Međunarodni simpozijum o eksperimentalnom tremoru: 1-3. april 1971. godine

Stern, Pavao

1972

Akademija nauka i umjetnosti Bosne i Hercegovine

https://bastina.anubih.ba/items/05bee08e-28ec-4b12-b10e-5c9e89b50461

AKADEMIJA NAUKA I UMJETNOSTI BOSNE I HERCEGOVINE

POSEBNA IZDANJA
KNJIGA XVII

ODJELJENJE MEDICINSKIH NAUKA
KNJIGA 4.

MEĐUNARODNI SIMPOZIJUM

O EKSPERIMENTALNOM TREMORU

1 — 3. APRIL 1971. GODINE

Urednik
PAVEL ŠTERN,
redovni član Akademije nauka i umjetnosti
Bosne i Hercegovine

SARAJEVO
1972

B. BOŠKOVIĆ, N. ROSIĆ AND V. VOJVODIĆ

SOME PHARMACOLOGICAL ACTIONS OF OXIMES AND CHOLINOLYTICS ON THE CARDIOVASCULAR EFFECTS PRODUCED BY OXOTREMORINE IN ANAESTHETIZED RATS.

The changes in arterial blood pressure are commonly seen after the administration of adequate doses of cholinergic drugs (anticholinesterase inhibitors, arecoline, pilocarpine, muscarine etc.) to most animal species (5, 6, 9). The rat appears to behave somewhat differently from other species. Anticholinesterase (anti-ChE) agents and other cholinomimetics cause a rise in blood pressure in rat, which is probably due to a direct action on the vasomotor center (4, 11, 14, 15).

Since the central actions of oxotremorine (OTR) may be blocked by atropine and related agents, it was reasonable to suppose that these are the manifestations of OTR muscarinic activity (3, 7, 8).

On the other hand, there are evidences that oximes could abolish the hypertensive effect in rats poisoned by anti-ChE compounds. This effect is probably due to direct anticholinergic actions of oximes, since it appears in animals poisoned by reactivatable and nonreactivatable organophosphorus compounds (12, 16).

Therefore, it was interesting to study the effects of oximes in cardiovascular changes induced by OTR. OTR was used instead of anti-ChE compounds in order to avoid the other effects these compounds may have, unrelated to their ability to inhibit cholinesterase.

MATERIAL AND METHODS

Male rats weighing between 200 and 250 grams were used. The animals were anaesthetized with urethane (0.7 ml of 25% urethane/100 gr., subcutaneously) and the arterial blood pressure was registered from the left carotid artery, using a mercury manometer (2). To avoid clotting,

heparin 500 i. u./100 gr., was given intraveneously. A T-shaped cannula was inserted into the trachea and one arm of the cannula was connected by a rubber tube to a Mare's tambur for kymographic registration of respiration.

All substances were injected into the jugular vein through a plastic cannula (internal diameter 1.0 mm, length 3 to 4 cm). Drugs were injected in a volume of 1 ml/kg, and the cannula was washed after each injection with an equal volume of 0.9% NaCl. The following substances were used:

— N, N' — trimethylenebis (pyridinium-4-aldoxime) dichloride (TMB-4 Cl_2).

— 1-Phenacyloxime-quinolinium chloride (F-oxime).

— Oxotremorine

— Atropine sulphate, and

— Atropine methylnitrate.

TMB-4 Cl_2 and F-oxime were synthetized by Ing. M. Milojević in our Institute. Oxotremorine was kindly provided by Prof. P. Stern, Sarajevo. Atropine sulphate and atropine methylnitrate were obtained from commercial sources.

All the substances were dissolved in an isotonic solution of NaCl before each experiment.

The ECG was registered by means of an »Cardi-all« type electrocardiograph, using the second lead.

RESULTS

The i. v. injection of OTR, 0.1 mg/kg, caused an immidiate transient fall of arterial blood pressure lasting 5 to 10 sec, followed by rise of arterial blood pressure reaching the maximum within one minute. Hypertensive effect of OTR was maintained at maximum level for more than 15 min. After that time, progressive decline of arterial blood pressure was registered, returning to control values 25 — 30 min after the injection. As shown in Table 1, the average increase of arterial blood pressure was 47 mm Hg. The height of hypertension was dose dependent, and 0.1 mg/kg of OTR produced submaximal effects.

OTR, 0.1 mg/kg, in addition to the efect on blood pressure, induced the following ECG changes: sinus bradycardia, reduction in the height of the P and T-wave. These changes were recorded only 2 to 3 min after the i.v. injection of OTR.

The results of the tested substances concerning the arterial blood pressure changes produced by OTR are presented in Table 1.

