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MECHANISM OF THE CENTRAL HYPOTENSIVE ACTION OF GUANETHIDINE

BY

K. P. BHARGAVA, B. P. JAJU AND K. K. TANGRI

From the Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow University, Lucknow, India

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Guanethidine is a potent hypotensive agent. It produces an initial short-lived hypertension due to catecholamine release which is followed by a prolonged hypotension (Maxwell, Plummer, Schneider, Povalski & Daniel, 1960). Furthermore, the prolonged hypotension is attributed to a peculiar " adrenergic-neurone blocking " action resulting in the lack of neurotransmitter at the adrenoceptive effector cells (Burn, 1961).

Since the guanethidine molecule is highly ionized, the possibility of a central locus of action of guanethidine has been considered unlikely. However, intraperitoneal injection of guanethidine decreases the noradrenaline content of brain (Pfeifer, Vizi & Satory, 1962 ; Sanan & Vogt, 1962 ; Dagirmanjian, 1963). Pfeifer *et al.* (1962) showed that guanethidine decreased the amphetamine-induced hypermotility in rats. These observations indicate that guanethidine does reach the central nervous system in amounts adequate to produce central effects. Introduction of guanethidine into the cerebral ventricular system of cats causes hypotension (Kaneko, McCubbin & Page, 1962). Similarly intraventricular administration of noradrenaline induces hypotension (Kaneko, McCubbin & Page, 1960). The peripheral action of guanethidine is intimately connected with the release of the adrenergic neurotransmitter. It was therefore planned to investigate the central component of the hypotensive action of guanethidine in dogs and to determine the role of brain catecholamines in the mediation of such a response.

METHODS

Fifty-six mongrel dogs were used. They were anaesthetized with pentobarbitone sodium (30 mg/kg, intravenously), bilaterally vagotomized and maintained on positive pressure artificial ventilation. Blood pressure was recorded from the right common carotid artery using a mercury manometer and a kymograph. A femoral vein was cannulated with an indwelling polyethylene tube for intravenous injections.

In order to avoid the complicating peripheral adrenergic-neurone blocking action of guanethidine, the drug was administered in a manner to localize the drug into the structures of the central nervous system, namely by intracerebroventricular injections and by topical application. The intracerebroventricular injection was made into the left lateral cerebral ventricle through a silver cannula introduced according to the technique of Bhargava, Gupta & Chandra (1961). Topical application of the drug was made on the floor of the fourth ventricle by means of a cotton pellet soaked in 1% solution of the drug.

The action of guanethidine on the medullary vasomotor centre was studied. The activity of the medullary vasomotor centre was assessed by centrally evoked pressor responses obtained by direct electrical stimulation of the vasomotor centre and by centrally mediated reflex pressor responses, namely the pressor responses to electrical stimulation of the central cut end of a vagus nerve and to occlusion of the common carotid artery. The direct stimulation of the medullary vasomotor centre was done by means of a stereotaxically oriented bipolar concentric electrode using the Horsley Clark stereotaxic instrument. The electrode placement was aided by the parameters described by Wang & Ranson (1939). Rectangular wave pulses were obtained from a Grass model S4 stimulator.

The central cut end of the vagus nerve was electrically stimulated using a tubular plastic electrode. The parameters of stimulation were adjusted so as to obtain pressor or depressor responses. The nictitating membrane response to preganglionic cervical sympathetic nerve stimulation was recorded on a kymograph by a frontal writing lever; these responses served as a test of the peripheral sympathetic neurone blocking action of guanethidine.

In some experiments, the effect of intraventricular injection of guanethidine was studied in animals which had been treated with reserpine (0.5 mg/kg, intraperitoneally for 2 days), tetrabenazine (30 mg/kg, intraperitoneally 4 hr before the experiment), α-methyldopa (200 mg, intracerebroventricularly for 4 days), cocaine (4 mg/kg, intravenously 30 min before the experiment), tranylcypromine (0.1 mg) or phenoxybenzamine (10 mg) or pronethalol (1 mg) (intracerebroventricularly 30 min before administration of guanethidine). In four dogs, the effect of noradrenaline on the blood pressure level was observed after prior intraventricular administration of guanethidine (5 mg daily for 2 days).

