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The action of *para*-methoxyphenylethylamine (PMPEA) on monosynaptic reflex transmission in the cat

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Summary

1. The intravenous injection of *para*-methoxyphenylethylamine (PMPEA) into cats produces an increase in the size of the spinal cord monosynaptic reflex. The reflex elevation occurs within 30 s of drug administration, reaches a peak within 2 min, and lasts about 20 min.

2. The action of PMPEA is similar for extensor (gastrocnemius-soleus) and flexor (posterior biceps-semitendinosus) monosynaptic reflexes.

3. Repeated doses of PMPEA give comparable effects. The degree of monosynaptic reflex elevation is dose related.

4 The action of PMPEA is antagonized by phenoxybenzamine and by methysergide or cyproheptadine. The combination of phenoxybenzamine with either of the latter is particularly effective in preventing the reflex facilitation by PMPEA.

5. It is concluded that PMPEA has a central action on the spinal cord. It seems likely that monoaminergic synapses are involved.

Introduction

There is now strong evidence that specific neurones in the brainstem contain monoamines and that the axones of some of these neurones project into the spinal cord (Brodal, Taber & Walberg, 1960; Andén, Carlsson, Hillarp & Magnusson, 1964; Andén, Häggendal, Magnusson & Rosengren, 1964; Carlsson, Falck, Fuxe & Hillarp, 1964; Andén, 1965; Dahlström & Fuxe, 1965; Anderson & Holgerson, 1966). It seems likely that noradrenaline and 5-hydroxytryptamine behave as transmitter substances at the synapses made by these pathways upon spinal cord neurones. The results of experiments in which monoamines have been released into the extracellular environment of spinal neurones by microelectrophoresis support this possibility (Biscoe, Curtis & Ryall, 1966; Engberg & Ryall, 1966; Weight & Salmoiraghi, 1966; DeGroat & Ryall, 1967; Phillis, Tebēcis & York, 1968).

If monoamines are transmitter substances within the spinal cord, there should be observable actions on spinal reflex activity by drugs which act at monoaminergic synapses, provided that such drugs can penetrate the blood-brain barrier. A number of recent studies have indicated that this is the case (McLennan, 1961; Andén,

Jukes & Lundberg, 1966 ; Andén, Jukes, Lundberg & Vyklický, 1966 ; Anderson & Shibuya, 1966 ; Anderson, Baker & Banna, 1967 ; Marley & Vane, 1967 ; Engberg, Lundberg & Ryall, 1968a, b ; Shibuya & Anderson, 1968 ; Banna & Anderson, 1968). A series of investigations has been started in our laboratory to learn more about the effects of compounds related in structure to noradrenaline and 5-hydroxytryptamine upon spinal reflex transmission. Observations on the action of *para*-methoxyphenylethylamine (PMPEA) on the monosynaptic reflex pathway are described here. A preliminary report of some of this work has been presented (Walker, Willis & Willis, 1969).

Methods

A total of fifty-one adult cats was used. Anaesthesia was induced with halothane (and sometimes methoxyflurane) delivered by flow of a mixture of 50% oxygen and 50% nitrous oxide. A vein in one limb was cannulated, and 80 mg/kg of alpha chloralose (Marley & Vane, 1963) was administered intravenously. The cannula was then used for injection of supplemental doses of chloralose, when required, and of maintenance fluids by slow drip. It also served as the route for drug injections. A tracheal cannula was inserted to permit artificial ventilation, and a carotid arterial cannula was employed for recordings of systemic arterial blood pressure.

The lumbosacral enlargement of the spinal cord was exposed by laminectomy. The spinal cord was transected at the thoraco-lumbar junction to eliminate actions descending from the rostral levels of the cord and from the brain. The dorsal roots L_6 to S_1 were routinely sectioned bilaterally, thereby minimizing input to the lumbosacral enlargement from peripheral sensory receptors. Although some input remained through intact dorsal roots, these were left undisturbed in order to preserve as much of the radicular blood supply as possible. In one experiment all the dorsal roots below the spinal transection were cut bilaterally as a test of the action of PMPEA, with no afferent input to the cord. Ventral roots were generally left intact. The L_7 and S_1 dorsal roots on one side were prepared for stimulation. Peripheral nerves were dissected in the hindlimb of the same side as that employed for root stimulation. Generally, two nerves were prepared for recording: posterior biceps-semitendinosus (PBST) and gastrocnemius-soleus (GS). This allowed a sampling of the activity of populations of flexor and of extensor motoneurones. The preparation was mounted on a rigid metal frame by clamps attached to vertebral bodies at two levels and to the iliac crests. Pools of warmed mineral oil were held by skin flaps of the back and hindlimb. Roots and nerves were lifted into the oil for stimulation or recording. The body temperature of the animal was further maintained by a warmed metal plate placed beneath the thorax and abdomen. The temperature of the oil pools was monitored periodically and that of the body continuously. The rectal temperature was kept near 37° C.

