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THE EFFECT OF GALANTAMINE ON THE BLOOD PRESSURE OF THE RAT

BY

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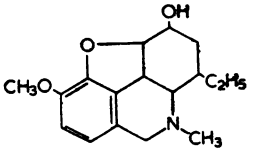
Several active substances have been isolated from the various species of *Galanthus* (Amarillidaceae) (Proskurnina & Areshkina, 1947; Mashkovski & Kruglikova-Lvova, 1951; Clemo & Felton, 1952; Proskurnina & Jakovlieva, 1952; Boit, 1954). These have been called tacitine, leucocitine, liquorine, galanthidine and galantamine (galanthamine). The chemical structure of galantamine is still uncertain. Proskurnina & Jakovlieva (1952) suggested that it is a derivative of 4-ethyl-5-methylphenanthridine, as follows:



This formula differs, however, from the structure proposed by Kobayashi, Shingu & Uyeo (1956).

Bubeva-Ivanova (1957) and Paskov (1962) isolated an active substance from *Galanthus nivalis* and called it Nivaline. Physicochemical and pharmacological studies have shown that galantamine and nivaline are identical (Paskov, 1962).

Physostigmine produces a blood pressure rise in rats during urethane anaesthesia, an effect attributed to central adrenergic activation (Varagić, 1955; Medaković & Varagić, 1957; Lešić & Varagić, 1961; Varagić, Lešić, Vučo & Stamenović, 1962; Varagić & Vojvodić, 1962). Other anticholinesterases containing a quaternary nitrogen were less potent and showed this effect only occasionally. Since galantamine has anticholinesterase activity (Paskov, 1962) and contains a tertiary nitrogen, we decided to investigate the action of this substance on the blood pressure of the rat and to compare it with the effect of physostigmine and synthetic anticholinesterase agents.

METHODS

Rats of either sex weighing 120 to 360 g were anaesthetized with urethane (0.7 ml./100 g body weight of a 25% solution, half of which was injected subcutaneously and the other half intramuscularly). Blood pressure was recorded from a polyethylene cannula inserted into the carotid

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artery and connected to a mercury manometer (Condon, 1951). Drugs were injected through a small polyethylene catheter in a jugular vein. Heparin (1 to 2 mg/100 g, intravenously) was injected at the start of the experiment. All drugs were injected in 0.1 to 0.3 ml. of 0.9% saline.

When necessary, the central nervous system was destroyed by introducing a needle through an orbit into the brain cavity. The needle was pushed downwards through the medulla into the spinal cord. After this procedure the spontaneous respiration ceased and the blood pressure fell to about 30 mm Hg.

For perfusion of the hindlegs of the rat a cannula was inserted into the abdominal aorta. Krebs solution was used for perfusion with addition of 5% Subsidon (a plasma substitute). The perfusion pressure was 65 to 95 mm Hg. The outflow was recorded with Stephenson's (1948) recorder.

The following drugs were used: galantamine (Nivaline) hydrobromide, physostigmine salicylate; 3-oxopentamethylenebis(allyldimethylphenyl)ammonium bromide (BW 284C51); (2-dimethylcarbamoyloxy-5-phenylbenzyl)trimethylammonium bromide (Ro-2-683); [3-*N*-*p*-chlorophenyl-(*N*-methylcarbamoyloxy)phenyl]trimethylammonium bromide (Ro-2-1250); neostigmine methylsulphate; nicotine hydrogen tartrate; phentolamine; phenoxybenzamine; cocaine hydrochloride; and atropine sulphate.

RESULTS

The effect of galantamine. Galantamine produced an increase of the blood pressure of the anaesthetized rat in fifteen experiments with doses of 0.2 to 3 mg/kg. The rise in blood pressure depended on the dose, ranged from 8 to 50 mm Hg and lasted from 5 to 29 min. The dose-dependent responses were obtained in five out of fifteen experiments, one of which is shown in Fig. 1. In the other ten experiments a tachyphylaxis towards the hypertensive response to galantamine was observed. This effect was particularly easy to produce with large doses of galantamine (3 mg/kg) but also occurred with repeated small doses (0.24 mg/kg) injected at short time intervals (Fig. 2).

