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DIFFERENCE BETWEEN THE BLOOD PRESSURE RESPONSES TO INTRAJUGULAR AND INTRACAROTID INJECTIONS OF PHYSOSTIGMINE, AND THE SYNDROME OF CONTRALATERAL TORSION IN THE RAT

BY

M. KRSTIĆ AND V. VARAGIĆ

From the Department of Pharmacology, Medical Faculty, Belgrade, Yugoslavia

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It has been repeatedly shown that physostigmine raises blood pressure in the rat anaesthetized with urethane (Varagić, 1955; Hornykiewicz & Kobinger, 1956; Medaković & Varagić, 1957; Lešić & Varagić, 1961; Varagić & Vojvodić, 1962). This effect of physostigmine was also present in the conscious rat, but it was absent or very much reduced in the spinal rat. This peculiar response is probably due to a central activation of adrenergic nervous elements (Lešić & Varagić, 1961; Varagić, Lešić, Vučo & Stamenović, 1962), the role of other factors being probably much less pronounced (Varagić & Beleslin, 1962). In all previous experiments physostigmine was injected only into a jugular vein. It was therefore of interest to compare the blood pressure responses to intrajugular and intracarotid injections of physostigmine; we have also compared these results with the frequency of production of the syndrome of contralateral torsion by intracarotid injections of physostigmine.

METHODS

Rats (220 to 380 g) of either sex were used. The animals were anaesthetized by subcutaneous injection of urethane (0.175 g/kg of body weight). To record blood pressure a cannula was inserted into a carotid artery and connected to a small capillary mercury-manometer (Condon, 1951). A small polyethylene catheter, 0.5 mm in diameter, was inserted into a jugular vein and was used for injecting drugs. The other carotid artery was cannulated with a polyethylene T-piece and was also used for injecting drugs. The carotid artery was widely exposed, so that it could be clamped either caudal or cephalad to the injection site so that the drug could be injected towards the head or towards the heart respectively. In some experiments the drugs were injected into the carotid blood stream without clamping the carotid artery. The cannulation of the carotid arteries was done so that alternate left and right carotid arteries were used for recording blood pressure and for injecting drugs respectively.

In a separate group of experiments physostigmine was injected into a carotid artery of conscious rats. These animals had been previously operated on, during ether anaesthesia, so that a polyethylene cannula had been inserted into the right or left carotid artery. This cannula was pushed under the skin of the neck, which was then sewn up.

RESULTS

Blood pressure responses to physostigmine. Intrajugular injection of physostigmine produced a larger blood pressure rise than did injection of the same dose into the blood stream of the right carotid artery. Fig. 1 illustrates an experiment in which 20 μg of physos-

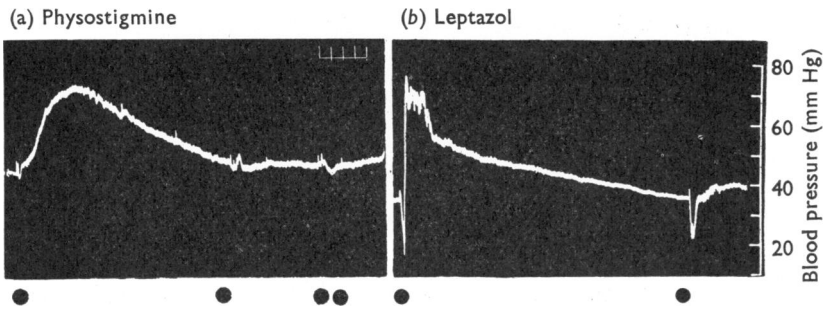

Fig. 1. The effect of intrajugular and intracarotid injections of physostigmine and leptazol on the blood pressure of a rat (230 g). (*a*) At the first dot, 20 μg of physostigmine were injected into a jugular vein; at the second dot, 20 μg were injected into the right carotid artery; at the double dot, 45 μg were injected into the right carotid artery. (*b*) At the first dot, 5 mg of leptazol were injected into the right carotid artery; at the second dot, the same dose was injected into a jugular vein. Time marks: 1 min.

tigmine were injected alternately into a jugular vein and into the blood stream of the right carotid artery. The intrajugular injection increased blood pressure, whereas even twice the dose of physostigmine injected into the right carotid artery produced no change in blood pressure. On the other hand, the intracarotid injection of 5 mg of leptazol produced a sustained blood pressure rise, whereas the intrajugular injection of the same dose of leptazol caused no change in blood pressure. This pattern of response was obtained in all four experiments.

A quite opposite effect was observed after injection of physostigmine into the right carotid artery towards the heart. This produced a larger response than intravenous injection of the same dose of physostigmine. Fig. 2 illustrates an experiment in which 20 μg of physostigmine were injected in turn into a jugular vein, into the right carotid artery towards the head, and into the same artery towards the heart. This pattern of response was obtained in all four experiments.

