenberg & Cooke (1967) found that mephenesin and chlormezanone extend the refractory period of skeletal muscle by an action at the neuromuscular junction. This effect may be particularly significant in view of the repetitive discharges characteristic of polysynaptic reflex activity (Eccles, 1957). The relative immunity of the monosynaptic reflex to depression could be due to the low frequency of the discharges in such a reflex (Eccles, 1957).

The present paper reports studies on the effects of mephenesin, methocarbamol and diazepam on contractions of the rat diaphragm and the cat tibialis anterior muscle elicited indirectly by nerve stimulation, or directly in fully curarized preparations. Effects of the drugs on nerve conduction were studied using the isolated rat phrenic nerve.

Methods

In vivo *preparations*

Experiments were performed on adult cats anaesthetized by the intraperitoneal injection of chloralose (80 mg/kg). The trachea was cannulated to facilitate artificial ventilation and carotid arterial blood pressure was recorded. The tibialis anterior muscle was prepared for the recording of contractions as described by Bowman, Goldberg & Raper (1962). Contractions were elicited by direct, indirect, or reflex stimulation.

In some experiments, contractions were recorded on a smoked drum using flat spring myographs. In others, isometric tension was recorded photographically from an oscilloscope (Tektronix RM 561 A) using a mechano-electric transducer valve (RCA 5734). In experiments where isometric tension was recorded, gross muscle action potentials from muscle belly-tendon leads were displayed simultaneously on the oscilloscope.

Indirectly elicited contractions were produced by stimulating the distal stump of the cut sciatic nerve with a bipolar platinum electrode using square wave pulses of 0.1 msec duration and of twice the strength required to produce a maximal response. Direct stimulation was applied to fully curarized muscles by means of platinum electrodes, one being inserted through the tendon of the muscle, the other being attached to the metal drill in the lower end of the femur. Square wave pulses of 1 msec duration and of sufficient strength to produce a contraction of the same height as that elicited by maximal indirect stimulation were used. In these experiments, the sciatic nerve was stimulated at intervals to verify that curarization was complete.

Polysynaptic reflex contractions were elicited at a frequency of 0.1 c/s by stimulation of the exposed ipsilateral femoral nerve with square wave pulses of 1 msec duration and of an intensity sufficient to cause a maximum withdrawal response of the tibialis anterior muscle. In these experiments the contralateral tibialis anterior muscle was stimulated through its motor nerve as described above.

In vitro *preparations*

Rat diaphragm

Isolated rat phrenic nerve-hemidiaphragms were prepared as described by Bülbring (1946). They were set up in a 50 ml. organ bath containing McEwen (1956) solution bubbled with 5% carbon dioxide in oxygen and kept at 37° C.

Contractions were elicited by stimulation of the phrenic nerve, or by direct stimulation applied between two platinum electrodes embedded in the costal border of the fully curarized preparation. The parameters of stimulation were identical with those used in the cat preparations.

Rat phrenic nerve

The apparatus used is shown in Fig. 1. Rats were killed by a blow on the head and approximately 5 cm of the left phrenic nerve was dissected free. The nerve was drawn through needle punctures in thin rubber diaphragms of the apparatus. These sealed around the nerve trunk producing three liquid tight chambers. The apparatus was placed in a water bath maintained at 37° C. The contents of the chambers were bubbled with 5% carbon dioxide in oxygen. The two outer chambers were filled with liquid paraffin and contained bipolar stimulating or recording electrodes which were applied to the nerve trunk. The centre chamber, to which drugs were added, was filled with McEwen solution. An indifferent unipolar platinum electrode was placed in contact with the nerve in this chamber to reduce the size of the stimulus artefact. The nerve was stimulated every 10 sec with square wave pulses of 1.0 msec duration and of a strength greater than that necessary to produce an action potential of maximal amplitude. After suitable amplification, the action potentials were displayed on an oscilloscope for photographic recording.