Galantamine potentiated the carotid sinus reflex induced by occlusion of the right carotid artery (Fig. 3). The duration and degree of potentiation of this effect was dose-dependent.

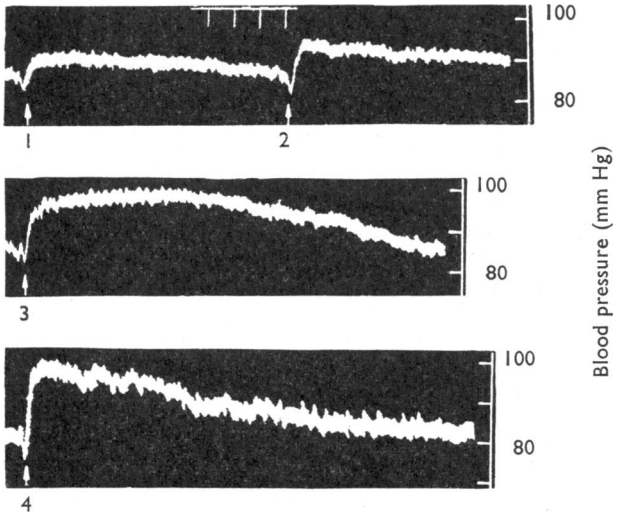

Fig. 1. The effect of increasing doses of galantamine on the blood pressure of the rat (120 g). At 1, 2, 3 and 4: 0.2, 0.5, 1 and 2 mg/kg respectively injected intravenously. Time: 90 sec.

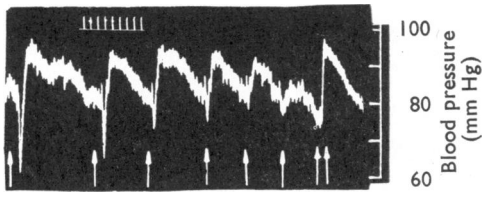

Fig. 2. The effect of galantamine on the blood pressure of the rat (250 g). The same dose of galantamine (0.24 mg/kg) was injected at each arrow. At the two close arrows, 1.2 mg/kg of galantamine. Time: 1 min.

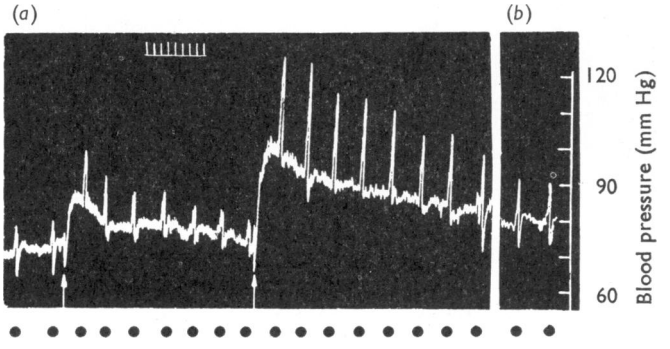

Fig. 3. The effect of galantamine on the carotid artery occlusion response in a rat (270 g). At the dots: occlusion of the right carotid artery for 15 sec, every 3.5 min. At first arrow, 1.1 mg/kg of galantamine, intravenously. At the second arrow, 2.2 mg/kg of galantamine. (*b*) was taken 48 min after (*a*). Time: 1 min.

Comparison between the effect of galantamine and the responses to other anticholinesterases. In nine experiments the response to galantamine was compared to that to physostigmine, neostigmine, Ro-2-683, Ro-2-1250 and BW 284C51. Only physostigmine and galantamine produced a hypertensive response, whereas the other substances produced little change in the blood pressure. The response to galantamine was quicker in onset than that to physostigmine, but its duration was usually less. The absence of the hypertensive response to synthetic anticholinesterases after injection of galantamine was not due to cross-tachyphylaxis because they had no effect when injected before galantamine.