TABLE 1

EFFECTS OF TMB-4 Cl_2, F-OXIME, ATROPINMETHYLNITRATE AND ATROPINE SULPHATE ON BLOOD PRESSURE IN RATS TREATED WITH OXOTREMORINE

Drugs	Arterial blood pressure, mmHg (X ∓ SE)	
	A	B
Controls	68.1 ± 4.0	68.1 ± 4.0
Oxotremorine	115.7 ± 6.2*	117.0 ± 5.4*
TMB-4 Cl_2	106.7 ± 5.1	122.0 ± 3.4
F-oxime	91.3 ± 4.2**	93.3 ± 3.8**
Atropinmethylnitrate	119.0 ± 7.3	115.0 ± 6.5
Atropin sulphate	82.5 ± 9.2**	62.5 ± 1.5**

Drugs

Column A = Tested drugs were given after oxotremorine.
Column B = Tested drugs were given before oxotremorine.

* $P < 0.05$ comparing with controls.
** $P < 0.05$ comparing with oxotremorine effects.

TMB-4 Cl_2, 10 or 20 mg/kg, had no influence on hypertension produced by OTR. When TMB-4 Cl_2 was injected before OTR, it failed to prevent or reduce the changes in arterial blood pressure produced by this substance.

On the other hand, F-oxime in a dose of 10 mg/kg, lowered the arterial blood pressure rised by OTR. This effect was obtained within 10 to 20 sec after the injection of F-oxime, and lasted more than 30 min. Given before OTR, F-oxime prevented the rise of arterial blood pressure (Table 1).

Atropin methylnitrate, in a dose of 2 mg/kg, had no influence on the hypertension produced by OTR; when injected before OTR, atropin methylnitrate failed to prevent or reduce hypertensive effect of this substance, but completely blocked hypotensive action of OTR. On the contrary, atropin sulphate, given in a dose of 2 mg/kg, either before or after OTR, completely blocked or returned to control values the changes in arterial blood pressure.

TMB-4 Cl_2 and F-oxime injected before OTR, lowered the intensity of bradycardia and abolished the other ECG disturbances produced by OTR. On the other hand, atropine sulphate or atropine methylnitrate, completely prevented bradycardia and the other ECG changes produced by OTR.

DISCUSSION

It can be seen from the results that the administration of OTR to rats caused initial transient fall in arterial blood pressure followed by hypertension. This finding suggests that, both, peripheral and central components of OTR actions, are responsable for the arterial blood pressure changes in rat. The changes in arterial blood pressure due to OTR could be prevented or blocked by atropine sulphate, while atropine methylnitrate was effective only in preventing hypotensive component. Inability of atropine methylnitrate to counteract the hypertensive effect of OTR, indicates that this hypertension is probably central in origin.

In our experiments, TMB-4 Cl_2 was unable to prevent or abolish the increased arterial blood pressure caused by OTR. On the other hand, previous findings that bispyridinium oximes (TMB-4 Cl_2 and others) could abolish cardiovascular changes, including hypertension, in rats poisoned by certain organophosphorus compounds, was suggested as direct antiacetylcholine action of oximes (6, 9, 10, 12, 13, 16). The diversity in TMB-4 Cl_2 actions found in our experiments and those described in poisoning by anti-ChE agents, could probably be explained by different mechanisms responsable for the hypertension in rat induced by OTR or anti-ChE agents, respectively.

In opposite to TMB-4 Cl_2, F-oxime lowered the arterial blood pressure rised by OTR. Since both oximes are quaternary ammonium compounds, it is expected that the rate of their penetration into the central nervous system is very similar. However, in relation to their peripheral action on the cardiovascular changes caused by OTR, both oximes were equally effective.

The greater effectiveness of F-oxime in relation to TMB-4 Cl_2 suggests that the former substance has some additional anticholinergic (probably atropine-like) actions, independently of whether these effects are directed to the centre or periphery of the nervous system (ganglia, etc.). This point of view is supported by the finding that an oxime very similar in structure to F-oxime (POMP-4) was, concerning ganglion-blocking activity, twice as effective as TMB-4 Cl_2 (13).

Unfortunately, our preliminary results are insufficient to furnisch a more complete pharmacological analysis of TMB-4 Cl_2 and F-oxime in relation to pharmacodynamic effects of OTR.

SUMMARY

The administration of OTR (0.05 — 0.1 mg/kg intravenously) to anaesthetized rats resulted in an immidiate, transient fall in arterial blood pressure, which after 5 to 10 sec was followed by an increase of arterial blood pressure. According to the dose used, an increased arterial blood pressure lasted from 25 to 30 min. The fall of arterial blood pressure was invariably accompained by pronounced bradycardia, and by the reduction in the height of the P and T-wave.

The oxime TMB-4 Cl_2 was ineffective in preventing or abolishing the changes of arterial blood pressure caused by OTR. F-oxime, was relatively effective in counteracting the changes in arterial blood pressure induced by OTR. Both oximes, given before OTR, lowered the intensity of bradycardia and abolished ECG disturbances.