The drugs used were mephenesin (Sigma), methocarbamol (A. H. Robins), diazepam (Roche) and procaine HCl (Drug Houses of Australia). Mephenesin and methocarbamol were dissolved in 50% polyethylene glycol 300 (Shell) in distilled water. Diazepam was dissolved in a mixture of glycofurol (Roche), benzyl alcohol and ethyl alcohol of the same composition as that used in the commercially available injectable preparation (Valium, Roche). Procaine was dissolved in distilled water. The stock solutions were diluted with a suitable volume of 0.9% w/v sodium chloride solution before injection. Control experiments in all preparations showed that the solvents were without effect at five times the concentration injected with the highest doses of the drugs used.

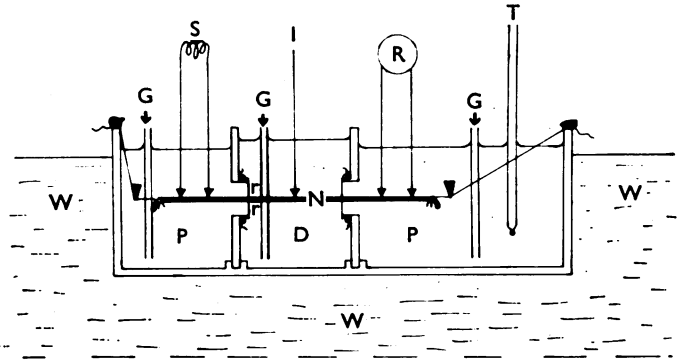

FIG. 1. Three chambered apparatus for the study of conduction in the isolated rat phrenic nerve. W, Constant temperature water bath; T, thermistor probe for temperature monitoring; G, inlets for aeration of the preparation; N, nerve; r, thin rubber diaphragm for provision of liquid tight seal between the chambers; S, stimulating; R, recording, and I, indifferent electrodes in contact with the nerve; P, liquid paraffin; D, drug in McEwen solution. For further details see text.

Results

Muscle contractions in response to single and paired stimuli

In these experiments the cat tibialis anterior muscle was stimulated once every 10 sec with alternating groups of single or paired pulses applied to the sciatic nerve. When the pulse separation was less than 0.5 msec the resulting contraction was of the same magnitude as that produced when the muscle was stimulated with single pulses. As the pulse separation of the paired stimuli was increased, some of the fibres within the muscle responded to both the first and the second stimulus with a consequent summation of the contraction. The summation of the developed tension became constant with greater pulse separations of the paired stimuli. This effect is shown in Fig. 2.

The increase in contraction with paired pulses was expressed as a percentage of the contraction obtained with single pulses. The pulse separation at which half of maximum summation occurred was taken as the mean refractory period of the system. This value was found to be 1.14 msec (S.E. $\pm$0.13 msec) in nine experiments with indirect stimulation.

Figure 2 shows the results of an experiment in which one tibialis anterior muscle was stimulated indirectly with groups of single or paired pulses while polysynaptic reflex contractions were elicited in the contralateral muscle. Doses of mephenesin were injected intravenously every 12 min and the records show the effects produced 4 min after total cumulative doses of 15, 20 and 120 mg/kg. Mephenesin increased