During the experiments, muscular contractions were eliminated by the use of gallamine triethiodide (initial dose of 10–20 mg/kg intravenously, followed by maintenance doses of 5 mg/kg each hour or as required). This drug did not seem to influence the results obtained by injections of the other drugs used in the study. Artificial respiration was employed. The arterial blood pressure was monitored with a pressure transducer whose output was displayed on a pen recorder by means of a carrier amplifier. The blood pressure was recorded continuously and served as a check of drug action.

Monosynaptic reflexes were evoked by stimulation of the L_7 or S_1 dorsal root or both roots together. The stimuli were rectangular pulses of 0·1 ms duration applied by a stimulator via an isolation unit. The voltage was chosen to be supramaximal for the production of the reflexes. The stimuli were repeated once every 3–5 s. Reflex discharges were recorded from peripheral nerves and observed on an oscilloscope. When desired, photographs were made. The output of one of the preamplifiers was led to a gating circuit (Thompson, Romans & Willis, 1967) which permitted the selection of a portion of the recorded waveform to be integrated electronically. For these experiments integration was timed to include just the monosynaptic reflex spike recorded from one of the peripheral nerves. The integral was led to the second channel of the pen recorder. A digital value for the amplitude of the integral could also be obtained by a system consisting of a voltage-to-frequency converter, a counter, a gate for controlling the counting duration, and a printer. Statistical comparisons were done using such digital values for the integrals of interest.

Drugs were administered intravenously. Dosages, except for noradrenaline, are given in terms of the salt. Solutions were generally in lactated Ringer's injection (*U.S.P.*, seventeenth edition) (lactated Ringer's, Abbott) or isotonic saline injected over a period of 30–90 s. Phenoxybenzamine HCl (Smith, Kline & French) was dissolved in 10 ml. of lactated Ringer's solution with gentle heating and stirring or in a dilute solution of acidified propylene glycol in saline. It was given over a period of 10–20 min. The noradrenaline solution employed was Levophed Bitartrate (Winthrop); it was diluted with 5% dextrose in Ringer's solution. *Para*-methoxyphenylethylamine HCl (Calbiochem) was the principal drug used. Others were methysergide (Sandoz) and cyproheptadine HCl (Merck). For some experiments, PMPEA was given by intravenous infusion, using a constant infusion pump (Harvard).

Results

Action of PMPEA on monosynaptic reflex

The effect of an injection of PMPEA on the monosynaptic reflex recorded from the posterior biceps-semitendinosus (PBST) nerve is shown in Fig. 1. The concomitant blood pressure change is also shown. Integrals of the monosynaptic reflex spike were recorded every 5 s as vertical lines in the pen recorder record at the lower margin of Fig. 1. PMPEA (5 mg/kg) was injected at the time indicated by the thick arrow. The reflex area increased to nearly twice its control size within a minute after the injection. The reflex was still elevated more than 10 min after the drug was given. Accompanying the change in the reflex was an increase in the systemic arterial blood pressure, as shown by the simultaneous record at the top of Fig. 1. The control level of blood pressure was reached before the reflex had resumed its initial level. The insets of Fig. 1 show sample photographic records taken at the times indicated by the thin arrows above the continuous record of the integrals. The upper oscilloscope trace is the integral. The middle trace is the reflex discharge, including an initial monosynaptic spike and a later asynchronous flexion reflex discharge. The third trace indicates by a pulse the timing of integration.

A similar increase in monosynaptic reflex transmission was seen in forty-seven of forty-eight separate experiments in response to injection of PMPEA. In each of the experiments, several doses were given, with comparable results. The onset of the increase generally occurred within 30 s of the beginning of the injection. The peak increase was observed 1–2 min later, and the reflex returned to the control level in about 20 min (range 7–50 min). There was a tendency for the response to last longer as the dose was increased. The action of PMPEA was similar in a completely deafferented animal to that in the partially deafferented preparations routinely employed. In one experiment PMPEA caused a small transient increase in the monosynaptic reflex, followed by a pronounced decrease lasting about 8 min.