Another type of response was observed when physostigmine was injected into the left carotid artery first towards the heart and then towards the head. The first two blood

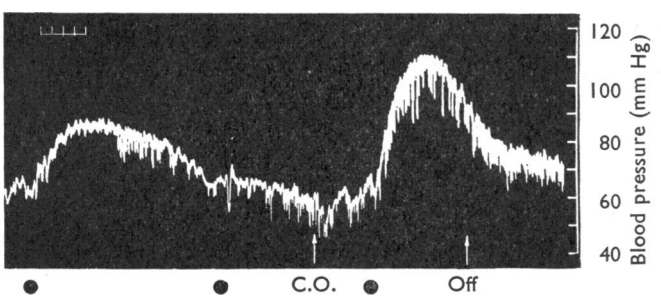

Fig. 2. The effect of intrajugular and intracarotid injections of physostigmine on the blood pressure of a rat (250 g). At the first dot, 20 μg of physostigmine were injected into a jugular vein; at the second dot, 20 μg were injected into the right carotid artery directed towards the head; at the first arrow (C.O.), the right carotid artery was occluded; at the third dot, 20 μg of physostigmine were injected into the right carotid artery directed towards the heart; at the second arrow (Off), the occlusion of the right carotid artery was removed. Time marks: 1 min.

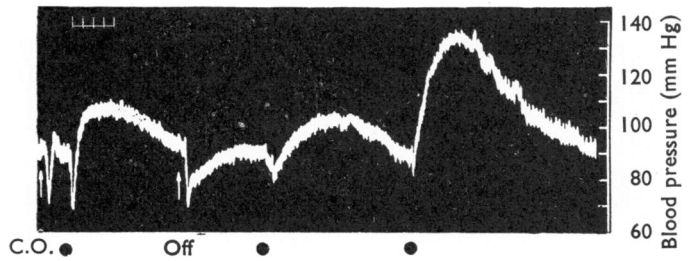

Fig. 3. The effect of intrajugular and intracarotid injections of physostigmine on the blood pressure of a rat (280 g). At the first arrow (C.O.), the left carotid artery was occluded; at the first dot, 30 μg of physostigmine were injected into the left carotid artery directed towards the heart; at the second arrow (Off), the occlusion of the left carotid artery was removed; at the second dot, 30 μg of physostigmine were injected into the left carotid artery towards the head; at the third dot, 30 μg were injected into a jugular vein. Time marks: 1 min.

pressure responses in Fig. 3 were obtained by injecting 30 μg of physostigmine towards the heart and then towards the head. It was also regularly observed that occlusion of the left common carotid artery caused a brief but clear fall of blood pressure. The third response in Fig. 3 was obtained by intrajugular injection of the same dose of physostigmine. This pattern of response was also obtained in all four experiments.

Vestibular response to intracarotid injection of physostigmine. Injection of physostigmine into the right carotid artery towards the heart of conscious rats caused a " sinistrotorsion." After doses of physostigmine ranging from 0.1 to 0.3 mg/kg this effect was observed in six of ten rats tested (60%). The phenomenon of sinistrotorsion consisted of an anti-clockwise circling of the animal. This effect usually started immediately after injection of

TABLE 1

THE EFFECT OF INTRACAROTID INJECTIONS OF PHYSOSTIGMINE ON THE INCIDENCE OF CONTRALATERAL TORSION IN THE RAT

On the left, incidence of sinistrotorsion after injection of physostigmine into the right carotid artery in the dose ranges (mg/kg of body weight) shown. On the right, dextrotorsion after injections into the left carotid artery. + = Positive effect; every + represents one complete turning of the animal. − = No contralateral torsion

No. of expt.	Sinistrotorsion for dose-range (mg/kg) 0·1–0·2	0·2–0·3	0·3–0·5	No. of expt.	Dextrotorsion for dose-range (mg/kg) 0·1–0·2	0·2–0·3	0·3–0·5
1	++++			1	+	−	
2	+++			2	−		−
3	−	−		3	−	−	
4	−	−	−	4		−	−
5	−	+		5	−		−
6	−	+	−	6	−		++++++
7	−	−		7	−	+	
8		−	−	8		−	−
9		+	+	9	−	−	
10		+		10		−	
				11		−	+
				12			−
				13		−	−
				14		++++++++	−
				15		−	−

physostigmine and usually lasted only 1 to 2 min. This contrasts with the same phenomenon observed in guinea-pigs, which lasted several minutes after intracarotid injection (De Jonge & Funcke, 1962). In the majority of experiments a forced movement of the head towards the right, lasting 2 to 20 min, was also observed immediately after injection of physostigmine. Injection of physostigmine into the left carotid artery towards the heart, using the same dose ranges as in previous experiments, caused " dextrotorsion "—a clockwise circling of the animal. This phenomenon was observed only in three of fourteen rats tested (21%), using the doses of physostigmine from 0.1 to 0.3 mg/kg.

