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The effects of dimethothiazine on muscle spindle activity in the decerebrate cat

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Summary

1. The effects of dimethothiazine have been studied on the response of afferent fibres from primary and secondary endings of muscle spindles in the soleus muscle of the decerebrate cat during stretching of the muscle under controlled conditions.

2. Dimethothiazine in doses of 1 to 4 mg/kg intravenously reduced the discharge frequency of primary and secondary endings. Higher doses of dimethothiazine had little further significant effect on the discharge frequency.

3. The discharge frequency recorded from de-efferented muscle spindles in soleus of the decerebrate cat were similar to the discharge frequencies obtained in preparations with intact ventral roots which had received a high dose of dimethothiazine.

4. Dimethothiazine had little significant effect on the discharge frequency of afferent fibres from muscle spindles in the soleus muscle of decerebrate preparations where the ventral roots were cut.

5. These effects of dimethothiazine on muscle spindle activity were not related to any changes in blood pressure of the decerebrate cat.

6. Dimethothiazine appears to reduce the effects of both the dynamic and static fusimotor fibres on the spindle.

7. The doses of dimethothiazine which effect spindle discharge frequency are similar to those required to reduce decerebrate rigidity.

Introduction

Dimethothiazine is a compound which reduces the rigidity of the cat decerebrated at the intercollicular level while having no significant inhibitory action on spinal interneurones of the anaesthetized cat and having low-potency in tests of central sedative action in rodents (Keary & Maxwell, 1967; Maxwell & Noblet, 1968). There is substantial evidence that the state of enhanced reflex extensor tonus of the intercollicular decerebrate cat is due to increased sensitivity of the stretch reflex produced by an increase in the rate of firing of fusimotor fibres (Eldred, Granit & Merton, 1953; Granit, 1955; Granit, Holmgren & Merton, 1955; Jansen, 1966). There is also evidence that the related compound chlorpromazine reduces fusimotor activity in both the decerebrate rabbit (Webster, 1965; Ellaway & Pascoe, 1965) and the intercollicular decerebrate cat (Henatsch & Ingvar, 1956). Furthermore, Keary & Maxwell (1967) showed that whereas dimethothiazine in a dose of 2–4 mg/kg intravenously produced a 20–30% inhibition of the patellar reflex in the cat

under chloralose anaesthesia no significant depression of spinal reflexes was seen in the spinal cat. It thus seemed possible that dimethothiazine reduced the rigidity of the cat decerebrated at the inter-collicular level by reducing fusimotor fibre activity supraspinally. Direct evidence was, however, lacking.

It is now well established (Matthews, 1962; Brown & Matthews, 1966) that fusimotor fibres to the muscle spindles can be separated into two divisions; the static and the dynamic fusimotor fibres. It appeared of interest to study the effects of dimethothiazine on fusimotor activity. There are two ways in which the effects of drugs on fusimotor discharge could be studied. The first and more direct method involves the recording of discharge of functionally single fusimotor fibres in subdivided ventral root filaments or in subdivided muscle nerve filaments. This has the disadvantage that it is sometimes difficult to distinguish unambiguously a fusimotor fibre from an α-fibre. Second, when fusimotor fibres are isolated from ventral root filaments their muscle of destination is usually unknown and, third, samples of isolated fusimotor fibres often tend to be biased in favour of those which are discharging spontaneously (Matthews, 1964; Hunt & Paintal, 1958). A further disadvantage of directly recording fusimotor activity is that it would probably be difficult to distinguish between effects of drugs on one type of fusimotor fibre (static or dynamic) as compared with the other. The alternative method of studying the effects of drugs on fusimotor activity is indirect and consists of recording the discharge of muscle spindle afferents. If, subsequently, it is shown that the drug in question does not depress the muscle spindle directly, then drug effects on activity of afferents from the muscle spindle may be attributed to a change in fusimotor activity (γ-bias). This latter method also has the advantage that the isolation of single, large afferents from dorsal root filaments is technically easier than that of single fusimotor fibres from muscle nerve filaments. Furthermore, the recording of an afferent discharge from a sensory ending indicates the joint action of several fusimotor fibres on the sensory ending; this is probably of more physiological importance than the discharge of an individual efferent fibre. The detailed studies of Crowe & Matthews (1964a, b), Brown & Matthews (1966) and Brown, Engberg & Matthews (1967) have provided much detailed information on the behaviour of afferents from muscle spindles while the muscle is undergoing stretch and provide a basis for distinguishing between possible drug effects on the dynamic and the static fusimotor fibre activity.

In the present experiments, the effects of dimethothiazine on the activity of afferent fibres from primary and secondary endings from soleus muscle in the decerebrate cat have been studied whilst the muscle was undergoing rapid controlled stretch. A preliminary communication of some of this work has been given to the Physiological Society (Maxwell & Rhodes, 1970).

