Role of the Adrenals in the Pressor Response to 1,1-Dimethyl-4-Phenylpiperazinium Iodide (DMPP) in the Rat[1] (34847)

C. CHINN AND L. J. WEBER[2]

Department of Pharmacology, School of Medicine, University of Washington, Seattle, Washington 98105

The pressor effect of ganglionic stimulants such as 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP) and 4(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride (McN-A-343) have been well described and reviewed by Trendelenburg (1) and Volle (2). These agents produce pressor or biphasic responses which consist of an initial transient fall and then rise of blood pressure. Nicotinic type of stimulant such as DMPP can be blocked by hexamethonium or tetraethylammonium whereas the response to the mucarinic type of agents such as McN-A-343 can be blocked by low doses of atropine. The vasopressor response to DMPP has been attributed to its powerful stimulatory effect on peripheral sympathetic ganglia and adrenal glands to the release of catecholamines whereas the effects of the muscarinic type of stimulants have been attributed mainly to the actions on sympathetic ganglia. The above conclusions are based on results obtained in dogs and cats. The observations described in this report indicate that in the rat the adrenals appear not to play a role in the pressor response to DMPP. The effects of DMPP are compared with those of the non-nicotinic ganglion-stimulating agents (McN-A-343) and *N*-benzl-3-pyrrolidyl acetate methobromide (AHR-602). A preliminary report of part of this work has been made to the Western Pharmacological Society (3).

Methods. Male or femal Sprague-Dawley rats weighing 260–360 g were anesthetized with sodium pentobarbital 40 mg/kg given intraperitoneally. Additional doses of 10 mg/kg were given when needed to maintain a steady state of anesthesia. In some experiments, urethane 1.75 g/kg given intraperitoneally, was used as the anesthetic agent. The trachea was cannulated to ensure a patent airway. Arterial blood pressure was recorded from the left common carotid artery via a polyethylene tubing using a Physiograph. Clotting in the cannula was prevented by filling it with about 0.1 ml heparin, (0.1 mg). Drugs were injected via the external jugular vein in volumes of 0.1–0.2 ml and washed with 0.2 ml normal saline. The interval between injections of ganglionic stimulants was a minimum of 20 min. The following drugs were used: *l*-epinephrine hydrochloride, *l*-norepinephrine bitartrate, 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP), 4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride (McN-A-343), *N*-benzyl-3pyrrolidyl acetate methobromide (AHR-602), bretylium tosylate, guanethidine monosulphate, physostigmine (eserine) salicylate, and 6-hydroxydopamine hydrobromide. Drug doses refer to the salts.

Adrenalectomy. In those experiments in which acute adrealectomies were performed, loose ligatures were placed around the blood vessels supplying the adrenals at the beginning of the experiments. After establishing control responses to various drugs, the vessels were tied and both adrenals removed. When the blood pressure had stabilized the drugs were again injected.

Chemical sympathectomy. Attempts to produce chemical sympathectomy using 6-hydroxydopamine were carried out according to the dosage used by Mueller *et al.* (4). Rats were given via the femoral vein two in-

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[2] Present address: Department of Pharmacology, School of Pharmacy, Oregon State University, Corvallis, Oregon 97331.

travenous injections of 6-hydroxydopamine (100 mg/kg in 10^{-3} *N* HCl) after anesthetization with ether. Next day, animals were prepared for blood pressure studies as described above, and responses were obtained 16–17 hr after the last doses of 6-hydroxydopamine.

Results. Blood pressure response to DMPP. Doses of DMPP between 20–50 μg/kg produced either a depressor response or no change in blood pressure (15 experiments). In one experiment 50 μg/kg produced a slight pressor response. The usual response to 75 μg/kg was a slight pressor response, sometimes preceded by a transient depressor response. Doses of 100 μg/kg or greater always produced marked pressor responses. These responses were blocked by hexamethonium but not by atropine. Thus, doses of DMPP required to produce marked pressor responses in the rat are approximately 10 times that required in the cat. In our hands, a dose of 10 μg/kg was found to produce a substantial pressor response in the pentobarbital anesthetized cat as reported in the literature.

Blood pressure response to McN-A-343. As reported in the cat and dog, McN-A-343 (50–100 μg/kg) produced initial depressor responses which were followed by more prolonged pressor responses. Both the pressor and depressor components were blocked by atropine but not by hexamethonium. Thus the blood pressure responses of the rat to the muscarinic ganglion stimulants are similar to the responses in the dog and cat.

Effect of acute adrenalectomy on the pressor responses to DMPP and McN-A-343. Increases in mean arterial blood pressures of 25–65 mm Hg were obtained by intravenous injections of 100–150 μg/kg DMPP. Acute bilateral adrenalectomy did not reduce the pressor response in nine experiments (Fig. 1). Similarly, in seven experiments the pressor response to McN-A-343 100–150 μg/kg (Fig. 1), or AHR-602 2 mg/kg (four experiments), was not reduced by acute bilateral adrenalectomy.

Effect of bretylium. Bretylium, 5 mg/kg, was injected intravenously three times at 15-min intervals. Five minutes after the last injection, the response to pressor doses of DMPP was completely abolished in four of eight experiments. In the other four experiments the pressor response was markedly reduced. The pressor response to McN-A-343, 100–150 μg/kg, was completely abolished in one experiment and markedly reduced in another. An experiment in which the pressor responses to DMPP and McN-A-343 were abolished is illustrated in Fig. 1.

