Brit. J. Pharmacol. (1965) **24**, 375–386.

AN ANALYSIS OF THE BLOCKING ACTION OF DIMETHYLPHENYLPIPERAZINIUM IODIDE ON THE INHIBITION OF ISOLATED SMALL INTESTINE PRODUCED BY STIMULATION OF THE SYMPATHETIC NERVES

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(*Received June* 15, 1964)

1,1-Dimethyl-4-phenylpiperazinium iodide (DMPP) is known to have a depolarizing action at nicotinic sites, acting mainly as a ganglion-stimulating or ganglion-blocking drug (Chen, Portman & Wickel, 1951; Page & McCubbin, 1953; Chen & Portman, 1954; Leach, 1957; Ling, 1959; Brownlee & Johnson, 1963), and as a skeletal neuromuscular-blocking agent (Kaller, 1956; Ling, 1959). More recently another action of DMPP has been reported. It has been shown for the small intestine of the rabbit (Bentley, 1962) and of the guinea-pig (Wilson, 1962) that DMPP abolishes the inhibitory effects produced by stimulation of the periarterial sympathetic nerves, although added adrenaline or noradrenaline still inhibit the intestine. This finding is consistent with the view that DMPP may produce an adrenergic neurone blockade of the postganglionic adrenergic nerves to the gut.

This paper presents evidence that DMPP abolishes the inhibitory effects of periarterial sympathetic nerve stimulation by an action which has features in common with the adrenergic neurone blocking actions of guanethidine and bretylium and which does not involve blockade of sympathetic ganglia.

Part of this work was communicated to the British Pharmacological Society in January, 1963.

METHODS

Preparations of guinea-pig or rabbit small intestine were made as described below and placed in organ-baths containing 20 ml. of Krebs solution at 37° C, bubbled with a mixture of 95% oxygen and 5% carbon dioxide. Longitudinal contractions were recorded on smoked paper with isotonic frontal-writing levers loaded with 0.75 to 1.0 g and having magnifications of ten-times. Throughout this work Multitone " Ten Pulse " stimulators were used.

The co-axially stimulated " Finkleman " preparation of the guinea-pig small intestine (*Wilson*, 1962). Adult guinea-pigs of either sex were stunned by a blow on the head and bled. The abdomen was opened in the midline and the entire small intestine with its attached mesentery and mesenteric arteries was removed. Preparations were made of short lengths of small intestine (approximately 3 cm long), each with its attached

mesenteric artery and periarterial sympathetic nerves; these were set up in the organ-bath for co-axial stimulation of the gut wall and for stimulation of the periarterial sympathetic nerves, using two independent stimulators, two sets of electrodes and different stimulation parameters.

Paton's (1955) technique, with a minor modification, was used for the co-axial stimulation: the intraluminal electrode was fixed to the supporting hook and the upper end of the small intestine was left open and attached by a cotton thread to the recording lever. The frequency of co-axial stimulation was one shock every 12 sec with rectangular stimuli of 0.1 or 0.3 msec duration, the voltage (2 to 4 V) being adjusted to give contractions about 80 to 90% of the maximal response. These twitches were inhibited by independent but simultaneous stimulation of the periarterial sympathetic nerves for periods of 35 or 45 sec at intervals of 6 to 15 min, using unshielded platinum wire annular electrodes. The frequencies of periarterial nerve stimulation were from 1 to 50 shocks/sec, with a pulse duration of 1 msec at supramaximal voltage (25 to 30 V).

The Finkleman preparation of the rabbit small intestine (*Finkleman*, 1930). Adult rabbits of either sex were stunned by a blow on the head and bled. The abdomen was opened in the midline and the entire small intestine with its attached mesentery and mesenteric arteries was removed. Short lengths of small intestine (approximately 3 cm long) were then set up as Finkleman preparations (Finkleman, 1930). Tone and pendular movements were inhibited by stimulating the periarterial sympathetic nerves for 20 sec every 3 min, using unshielded platinum wire annular electrodes: the stimulus frequencies were from 3 to 50 shocks/sec, with a pulse duration of 1 msec at supramaximal voltage (30 to 50 V).

Drugs. Bretylium tosylate, dexamphetamine sulphate, dimethylphenylpiperazinium iodide (DMPP), dopamine hydrochloride, guanethidine sulphate, hexamethonium bromide, nicotine hydrogen tartrate, (−)-noradrenaline bitartrate and procaine hydrochloride were used. All concentrations are expressed as final bath concentrations in g/ml. of base. Unless otherwise stated, each drug was tested on separate preparations from at least six animals.