Methods

Preparation

Cats were anaesthetized with ether or halothane. The carotid arteries were clamped and the mid-brain sectioned approximately between the colliculae. Anaesthesia was then discontinued. The leg and hip muscles were extensively denervated, the nerve to soleus remaining intact. A laminectomy was then carried out from S2 to approximately L6, the spinal theca were sectioned and the exposed cord was

bathed in paraffin (at 37° C). The laminectomy was assisted by the administration of ether or halothane to the animal during the surgical procedure. The dorsal roots of L6, L7, S1 and S2 on the left side were cut and thin dorsal root filaments from L7 were separated under paraffin. In some experiments the corresponding ventral roots were also sectioned.

Myography

The leg of the cat was held rigid by pins in both femurs. A string was tied to the tendon of soleus. The animal was supported by placing the head in a Czermak head-holder and the vertebral column of the animal was held rigid by a circular metal ring sewn into the dorsal muscles and clamped. The tension in soleus was measured by attaching the string from the tendon to a Grass force displacement transducer which itself was mounted on the shaft of a linear motor (Plessey 5W/305). The characteristics of this motor are such that it gives linear displacements with time. The linear characteristics of the motor were checked in preliminary experiments in which the force displacement transducer was attached to a helical spring and the tension developed displayed on an oscilloscope. A linear relationship between tension and time was obtained. In most experiments soleus was stretched through a distance of 2·0 cm in 1·0 s. The muscle was maintained at this extension for 2–3 s and then released.

Recording

The action potentials of the afferent fibre studied were amplified by conventional means and displayed on a Nagard 311 double beam oscilloscope. One beam (the upper) was used to display the action potentials while the lower beam displayed the tension in soleus as recorded by the strain gauge. Permanent records were obtained by displaying a fixed spot and recording the action potentials on a film moving at 6·60 (nominally 6·35) cm per second. The time scale was calibrated by means of an electrophysiological stimulator which was itself calibrated against a Decatron counter. Measurements of discharge frequency were made by counting the number of spikes occurring in 0·635 cm lengths of the developed film strip.

Conduction velocities

Conduction velocities were determined by stimulating the nerve to soleus and recording the action potential produced in the dorsal root filament under study. The time lag between stimulation and the arrival of the action potential at the recording electrodes is the conduction time for this length of neurone. The conduction distance was determined at the end of the experiment by dissecting out the sciatic nerve with its attached dorsal roots. The possible source of error in determination of conduction velocities discussed by Harvey & Matthews (1961) did not appear to occur in the present series of experiments.

Blood pressure recordings

In some of the experiments, arterial pressure was recorded in mmHg (1 mmHg≡ 1·333 mbar) from the brachial artery by means of a thin polythene catheter leading to a mercury manometer.

Drugs

Dimethothiazine (as the methanesulphonate) and gallamine triethiodide ("Flaxedil", M&B) were used. The drugs were dissolved in saline immediately before use, care being taken to keep the dimethothiazine out of sunlight.

Dimethothiazine was administered by slow intravenous infusion (Palmer infusion apparatus) at the rate 1 (mg/kg)/min into a cannulated cephalic vein. Gallamine was administered by rapid intravenous injection into a cephalic vein.

Experimental procedure

In the majority of experiments, spindle discharge was recorded during three or more control stretch responses. A known dose of dimethothiazine was then infused intravenously. The infusion was stopped and 2 min after the end of infusion, two further stretch responses were recorded. The infusion was then recommenced until the next dose of dimethothiazine had been administered. In general, doses of 0·5, 1·0, 2·0, 4·0, 8·0 etc. mg/kg were studied.

In the present experiments, twenty-six endings were studied. In some cases, the conduction velocity was not recorded and in these the ending has been classified as primary or secondary on the basis of its dynamic sensitivity. The range of conduction velocities observed in these experiments was from 110 to 30 m/s. A conduction velocity of 70 m/s has been taken as the dividing line between afferents from primary and afferents from secondary endings (Harvey & Matthews, 1961). On this basis, fifteen experiments were on primary endings and seven on secondary endings in preparations with intact ventral roots. In addition, four experiments were performed on primary endings employing preparations in which both dorsal and ventral roots were cut before drug infusion was begun.

Reduction of decerebrate rigidity

In three separate experiments the effect of dimethothiazine on the rigidity of the decerebrate cat as objectified by reduction of the electromyographic (e.m.g.) response to stretch of quadriceps was studied. The procedure was similar to that described previously (Keary & Maxwell, 1967) except that the e.m.g. was also integrated. The rate of infusion of dimethothiazine was identical to that used in the experiments on spindle discharge. The reduction in decerebrate rigidity produced by a particular dose of dimethothiazine was determined from the ratio of the integrated e.m.g. after that dose and that during the control period.

