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The treatment of hypertensive disorders has been revolutionized in recent years by the discovery and use of compounds which inhibit the release of neurohormones from the postganglionic sympathetic nerve endings.

Recently guanethidine was introduced for the treatment of hypertension in human being.\(^5\) This compound has been used and seems to help hypertension by preventing the release of the sympathetic transmitter.\(^3\) In addition, it produces a depletion of tissue stores of catecholamines.

In preceding reports,\(^5\) the authors have synthesized several analogues of guanethidine and evaluated them for their activities in blocking the sympathetic nervous system and were able to demonstrate that [2-(methylphenylamino)ethyl]guanidine sulfate (MPG) displayed many of the effects that were similar to guanethidine.

Actions common to both are:
1) inhibition of the contraction of the nictitating membrane which are evoked by preganglionic electrical stimulation given to the cervical sympathetic nerve and both drugs also produce an immediate and protracted increase in the tonus of the nictitating membrane, 2) potentiation of the norepinephrine- and epinephrine-induced contractions, and inhibition of the tyramine-induced contraction in the cat nictitating membrane, 3) potentiation of the norepinephrine- and epinephrine-induced hypertensions, and inhibition of the tyramine-induced hypertension in the rat, 4) inhibition of the decreasing motility of the isolated rabbit ileum caused by electrical stimulation given to the sympathetic nerve.

In this report, the authors investigated mainly the pharmacological properties of MPG in the sympathetic nervous system. MPG differs structurally from guanethidine, namely MPG possesses methylphenylamino group instead of octahydro-1-azocinyl group of guanethidine.

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Methods

MPG is a white crystalline powder with a molecular weight of 241.31. It melts at 155-156.5\(\circ\) with decomposition. It is easy to dissolve in water.

Cats and rats of both sexes were anesthetized with urethane (1.4 g./kg.) subcutaneously. According to the Burn’s method,\(^7\) spinal cats were prepared under ether anesthesia. For the examination of the effect

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on the heart rate, dogs of both sexes were anesthetized with intravenous injections of sodium pentobarbital (40 mg./kg.) and vagotomized bilaterally.

Arterial pressure was recorded either by a mercury manometer or by an electromanometer connected to a cannulated carotid artery.

The cervical sympathetic chain, the greater splanchnic nerve and the celiac ganglion were stimulated with supramaximal rectangular pulses using Nihon Koden MSE20 stimulator.

Isotonic lever systems were used for the study of the nictitating membrane responses in cats.

All drugs were dissolved in 0.9% aqueous sodium chloride and injected into a cannula tied into a femoral vein unless otherwise stated.

The following drugs were used: [2-(methylphenylamino)ethyl]guanidine sulfate (MPG), 1-[2-(octahydro-1-azocinyl)ethyl]guanidine sulfate (guanethidine), dl-norepinephrine hydrochloride, l-epinephrine hydrochloride, dl-amphetamine sulfate, tyramine hydrochloride, 2-(N-m-hydroxyphenyl-p-toluidinomethyl)imidazoline methanesulfonate (phenotamine) and 1,1-dimethyl-4-phenylpiperazinium iodide.

All doses are expressed as weights of salts.

Results

Effects of MPG on the Cat Blood Pressure and Nictitating Membrane

Intravenous injection of 5~10 mg./kg. produced a fall in blood pressure and a prolonged contraction of the nictitating membrane of urethane anesthetized cats. In most experiments the blood pressure returned to normal within 5 min. or so, but the contraction of the nictitating membrane persisted for 3 hr. or more (Fig. 1).

Effects of MPG on the Sympathetic Efferent Transmission in Cats

One mg./kg. of MPG given intravenously resulted in an immediate suppression of the contraction of the nictitating membrane which were evoked by postganglionic electrical stimulation (5~50 c.p.s., 0.7 msec., supramaximal voltage for 15 sec.) of the cervical sympathetic nerve. The blocking action was still detected for about 3 hr. after 5 mg./kg.