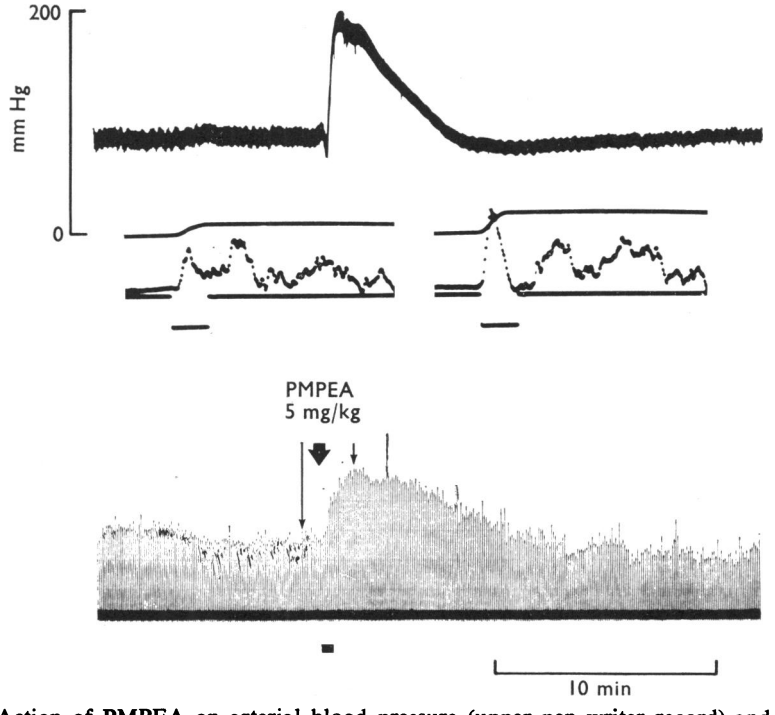

FIG. 1. Action of PMPEA on arterial blood pressure (upper pen writer record) and on PBST monosynaptic reflex (lower pen writer record). PMPEA injected at the time indicated by the thick arrow. The insets show photographs of oscilloscope traces made at the times indicated by the thin arrows. See text for details.

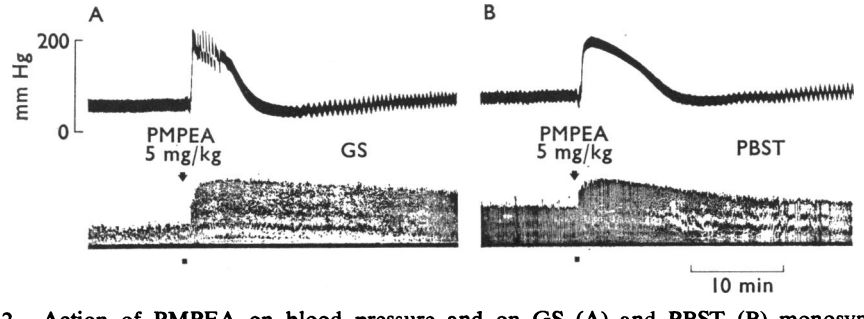

FIG. 2. Action of PMPEA on blood pressure and on GS (A) and PBST (B) monosynaptic reflexes in the same experimental animal.

The predominant action of PMPEA on the blood pressure at doses below 10 mg/kg was a pressor effect. This was often preceded by small, short-lasting changes in either direction (Figs. 1–3). Infusions of PMPEA produced an initial marked elevation in blood pressure, followed by a maintained elevation at a lower level (Fig. 7A).

PMPEA and monosynaptic reflexes of extensor and flexor motoneurones

The facilitatory action of PMPEA was similar for monosynaptic reflexes recorded from either the gastrocnemius-soleus (GS) nerve or the PBST nerve. Thus, there was a similar response for extensor and flexor monosynaptic reflex pathways. An experiment in which the action of the drug was recorded for both the GS and the PBST nerve is illustrated by Fig. 2. The reflexes were recorded simultaneously by photographs of the potentials, but it was possible to integrate only one reflex at a time. Thus, Fig. 2A represents the action of one dose of PMPEA (5 mg/kg) on the GS reflex and on the blood pressure, while Fig. 2B shows the action of a later dose of PMPEA (again 5 mg/kg) on the PBST monosynaptic reflex and on the blood pressure. The monosynaptic reflexes of both GS and PBST motoneurones were consistently increased by the drug in this and in other experiments. There was no evidence of a consistent difference in the intensity or time course of response of the PBST and GS monosynaptic reflexes to PMPEA from experiment to experiment.