RESULTS

The co-axially stimulated "Finkleman" preparation of the guinea-pig small intestine

Maximal twitches to co-axial stimulation were always obtained with voltages greater than 10 V and the height of the contractions often increased for the first hour. Responses

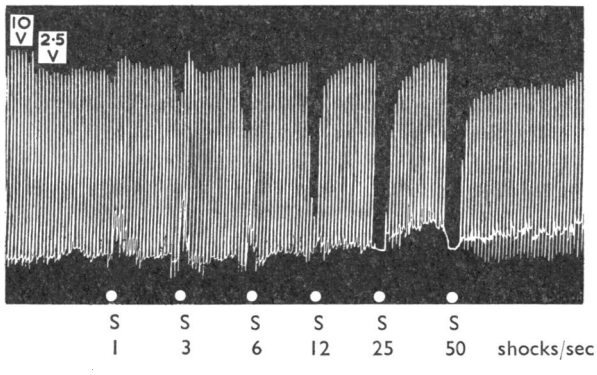

Fig. 1. The co-axially stimulated preparation of guinea-pig small intestine inhibited by periods of simultaneous periarterial sympathetic nerve stimulation at different frequencies. The intestine was stimulated co-axially at a frequency of 5 shocks/min with a pulse duration of 0.1 msec. The voltage for co-axial stimulation was initially 10 V and gave maximal transmural twitches; just submaximal contractions were then obtained by reducing the voltage to 2.5 V for the remainder of the experiment. At the white dots (S) the periarterial sympathetic nerves were stimulated for 35 sec at supramaximal voltage, with a pulse duration of 1 msec at the frequencies indicated (shocks/sec). There was an increase in the inhibition of the transmural twitches with increasing frequency of sympathetic nerve stimulation.

approximately 80 to 90% of the maximum were then obtained by reducing the voltage to 2 to 4 V and, with occasional changes of the bath fluid, these contractions remained uniform for several hours.

When the periarterial sympathetic nerves were stimulated with increasing stimulus frequency there was an increase in the inhibition of the submaximal transmural twitches, from a minimal inhibition at frequencies of 1 to 3 shocks/sec to complete inhibition at frequencies of 25 to 50 shocks/sec (Fig. 1). With intervals of 6 min or more between successive periods of sympathetic nerve stimulation the inhibition of the transmural contractions was reproducible for 5 hr or longer.

DMPP. Concentrations of 2.5 to 10×10^{-6} DMPP produced a brief contraction of the preparation followed by depression of the transmural twitches. The height of the transmural

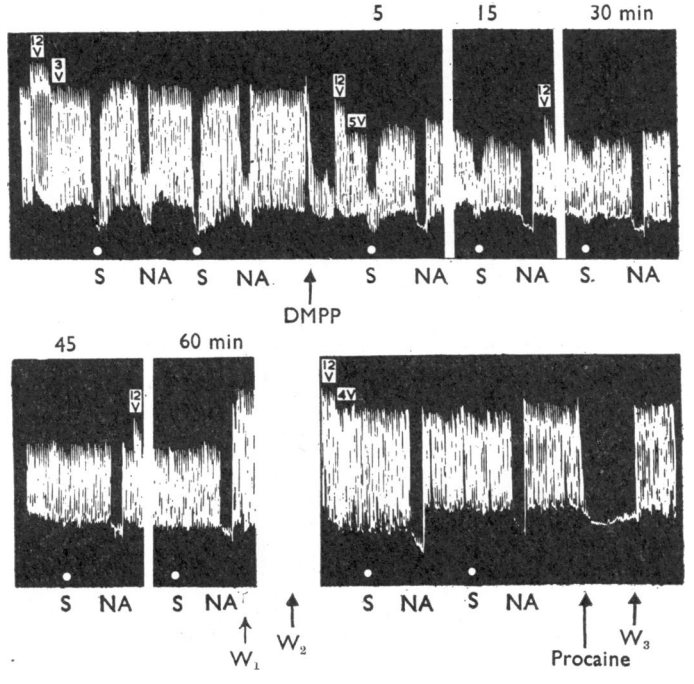

Fig. 2. The effect of DMPP on the inhibitory responses of the co-axially stimulated guinea-pig small intestine to stimulation of the periarterial sympathetic nerves and to added noradrenaline. The intestine was stimulated co-axially as in Fig. 1. At the white dots (S) the periarterial sympathetic nerves were stimulated at a frequency of 50 shocks/sec with 1 msec duration at supramaximal voltage (30 V) for 45 sec. At NA, noradrenaline (2×10^{-8}) was added for a contact time of 45 sec before washing out the drug. S and NA were alternated throughout the experiment. At the first arrow, DMPP (5×10^{-6}) caused a contraction of the intestine and then reduced the size of the transmural twitches; raising the voltage of the co-axial stimulation partially restored the height of the transmural contractions. During 1-hr contact of the intestine with DMPP, the inhibitory effect of periarterial nerve stimulation was blocked, but the inhibitory effect of noradrenaline was increased. At W_1 the DMPP was washed out of the bath and at W_2 the preparation was washed thirty times during 1 hr: the inhibitory effect of sympathetic nerve stimulation remained blocked whilst that of added noradrenaline was still increased. At the fourth arrow, procaine (1×10^{-6}) was added and blocked the transmural twitches produced by co-axial stimulation of the parasympathetic nerves; at W_3 the procaine was washed out. Numbers above the records give times in minutes from the addition of DMPP.

twitches could partially be restored by raising the voltage of the co-axial stimulation (Fig. 2, upper record). Even after prolonged contact with DMPP, on washing out the drug there was a rapid return of the transmural twitches to their original size, although the voltage required for just submaximal stimulation was often greater than that needed initially (Fig. 2, lower record).