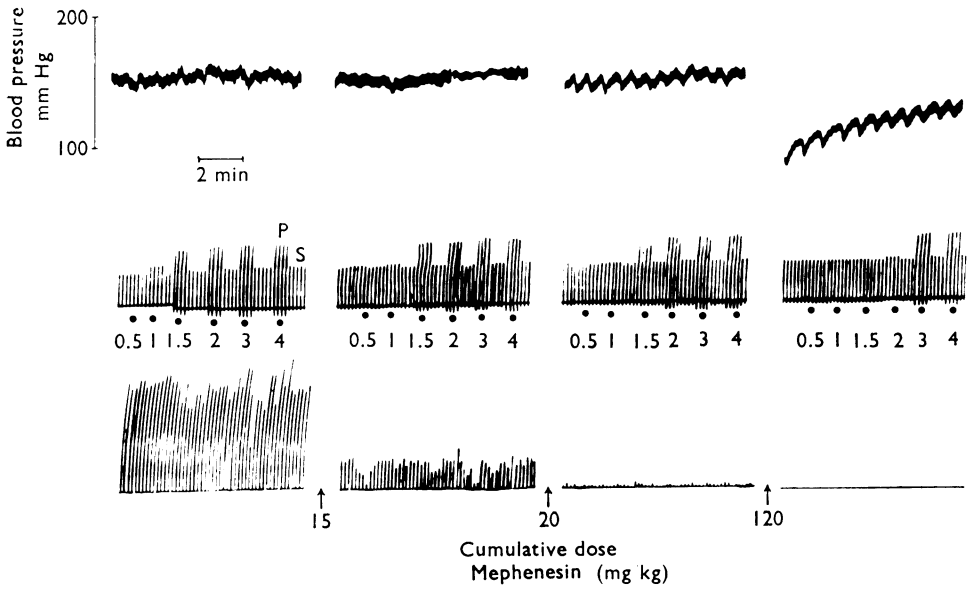

FIG. 2. Cat, chloralose anaesthesia. Records of blood pressure and contractions produced by indirect and reflex stimulation of the tibialis anterior muscles. Flexor reflexes (lower trace) were elicited once every 10 sec by stimulation of the ipsilateral femoral nerve. The contralateral muscle (centre trace) was stimulated through its motor nerve once every 10 sec with groups of single (S) and paired stimuli (P). Numbers indicate the pulse separation of the paired stimuli in msec. The records show the effects produced by a cumulative dose of mephenesin 15, 20 and 120 mg/kg.

the refractory period of the indirectly stimulated muscle as shown by the decreased tension responses at small pulse separations during paired stimuli. Increases in refractory period produced by mephenesin occurred at dose levels below those necessary to cause complete blockade of polysynaptic reflex contractions. Methocarbamol produced similar effects to those described for mephenesin. Diazepam had no effect on the refractory period of the indirectly stimulated muscle but, like mephenesin and methocarbamol, it abolished the polysynaptic reflex contractions.

Figure 3 shows graphically the changes in mean refractory period and the depression of reflex contractions produced by cumulative doses of mephenesin, methocarbamol, and diazepam. Each point is the mean of the results from three experiments with each drug.

The twitch tension produced by motor nerve stimulation with single pulses was unaffected by the highest doses used of mephenesin (180 mg/kg), methocarbamol (200 mg/kg), and diazepam (400 μg/kg).

Experiments in which the isolated rat diaphragm was stimulated indirectly with alternating groups of single or paired pulses showed that the mean refractory period in nineteen preparations was 1.8 msec (S.E. $\pm$0.09 msec). As with the cat tibialis anterior muscle, mephenesin and methocarbamol increased the refractory period whereas diazepam was without effect.

In rat diaphragm preparations, twitches produces by stimulating the motor nerve with single pulses were unaffected by the highest concentrations used of mephenesin (1 mg/kg), methocarbamol (1 mg/ml.) and diazepam (100 μg/kg).

With directly stimulated fully curarized cat tibialis anterior and rat diaphragm preparations, the mean refractory periods were 1.03 msec (S.E. $\pm$0.14 msec) and 1.43 msec (S.E. $\pm$0.15 msec), respectively.