Fig. 2. Effect of [2-(methylphenylamino)ethyl]guanidine Sulfate (MPG) on the Contraction Responses of the Nictitating Membrane evoked by Postganglionic Cervical Sympathetic Nerve Stimulation in a Urethane Anesthetized Cat (3 kg.)

Postganglionic nerve was stimulated with rectangular pulses of supramaximal voltage and 0.7 msec. duration, at frequencies of 5~50 c.p.s. for 15 sec. (Circles: 5 c.p.s., Dots: 10 c.p.s., Triangles: 20 c.p.s., Squares: 50 c.p.s.) A is control responses. Between A and B, 1 mg./kg. of MPG was injected intravenously. B and C are responses at 10 min. and 30 min. after injection of MPG. Between C and D, 0.5 mg./kg. of amphetamine was injected intravenously. D and E are responses at 10 min. and 30 min. after injection of amphetamine.
of MPG were injected intravenously. These reduced responses caused by 1 mg./kg. of MPG were recovered almost completely following the intravenous administration of 0.5 mg./kg. ofamphetamine. The typical responses are illustrated in Fig. 2.

The pressor responses elicited by electrical stimulation of the left greater splanchnic nerve (20 c.p.s., 1 msec., supramaximal voltage for 30 sec.) and the left celiac ganglion (20 c.p.s., 1 msec., supramaximal voltage for 20 sec.) in 2 cats were greatly diminished following the intravenous administration of 10 mg./kg. of MPG. These reduced responses also recovered almost completely following the intravenous administration of 2 mg./kg. ofamphetamine. Some examples of these experiments are shown in Fig. 3.

![Graph showing pressor responses](image)

**Fig. 3.** Effects of [2-(methylphenylamino)ethyl]guanidine Sulfate (MPG) on the Pressor Responses evoked by Electrical Stimulation to the Celiac Ganglion and the Splanchnic Nerve in Urethane Anesthetized Cats

a) Stimulation of the celiac ganglion (20 c.p.s., 1 msec. for 20 sec. at supramaximal voltage) at dots. A is control response. Between A and B, 10 mg./kg. of MPG was injected intravenously. B and C are responses at 30 min. and 45 min. after injection of MPG. Between C and D, 2 mg./kg. ofamphetamine was injected intravenously. D and E are responses at 30 min. and 140 min. after injection ofamphetamine.

b) Stimulation of the splanchnic nerve (20 c.p.s., 1 msec., for 30 sec. at supramaximal voltage) at dots. A is control response. Between A and B, 10 mg./kg. of MPG was injected intravenously. B and C are responses at 30 min. and 45 min. after injection of MPG. Between C and D, 2 mg./kg. ofamphetamine was injected intravenously. D is response at 60 min. after injection ofamphetamine.

**Effects of MPG on the Pressor Responses to Norepinephrine, Epinephrine, Tyramine, and Dimethylphenylpipеразинum in Cats**

Intravenous injection of 10 mg./kg. of MPG markedly potentiated the pressor response to an intravenous injection of 5 μg./kg. of norepinephrine, while the pressor response to 5 μg./kg. of epinephrine was moderately potentiated in all cats studied. The pressor responses to tyramine and dimethylphenylpipеразинum were markedly suppressed in three cats. Some typical examples are illustrated in Fig. 4 (a)~(c).

