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

N. ROSIĆ, B. BOŠKOVIĆ AND V. VOJVODIĆ

DEPRESSION OF ACTIVE AVOIDANCE BEHAVIOR IN RATS BY SMALL DOSES OF OXOTREMORINE

Chalmer and Erickson (2) have demonstrated that subtremorogenic doses of tremorine produced a blockade of avoidance responding, both in Warner shuttle-boxes and in Skinner-boxes (Sidman avoidance). This blockade of avoidance responses (AA responses) could be prevented by atropine, but not by methantheline, a quaternary anticholinergic drug. These experiments, as well as many others (7, 1), confirmed a cholinergic nature of avoidance behavior and supported the hypothesis given by Carlton (1), that cholinergic system in brain is involved in control of animal behavior.

As concerns cholinesterase reactivators the evidence available to date indicates that certain compounds can cross blood-brain barrier, and counteract at least in the part the central effects of some anticholinesterase inhibitors (3, 5, 6, 8).

Present paper deals with the effects of oxotremorine (OTR) on AA behavior in rats. It was assumed that OTR, as active metabolite of tremorine, would also produce a blockade of AA responses. The efforts were made to find out a minimal dose of OTR, which will provoke blockade of AA responses in well trained rats (Experiment 1). In experiment 2, the interaction between TMB-4, F-oxime and OTR were studied.

METHOD

Subjects. Adult male rats of Wistar-derived strain were used.

Apparatus. The apparatus consisted of series of automatically operated shuttle-boxes (commercial product of Ugo Basile — Milano). The source of conditioned signal (CS) was light mounted on the centre of ceiling. The stimulus lacked directional properties.

AA pretraining. The rats were pretrained in sessions, each consisting of 50 trials at 30-second intervals. The interval between sessions was 24 hours. The other conditions of test were: CS-US (unconditioned stimulus) = 7 seconds. CS precedes US for 3 seconds. US = 1.5 mA scrambled footschook. CS terminated by avoidance response; an escape response

terminated both, CS and US. If animal does not cross from one to another part of shuttle-box during the presentation of CS-US, both stimula terminated automatically. Such training was continued until the animals reached a stable performance with 40 or more AA responses per session.

Drug treatment. OTR in water solution was injected subcutaneously, while all other tested drugs were given intraperitoneal. Total volume of each injection was 0.1 ml/100 gr. of body weight.

In all experiments behavioral tests without treatment were carried out in the days before and after treatment sessions.

RESULTS

Experiment 1

In these series of experiments the dose response relationship and time course of OTR effects on AA behavior were investigated. All experiments were carried out with groups of well trained animals assigned at random to either dose of OTR, or to a time of testing after administration of drug. Doses of 0.025, 0.05 and 0.075 mg/kg of OTR were used, respectively. Fifteen minutes after single injection of OTR, all groups of rats were tested in shuttle-boxes. The results of these experiments are shown in Fig. 1.