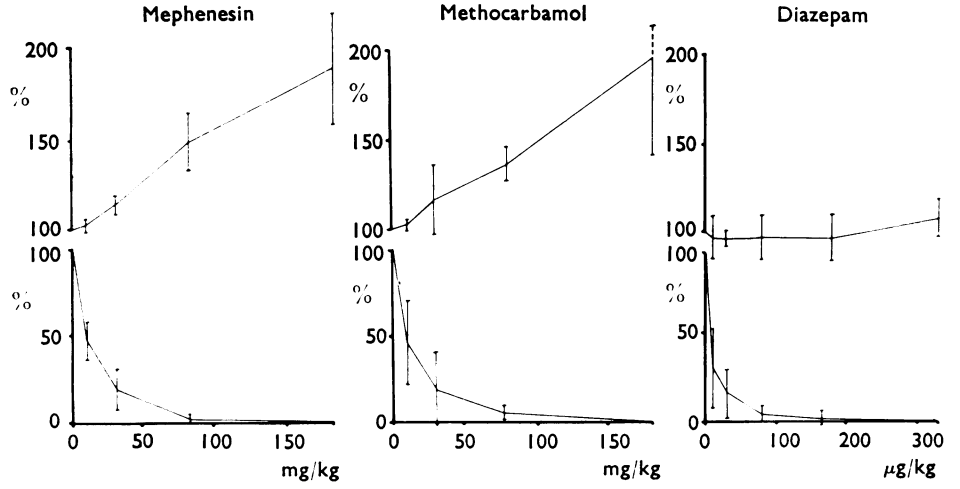

FIG. 3. Graphs showing percentage change in the mean refractory period (upper graph) and percentage reduction in the flexor reflex contractions (lower graph) in chloralose anaesthetized cats produced by cumulative intravenous doses of mephenesin, methocarbamol and diazepam. Each point represents the mean from the results of three experiments. The vertical lines indicate the standard errors of these means.

As in the indirectly stimulated preparations, mephenesin and methocarbamol increased the mean refractory period of the preparations, whereas diazepam was without effect. Figure 4 shows the effect of methocarbamol on a directly stimulated rat diaphragm preparation.

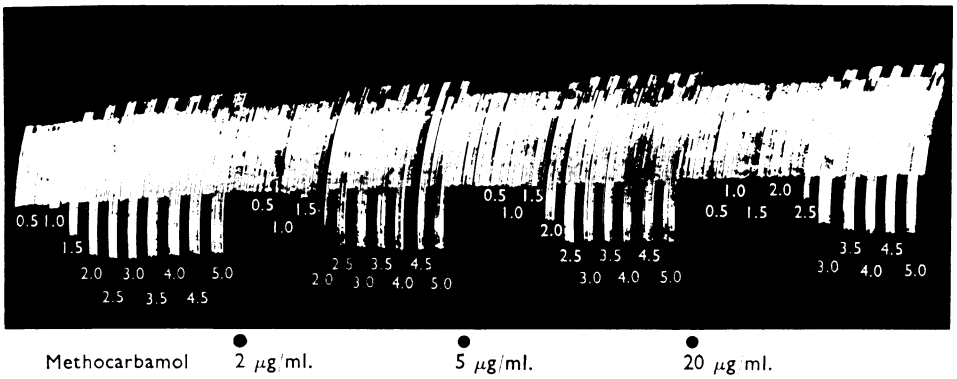

FIG. 4. Contractions of the isolated rat diaphragm produced once every 10 sec by direct stimulation of the fully curarized preparation with alternating groups of single or paired stimuli. The numbers indicate the pulse separation between the paired stimuli in msec. Effects produced before and after the total cumulative doses of methocarbamol 2, 5 and 20 μg/ml.