Repeated doses of PMPEA

When PMPEA was given in repeated doses, a comparable facilitation of the monosynaptic reflex was observed each time. An experiment in which six consecutive doses of PMPEA were given at intervals of approximately 45 min is shown in Fig. 3. The records of the monosynaptic reflex of the PBST nerve and of the systemic arterial blood pressure are shown in Fig. 3A, B and C for the first, fourth and sixth doses (10 mg/kg each). Noradrenaline was given in two different doses at the conclusion of the experiment (Fig. 3D). It produced no effect on the reflex, although the pressor action was comparable in amplitude with that caused by the PMPEA. It was noted that there was a tendency for the control level of the reflex to increase during the course of the experiment. This might have been due to a failure to allow full recovery between doses, although long-term changes in reflex excitability could not be ruled out. The pressor effect of PMPEA showed slight

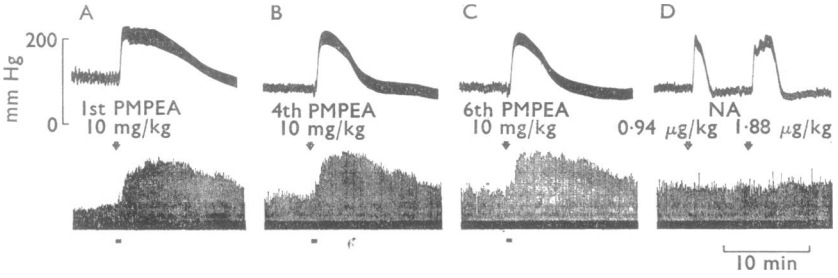

FIG. 3. Effect of repeated doses of PMPEA on a PBST monosynaptic reflex. A-C show the effects of the first, fourth and sixth of six consecutive doses of 10 mg/kg. D illustrates the lack of action of noradrenaline (NA) upon the monosynaptic reflex. The second dose of noradrenaline was injected slowly to produce a longer lasting blood pressure elevation than that caused by the first dose.

tachyphylaxis (Fig. 3A and B). Similar findings were obtained in two other experiments in which repeated doses of 5 mg/kg were used.

Dose-response relationship

The degree of facilitation of the monosynaptic reflex by PMPEA was a function of the dose given. This is shown for a series of experiments in Fig. 4. The dose-response curves are roughly parallel. In some of the experiments more doses were given, but the responses plotted were just those in which the control reflexes were of comparable size. The monosynaptic reflex size depends upon the fraction of a population of motoneurones which discharges following an afferent volley, and it is hazardous to compare responses when the control values differ (Anderson & Shibuya, 1966).

Action of blocking agents

A series of experiments was done to test the effects of blocking agents on the facilitatory action of PMPEA on the monosynaptic reflex. The drugs employed were blockers of α-adrenoceptors (phenoxybenzamine) and of 5-hydroxytryptamine receptors (methysergide, cyproheptadine).

The effect of phenoxybenzamine followed by methysergide is illustrated for one experiment in Fig. 5. The second of two control PMPEA responses is shown in Fig. 5A. Phenoxybenzamine was given (20 mg/kg). It had little effect on the monosynaptic reflex, although the blood pressure was lowered slightly (Fig. 5B). A test dose of PMPEA showed that the phenoxybenzamine partially blocked the reflex response (Fig. 5C). After administration of methysergide (2 mg/kg) (Fig. 5D), the reflex facilitatory action of PMPEA was completely blocked at the dose used