DMPP and noradrenaline. Concentrations of 2.5 to 5×10^{-6} DMPP gradually reduced and finally abolished the inhibitory effect of periarterial nerve stimulation, whereas the inhibitory effect of added noradrenaline was either unchanged or increased (Fig. 2). After repeated washing of the preparations for periods up to 2 hr, the inhibitory effect of sympathetic nerve stimulation remained blocked and the inhibitory effect of added noradrenaline remained unchanged or potentiated.

The Finkleman preparation of the rabbit small intestine

When the periarterial sympathetic nerves were stimulated with increasing stimulus frequency there was an increase in the inhibition of tone and pendular movements from a minimal inhibition at frequencies of 3 to 6 shocks/sec to complete inhibition at frequencies

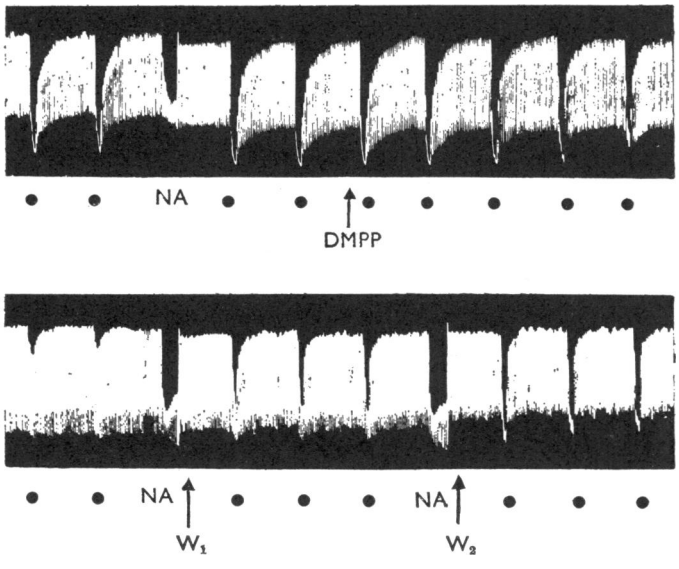

Fig. 3. The effect of a low concentration of DMPP on the inhibitory responses of the rabbit small intestine to stimulation of the periarterial sympathetic nerves and to added noradrenaline. At the black dots the periarterial sympathetic nerves were stimulated at a frequency of 25 shocks/sec with 1 msec duration at supramaximal voltage (36 V) for 20 sec; the interval between successive periods of sympathetic nerve stimulation was 3 min. At NA, noradrenaline (2.5×10^{-9}) was added for a contact time of 1 min before washing out the drug. At the first arrow, DMPP (2×10^{-7}) was added and remained in contact with the preparation for 45 min until washed out at W_1. There is a gap of 20 min between the upper and the lower records. The DMPP gradually reduced (upper panel) but did not abolish (lower panel) the inhibitory effect of periarterial nerve stimulation, whilst at the same time the inhibitory effect of added noradrenaline remained unchanged. After two periods of repeated washing, at W_1 (ten times in 40 min) and W_2 (five times in 10 min), there was a pronounced but incomplete recovery of the inhibitory effects of periarterial nerve stimulation.

of 25 to 50 shocks/sec. With intervals of 3 min between successive periods of sympathetic nerve stimulation, and with occasional changes of the bath fluid, the inhibition was reproducible for 6 hr or longer.

DMPP. Concentrations of 2 to 50×10^{-7} DMPP progressively reduced and finally abolished the inhibitory effects of periarterial nerve stimulation. Concentrations of 2 to 10×10^{-7} caused no change in the tone or pendular movements of the intestine and, with the lowest concentrations of the drug, the block of the sympathetic inhibition was incomplete after 45 min contact (Fig. 3). Concentrations of 2 to 5×10^{-6} DMPP produced a contraction of the intestine initially, and then caused a rapid sympathetic blockade which was usually complete after 30 min contact (Fig. 4); in some experiments, concentrations of 5×10^{-6} DMPP also reduced the size of the pendular movements.

After 45 min contact of the preparation with DMPP, the partial sympathetic blockade produced by low concentrations of the drug was slowly reversed by washing (Fig. 3), but the complete blockade produced by high concentrations of DMPP was not reversed by repeated washing for up to 2 hr.