**Effect of MPG on the Hypertension produced by the Carotid Oclusion Reflex**

Intravenous administration of 10 mg./kg. of MPG in three cats resulted in a reduction of the pressor responses caused by the carotid occlusion within 15 min. and this reduction lasted for 2 hr. or more. A typical example is illustrated in Fig. 4 (d).
Effect of MPG and Guanethidine on the Pressor Responses to Norepinephrine and Tyramine in Rats

The effects of MPG on the pressor responses of both amines are compared with those of guanethidine in rats. All rats were pretreated with MPG (10 mg./kg., i.v.) or guanethidine (10 mg./kg., i.v.) 30~60 min. prior to the experiment. The pressor response to norepinephrine (5 μg./kg., i.v.) was significantly potentiated by both compounds, while the pressor response to tyramine (1 mg./kg., i.v.) was significantly suppressed by both compounds. The pressor response to tyramine was considerably reduced by pretreatment with MPG but after pretreatment with guanethidine at the same dose level, the reduction in pressor response of tyramine was less pronounced.

The results of these experiments are summarized in Table I.

Effect of Chronic Administration of MPG on the Cat Nictitating Membrane

20 mg./kg. of MPG was administered subcutaneously on the first day, the fourth day and the seventh day (total 60 mg./kg.) in an unanesthetized cat. This brought about moderate relaxation of the nictitating membrane. In this cat, anesthetized with urethane, the preganglionic electrical stimulation of the sympathetic nerve resulted in very small contractions of the nictitating membrane compared with the contractions produced in untreated animals in which the same lever system was employed. In addition, an intravenous injection of 5 μg./kg. of norepinephrine in a pretreated cat produced a clearly defined contraction of the membrane, while intravenous injection of 0.5 mg./kg. and 1 mg./kg. of tyramine produced almost no contraction. These same doses, however, in untreated cats produced very small or no detectable contraction of the nictitating membrane with 5 μg./kg. of norepinephrine and membrane with 0.5 mg./kg. and 1 mg./kg. of

Effect of MPG on the Cat Nictitating Membrane pretreated with Phentolamine

One cat was injected intravenously with 1 mg./kg. of phentolamine 30 min. prior to the experiment, which moderately suppressed the contraction of the nictitating membrane produced by 10 mg./kg. of MPG injected intravenously. In two cats,

Fig. 4. Effects of [2-(methylphenylamino)ethyl]-guanidine Sulfate (MPG) on the Pressor Responses to Intravenous Injections of Norepinephrine (NE., 5 μg./kg.), Epinephrine (E., 5 μg./kg.), Tyramine (Tyr., 1 mg./kg.), Dimethylphenylpiperazinium (DMPP., 20 μg./kg.) and evoked by the Carotid Occlusion for 30 sec. (C.O.) in Urethane Anesthetized Cats

A shows control responses and B shows the responses after 10 mg./kg. of MPG injected intravenously.

a) B is recorded after 90 min. (2.5 kg.)
b) B is recorded after 60 min. (2.7 kg.)
c) B is recorded after 70 min. (2.0 kg.)
d) B and C are recorded after 15 min. and 45 min., respectively. (0.55 kg.)

marked contractions of the nictitating tyramine in every case. See Fig. 5.
Table I. Effect of [2-(Methylphenylamino)ethyl]guanidine Sulfate (MPG) and Guanethidine on Norepinephrine- and Tyramine-induced Pressor Responses in Urethane Anesthetized Rat

<table>
<thead>
<tr>
<th>Compounds (Dose, i.v.)</th>
<th>Pressor amines</th>
<th>Pressor Responses (mean ± S. E. mm. Hg)</th>
<th>Before treatment</th>
<th>After treatment(*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPG (10 mg./kg.)</td>
<td>Tyr.</td>
<td>37.0 ± 3.41(6)</td>
<td>0.50 ± 0.50(6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NE.</td>
<td>28.7 ± 1.37(9)</td>
<td>44.2 ± 2.23(9)</td>
<td></td>
</tr>
<tr>
<td>Guanethidine (10 mg./kg.)</td>
<td>Tyr.</td>
<td>42.8 ± 1.37(5)</td>
<td>20.0 ± 3.28(5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NE.</td>
<td>32.8 ± 3.20(5)</td>
<td>64.0 ± 4.98(5)</td>
<td></td>
</tr>
</tbody>
</table>

Tyr.: tyramine 1 mg./kg., i.v.  NE.: norepinephrine 5 mg./kg., i.v.  ( ) : number of rats

* These responses were obtained 30 min. ~ 1 hr. after intravenous injection of MPG or guanethidine.

