

GANGLIONIC BLOCKING ACTION OF DIMETHYLPHENYL-PIPERAZINIUM (DMPP)

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Received July 31, 1957

Dimethylphenylpiperazinium iodide (DMPP) blocks transmission of preganglionic nerve impulses at the superior cervical ganglion of the cat. This effect is augmented by subsequent addition of acetylcholine. It also depresses the emptying reaction, but has no effect on the longitudinal muscle contraction, caused by transmural stimulation of the guinea pig ileum. DMPP appears to block transmission in the same way as does tetramethylammonium, and large doses of acetylcholine.

EXPERIMENTAL

Addendum

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This Journal, 1957, 9, 747

After the summary, p. 747, insert the following paragraph:

Chen, Portman and Wickel¹ described the ganglionic stimulating action of dimethylphenylpiperazinium iodide but made no reference to its blocking action. In the intervening six years the impression has gained ground that the drug stimulates only, and the view is widely held that DMPP has no blocking action. This is not my experience.

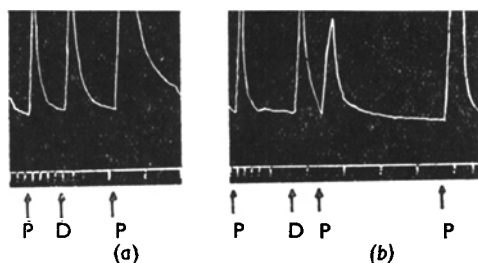


FIG. 1. Cat 3 kg. Responses of right nictitating membrane (lower record) to preganglionic stimulation (P) for five seconds at 3/sec. every two minutes. (a) Close arterial injection of 10 μ g. D.M.P.P. (D). (b) Close arterial injection of 20 μ g. D.M.P.P. Control responses of opposite membrane upper record. Time = 30 sec.

tympanic bulla, and the pre-ganglionic nerves by exposing the peripheral end of the cut sympathetic nerve. Movements of both nictitating membranes were isotonicly recorded.

Stimulation was by square wave stimuli of 0.03 msec. duration, at 4 to 10 volts, at a frequency shown in the figures.

Guinea pig ileum. The ileum was prepared by Paton's method². The longitudinal movements were measured by an isometric mirror-lever; movements were amplified by photocell d.c. amplifier and recorded on smoked paper by a direct-writing galvanometer.

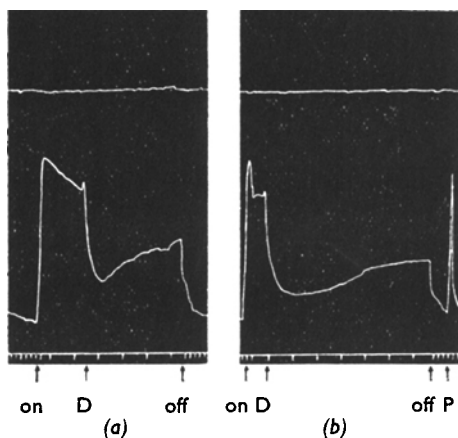


FIG. 2. Cat 3 kg. Effect of D.M.P.P. (D) on the continuously stimulated preganglionic nerve to right nictitating membrane at 3/sec. (a) Close arterial injection of 10 μ g. D.M.P.P. (b) Close arterial injection of 20 μ g. D.M.P.P. End of stimulation. Control membrane, upper record. Time = 30 sec.

Changes in volume were recorded hydraulically with a sensitive float recorder; in this way simultaneous records of longitudinal and volume changes were made.

Emptying reaction. An emptying reaction was obtained by distending the ileum with a pressure of about 1.5-2 cm. of water, and stimulating transmurally with square waves of 0.03 msec. duration, at 15 volts, and 1 sec. frequency, for a period of five seconds.

Peristaltic reflex. By raising the hydrostatic pressure for periods of 30 seconds to about 6 to 8 cm. of water from a constant head device, a peristaltic reflex was developed.

Blood pressure. The carotid blood pressure was recorded by mercury manometer and the splanchnic nerves to the suprarenal medulla stimulated by an electrode inserted through an opening in the abdominal wall.

RESULTS

Nictitating membrane. 3 kg. cat. The retrograde intra-arterial injection of 5 to 10 μ g. of DMPP iodide stimulates the ganglion causing retraction of the nictitating membrane (Fig. 1a). Doses of 20 μ g. stimulate, and produce an immediate blockade of preganglionic nerve stimulation (Fig. 1b).

A dose of 10 μ g. of DMPP lyses the contracture of the nictitating membrane stimulated preganglionically (Fig. 2a); with 20 μ g. the blockade is more evident (Fig. 2b).

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The lysis of contracture of the nictitating membrane stimulated through its preganglionic nerve by 5 μg . DMPP is added to by a dose of 10 μg . of acetylcholine (Fig. 3a); under the same conditions 10 μg . of acetylcholine opposes the block caused by 2.5 μg . of hexamethonium.