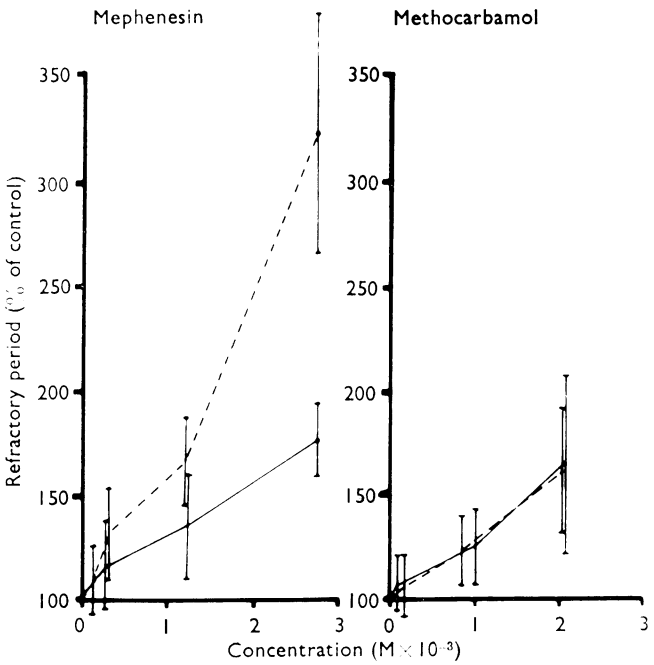

FIG. 5. The effects of mephenesin and methocarbamol on the mean refractory period of isolated rat diaphragm preparations during direct (——) or motor nerve (– – –) stimulation. The ordinate gives the refractory period as a percentage of the control value. Each point represents the mean from the results of five experiments. The vertical lines indicate standard errors of these means.

In the cat tibialis anterior muscle, the changes in the refractory period produced by the drugs were similar when either direct or motor nerve stimulation was used. In the rat diaphragm, however, mephenesin produced greater increases in the refractory period when motor nerve stimulation was used. These results are shown graphically in Fig. 5. On a molar basis, it can be seen that mephenesin and methocarbamol have a similar potency in increasing the mean refractory period of directly stimulated preparations. In the rat diaphragm, the larger changes in refractory period produced by mephenesin when motor nerve stimulation rather than direct stimulation was used suggests that the drug has some action on the nerve or on the neuromuscular junction as well as on the muscle fibres. In the cat this effect was not

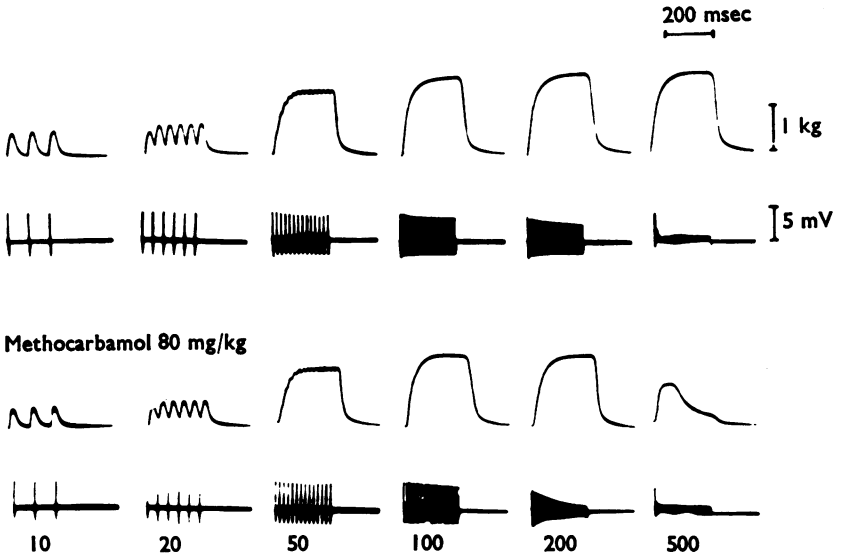

FIG. 6. Cat, chloralose anaesthesia. Records of isometric tension and gross muscle action potentials from the tibialis anterior muscle taken before (upper records) and after (lower records) the intravenous injection of a total cumulative dose of mephenesin (80 mg/kg). The muscle was stimulated through its motor nerve for periods of 250 msec at the frequencies (c/s) indicated under the lower records.