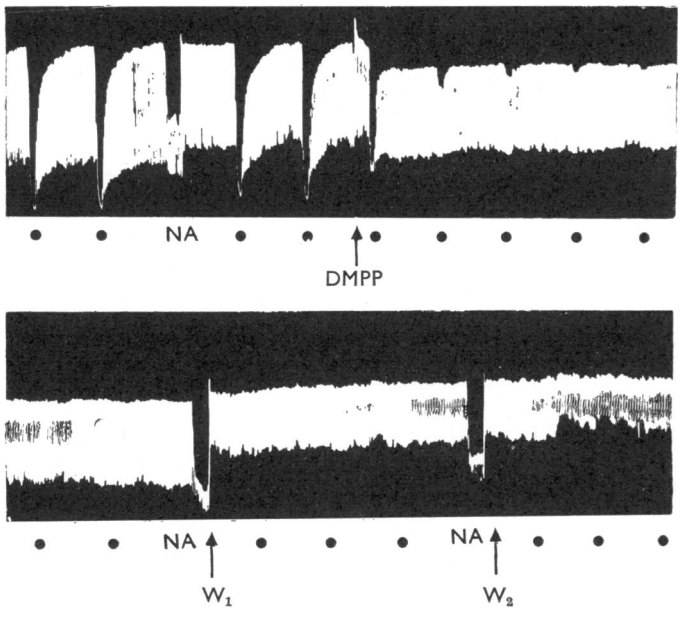

Fig. 4. The effect of a high concentration of DMPP on the inhibitory responses of the rabbit small intestine to stimulation of the periarterial sympathetic nerves and to added noradrenaline. The intestine was taken from the same animal as that used for Fig. 3, and the parameters and intervals of sympathetic nerve stimulation and the concentrations of added noradrenaline were also the same. At the first arrow, DMPP (5×10^{-6}) was added and remained in contact with the preparation for 45 min, until washed out at W_1. There is a gap of 20 min between the upper and the lower records. The DMPP initially caused a brief contraction and then rapidly reduced (upper panel) and finally abolished (lower panel) the inhibitory effect of periarterial nerve stimulation, whilst at the same time the inhibitory effect of added noradrenaline was increased. After two periods of repeated washing, at W_1 (ten times in 40 min) and W_2 (five times in 10 min), there was no recovery of the inhibitory effects of periarterial nerve stimulation, but added noradrenaline still inhibited.

DMPP and noradrenaline. Concentrations of DMPP which greatly reduced or abolished the inhibitory effects of periarterial nerve stimulation did not reduce (Fig. 3) and in some experiments potentiated (Fig. 4) the inhibition of tone and pendular movements produced by added noradrenaline.

Ganglionic blocking drugs and DMPP. Hexamethonium (1×10^{-4}) increased the height of the pendular movements and, when present for 1 hr, did not reduce the inhibitory effects of periarterial nerve stimulation (Fig. 5). In four of five rabbits, 5×10^{-4} hexamethonium present for 1 hr slightly reduced the inhibition produced by maximal stimulation of the periarterial sympathetic nerves. Neither concentration of hexamethonium, present for 1 hr, prevented DMPP from producing a block of the sympathetic inhibition (Fig. 5).

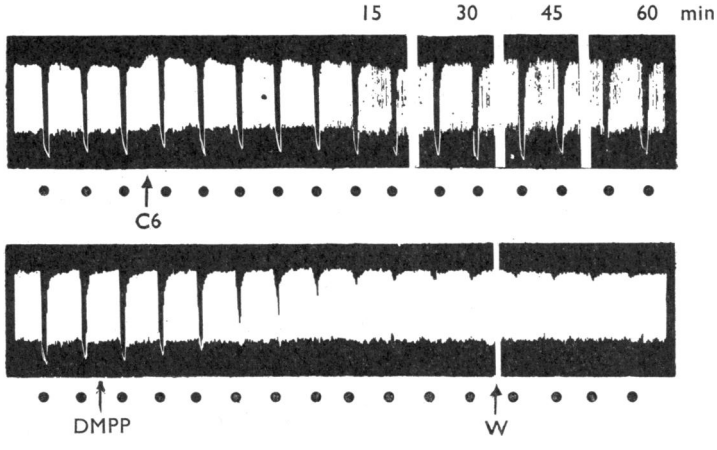

Fig. 5. The effect of DMPP on sympathetic inhibition of rabbit small intestine in the presence of hexamethonium. At the black dots the periarterial sympathetic nerves were stimulated with the same parameters and intervals of stimulation as in Fig. 3. At C6, hexamethonium (1×10^{-4}) caused a slight increase in the height of the spontaneous contractions but caused no reduction in the inhibitory effects of sympathetic nerve stimulation, even after 1-hr contact with the preparation. Without washing out the hexamethonium, DMPP (8×10^{-7}) was added at the second arrow and progressively reduced the inhibitory effect of periarterial nerve stimulation. At W the preparation was washed twenty-times in 30 min but there was no return of the sympathetic inhibition.