Results

Effects on spindle discharge

Typical recordings of the discharge of an afferent fibre from a secondary ending undergoing stretch and the modification produced by dimethothiazine are illustrated in Fig. 1. Figure 2 shows the effect of a single dose of dimethothiazine on a primary ending with a high dynamic sensitivity. There are four parameters which could be used to measure a drug effect (Fig. 2). These are: (i) the resting frequency before stretch of soleus; (ii) the maximum frequency during the dynamic phase of stretch; (iii) the discharge frequency during maintained stretch; (iv) the discharge frequency on relaxation of the muscle tension. In the present experiments the drug

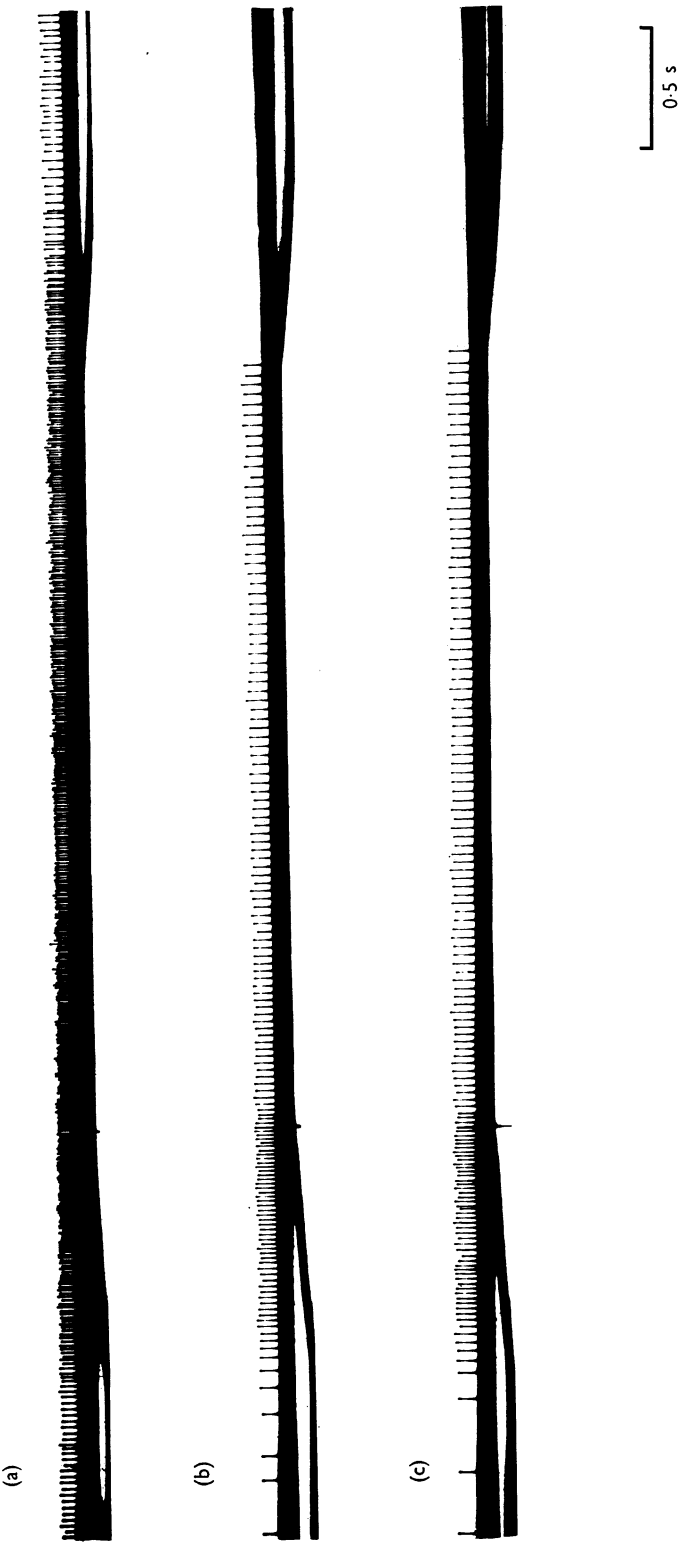

FIG. 1. Effect of intravenous dimethothiazine on the discharge of an afferent fibre from a secondary ending (conduction velocity 58 m/s) in the soleus muscle of an intercollicular decerebrate cat (2·3 kg) while soleus was being stretched. Dorsal roots (L6 to S2) cut, ventral roots intact. In each panel the upper trace is the spike discharge in a dorsal root filament and the lower trace is the tension in soleus (arbitrary scale). (a) Control response (arterial pressure 93 mbar); (b) after 2 mg/kg dimethothiazine (arterial pressure 93 mbar); (c) after 4 mg/kg dimethothiazine (arterial pressure 93 mbar).

effects on the first three of these parameters termed respectively resting, dynamic, and static frequencies, were studied.