5 mg./kg. of phentolamine completely suppressed the contraction of the nictitating membrane produced by 10 mg./kg. of MPG injected intravenously. In all untreated cats, however, 10 mg./kg. of MPG injected intravenously produced marked contractions in every case.

Some typical examples are illustrated in Fig. 6 (a) ~ (c).

Effect of MPG on the Cat Nictitating Membrane pretreated with Reserpine

In three cats, 3 mg./kg. of reserpine injected subcutaneously 24 hr. prior to

![](image)

Fig. 5. Effect of [2-(Methylphenylamino)ethyl]guanidine Sulfate (MPG) injected subcutaneously on the Contraction Responses of the Cat Nictitating Membrane evoked by Electrical Stimulation of the Preganglionic Cervical Sympathetic Nerve (20 c.p.s., 0.7 msec. for 15 sec. at supramaximal voltage) and Intravenous Injection of Tyramine (Tyr<sub>0.5</sub>: 0.5 mg./kg., Tyr<sub>1</sub>: 1 mg./kg.) and Norepinephrine (NE.: 5 μg./kg.)

a) Typical response of untreated cat nictitating membrane (2.5 kg.)
b) Typical response of a cat which was pretreated with MPG (three times, 20 mg./kg. of MPG on the first day, the fourth day and the seventh day) injected subcutaneously (2.6 kg.)

Fig. 6. Effect of [2-(Methylphenylamino)ethyl]guanidine Sulfate (MPG) injected intravenously on the Nictitating Membrane in Urethane Anesthetized Cats

10 mg./kg. of MPG was injected at dots.

a) Typical response in an untreated cat (3 kg.)
b) Cat pretreated with 1 mg./kg. of phentolamine injected intravenously 30 min. prior to experiment (2.8 kg.)
c) Cat pretreated with 5 mg./kg. of phentolamine injected intravenously 30 min. prior to experiment (3.1 kg.)
d) Cat pretreated with 3 mg./kg. of reserpine injected subcutaneously 24 hr. prior to experiment (2.6 kg.)

experiments, significantly suppressed the contractions of the nictitating membrane produced by 10 mg./kg. of MPG injected intravenously. A typical example is illustrated in Fig. 6 (d).
Effect of MPG on the Heart Rate in Dogs and Cats

2 mg./kg. of MPG, which was injected intravenously during 2 min. on pentobarbital anesthetized dog, produced an increase in the heart rate which persisted for about 90 min. Either a urethane anesthetized cat or a spinal cat was injected with 5 mg./kg. of MPG during 2 min., this produced an increase in the heart rate which persisted for about 30 min. In contrast to the hypotensive response in a urethane anesthetized cat, a hypertensive response was obtained in a spinal cat which parallels with the chronotropic action. The typical responses are illustrated in Fig. 7.

![Graphs showing heart rate and blood pressure responses to MPG administration in dogs and cats.](image)

**Fig. 7.** Effect of Intravenous Injections of [2-((Methylphenylamino)ethyl]-guanidine Sulfate (MPG) on the Heart Rate and the Blood Pressure in Dog (a) and Spinal Cat (b).

2 μg./kg./min. of isoproterenol (Iso) and 1 mg./kg./min. or 2.5 mg./kg./min. of MPG were injected in a dog and a spinal cat during 2 min. respectively.

Discussion

MPG blocks the smooth muscle response to adrenergic nerve stimulation in a variety of preparations, that is, the inhibition of the response of the cat nictitating membrane to postganglionic sympathetic nerve stimulation and the inhibition of the pressor responses of the cat blood pressure to the celiac ganglion and the splanchnic nerve stimulation. This lasting depression of many excitatory responses evoked by electrical stimulation of the peripheral sympathetic nerve, may be caused by impairing the conduction of impulses in adrenergic neurone with consequent failure of the norepinephrine and epinephrine release.