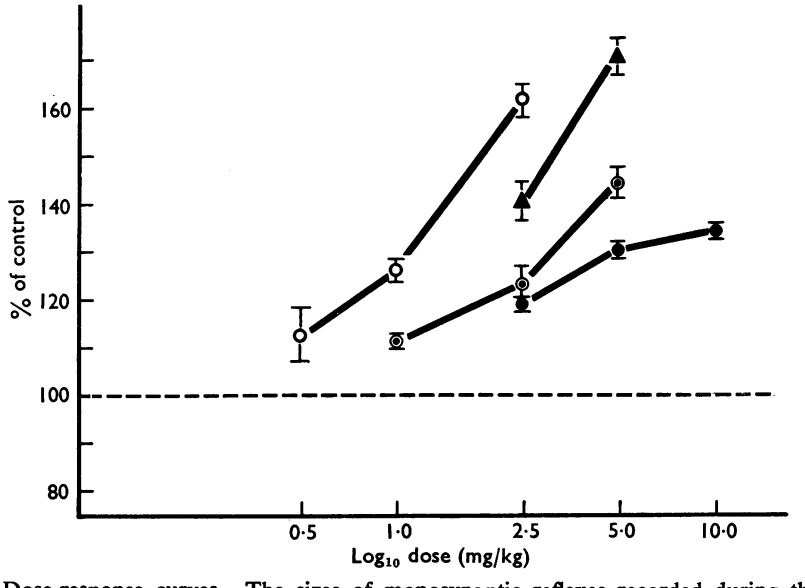

FIG. 4. Dose-response curves. The sizes of monosynaptic reflexes recorded during the peak action of graded doses of PMPEA are plotted as a percentage of the control sizes. The points are the means of twenty responses, and the vertical bars indicate ±1 S.D. The abscissa represents $\log_{10}$ of the dose (mg/kg). ○, Experiment 1 ; ▲, experiment 2 ; ⊙, experiment 3 ; ●, experiment 4.

originally (5 mg/kg), although higher doses produced some increase in the reflex (10 and 20 mg/kg). It should be noted that the methysergide itself decreased the monosynaptic reflex, as in the experiments of Banna & Anderson (1968).

Reversing the sequence of injection of the blocking agents had a similar result, as indicated for another experiment in Fig. 6. The actions of two control doses of PMPEA are shown (Fig. 6A and B). Methysergide (3 mg/kg) reduced the size of the reflex and also produced a partial block of a test dose of PMPEA (Fig. 6C). Phenoxybenzamine (20 mg/kg) had little effect itself on the reflex, although it did lower the arterial blood pressure (Fig. 6D). Test doses of PMPEA, however, showed that the phenoxybenzamine had greatly intensified the blockage (Fig. 6E and F for 5 and 20 mg/kg).

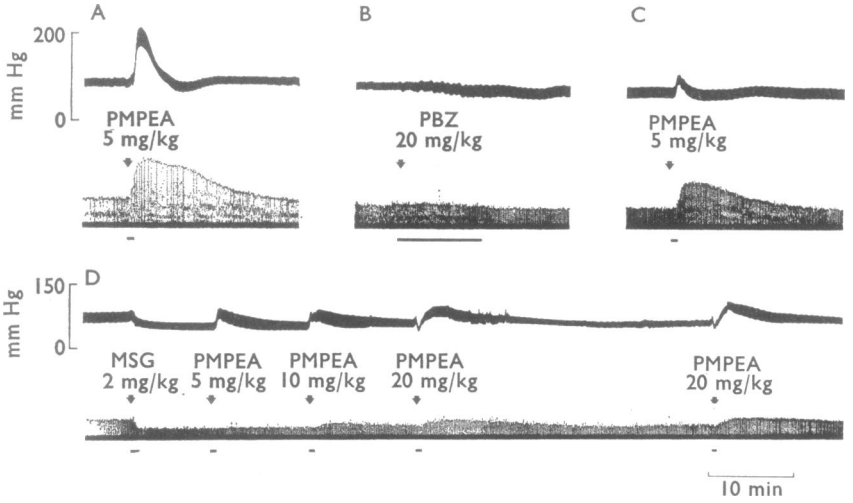

FIG. 5. Antagonism of the action of PMPEA by phenoxybenzamine (PBZ) and by methysergide (MSG). Phenoxybenzamine produced a partial antagonism (compare C and A), while the addition of methysergide increased the degree of block (D).