Doses between 1 to 4·0 mg/kg of dimethothiazine (Fig. 3) produced marked reductions in all three parameters being studied. Larger doses of between 4 and 16 mg/kg had little further effect on the frequency of response of a primary ending to stretch. A similar effect was seen in the smaller number of experiments carried out with afferents from secondary endings (Figs. 4 and 5).

The effect of dimethothiazine was investigated in four preparations in which the ventral roots had been sectioned and in all four preparations the responses of afferents from primary endings in soleus were studied. Since section of the ventral roots caused a fall in the discharge frequency it is more objective to compare drug effects in innervated and denervated preparations expressing the data as a percentage of the control, rather than the actual discharge frequency. No significant effect of dimethothiazine was observed in these four experiments (Fig. 6) up to doses of 16 mg/kg, doses which cause a considerable reduction (see Figs. 3 and 5) in the activity of primary and secondary endings from muscle spindles in preparations where the ventral roots are intact.

In one experiment gallamine triethiodide (5 mg/kg intravenously) was administered after a dose of 8 mg/kg of dimethothiazine had been administered to a preparation with intact ventral roots in which a primary ending was studied. This dose of gallamine inhibits the effect of fusimotor fibres on the intrafusal muscle fibres of the spindle, thus producing functional de-efferentation. In this one experiment, gallamine produced a very slight further depression from that seen with dimethothiazine.

As mentioned in the introduction, the working hypothesis of the present experiments was that dimethothiazine might reduce decerebrate rigidity by abolishing the effects of fusimotor activity on the muscle spindle. It was known from the work

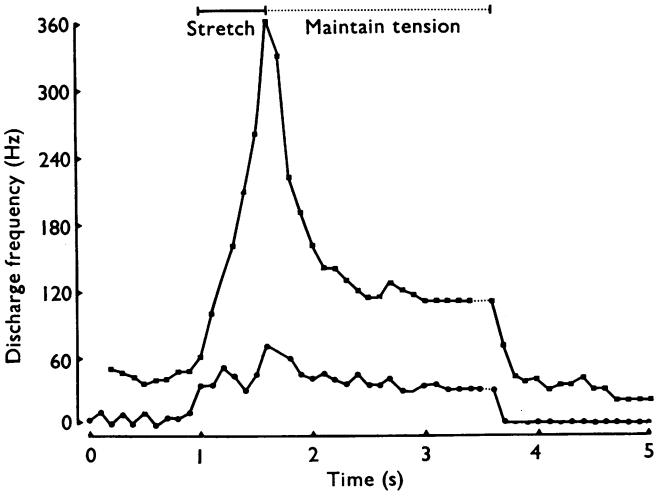

FIG. 2. Decerebrate cat (1·7 kg). Dorsal roots (L6, L7, S1) cut. Effect of dimethothiazine on discharge of primary spindle ending (conduction velocity 83 m/s) from soleus undergoing 2 cm stretch at 20 mm/s. ■, Control; ●, dimethothiazine 1 mg/kg intravenously.