Dopamine and DMPP. Dopamine (5×10^{-6}) decreased the height of the spontaneous contractions and the tone of the intestine and did not potentiate a submaximal sympathetic inhibition. When added to preparations in which a block of the sympathetic inhibition had been induced by DMPP, dopamine (5×10^{-6}) restored the inhibitory effects of periarterial nerve stimulation (Fig. 6). This reversal of blockade due to DMPP was not always well maintained after washing out the dopamine.

Noradrenaline and DMPP. Noradrenaline in a concentration of 1×10^{-5} in contact with the gut for 15 min abolished the tone and pendular movements initially; towards the end of the period of contact, small spontaneous contractions often reappeared. When this concentration of noradrenaline was added to a preparation in which sympathetic inhibition had been blocked by DMPP, there was, on washing out the noradrenaline to re-establish

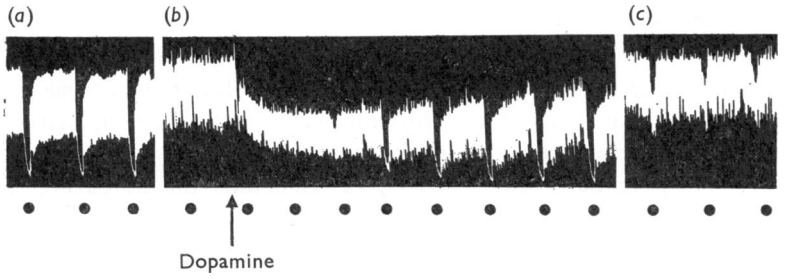

Fig. 6. The effect of dopamine on the sympathetic blockade of rabbit intestine produced by DMPP. At the black dots the periarterial sympathetic nerves were stimulated at 25 shocks/sec, with pulse duration 1 msec at supramaximal voltage (40 V) for 20 sec; the interval between successive periods of sympathetic nerve stimulation was 3 min. (*a*) Shows the inhibitory responses of the normal preparation; between (*a*) and (*b*) DMPP (5×10^{-6}) was present for 45 min, followed by washing (ten-times in 1.5 hr). (*b*) Shows the persistent sympathetic blockade and the addition of dopamine (5×10^{-6}) which decreased the tone and pendular movements of the preparation and produced a rapid return of the inhibitory effects of periarterial nerve stimulation. The sympathetic inhibition was not well maintained on washing out the dopamine, which was done five-times in 10 min between (*b*) and (*c*).

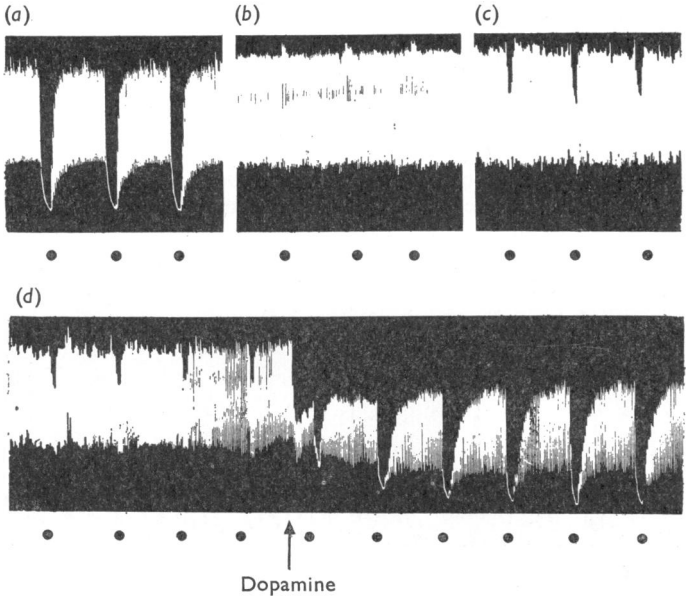

Fig. 7. The effect of prolonged exposure to a high concentration of noradrenaline on the sympathetic blockade of rabbit small intestine produced by DMPP. At the black dots the periarterial sympathetic nerves were stimulated with the same parameters and intervals of stimulation as in Fig. 6. (*a*) Shows the inhibitory response of the normal preparation and (*b*) shows the persistent block of sympathetic inhibition induced by contact with DMPP (2×10^{-6}) for 1 hr, followed by repeated washing (sixteen-times) for 1 hr. Between (*b*) and (*c*) the preparation was soaked in noradrenaline, 1×10^{-5} for 15 min, and then washed (nine-times in 15 min) until the tone and pendular movements returned to normal. There was a partial restoration of the inhibitory effects of periarterial nerve stimulation and the inhibition was maintained on further washing which was done nine-times in 30 min between (*c*) and (*d*). At the arrow, dopamine (5×10^{-6}) produced a rapid return of the sympathetic inhibition.

normal tone and pendular movements, a maintained but partial restoration of the inhibitory effects of periarterial nerve stimulation (Fig. 7).