Guinea pig Ileum. A dose of 1.0 to 1.5 $\mu\text{g}/\text{ml}$. increased the tone and rhythmic movements of the gut subjected to an internal hydrostatic pressure of 1 to 1.5 cm. of water, larger doses depressed (Fig. 4).

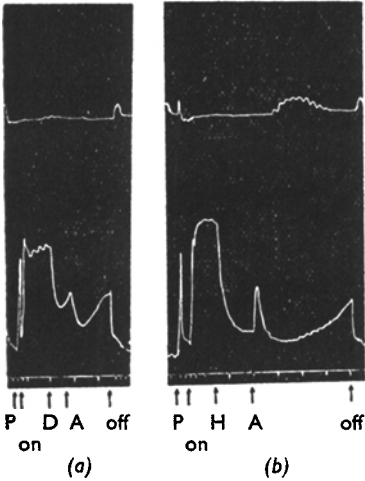


FIG. 3. Cat 3 kg. Effect of subsequent close arterial injections of acetylcholine (A) after ganglionic blockade to the preganglionically stimulated right nictitating membrane (lower record) at 0.5/sec. (a) Close arterial injection of 5 μg . D.M.P.P. (D) and response of ganglion to 10 μg . acetylcholine. (b) Close arterial injection of 2.5 μg . hexamethonium (H) and response of ganglion to 10 μg . acetylcholine. Animal previously treated with 500 μg . tetra-ethyl pyrophosphate. Time = 30 sec.

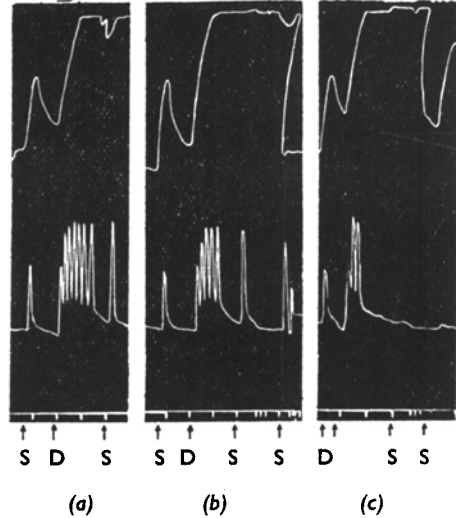


FIG. 4. Effect of D.M.P.P. (D) on the emptying reaction of guinea pig ileum suspended in Krebs's at 32°. Hydrostatic pressure inside lumen 2 cm. of water, transmural stimulation (S) at 1/sec. for five seconds. Upper record longitudinal muscle movements, lower one changes in intestinal volume. (a) D.M.P.P. 1.5 $\mu\text{g}/\text{ml}$. (b) D.M.P.P. 2.0 $\mu\text{g}/\text{ml}$. (c) D.M.P.P. 3.0 $\mu\text{g}/\text{ml}$. Preparation washed between each addition of drug. Time = 30 sec.

Emptying Reaction. Guinea pig ileum. The emptying reaction of the transmurally stimulated ileum is first stimulated by 1.5 to 2.0 $\mu\text{g}/\text{ml}$. and then blocked by 2.5 to 3.0 $\mu\text{g}/\text{ml}$. of DMPP (Fig. 4).

Peristaltic Reflex. Guinea pig ileum. The peristaltic reflex is blocked by 3.0 to 5.0 $\mu\text{g}/\text{ml}$. (Fig. 5).

Blood Pressure responses. Chloralose 65 mg./kg. cat. Atropine 1.5 mg./kg.

With doses of 5 to 10 $\mu\text{g}/\text{kg}$. there is seen a biphasic response; first depressor then pressor (Fig. 6a); larger doses of up to 2 mg./kg. still show evidence of the depressor response but with high secondary pressor

components. In the range 0.5 to 2 mg./kg. there is seen some evidence for the onset of a nicotine-like block of the pressor response.

Stimulation of the greater splanchnic branch to the left adrenal medulla showed no diminution in pressor effect with increasing doses of DMPP until the range of 1 to 2 mg./kg. was reached (Fig. 6*b*).

DISCUSSION

Small doses of DMPP injected intra-arterially into the superior cervical ganglion stimulates the ganglion. Larger doses, themselves stimulatory, block the effects of stimulating the preganglionic nerves; that the effect is located at the synapse is shown by the integrity of the post-ganglionic stimulation.

The ganglionic block by DMPP differs from that by hexamethonium in being added to by the acetylcholine. These two pieces of evidence, taken together, suggest that DMPP stimulates and depresses ganglionic transmission at the superior cervical synapse in the same way as does acetylcholine and tetramethylammonium³.

DMPP stimulated both the longitudinal and circular muscle of the guinea pig ileum; the effect on the circular muscle was abolished by hexamethonium, and also by increasing the dose of DMPP. Both observations are consistent with ganglion stimulating and blocking actions.