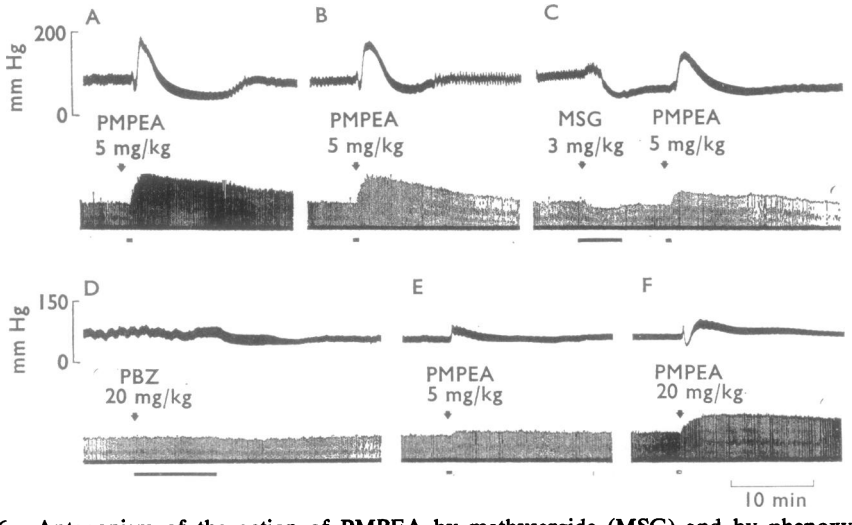

FIG. 6. Antagonism of the action of PMPEA by methysergide (MSG) and by phenoxybenzamine (PBZ). Methysergide produced a partial block of the effects of PMPEA at 5 mg/kg (compare C with A and B). The addition of phenoxybenzamine enhanced the degree of antagonism (E and F).

Similar results were obtained when cyproheptadine was substituted for methysergide. Cyproheptadine itself has minimal effects upon the monosynaptic reflex and upon the cardiovascular system (Banna & Anderson, 1968). Since it was difficult to judge the duration of action of cyproheptadine, the experimental procedure was altered. Infusions of PMPEA were shown in preliminary experiments to cause a maintained increase in the monosynaptic reflex. Successive infusions at the same rate produced similar changes in reflex amplitude, and infusions at different rates produced dose-related increases in the plateau size of the reflex. Figure 7A shows the increase of a PBST monosynaptic reflex that was produced by the infusion of PMPEA at a rate of 1·4 mg/kg per min. A second infusion of PMPEA at the same rate (Fig. 7B) had less effect upon the blood pressure, but it produced a similar increase in the reflex size until the injection of cyproheptadine (0·5 mg/kg at the time indicated by the arrow). The cyproheptadine appeared to prevent much of the increase in reflex size expected by comparison with the control infusion (as shown by the dashed line in Fig. 7B), and it even reduced the reflex transiently. Following this, phenoxybenzamine was injected (10 mg/kg), and 1 hr later another infusion was given at the same rate as above. Figure 7C shows that this infusion had only a minimal action. Comparable results were obtained in several other experiments.

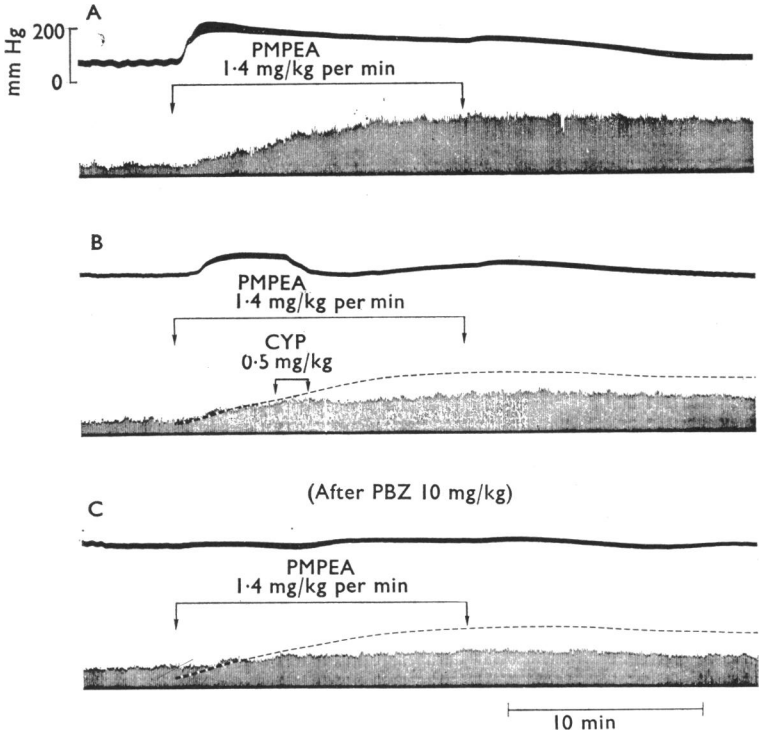

FIG. 7. Antagonism of the action of PMPEA by cyproheptadine (CYP) and by phenoxybenzamine (PBZ). PMPEA was given by continuous infusion, producing a prolonged rise in blood pressure and in the size of the monosynaptic reflex (A). The injection of cyproheptadine caused a transient decrease in the reflex (B) and prevented it from attaining the amplitude expected by comparison with the effect of the control infusion (dashed line in B). Phenoxybenzamine increased the antagonism (C).