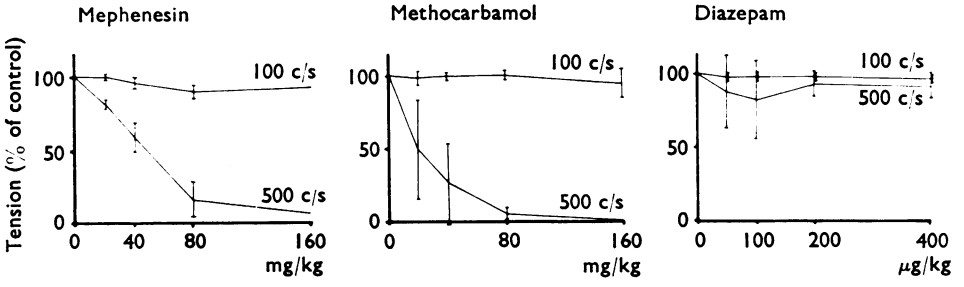

FIG. 7. Graphical records of the effects produced by cumulative doses of mephenesin, methocarbamol and diazepam on the isometric tension developed by the indirectly stimulated tibialis anterior muscle at the end of a tetanus of 250 msec duration at frequencies of 100 and 500 c/s. Each point represents the mean (±S.E.) of the results from three experiments. Only two results were obtained with the highest dose of mephenesin. In the third experiment this dose produced a marked fall in blood pressure and the result was therefore discarded.

seen with the dose levels used. Diazepam, at the highest dose level used in these experiments (100 μg/kg) produced no changes in the refractory period of directly or indirectly stimulated diaphragms.

In four preparations, procaine up to a concentration of 50 μg/ml. did not effect contractions of the rat diaphragm in response to direct or motor nerve stimulation with single pulses. Motor nerve stimulation with paired pulses, however, showed that the mean refractory period was prolonged by procaine in a concentration of 20 μg/ml. When direct stimulation was used, the mean refractory period was not affected by concentrations up to 100 μg/ml.

The increase in the mean refractory period produced by mephenesin and methocarbamol might be expected to produce a decrease in the tension produced during high frequency tetanic stimulation. In the rat diaphragm, "fatigue" and non-maintenance of tetanic tension occurred rapidly in control conditions. In the indirectly stimulated cat tibialis anterior muscle, however, the degree of fatigue produced after a series of tetanic stimuli was only slight, and this preparation was therefore used in further studies. Figure 6 shows records of isometric tension and gross muscle action potentials produced once every 10 sec by repetitive stimulation with trains of 250 msec duration. Frequencies of 10 to 500 c/s were used. The records show the effect of a cumulative intravenous dose of methocarbamol 80 mg/kg.

Despite the fatigue produced by the tetanic stimuli, it can be seen that at frequencies below 200 c/s the tetanic responses were essentially unchanged by methocarbamol. At 500 c/s tension was reduced and waned during tetanic stimulation in the presence of the drug. Mephenesin produced an effect similar to that shown for methocarbamol, whereas diazepam was without effect on the tension produced during high frequency tetanic stimulation. Figure 7 shows the actions of the three drugs, each given in cumulative doses at 15 min intervals, on tetanic responses to stimulation of 100 and 500 c/s. The tension developed at the end of the stimulation period was expressed as a percentage of the maximum tetanic tension developed in the absence of the drug. Each point shows the mean (±S.E.) of the results of three experiments with each drug. Only two results were obtained for the highest dose of mephenesin used, the third being discarded because of the low arterial blood pressure. Both mephenesin and methocarbamol significantly depressed the tension developed at 500 c/s stimulation while leaving that developed during stimulation at 100 c/s unaffected. Diazepam was without significant effect on the tension developed at either frequency.

Attempts to produce these effects in directly stimulated fully curarized muscles were unsuccessful. Results with frequencies greater than 100 c/s, both in the absence or the presence of any drug, were very inconsistent. The high frequencies used and the large currents required for direct stimulation probably accounted for this erratic behaviour and these experiments were discontinued.

Isolated rat phrenic nerve preparations

Using the apparatus illustrated in Fig. 1, rat phrenic nerves were stimulated with alternate single and paired pulses once every 10 sec. The result of increasing the pulse interval during the paired stimuli is illustrated in Fig. 8. The peak voltage of the gross action potential produced by the second impulse of the paired stimuli

increased as the pulse interval widened. Figure 9 shows the effects of cumulative doses of mephenesin, methocarbamol and diazepam on gross action potentials produced by paired stimuli of 1.5 msec pulse separation. Each record was taken 4 min after addition of the drug to the central chamber of the apparatus. Five such experiments were performed with each of the three drugs.