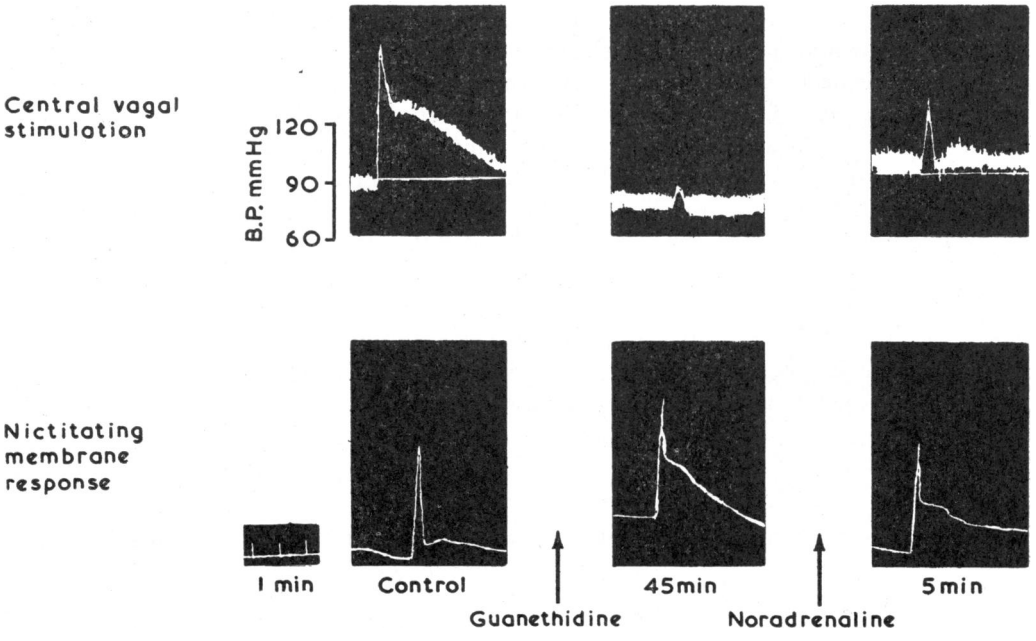

Fig. 1. Record showing the effect of intracerebroventricular (i.c.v.) injection of guanethidine (5 mg) on the pressor responses (upper panels) to central vagal stimulation (8 V, 60 shocks/sec for 15 sec) in a dog anaesthetized with pentobarbitone sodium (30 mg/kg) and vagotomized. The lower panels show the responses of the nictitating membrane to preganglionic stimulation. After 45 min there was a fall in blood pressure (20 mm Hg) and marked inhibition of central vagal pressor responses without any diminution of nictitating membrane responses. The last panels show complete recovery of blood pressure and partial recovery of central vagal pressor response after i.c.v. injection of noradrenaline (200 μg).

RESULTS

Effect of intracerebroventricular guanethidine on reflex vasomotor responses in untreated dogs

The effect of intracerebroventricular injection of guanethidine was studied on the pressor responses to stimulation of the central cut end of a vagus nerve and on the nictitating membrane responses to preganglionic sympathetic stimulation in untreated dogs. Guanethidine (1 and 2.5 mg) had no effect on blood pressure and there was no change in the reflex excitability of the vasomotor centre. However, a higher dose of guanethidine (5 mg) consistently produced a fall in blood pressure and an inhibition of the reflex vasomotor responses although the nictitating membrane responses to preganglionic sympathetic stimulation remained unaltered (Fig. 1). Usually the peak hypotensive effect of guanethidine was observed in about 45 min and the recovery was not apparent up to 300 min from the injection. Noradrenaline (200 μg), injected into the lateral cerebral ventricles at the peak hypotensive effect of guanethidine, immediately reversed the hypotensive action, and the pressor response to central vagal stimulation also tended to recover. The nictitating membrane responses were unaltered (Fig. 1). Similarly in the guanethidine-treated dogs intraventricular injection of noradrenaline elicited a pressor response instead of the usual hypotensive response.