Discussion

Para-methoxyphenylethylamine appears to have an action on the spinal cord which leads to an increase in monosynaptic reflex transmission. The monosynaptic reflexes of both extensor and flexor motoneurones are similarly affected. A possible mechanism for changing monosynaptic reflexes is an alteration of afferent input by drug interactions with peripheral receptor organs. This is unlikely in these experiments, since most of the afferent input (L_6–S_1) was interrupted, bilaterally. In one experiment, all the dorsal roots below the spinal transection were cut, with no change in the response to PMPEA. Arterial blood pressure changes were not related to the reflex alterations. For instance, noradrenaline in a dose which raised the blood pressure as much as did PMPEA had no effect upon the monosynaptic reflex (Fig. 3D). Furthermore, PMPEA could still cause a large enhancement of the reflex when a blocking agent, phenoxybenzamine, greatly reduced its pressor effect (Fig. 5C). Other workers have indicated that reflex transmission is generally unaffected by blood pressure changes within wide limits (Marley & Vane, 1967). However, actions mediated by local vasomotor changes cannot be ruled out.

Repeated injections of a given dose of PMPEA produced comparable changes in reflex transmission, indicating the absence of tachyphylaxis. Minimal alterations in reflex height occurred after a dose of about 1 mg/kg, while maximum effects could be observed with 10 mg/kg. The limiting factor for maximal action, however, may have been the size of the subliminal fringe of motoneurones, rather than the availability of receptors, because the largest reflexes after PMPEA could exceed the maximum size of the reflex during post-tetanic potentiation.

A question of considerable interest is the site of action of PMPEA in the spinal cord. The structure of PMPEA resembles that of noradrenaline, and its peripheral actions are sympathomimetic in the cat (Epstein, Gunn & Virden, 1932). It would be reasonable to suppose that the central action would be mediated by excitation of receptors for catecholamines, possibly located on neurones receiving terminals of adrenergic axones descending from the brain (Carlsson *et al.*, 1964 ; Dahlström & Fuxe, 1965). The observation of antagonism of the PMPEA facilitation of monosynaptic reflex transmission by phenoxybenzamine (Figs. 5–7) would be consistent with this hypothesis. A block of the facilitatory action of PMPEA by agents which interfere with 5-hydroxytryptamine receptors was also observed (Figs. 5–7). It is possible that this was due to non-specific blockage of receptors for catecholamines (Banna & Anderson, 1968). Alternatively, PMPEA may act by excitation of receptors for catecholamines and tryptamines. Precursors of both noradrenaline and 5-hydroxytryptamine cause an increase in the size of the monosynaptic reflex (Baker & Anderson, 1965 ; Anderson & Shibuya, 1966 ; Anderson *et al.*, 1967), so the observation of an increase due to PMPEA is consistent with an action on either or both classes of receptor.

A further issue is whether PMPEA itself acts upon postsynaptic receptors or causes the release of endogenous monamines (Cession-Fossion, 1963). Experiments designed to help answer this question are in progress.

The finding that PMPEA has a powerful central nervous system action in the cat is of considerable general interest, because there has been some recent speculation about the possible role of methoxylated phenylethylamines, such as PMPEA and dimethoxyphenylethylamine (DMPEA), in the pathogenesis of schizophrenia and of

Parkinsonism (for a review of the " pink spot " controversy, see Barbeau, 1967). The psychotomimetic action of the trimethoxy compound, mescaline, is well known. Although neither PMPEA nor DMPEA appear to have much effect when injected intravenously in human volunteers (Hollister & Friedhoff, 1966 ; Brown, McGeer & Moser, 1968), they do produce marked behavioural changes in animal subjects (Epstein *et al.*, 1932 ; Ernst, 1962). Evidently, continued study of these and related compounds may be important for the understanding of central nervous system changes induced by drugs or by disease.

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