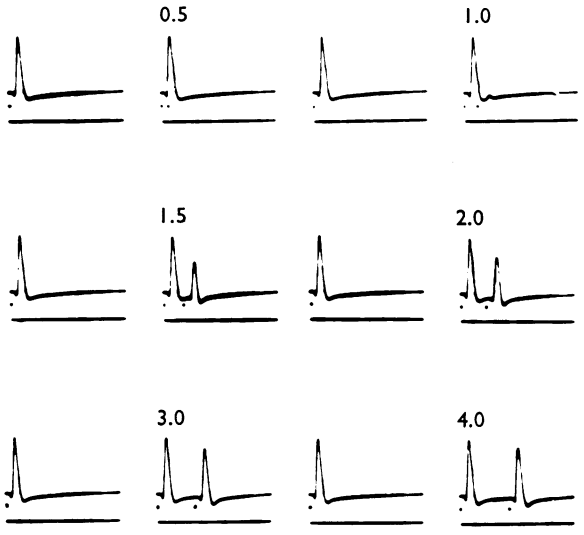

FIG. 8. Oscilloscope records of gross nerve action potentials from the isolated rat phrenic nerve in response to alternate single and paired stimuli. The numbers indicate the pulse interval in msec between the paired stimuli.

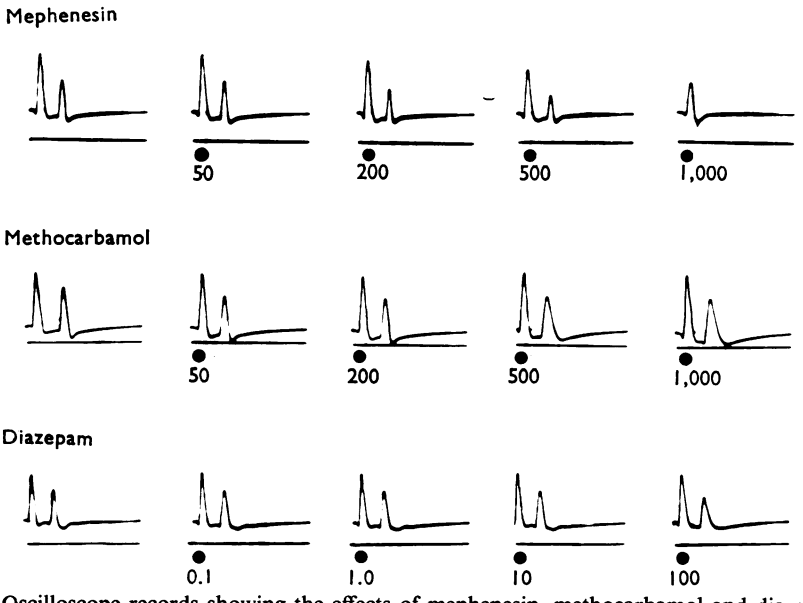

FIG. 9. Oscilloscope records showing the effects of mephenesin. methocarbamol and diazepam on phrenic nerve action potentials produced by paired stimuli of 1.5 msec pulse separation. Numbers indicate doses of the drugs in μg/ml.

With mephenesin, the peak voltage of both the first and the second action potentials of the pair was reduced with increasing concentrations of the drug. The peak voltage of the second action potential of the pair was reduced to a greater extent than that of the first. At a concentration of 1 mg/ml., mephenesin completely abolished the second nerve action potential. At this concentration the mean peak voltage of the first action potential was reduced to 26% (S.E. $\pm$23%) of the control. Procaine (0.1 mg/ml.) produced similar effects to those of mephenesin on both the first and the second action potential. Methocarbamol did not significantly affect the peak voltages of either the first or the second action potential at any concentration up to the highest used in these experiments (1 mg/kg). Diazepam was without significant effect on the peak voltage of the first action potential at concentrations of up to 100 μg/ml. The peak voltage of the second action potential was reduced to 42% (S.E. $\pm$13%) of that of the control by diazepam 100 μg/ml. This effect, recorded in the isolated nerve, did not seem to contribute to changes in the tension responses of the indirectly stimulated rat diaphragm preparation, as these were unaffected by the same concentrations of the drug.