Antagonism between galantamine and physostigmine. Galantamine antagonized the hypertensive response to physostigmine (Fig. 4). If galantamine was injected during the response to physostigmine, no immediate antagonistic action of galantamine occurred. However, the next injection of physostigmine produced a smaller rise in blood pressure than before (Fig. 4). This antagonism was always reversible, lasted from 10 to 60 min and was observed in eleven experiments.

Galantamine and ganglion-blocking agents. Hexamethonium (65 to 100 mg/kg) did not depress, but sometimes potentiated, the hypertensive action of galantamine (four experiments). In two experiments, pentolinium (50 mg/kg) did not affect the action of galantamine. However, nicotine (five experiments) invariably depressed the hypertensive

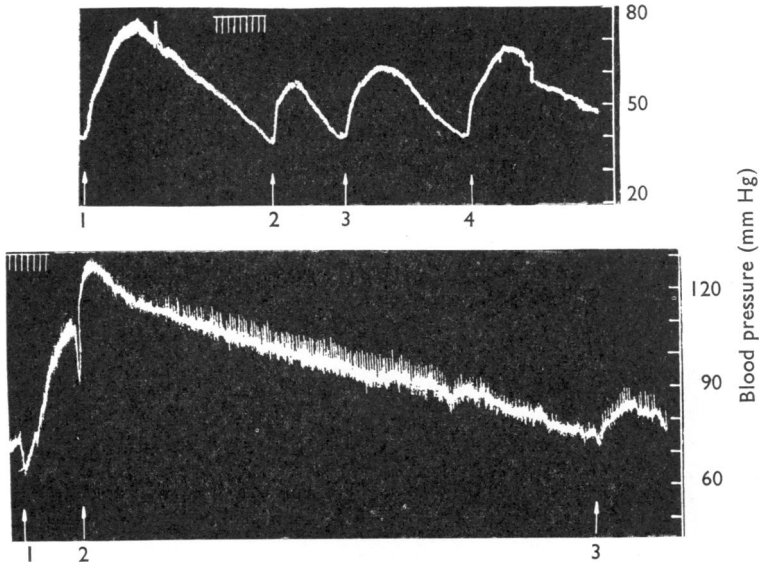

Fig 4. Antagonism between galantamine and physostigmine. Top tracing : blood pressure of a rat (260 g). At 1, 3 and 4: 0.15 mg/kg of physostigmine, intravenously. At 2, 2 mg/kg of galantamine. Time: 1 min. Bottom tracing: blood pressure of a rat (240 g). At 1 and 3: 0.15 mg/kg of physostigmine, intravenously. At 2, 1 mg/kg of galantamine. Time: 75 sec.

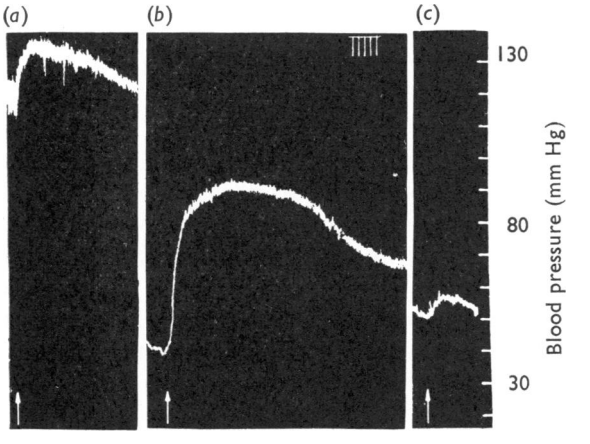

Fig. 5. The effect of hexamethonium and nicotine on the blood pressure response to galantamine in a rat (220 g). At the arrows, 1 mg/kg of galantamine, intravenously. Between (*a*) and (*b*), 100 mg/kg of hexamethonium in divided doses. Between (*b*) and (*c*), 3.25 mg of nicotine in divided doses. Time 1 min.

response to galantamine. In the experiment of Fig. 5 the response to galantamine was potentiated by hexamethonium, but after nicotine the effect of galantamine was almost completely blocked.