Atropine methylnitrate, given before OTR, completely prevented hypotension, but was unable to prevent or abolish the hypertensive action of OTR. Atropin sulphate, completely prevented or abolished changes in arterial blood pressure caused by OTR. Both, atropine methylnitrate and atropine sulphate effectively prevented bradycardia and the other ECG changes produced by OTR.

B. BOŠKOVIĆ, N. ROSIĆ I V. VOJVODIĆ

NEKA FARMAKOLOŠKA DJELOVANJA OKSIMA I HOLINOLITIKA NA KARDIOVASKULARNE EFEKTE IZAZVANE POMOĆU OKSOTREMORINA NA ANESTETIZIRANIM ŠTAKORIMA

KRATAK SADRŽAJ

Administracija OTR (0,05 — 0,1 mg/kg i. v.) na anesteziranim štakorima je prouzrokovala neposredan, tranzitorni pad arterijskog krvnog pritiska, iza čega je, poslije 5 do 10 sec., slijedio njegov porast. Zavisno od upotrijebljene doze, povišeni arterijski krvni pritisak je trajao od 25 do 30 min. Pad arterijskog krvnog pritiska je u svim slučajevima bio praćen izraženom bradikardijom i smanjenjem visine P- i T-talasa.

Oksim TMB-4 Cl_2 nije mogao da spriječi promjene arterijskog krvnog pritiska prouzrokovane sa OTR. F-oksim je imao nekog efekta u ovom smislu. Ako se oba oksima daju prije OTR smanjuju intenzitet bradikardije i sprečavaju poremećaje u ECG.

Atropin metilnitrat, ako se dâ prije OTR, sprečava pojavu hipotenzije, ali nije u stanju da suzbije njegovo hipertenzivno djelovanje. Atropin sulfat je potpuno spriječio promjene arterijskogg krvnog pritiska izazvanog sa OTR. Oba atropina, metilnitrat i sulfat, spriječili su nastajanje bradikardije i druge ECG promjene izazvane sa OTR.

REFERENCES

1. Cho, A. K., Haslett, W. L. and Jenden, D. J.: The peripheral actions of oxotremorine, a metabolite of tremorine. J. Pharmacol. 138: 249 — 257, 1962.

2. Condon, N. E.: A modification of the conventional mercury manometer for blood pressure recordings. Br. J. Pharmac. 6: 19 — 20, 1951.

3. Cox, B. and Potkonjak, D.: The relationship between tremor and change in brain acetylcholine concentration produced by injection of tremorine or oxotremorine in the rat. Br. J. Pharmac. **35:** 295 — 303, 1969.

4. Dirnhuber, P., Cullumbine, H.: The effect of anticholinesterase agents on the rat's blood pressure. Br. J. Pharmac. **10:** 12 — 15, 1955.

5. Goodman, L. S. and Gilman, A.: The Pharmacological Basis of Therapeutics. The Macmillan Company, New York, 1966.

6. Holmstedt, B.: Pharmacology of organophosphorus cholinesterase inhibitors. Pharmacol. Rev. **11:** 567 — 688, 1959.

7. Holmstedt, B.: Mobilization of acetylcholine by cholinergic agents. N. Y. Acad. Sci. **144:** 433 — 458, 1967.

8. Jenden, D. J.: Testing of drugs for therapeutic potential in Parkinson's disease, in »Selected Pharmacological Testing Methods« (A. Burger Ed.) Marcel Dekker, Inc., New York, 1968.

9. Koelle, G. B.: »Handbuch der Experimentellen Pharmakologie«, Cholinesterases and Anticholinesterase Agents. Berlin — Göttingen — Heidelberg, Springer Verlag, 1963.

10. Lindgren, P. and Sundwall, A.: Parasympatholytic effects of TMB-4 /1,l'-trimethylenbis/ 4-formylpyridinium bromide /-dioxime/ and some related oximes in the cat. Acta Pharmacol. (Kbh.) **17:** 69 — 83, 1960.

11. Medaković, M. and Varagić, V.: The effect of eserine and neostigmine on the blood pressure of conscious rats. Br. J. Pharmac. **12:** 24 — 27, 1957.

12. Milošević, M. P.: The effect of oxime on the hypertensive action of paraoxon and physostigmine in nonanaesthetized rats. Med. Pharmacol. Exp. **16:** 6 — 10, 1967.

13. Milošević, M. P., Terzić, M. und Simić, D.: Ganglionäre Wirkungen einiger oxime. Naturwisch. **55:** 134 — 135, 1968.

14. Varagić, V.: The action of eserine on the blood pressure of the rat. Br. J. Pharmac. **10:** 349 — 353, 1955.

15. Varagić, V. and Krstić, M.: Adrenergic activation by anticholinesterases. Pharmacol. Rev. **18:** 799 — 800, 1966.

16. Vojvodić, V. and Milošević, M.: Some pharmacological actions of oximes and atropine on the cardiovascular effects produced by pinacolyl methylphosphonophluoridate (soman) in rats. Iugoslav. Physiol. Pharmacol. Acta **7:** 439 — 446, 1971.