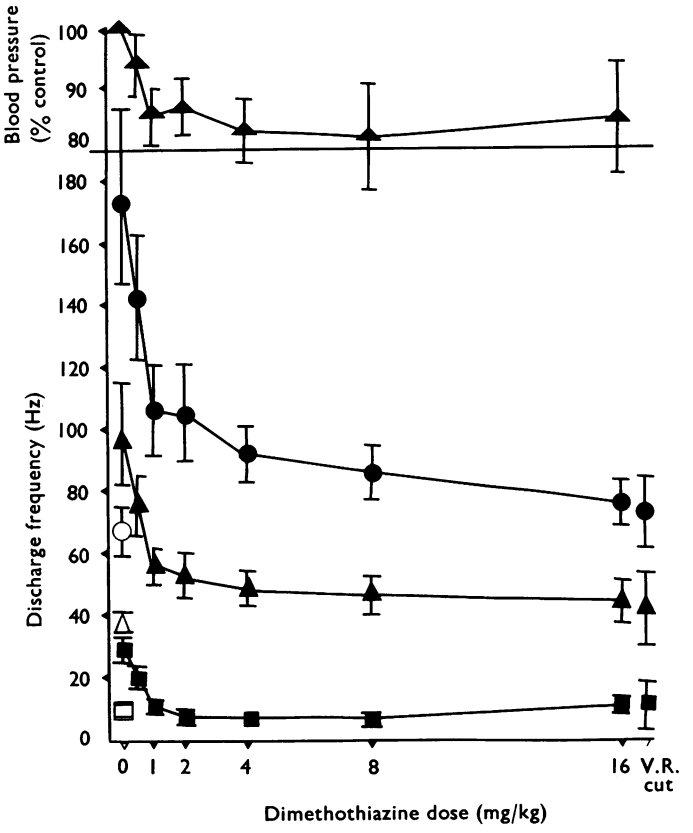

FIG. 3. Effect of dimethothiazine on the discharge frequency of muscle spindle primary endings in response to stretch. Mean value for fifteen experiments. Decerebrate cats with cut dorsal roots (L6 to S2) and intact ventral roots. Upper curve shows mean arterial blood pressure change during nine experiments. Open symbols indicate mean control value for four experiments with ventral and dorsal roots cut and with no drug administered. Vertical lines indicate standard error. V.R. cut, Ventral roots cut at the end of infusion (four experiments); ●, dynamic discharge frequency; ▲, static discharge frequency; ■, resting discharge frequency.

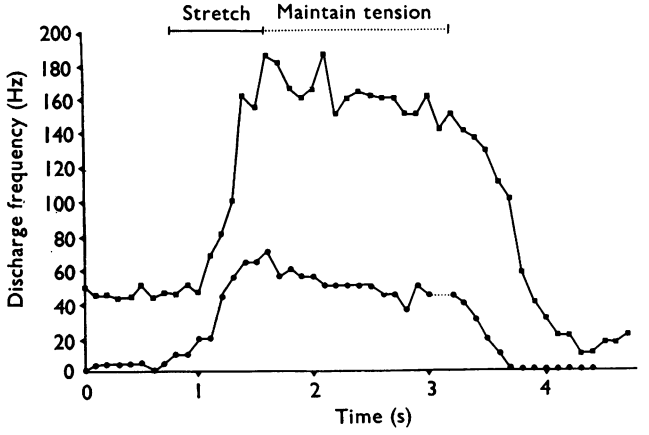

FIG. 4. Effect of dimethothiazine on the discharge of a muscle spindle secondary ending (conduction velocity 58 m/s) from soleus undergoing 2 cm stretch at 20 mm/s. Cat decerebrate, 1·9 kg, dorsal roots (L6 to S1) cut. Ventral roots intact. ■, Control; ●, dimethothiazine 4 mg/kg.

of Crowe & Matthews (1964a, b), Brown & Matthews (1966) and others that efferent fibres to muscle spindles may be subdivided into static and dynamic fusimotor fibres. It was of interest to attempt to determine whether dimethothiazine was having any preferential effect on one type of fusimotor fibre.

There are three ways in which such a differential drug effect could be determined. These are, first, the effects of the drug on the dynamic index. This is defined (Brown & Matthews, 1966) as the fall in the discharge of the ending which occurs in the first half second after completing the dynamic phase of stretching; that is, it is the difference between the discharge at the end of the dynamic phase of stretching and that occurring when the muscle has been at the final length for 0·5 seconds. Second, Appelberg, Bessou & Laporte (1966) have shown that the secondary afferent ending of the spindle is acted on by the static fusimotor fibres alone. Hence a drug effect on the sensitivity of secondary afferents from the muscle spindle probably results from an inhibitory effect on the static fusimotor fibres provided the drug is not acting on the muscle spindle directly. Third, the resting phase of discharge of a muscle spindle primary ending when the muscle is not under stretch is con-