Effect of topical application of guanethidine on the stereotaxically evoked medullary pressor responses

Pressor responses were evoked by electrical stimulation of the medullary vasomotor centre and the effect of guanethidine (1%) applied topically at the site of electrode

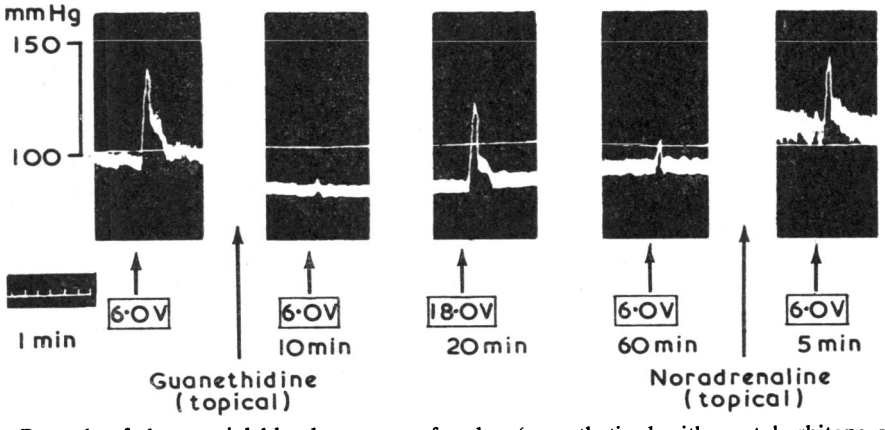

Fig. 2. Records of the arterial blood pressure of a dog (anaesthetized with pentobarbitone sodium, 30 mg/kg, and vagotomized) showing the effect of topical application of guanethidine (1%) on the pressor responses to direct electrical stimulation (100 shocks/sec for 10 sec) of the medullary vasomotor centre. The first panel shows the control response (6 V). Ten minutes after guanethidine (second panel) there was a fall in blood pressure and marked inhibition of medullary pressor responses. However, with a stimulus of 18 V, a vasopressor response (third panel) comparable to control response could still be elicited. At 60 min (fourth panel) slight recovery is seen. After topical application of noradrenaline (0.01%) to the floor of the fourth ventricle there is complete recovery (fifth panel) of the blood pressure and the medullary pressor response.

penetration was studied in five dogs. In Fig. 2 are shown the results of a typical experiment. Guanethidine produced a fall in blood pressure and inhibition of the pressor response within 10 min. However, a pressor response equal in magnitude to the control could be obtained with three times the control voltage. Only slight recovery of the blood pressure level and of the medullary pressor response could be seen at the end of 1 hr. At this time topical application of noradrenaline (0.01%) immediately reversed the hypotensive effect of guanethidine and the pressor response to stimulation of the vasomotor centre recovered completely.

Effect of intracerebroventricular guanethidine on reflex vasomotor and nictitating membrane responses in dogs treated with various drugs

Treatment of dogs with reserpine, tetrabenazine, α-methyldopa and cocaine rendered the animals refractory to the hypotensive effect of intracerebroventricular injection of guanethidine (5 mg) and to the inhibitory effect on the reflex responses to carotid arterial occlusion and stimulation of the central end of a cut vagus. The β-receptor blocking drug, pronethalol, had a similar action in preventing the effects of guanethidine. However, the usual action of intracerebroventricular guanethidine (5 mg) on the blood pressure level and the reflex vasomotor response to afferent vagal stimulation was present in animals previously treated with phenoxybenzamine (10 mg), an α-receptor blocking agent. Intracerebroventricular injection of 100 μg of tranylcypromine made a previously ineffective dose of guanethidine active in depressing the reflex vasomotor responses, although there was no change in the responses of the nictitating membrane to preganglionic stimulation.

TABLE 1

EFFECTS OF INTRACEREBROVENTRICULAR INJECTION OF GUANETHIDINE AND NORADRENALINE ON BLOOD PRESSURE AND REFLEX VASOMOTOR RESPONSES IN NORMAL AND DRUG-TREATED DOGS

Preparation	No. of animals	Drugs	Intracerebroventricular dose (mg)	Effect on blood pressure	Effect on reflex vasomotor responses
(*a*) *Untreated dogs*	4	Guanethidine	1 to 2·5	No effect	No effect
	5	Guanethidine	5 or more	Fall	Depression
	3	Noradrenaline	0·2	Fall	Depression
(*b*) *Treated dogs:*					
Guanethidine	4	Noradrenaline	0·2	Rise	Facilitation
Reserpine	3	Guanethidine	5·0	No effect	No effect
Tetrabenazine	3	Guanethidine	5·0	No effect	No effect
α-Methyldopa	4	Guanethidine	5·0	No effect	No effect
Cocaine	2	Guanethidine	5·0	No effect	No effect
Parnate	2	Guanethidine	1·0	No effect	Depression
Phenoxybenzamine	3	Guanethidine	5·0	Fall	Depression
Pronethalol	5	Guanethidine	5·0	No effect	No effect