Dexamphetamine and DMPP. In six of nine rabbits, dexamphetamine (1 or 5×10^{-6}) potentiated a submaximal sympathetic inhibition. The inhibition remained potentiated in the presence of the drug and reverted slowly to its original level on washing out the dexamphetamine. No potentiation was seen greater than that illustrated in Fig. 8. When added to preparations in which a block of sympathetic inhibition had been established with DMPP, dexamphetamine (5×10^{-6}) always produced a rapid and complete return of the inhibitory effects of periarterial nerve stimulation (Fig. 9). This reversal of the blockade due to DMPP was well maintained on washing out the dexamphetamine.

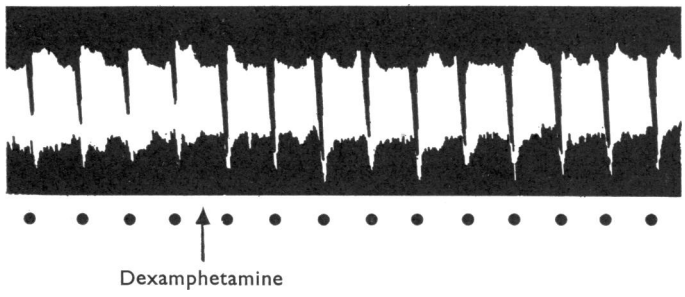

Fig. 8. The effect of dexamphetamine on a submaximal sympathetic inhibition of rabbit small intestine At the black dots the periarterial sympathetic nerves were stimulated at a frequency of 12 shocks/sec with a pulse duration of 1 msec at supramaximal voltage (30 V) for 20 sec; the interval between successive periods of sympathetic nerve stimulation was 3 min. Dexamphetamine, to a final bath concentration of 1×10^{-6}, was added at the arrow, and increased the inhibitory effect of sympathetic nerve stimulation.

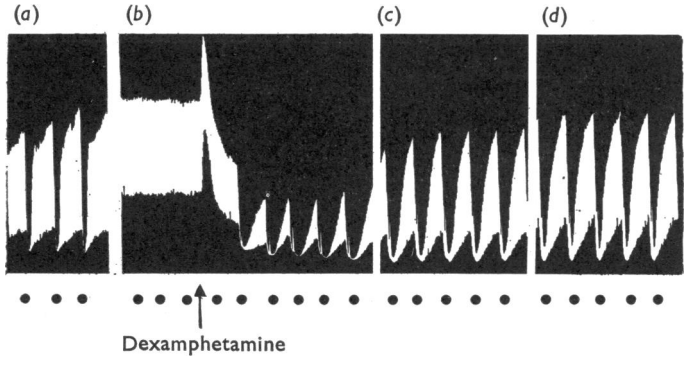

Fig. 9. The effect of dexamphetamine on the sympathetic blockade of rabbit small intestine produced by DMPP. At the black dots the periarterial sympathetic nerves were stimulated at 25 shocks/sec with a pulse duration 1 msec at supramaximal voltage (50 V) for 20 sec; the interval between successive periods of sympathetic nerve stimulation was 3 min. (*a*) Shows the inhibitory responses of the normal preparation; between (*a*) and (*b*), DMPP (2×10^{-6}) was present for 1 hr, followed by washing (six-times) for 1 hr. (*b*) Shows the persistent sympathetic blockade and the addition of dexamphetamine (5×10^{-6}), which produced a rapid return of the inhibitory effects of periarterial nerve stimulation. The sympathetic inhibition was well maintained on washing out the dexamphetamine, which was done four times between (*b*) and (*c*) and four times between (*c*) and (*d*).

Bretylium and guanethidine. Bretylium (1 to 8×10^{-6}) or guanethidine (5 to 50×10^{-7}) gradually reduced and eventually abolished the inhibitory effects of periarterial nerve stimulation. Repeated washing for 2 hr did not reverse the blockade produced by guanethidine, but did reverse the blocking action of bretylium. With bretylium the degree of reversal of the blockade on repeated washing was related to the concentration used (Fig. 10).