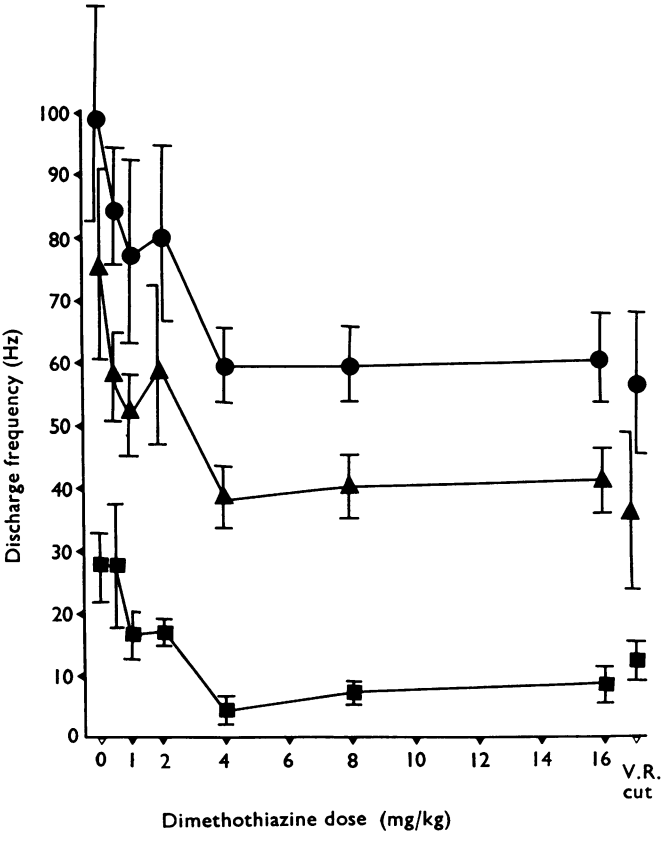

FIG. 5. Effect of dimethothiazine on the discharge frequency of muscle spindle secondary endings in response to stretch. Mean of seven experiments with dorsal roots cut and ventral roots intact. Vertical lines are standard errors. V.R. cut, Ventral roots cut at end of infusion; ●, dynamic discharge frequency; ▲, static discharge frequency; ■, resting discharge frequency.

trolled by the frequency of discharge of the static fusimotor fibres (Brown & Matthews, 1966). It was, therefore, of interest to study the effects of dimethothiazine on these three properties.

In preparations with intact ventral roots, doses of 4 to 8 mg/kg of dimethothiazine produce a significant fall in dynamic index, the final value being close to that seen in preparations with cut dorsal and ventral roots (Fig. 7). Thus dimethothiazine seems to reduce dynamic fusimotor activity. It is shown above that dimethothiazine reduces the frequency of discharge of afferent fibres from secondary endings in the muscle spindle but does not depress the muscle spindle directly. The effect of the drug on the resting discharge has previously been referred to (Figs. 3 to 5) and a reduction is seen. It thus seems that dimethothiazine reduces the activity of static and of dynamic fusimotor fibres.

If the effects of dimethothiazine on spindle discharge are comparable with those produced by de-efferentation of the muscle spindle, then the values of the various parameters being discussed in a preparation with cut ventral roots should be equal, within the limits of experimental error, to the values obtained after the maximal effective dose of dimethothiazine. Points for the values of these parameters obtained

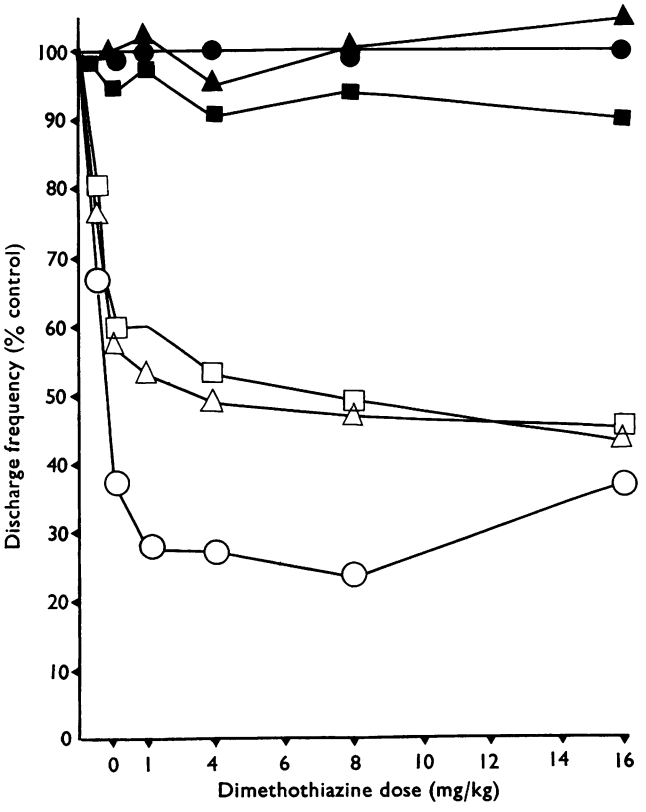

FIG. 6. Effect of dimethothiazine on the discharge frequency of primary endings in preparations with intact ventral roots compared with the effect on preparations with cut ventral roots (L6 to S2). All preparations had cut dorsal roots (L6 to S2). The mean of fifteen experiments is shown with intact ventral roots. The data on preparations with cut ventral roots refers to the mean of four experiments. Closed symbols refer to cut ventral roots, open symbols to intact ventral roots. □ ■, Dynamic discharge frequency; △ ▲, static discharge frequency; ○ ●, resting discharge frequency.

in preparations with the ventral roots cut are inserted in Figs. 3, 5 and 7. In general, the agreement is fairly good but it is possibly significant that the agreement is not exact, in that the frequency of discharge in preparations where the ventral roots were cut was in general slightly less than that seen after a maximal dose of dimethothiazine.