Effect of guanethidine. Using a dose of 15 mg/kg, guanethidine completely blocked the response to DMPP in three of four experiments. In the fourth experiment, guanethi-

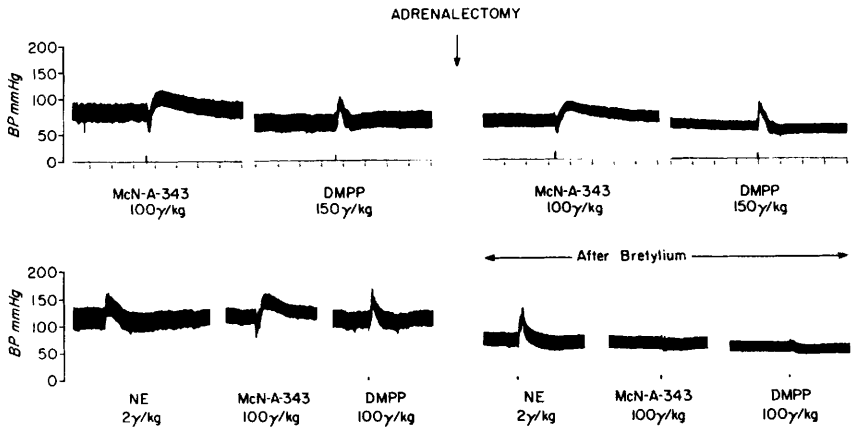

FIG. 1. Upper. The effect of adrenalectomy on the pressor responses to McN-A-343 and DMPP. Female rat, 300 g, anesthetized with urethane. Time markers indicate 1 min. Lower. The effect of bretylium on the pressor responses to McN-A-343 and DMPP. Female rat (different from the one above, 300 g, anesthetized with urethane. Paper speed is same as above.

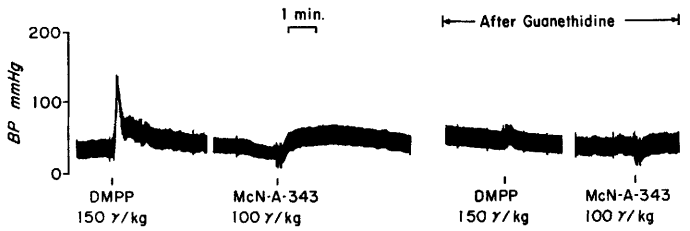

FIG. 2. The effect of guanethidine on the pressor responses to DMPP and McN-A-343. The effect of guanethidine was tested 10 min after a dose of 15 mg/kg into the jugular vein.

dine virtually abolished the pressor response to DMPP. The pressor response to McN-A-343 was completely blocked by guanethidine in all four experiments. The results of one of these experiments are shown in Fig. 2.

Effect of chemical sympathectomy by 6-hydroxydopamine. Four rats were treated as described in *Methods* to produce a chemical sympathectomy. In two rats the pressor response to DMPP (100 μg/kg) was completely abolished; in two others, the pressor response was markedly reduced. In these two latter rats, however, the pressor response to eserine was still partially present, indicating that sympathectomy was incomplete in the animals. Eserine has been shown by Lesic and Varagic (5) to produce a pressor response which is centrally mediated, and that adrenal medullary discharge plays no part in the response. Cass and Spriggs (6) have found eserine to be a useful agent for testing sympathetic function. The response to McN-A-343 was completely abolished in all four animals.

Discussion. Stimulation of the adrenal medulla by the ganglionic stimulant, DMPP, contributes largely to the pressor effect of this agent in the cat and dog. Thus, in spinal cats, the pressor response to DMPP was greatly reduced shortly after adrenalectomy (7). Similarly in the anesthetized dog, the pressor effect of DMPP was markedly reduced when tested 4 hr after bilateral adrenalectomy (8). The results of experiments presented in this paper indicate that the adrenal medulla does not appear to play a part in the pressor response to DMPP in the rat at doses which produce substantial pressor responses. Thus, the pressor response to DMPP did not diminish when tested 30–60 min after bilateral adrenalectomy. Sympathetic blockade by guanethidine abolished the pressor response to DMPP. Bretylium either abolished completely or markedly reduced the pressor response. Since guanethidine has been shown to produce sympathetic block without blocking the release of amines from the adrenal medulla of the rat (6) and bretylium has been demonstrated to possess a similar neurone blocking action (9), our results using these two agents, therefore, indicate a lack of contribution from the adrenals in the pressor response to DMPP in the rat.

Experiments in which chemical sympathectomy was attempted by treatment with 6-hydroxydopamine yielded results which were not unequivocal. In two rats the pressor response to DMPP was completely abolished, whereas in two others the response was markedly reduced after treatment with 6-hydroxydopamine. Despite the report that 6-hydroxydopamine produces a depletion of cardiac norepinephrine to undetectable levels and tyrosine hydroxylase activity to zero (4), complete loss of sympathetic activity has not been reported. On the contrary, the pressor response to eserine was still present in these rats treated with 6-hydroxydopamine, indicating that sympathectomy was not complete at a time when tissue norepinephrine was reported to be absent.

It appears that the adrenal medulla of the rat is relatively insensitive to the stimulatory actions of DMPP as compared to the cat and dog. This is not the first instance in which such a difference in the response of the adrenal medulla of the rat has been reported. Stewart and Rogoff (10) have reported that eserine stimulates the adrenal medulla of

the cat to release catecholamines, whereas Lesic and Varagic (5) found eserine not to stimulate the rat adrenal.

Summary. The blood pressure response of the rat to the ganglionic stimulant 1,1-dimethylphenylpiperazinium iodide (DMPP) was much less sensitive than that of the cat. Acute bilateral adrenalectomy did not diminish the pressor response to DMPP in the rat. Bretylium or guanethidine completely or virtually abolished the pressor response produced by DMPP. It was concluded that, in the rat, the adrenals appear not to play a role in the pressor response produced by DMPP.

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