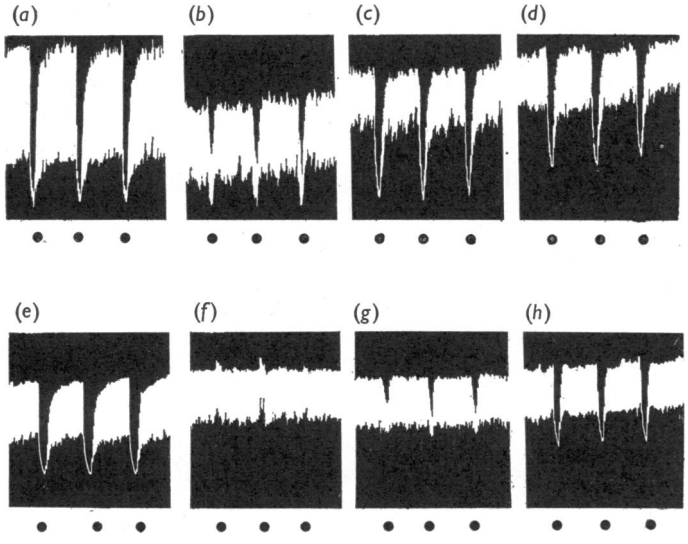

Fig. 10. The effect of repeated washing on the sympathetic blockade of rabbit small intestine produced by bretylium. At the black dots the periarterial sympathetic nerves were stimulated with the same parameters and intervals of stimulation as in Fig. 6. Between (*a*) and (*b*), bretylium (2×10^{-6}) was added for 1 hr and produced a complete block of the sympathetic inhibition; the preparation was then washed five times in 20 min and there was the partial return of sympathetic inhibition shown in (*b*). (*c*) and (*d*) show full restoration of the sympathetic inhibition after further washing, which was done five-times in 25 min between (*b*) and (*c*) and five-times in 10 min between (*c*) and (*d*). The lower record shows an experiment on a preparation of intestine from the same rabbit, but with a high concentration of bretylium (8×10^{-6}) added between (*e*) and (*f*); in all other details the experiment is identical with that in the upper record. (*f*) Shows a persistent sympathetic blockade after washing out the bretylium; (*g*) and (*h*) show progressive but incomplete restoration of the sympathetic inhibition with further washing.

In four rabbits, the block of sympathetic inhibition produced by guanethidine or bretylium was reversed by dexamphetamine (5×10^{-6}) or dopamine (5×10^{-6}). Noradrenaline in a concentration of 1×10^{-5} in contact with the preparation for 15 min caused no change or partially reversed the blocking action of guanethidine.

Bretylium, guanethidine and DMPP. Experiments were made to compare the block of sympathetic inhibition produced by contact with each of the three drugs for 30 min. When a range of concentrations of each drug was tested on separate preparations from the same rabbit, the rates of progression and the final amounts of block produced were almost equal with bretylium (2×10^{-6}), guanethidine (1×10^{-6}) and DMPP (4×10^{-7}).

DISCUSSION

We have confirmed the reports of Bentley (1962) for the rabbit and Wilson (1962) for the guinea-pig, that in the small intestine the inhibitory effects of periarterial sympathetic nerve stimulation are blocked by DMPP. What is the site and mechanism of this blocking action ?

The experiments in which the sympathetic inhibition was blocked, but the inhibition produced by noradrenaline was either unchanged or potentiated, indicate that the blockade due to DMPP is due to a reduction in the amount of transmitter reaching the sympathetic receptors. This reduction is probably the result of an action of DMPP on some part of the sympathetic innervation, so causing a decrease in the amount of sympathetic transmitter liberated, although we have made no direct measurements of noradrenaline output from the intestine.

When the possible sites and mechanisms of the sympathetic blocking action of DMPP are considered, the known ganglion-blocking property of the drug (Chen & Portman, 1954; Leach, 1957; Ling, 1959; Brownlee & Johnson, 1963) must be taken into account. Are there ganglionic synapses in the periarterial sympathetic nerves, an anatomical arrangement known to occur in the sympathetic nerves to the vas deferens of the guinea-pig (Bentley & Sabine, 1963; Birmingham & Wilson, 1963), and could the sympathetic blocking action of DMPP be the result of ganglion blockade ?

That the periarterial sympathetic nerves of the rabbit Finkleman preparation are postganglionic fibres was confirmed by experiments using concentrations of hexamethonium greater than those known to block ganglia (Feldberg, 1951); these concentrations of hexamethonium had no blocking action on the sympathetic inhibition. Similarly there is good evidence that the periarterial sympathetic nerves of the Finkleman preparation of the guinea-pig are postganglionic fibres. Thus, ganglion-blocking concentrations of hexamethonium have no sympathetic blocking action (Wilson, 1962) and, although concentrations of DMPP which block ganglia also block sympathetic inhibition, the ganglion blockade by DMPP occurs rapidly (Brownlee & Johnson, 1963) and precedes block of the inhibitory effects of periarterial nerve stimulation (Wilson, 1962). These results show that the site of the sympathetic blocking action of DMPP must be on postganglionic nerves, a conclusion which is supported by the observation that in the rabbit intestine ganglion-blocking concentrations of hexamethonium did not prevent DMPP from blocking the sympathetic inhibition.

The blocking action is not due to a conventional local anaesthetic effect, since in the small intestine of the guinea-pig the DMPP blockade was selective for the sympathetic nerves. When the inhibitory effects produced by stimulation of the sympathetic nerves were blocked, the transmural twitches produced by stimulation of the parasympathetic nerves (Paton, 1955) were reduced, but only by an amount consistent with the ability of DMPP to depress the contractions produced by added acetylcholine (Brownlee & Johnson, 1963).