DISCUSSION

The results of the present study are summarized in Table 1. Intracerebroventricular administration of guanethidine (5 mg) consistently caused a fall in blood pressure and depressed the responses to stimulation or activation of the vasomotor neurones. In view of the doubt regarding the penetration of guanethidine into the cerebrospinal fluid it is impossible to state the clinical significance of the central component of the hypotensive action of guanethidine.

It is our contention that the central vasomotor effects of guanethidine are mediated through a release of catecholamines from the structures of the central nervous system, particularly the medulla oblongata. The responses of the vasomotor centre were depressed by topical application of guanethidine to the floor of the fourth ventricle and recovery occurred immediately upon the application of noradrenaline (see Fig. 2). Previous treatment of the animal with guanethidine reversed the depressor action of intraventricular noradrenaline into pressor. Similar results have been reported for reserpine (Share & Melville, 1963). Reserpine is a well-known releaser and depleter of biogenic amines and it appears that the same action may be responsible for the reversal of noradrenaline responses by guanethidine. In reserpinized animals, guanethidine was ineffective. It is possible that, besides catecholamines, 5-hydroxytryptamine may be concerned in the central hypotensive action of reserpine (Bhargava & Tangri, 1959) and also of guanethidine. Since tetrabenazine alone was effective in blocking the hypotensive action of intracerebroventricular guanethidine, it may be concluded that the central hypotensive action of guanethidine is mediated through catecholamines and not 5-hydroxytryptamine. α-Methyldopa has been reported to be a potent decarboxylase inhibitor (Sourkes, 1954) and thereby reduces the synthesis of catecholamines. In dogs treated with α-methyldopa intraventricular guanethidine did not produce hypotension. It is possible that after α-methyldopa the amount of noradrenaline available to be released by guanethidine is inadequate to produce the hypotensive effect. Furthermore, cocaine, which blocks the release of catecholamines (MacMillan, 1959) also blocked the hypotensive action of intracerebroventricular guanethidine.

That monoamine oxidase inhibition by tranylcypromine was able to potentiate the action of guanethidine again indicates an accumulation of released catecholamines in the brain which may be responsible for the depression of the vasomotor centre.

The hypotension caused by intracerebroventricular injections of noradrenaline and isoprenaline is not blocked by phenoxybenzamine but is successfully blocked by pronethalol (unpublished observations). Similarly, the central hypotensive action of guanethidine can be blocked by pronethalol but not by phenoxybenzamine. It appears that the central receptors for the hypotensive action of catecholamines may be of the β-type in terms of Ahlquist's (1948) classification, and guanethidine acts on these receptors through the liberation of catecholamines. It is, however, possible that guanethidine may also have a direct action on the β-receptors situated in the central nervous system.

SUMMARY

1. The central vasomotor effects of guanethidine have been investigated and the mechanism of depression of the vasomotor centre by guanethidine has been studied.

2. Intracerebroventricular guanethidine produced a fall in blood pressure and inhibited reflexly mediated vasomotor responses. These effects of guanethidine were reversed by intracerebroventricular noradrenaline.

3. Topically applied guanethidine raised the threshold of the medullary vasomotor centre to electrical stimulation. This effect was also reversed by noradrenaline.

4. Previous treatment of the animal with reserpine, tetrabenazine, α-methyldopa or cocaine rendered the animals refractory to the central hypotensive action of guanethidine.

5. Inhibition of monoamine oxidase by tranylcypromine potentiated the central hypotensive action of guanethidine.

6. The central vasomotor effects of guanethidine were blocked by pronethalol, a β-receptor blocking agent, but not by phenoxybenzamine, an α-receptor blocking agent. Correspondingly the inhibition of vasomotor tone by intracerebroventricular noradrenaline was blocked by pronethalol but not by phenoxybenzamine.

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