In common with xylocholine, guanethidine and bretylium, MPG blocks, the inhibiting effect of MPG on the response to postganglionic stimulation in the cat nictitating membrane is abolished by amphetamine, which suggests a common mechanism of action for xylocholine, guanethidine, bretylium and MPG at postganglionic adrenergic nerve endings. The same mechanism may be involved in the phenomenon that the antagonistic effect on the pressor responses produced by the stimulation of the celiac ganglion and the splanchnic nerve was abolished by amphetamine.

MPG potentiated the pressor responses of norepinephrine and epinephrine. If one assumes that MPG depletes catecholamine stores, as guanethidine does, or inhibits the

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uptake of catecholamines to tissue, as cocaine, the potentiation of catecholamines by MPG may be understandable. But the possibility that MPG alters directly the sensitivity of receptor to catecholamines or other unknown mechanisms would not be excluded.

The inhibition of tyramine by MPG was compared with that of guanethidine in rat blood pressure. The results showed that the antityramine action by MPG is more potent than that of guanethidine when 10 mg./kg. of these compounds were injected intravenously. Amine depletion from catecholamine stores and antagonism to the uptake of tyramine by the norepinephrine stores, is the same as cocaine, may also be partially responsible for the antityramine action of MPG.

MPG also causes a sympathomimetic effect. This property of MPG is similar to that of bretylium and guanethidine. The sympathomimetic effect of MPG is shown by the contraction of the cat nictitating membrane, the rise of the blood pressure in spinal cat and the increase in the heart rate in cat and dog. These responses, like those due to bretylium or guanethidine, may be due to the release of sympathomimetic amines, since the contraction of the cat nictitating membrane by MPG injected intravenously was completely suppressed by phentolamine and the pretreatment of reserpine.

The prolonged amine release would possibly lead to amine depletion and interfere with sympathetic transmission. But the sympathetic blocking effect of MPG, which was demonstrated in an acute experiment, is not considered to be a result from such a release. McCubbin _et al._ have suggested that the acute effect of guanethidine depends upon the interference with the sympathetic effector system primarily through an action at the nerve endings. The chronic effect, however, may depend in part upon an ability to deplete stores of endogenous catecholamines. The acute effect of MPG is similar to the effect of guanethidine and may be interpreted by the same mechanisms mentioned above.

The authors express their deep gratitude to Dr. Y. Gomi of this institute for his kind advice.

**Summary**

The effect of [2-(methylphenylamino)ethyl]guanidine sulfate (MPG) on sympathetic nervous system was studied and the following results were obtained:

1) intravenous injection of MPG caused a fall of blood pressure and sustained contraction of the nictitating membrane in urethane anesthetized cat, 2) MPG caused a lasting depression of many excitatory responses, evoked by electrical stimulation of the peripheral sympathetic nerves, that is, inhibition of the response of the cat nictitating membrane to postganglionic sympathetic nerve stimulation and inhibition of the pressor responses in cat to the celiac ganglion or splanchnic nerve stimulation. In addition, these reduced responses were abolished by amphetamine, 3) MPG also caused the potentiation of the pressor responses to norepinephrine and epinephrine, but caused a potent antagonistic action to pressor responses produced by tyramine, dimethylphenylpiperazinium and the occlusion of the carotid artery in cat, 4) injection of high doses of MPG caused a sympathomimetic effect on the cat nictitating membrane, the heart rate of cat and dog and the blood pressure in spinal cat. The contraction of the cat nictitating membrane by MPG was abolished by phentolamine and pretreatment with reserpine. From the results mentioned above, it is concluded that MPG has adrenergic neurone blocking action and sympathomimetic action resembling those of guanethidine and bretylium.

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