Discussion

Mephenesin, methocarbamol and diazepam all abolished polysynaptic reflex contractions, confirming the work of previous authors. Diazepam differed from both mephenesin and methocarbamol in that it seemed to have no peripheral activity on skeletal muscle. Mephenesin and methocarbamol produced an increase in the mean refractory period of skeletal muscle in both *in vivo* and *in vitro* preparations. The doses of these drugs required to produce changes in refractory period were less than those necessary for the complete abolition of contractions elicited by polysynaptic reflex stimulation. These doses fall within the range of those used clinically to alleviate muscle spasm (Schwab, 1964; Feinberg, Carey, Hussussian & Arias, 1962). The site of action of mephenesin and methocarbamol in producing these peripheral effects appears to be the muscle fibres themselves.

In the cat, the increases in the mean refractory period were similar in preparations stimulated directly or through their motor nerves. These results were confirmed in the isolated rat diaphragm preparation. In this preparation, however, mephenesin, unlike methocarbamol, produced greater effects when motor nerve stimulation was used. Experiments using isolated phrenic nerves showed that mephenesin produced a depression of conducted nerve action potential whereas methocarbamol was without effect. A local anaesthetic action of mephenesin has previously been described by Feinstein & Libet (1953), and in the present experiments procaine and mephenesin had similar effects on the conducted nerve action potentials. This pre-junctional action of mephenesin might explain its greater effect on the refractory period in diaphragms stimulated through their motor nerves diaphragm preparations. This suggestion is further supported by the finding that procaine changed the refractory period of the indirectly stimulated diaphragm in a similar manner to mephenesin, but it had no effect on the mean refractory period of the directly stimulated diaphragm.

Rosenberg & Cooke (1967) have recently shown that both mephenesin and chlormezanone increase the refractory period in the cat tibialis anterior muscle. They suggest that the site of action of both these drugs is at the neuromuscular junction, for neither drug influenced nerve conduction or produced changes in the

refractory period of directly stimulated, curarized, or chronically denervated muscles. The reason for the discrepancy between the latter results and those in the present paper is not obvious. Goodman (1954) has described a decrease in the excitability of fully curarized frog muscle with mephenesin, as evidenced by an increase in rheobase. If the same effects are produced in mammalian muscle, the loss of excitability does not seem to be sufficient to decrease contractility in response to single supra-maximal shocks. Repolarization of the muscle is, however, possibly delayed with a consequent increase in refractory period. Further work is required to determine the mode of action of the drugs in producing these changes.

The increase in refractory period produced within the muscle could well account for the reduction in tetanic tension produced by mephenesin and methocarbamol during high frequency tetanic stimulation especially if a cumulative increase in refractory period occurred during the train of tetanic impulses. The fact that diazepam did not share the peripheral effects of mephenesin and methocarbamol indicates that these effects are not common to all drugs that abolish polysynaptic reflex contractions.

The contribution of the peripheral actions of the drugs to their ability to abolish polysynaptic reflexes and to relieve skeletal muscle spasm is worthy of comment. In both states, rapid repetitive discharges occur (Denny-Brown & Foley, 1948; Eccles, 1957). Increases in the refractory period occurring at the muscle itself might explain, at least in part, the ability of the drugs to reduce muscle spasm. It is possible that the prolongation of the refractory period as seen post-junctionally in muscle might reflect similar actions of the drugs at other sites involved in the genesis of muscle contraction, such as spinal interneurones or α-motoneurones. This possibility is at present under investigation.

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