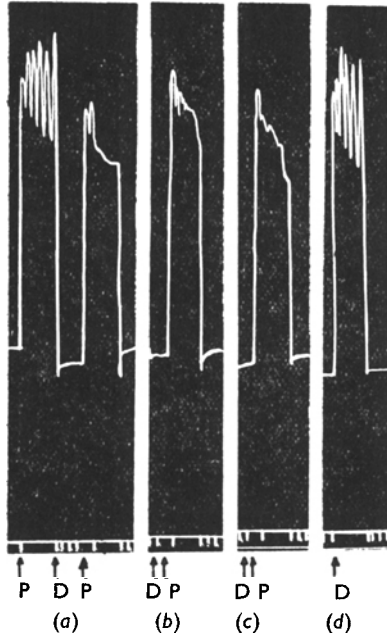


Fig. 5. Effect of D.M.P.P. (D) on the peristaltic reflex (P). Hydrostatic pressure increased to 9 cm. of water. (a) Control response and effect of 3.0 $\mu\text{g./ml.}$ D.M.P.P. (b) D.M.P.P. 4.5 $\mu\text{g./ml.}$ (c) D.M.P.P. 6.0 $\mu\text{g./ml.}$ (d) Control response after washing. Time = 30 sec.

The electrically stimulated emptying reaction of the guinea pig ileum is readily blocked by DMPP, whilst the response of longitudinal muscle is unaltered. To depress the longitudinal contraction, drugs affecting responses at post-ganglionic cholinergic synapses have to be used². Larger doses of DMPP also depress the peristaltic reflex, an effect shared by other drugs which depress ganglionic transmission.

The effects of DMPP on the blood pressure are overwhelmingly stimulatory; very large doses are needed before diminution in response to repeated injections is seen. The effect is reminiscent of nicotine but the stimulatory component is more pronounced.

The adrenal medulla seems to be more easily affected in the cat than the other sympathetic abdominal ganglia; the rise of blood pressure seen after

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stimulating the left sympathetic nerve to the adrenal gland is reduced after large intravenous doses of DMPP.

In the atropinised cat (1.5 mg./kg.) small and large doses showed a marked vasodilator component which preceded the rise of blood pressure.

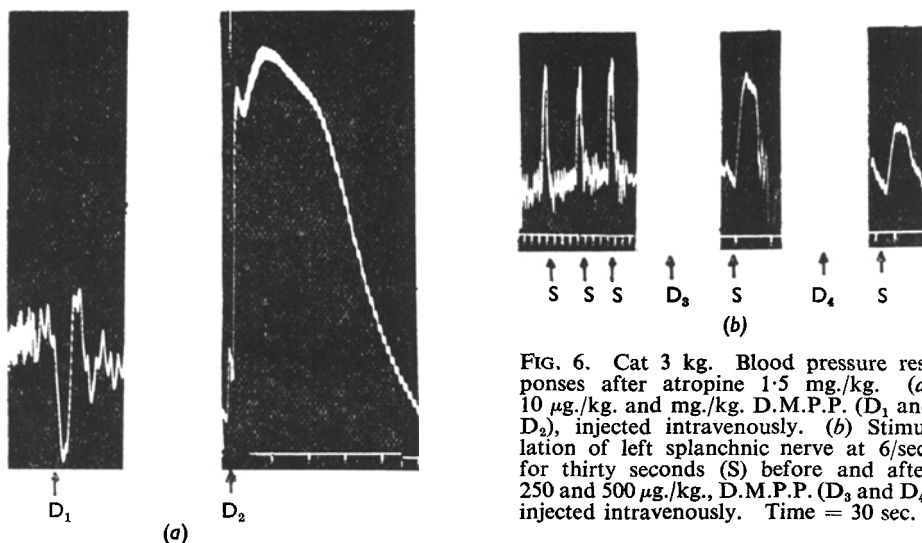


FIG. 6. Cat 3 kg. Blood pressure responses after atropine 1.5 mg./kg. (a) 10 µg./kg. and mg./kg. D.M.P.P. (D₁ and D₂), injected intravenously. (b) Stimulation of left splanchnic nerve at 6/sec. for thirty seconds (S) before and after 250 and 500 µg./kg., D.M.P.P. (D₃ and D₄) injected intravenously. Time = 30 sec.

It is concluded that DMPP stimulates and depresses ganglia. The drug must be injected directly into the ganglion or used in large doses to demonstrate its blocking action. Its mode of action seems to be similar to that of other drugs which stimulate before depressing the activity of ganglion cells.

REFERENCES

1. Chen, Portman and Wickel, *J. Pharmacol.*, 1951, 103, 330.
2. Paton, *J. Physiol.*, 1955, 127, 40P.
3. Paton and Perry, *J. Physiol.*, 1953, 119, 43.