Is this selective sympathetic blockade by DMPP similar to the adrenergic neurone blockade produced by bretylium or guanethidine ? Some similarity in the blocking actions of these three drugs was suggested by the experiments in which equipotent doses of DMPP, bretylium or guanethidine gave equivalent rates of blockade; the similarity was supported by the response of blocked preparations to sympathetic nerve stimulation after the addition of dopamine or dexamphetamine.

Dopamine, in concentrations which themselves caused no change in the inhibitory response of the rabbit ileum to sympathetic nerve stimulation, reversed the adrenergic neurone blocking actions of bretylium or guanethidine (Day, 1962). We obtained similar results and found that dopamine also restored the inhibitory effects of periarterial nerve stimulation in preparations which had been blocked by DMPP.

Day (1962) showed that dexamphetamine reversed the sympathetic blocking actions of bretylium or guanethidine on the rabbit ileum. We have confirmed this finding and have shown that dexamphetamine (5×10^{-6}) also rapidly reversed the sympathetic blocking action of DMPP. Control experiments demonstrated that dexamphetamine (1 to 5×10^{-6}) could increase a submaximal sympathetic inhibition but the reversal by dexamphetamine of the blockade due to DMPP was more uniform and more complete than could be accounted for solely by this potentiating effect. It seems likely that dexamphetamine reverses a blockade due to DMPP by a mechanism similar to that proposed (Day, 1962; Day & Rand, 1962; Day & Rand, 1963) for the reversal of guanethidine.

The degree of reversal of the sympathetic blockade produced by repeated washing or by soaking the preparation in a high concentration of noradrenaline suggested that the properties of the blockade induced by DMPP are more like those of guanethidine than those of bretylium. Boyd, Gillespie & MacKenna (1962) reported that sympathetic inhibition is restored by soaking blocked preparations in noradrenaline, 1×10^{-5}, for 15 min; their kymograph record shows what seems to be a complete reversal of the blockade due to bretylium, but only a partial reversal of the blockade produced by guanethidine. We have shown that a blockade due to guanethidine may be partially reversed by this treatment with noradrenaline, but in experiments with bretylium we found that the amount of washing needed to restore the tone and spontaneous movements of a preparation after soaking in noradrenaline was often sufficient itself to reverse the block of the sympathetic inhibition. Although Day (1962) considered that the sympathetic blocking actions both of guanethidine and of bretylium are normally very persistent in the rabbit isolated ileum, Boyd *et al.* (1962) have also noted the difference between blockade by bretylium, which was easily reversed by washing, and blockade by guanethidine which was long-lasting and not reversed. In our experiments, the blockade due to DMPP, unlike that due to bretylium but like that due to guanethidine, was persistent on washing out the drug and was only partially reversed by soaking in noradrenaline.

The evidence suggests that, in the small intestine of the rabbit or guinea-pig, DMPP blocks the inhibitory effects of periarterial nerve stimulation by an adrenergic neurone blocking action; this blocking action can occur with concentrations of DMPP which are, in most instances, lower than those used to stimulate ganglia (Chen *et al.*, 1951; Leach, 1957; Ling, 1959; Brownlee & Johnson, 1963), to block ganglia (Chen & Portman, 1954; Leach, 1957; Ling, 1959; Brownlee & Johnson, 1963) or to block the skeletal neuromuscular junction (Kaller, 1956; Ling, 1959).

SUMMARY

1. The blocking action of dimethylphenylpiperazinium iodide (DMPP) on the inhibition of the small intestine produced by stimulation of the periarterial sympathetic nerves was analysed on Finkleman preparations of rabbit small intestine and of co-axially stimulated guinea-pig small intestine.

2. DMPP (2 to 50×10^{-7}) abolished the inhibitory effects of sympathetic nerve stimulation but did not reduce the inhibitory effects of added noradrenaline.

3. In the presence of ganglion-blocking concentrations of hexamethonium, which themselves did not block the inhibitory response of the rabbit intestine to periarterial nerve stimulation, DMPP still caused sympathetic blockade.

4. The sympathetic blocking action of DMPP, like that of guanethidine, was persistent on repeated washing, whereas the blocking action of bretylium was more readily reversed.

5. The sympathetic blocking action of DMPP on the rabbit intestine, like that of bretylium or guanethidine, was readily reversed by dopamine or by dexamphetamine but, like that of guanethidine, was only partially reversed by a high concentration of noradrenaline.

6. In the rabbit, DMPP was more potent than guanethidine or bretylium and resembled guanethidine more closely than bretylium in the properties of its blockade.

7. The results show that in the small intestine of the rabbit or guinea-pig DMPP produces an adrenergic neurone blockade.

We wish to thank Professor George Brownlee for his help with the preparation of this paper.

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