The incidences of contralateral torsion after injections of physostigmine into the right or left carotid artery are shown in Table 1.

DISCUSSION

Intrajugular injection of physostigmine regularly caused a larger blood pressure response than did intracarotid (either right or left) injection directed towards the head. On the other hand, leptazol produced a larger blood pressure increase if injected into a carotid artery towards the head than after intrajugular injection. A different pattern of response was observed when physostigmine was injected into a carotid artery towards the heart. Such an injection into the right carotid artery invariably caused a larger blood pressure response than did intravenous injection of the same dose of physostigmine. On the other hand, injection of physostigmine into the left carotid artery towards the heart caused a smaller rise of blood pressure than did intravenous injection of the same dose. Thus, only when

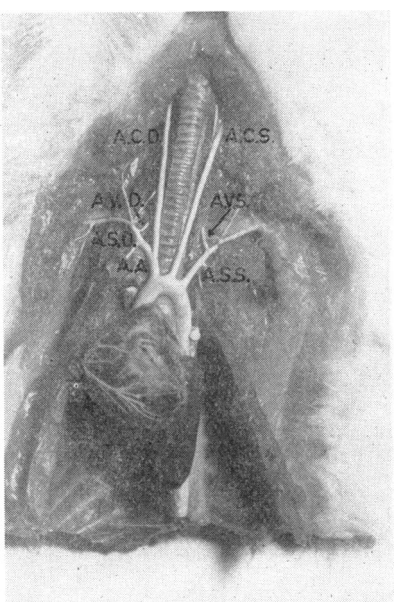

Fig. 4. Photograph of the large arteries arising from the aortic arch of the rat. A.C.D., right carotid artery; A.C.S., left carotid artery; A.A., innominate artery; A.S.D., right subclavian artery; A.S.S., left subclavian artery; A.V.D., right vertebral artery; and A.V.S., left vertebral artery.

the dose of physostigmine was injected into the right carotid artery in the direction of the heart did the pressure response exceed that produced by injecting the same dose into a jugular vein.

These differences in effects are probably due to anatomical differences in the arborization of great blood vessels (Fig. 4). The right common carotid artery arises in the rat from the innominate artery close to the origin of the right subclavian artery, while the left carotid artery arises directly from the aorta. A similar anatomical distribution of the great blood vessels is present in the guinea-pig (Diamant, 1954). The vertebral arteries arise from the subclavian arteries. It is probable that most of the physostigmine injected into the right carotid artery towards the heart first reaches the right subclavian and then the right vertebral artery. The amount of physostigmine which can reach the left vertebral artery after injection into the left carotid artery towards the heart is probably much smaller, the majority of the drug going into the aorta and general circulation, where it is probably inactivated. After injection of physostigmine into a jugular vein the drug passes through the pulmonary circulation, and quickly reaches the aorta and thence both left and right vertebral arteries in significant amounts. It is therefore possible that the regions of the brain supplied by the common carotid arteries are functionally less important for the hypertensive response to physostigmine than are the regions supplied by the vertebral arteries.

Diamant & Tammelin (1953) have shown that the inhibition of cholinesterase activity after injection of anticholinesterases into the right carotid artery was greatest in the right half of the pons and medulla. This result was interpreted as probable evidence for cholinergic transmission in the central vestibular system (Diamant, 1954). The method of causing sinistrotorsion by physostigmine in guinea-pigs was even used for screening central anticholinergic activity (De Jonge & Funcke, 1962). Our experiments suggest that the vestibular syndrome of contralateral torsion could be induced in the rat more easily by injection of physostigmine into the right carotid artery towards the heart than into the left carotid artery towards the heart. Thus, the experiments with intracarotid injections of physostigmine agree with regard to both blood pressure and vestibular responses. Both groups of experiments seem to indicate a greater functional significance for the hypertensive response to physostigmine of the pons and medulla compared with regions supplied by the common carotid arteries.

SUMMARY

1. The blood pressure responses to intrajugular and intracarotid injections of physostigmine into the rat anaesthetized with urethane were compared.

2. Intrajugular injection produced a larger blood pressure rise than did injection of the same dose into the blood stream of the left or right carotid artery. Injection into the occluded right carotid artery, directed towards the heart, produced a larger blood pressure response than did intrajugular injection of the same dose. Injection of physostigmine into the left carotid artery towards the heart produced a smaller effect than did intrajugular injection.

3. Injection into the right carotid artery towards the heart in the conscious rat produced a syndrome of contralateral torsion of the head more frequently than did injection into the left carotid artery towards the heart.

4. It is concluded that the pons and medulla, supplied by the vertebral arteries, are of greater functional importance for the hypertensive blood pressure response to physostigmine than are regions supplied by the common carotid arteries.

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