Reduction of decerebrate rigidity and effect on spindle discharge

The doses of dimethothiazine which produced a reduction in discharge frequency of spindles in soleus were comparable to those required to reduce decerebrate rigidity (Fig. 8), as measured by e.m.g. changes in quadriceps. It appeared, however, that low doses of dimethothiazine produced a greater reduction in the frequency of discharge of primary endings than of secondary endings. The reduction in the discharge frequency of secondary endings seemed to correspond more closely to the reduction of decerebrate rigidity than did the reduction in the discharge frequency of the primary endings. Further work would, however, be required to determine whether there is any significant difference in the effect of dimethothiazine on the frequency of discharge of primary as compared to secondary endings, and to relate this to reduction of decerebrate rigidity.

Effects on arterial pressure

In nine experiments, arterial pressure was recorded from the brachial artery. In four of these, the intravenous infusion of doses of 0·5–4·0 mg/kg of dimethothiazine had little significant effect on blood pressure (fall of less than 13 mbar) (Fig. 3).

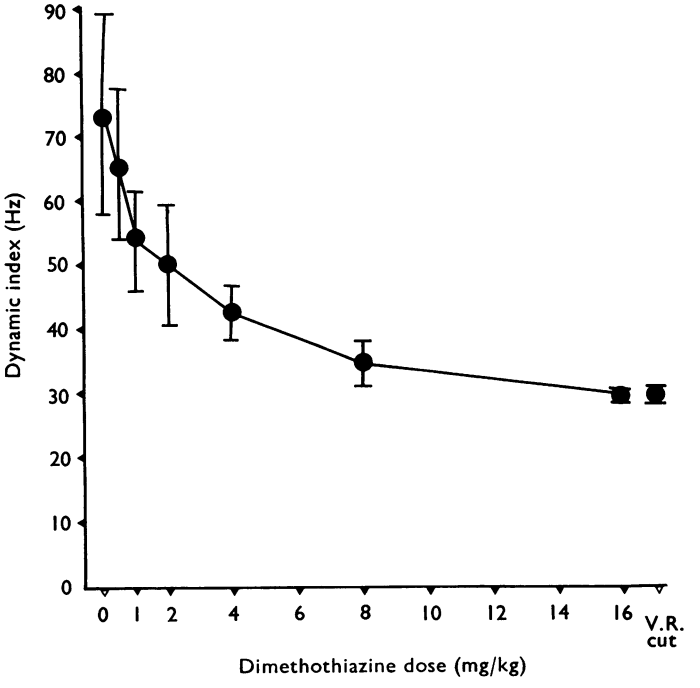

FIG. 7. Effect of dimethothiazine on the dynamic index of the muscle spindle primary ending response to stretch. Closed circles represent means for fifteen experiments with cut dorsal roots and intact ventral roots. Vertical lines show standard error. V.R. cut, Ventral roots cut at the end of infusion.

Higher doses of 8–16 mg/kg in one of the four experiments produced a fall of between 10 and 45 mbar. In the five other experiments a fall of blood pressure of greater than 13 mbar was observed following infusion of 0·5–4·0 mg/kg (Fig. 3). There appeared to be no correlation between the effect on blood pressure and muscle spindle activity.

Discussion

The main purpose of the experiments being reported here was to investigate the mode of action of dimethothiazine in reducing decerebrate rigidity and, in particular, to attempt to obtain evidence that this drug may act in the intercollicular decerebrate cat by reducing and, in high doses, by abolishing the effects of fusimotor activity on the muscle spindle, whilst having little depressant activity on the spindle itself.

That dimethothiazine does not reduce decerebrate rigidity by inhibiting transmission in spinal interneurones has been established in experiments (Keary & Maxwell, 1967) in which the effect of this drug on the polysynaptic flexor reflex and