Galantamine and adrenergic-blocking agents. Phentolamine (2.5 mg/kg; three experiments) and phenoxybenzamine (3 mg/kg; two experiments) blocked the

hypertensive effect of galantamine (1 mg/kg). In one other experiment the action of galantamine was not affected by phenoxybenzamine.

The effect of adrenalectomy. In four adrenalectomized rats the hypertensive response to galantamine was still present, although somewhat smaller than in normal ones.

The effect of cocaine and atropine. In two out of three experiments cocaine (2.5 to 5 mg/kg) potentiated the hypertensive effect of galantamine (1 mg/kg), whereas in one experiment it had no action.

Atropine (2.5 to 5 mg/kg) blocked the hypertensive action of galantamine (1 mg/kg) in all of three experiments.

The effect of galantamine in the pithed rat. In four pithed rats galantamine had no hypertensive effect.

The effect of galantamine on the perfused hindlegs of the rat. When galantamine was injected into the perfused hindlegs of the rat, no vasoconstrictor response was observed. The doses of galantamine ranged from 0.2 to 1 mg. In the same preparation adrenaline (5 to 10 ng) gave a significant vasoconstrictor response lasting up to 20 min.

DISCUSSION

Our experiments suggest that the anticholinesterase drug galantamine produced a hypertensive effect in the rat through central stimulation of the sympathetic nervous system. Thus the effect could not be obtained in the pithed rat, galantamine had no vasoconstrictor effect in the perfused hindlegs, and the rise of blood pressure was potentiated by cocaine and prevented by phentolamine and phenoxybenzamine. That adrenalectomy did not substantially reduce the hypertensive effect of galantamine suggests that liberation of catechol amines from the adrenal medulla plays a minor role in the response. In many respects the rise of blood pressure produced by galantamine was similar to that produced by physostigmine (Varagić, 1955), an effect also mediated by central stimulation. However, the hypertension induced by galantamine was quicker in onset and shorter in duration than that due to physostigmine. Furthermore injections of galantamine antagonized subsequent injections not only of galantamine, showing tachyphylaxis, but also of physostigmine, suggesting cross-tachyphylaxis.

The peripheral pathway mediating the hypertensive response to physostigmine and galantamine must be an unusual one, as suggested for physostigmine by Gokhale, Gulati & Joshi (1964), since hexamethonium and pentolinium blocked neither the action of galantamine in our present experiments nor the action of physostigmine (Varagić, 1955; Gokhale *et al.*, 1964). Two drugs, however, did block the hypertensive response to galantamine. One was nicotine, which prevents ganglionic transmission by depolarization (Paton & Perry, 1953; Trendelenburg, 1957), and the other was atropine. Volle (1962) and Takeshige & Volle (1964) have suggested at least three pharmacologically distinct cholinoceptive sites in the sympathetic ganglia, one of which is sensitive to atropine (Jones, 1963; Takeshige & Volle, 1964). Thus it is possible that both nicotine and atropine antagonize the hypertensive response to galantamine (and to physostigmine) either by an effect at ganglia or by a more central antagonism.

SUMMARY

1. Galantamine (an alkaloid from *Galanthus nivalis*) produced a rise in blood pressure of the rat during urethane anaesthesia. Tachyphylaxis towards the effect was also observed.

2. Among the six anticholinesterases tested only the tertiary bases galantamine and physostigmine produced the hypertensive response. The quaternary substances had no effect.

3. Hexamethonium and pentolinium did not block the hypertensive action of galantamine, whereas nicotine did.

4. Adrenalectomy depressed the hypertensive action of galantamine only to a small extent. Atropine and adrenergic-blocking agents blocked it, whereas cocaine occasionally caused its potentiation. The effect of galantamine was absent in the pithed rat. No significant vasoconstrictor response to galantamine was seen in the perfused hindlegs of the rat.

5. It is concluded that the pressor response to galantamine is similar to the pressor effect of physostigmine and is due to a central stimulation of adrenergic nervous elements.

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