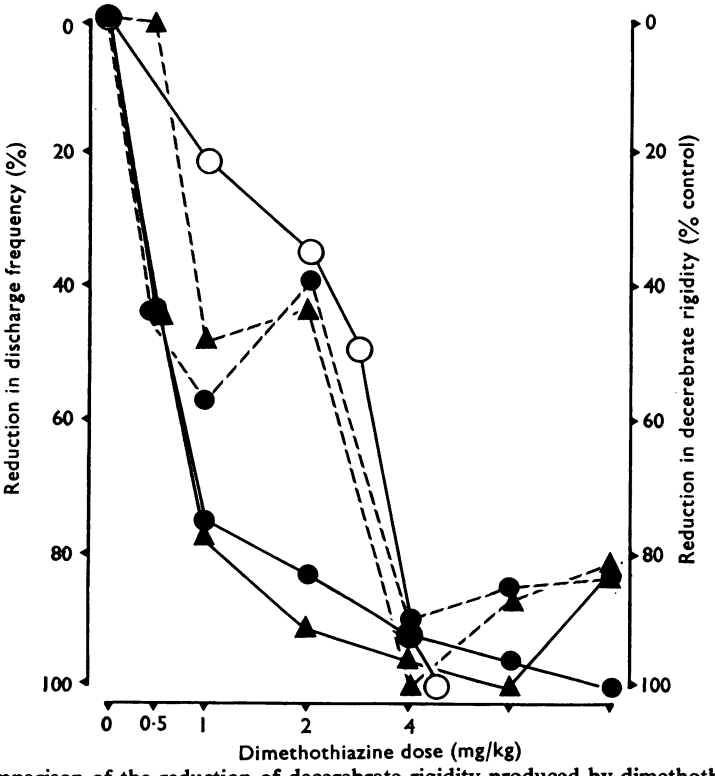

FIG. 8. Comparison of the reduction of decerebrate rigidity produced by dimethothiazine with its effect in reducing the frequency of discharge of primary and secondary endings in soleus while that muscle was resting and during maintained stretch. For comparison with reduction of decerebrate rigidity change in discharge frequency at a dose, d, of dimethothiazine is expressed as $R_d = \frac{F_c - F_d}{F_c - F_{vr}} \times 100$, where F_c, F_d and F_{vr} refer, respectively, to the discharge frequencies under the control conditions; following a dose, d, of dimethothiazine; and when the ventral roots are cut. ○——○, Reduction of decerebrate rigidity (mean of three experiments); ●——●, primary ending, resting ($n=15$); ▲——▲, primary ending, static ($n=15$); ●- - -●, secondary ending, resting ($n=7$); ▲- - -▲, secondary ending, static ($n=7$).

the monosynaptic patellar reflex was studied. These experiments indicate that dimethothiazine had little significant effect on the flexor reflex whilst producing a 20–30% depression of the patellar reflex in preparations with intact central nervous systems.

In spinal preparations dimethothiazine has been found to have no effect on the patellar reflex, an observation consistent with a possible supraspinal site of drug action.

If dimethothiazine is acting by depressing fusimotor activity, one would expect no significant drug effect in preparations where the ventral roots are sectioned. This indeed is what has been observed in the present studies. Our experiments show that dimethothiazine reduces the sensitivity of the muscle spindle to stretch in preparations with intact ventral roots. The discharge pattern of the muscle spindle in response to stretch after a high dose of dimethothiazine was comparable, but not identical with, that seen in preparations with cut ventral roots. The fact that the frequency of discharge seen in preparations following the maximal effective dose of dimethothiazine and that seen following sectioned ventral roots were not identical suggests that dimethothiazine may not be producing complete abolition of fusimotor activity.

It is now known that the efferent fibres to the muscle spindle may be subdivided into static and dynamic fusimotor fibres, so it was of interest to determine whether dimethothiazine had any preferential effect on one group of these efferent fibres. Furthermore, it is thought (Jansen & Matthews, 1962) that the areas of the central nervous system controlling the activity of these two groups of fusimotor fibres may be different, suggesting that a specific drug effect on one group of fusimotor fibres may indeed be possible.

That dimethothiazine reduces the dynamic index of primary endings indicates that it is reducing the activity of the dynamic fusimotor fibres. Its action in reducing the discharge frequency of secondary endings and its effect in reducing the discharge frequency of both primary endings and secondary endings in the resting state indicates that it is reducing the activity of the static fusimotor fibres.

The comparison of the effects of dimethothiazine on the discharge frequency of primary endings and its effects on decerebrate rigidity suggests that considerable reduction in the discharge frequency of primary endings is required to produce reduction in decerebrate rigidity. It should be remembered, however, that different muscles (soleus ; quadriceps) were used in the recording spindle sensitivity and decerebrate rigidity. There is evidence (Matthews, 1969) that the secondary as well as the primary endings of the muscle spindles may be responsible for the tonic stretch reflex of the decerebrate cat. Further studies would be required to establish whether there was any significant difference in the effects of dimethothiazine on the primary as compared to the secondary endings.

These experiments indicate that dimethothiazine is an example of a drug which has little sedative activity and which reduces decerebrate rigidity in the cat probably by reducing or abolishing the effects of both static and dynamic fusimotor activity on the muscle spindle. There is no evidence that the drug effects one group of fusimotor fibres preferentially to the other. It is however possible that drugs may be developed with such a preferential effect, and the methods described here provide a means of investigating them.

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