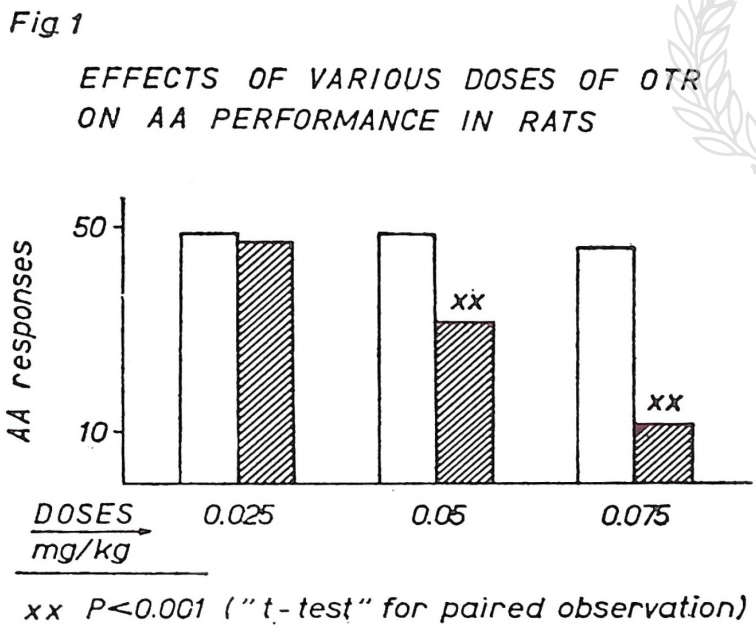


Fig. 1

Effects of various doses of OTR on AA performance in rats. All animals were tested 15 minutes after OTR administration. Columns refer to mean numebrs of AA responses given before OTR treatment (white columns) and after OTR injection (shaded columns).

The subcutaneous injection of 0.05 and 0.075 mg/kg of OTR provoked marked depression of AA responses in rats, while the dose of 0.025 mg/kg failed to show any effect. The depressant effect on learned behaviour was shown, both by loss of AA responses and by return to an escape pattern, without motor incapacitation of treated rats. The symptoms of OTR intoxication (tremor, salivation, etc) were negligible.

The time course of OTR depressant effects was studied in rats treated with 0.075 mg/kg. Immediately after drug administration, animals were *continously* tested in shuttle-boxes until a full recovery of AA responses were recorded.

As it is shown on Fig. 2, the depression of AA responses occures 5 minutes after drug administration, reaching a maximum between 15 and 20 minutes. After this time, slow, but progressive recovery of

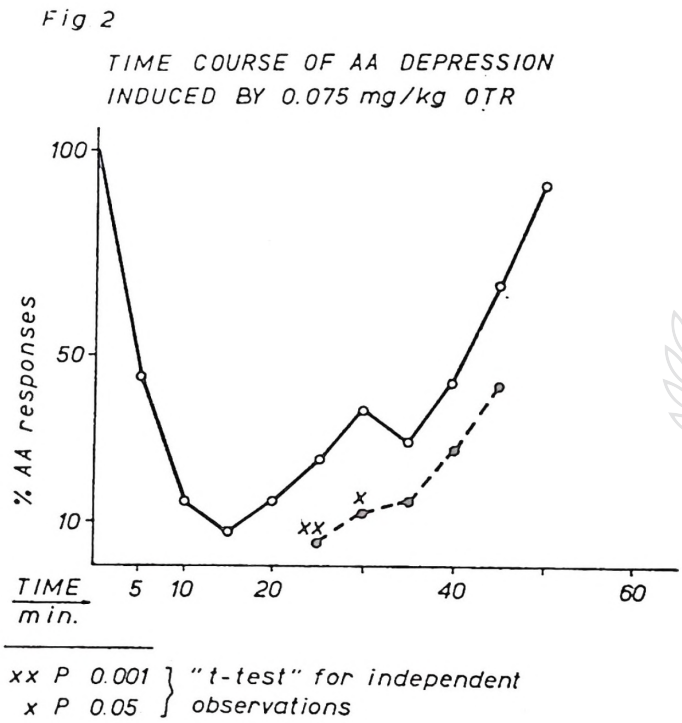


Fig. 2

Time course of AA depression induced by OTR (0.075 mg/kg). The curves show average percentage of given AA responses in blocks of 5 minutes of performance. Upper curve=performance of rats which have been tested continously immediately after OTR injection. Lower curve = performance of animals which have been tested 20 minutes after OTR injection.

AA responses was registrated. The number of AA responses reached the normal values about one hour of testing. In order to exclude the influence of relearning factor during the continous testing, a separate group of trained animals were injected with same dose of OTR and

tested 20 minutes later. In this group of rats a more marked depression was recorded (lower curve on Fig. 2) comparing with »continuously« tested group of animals. Mathematical analysis of blocks of AA responses (5 minutes performance per one block), has shown significant differences between means of AA responses in two experimental groups. However, this difference was significant only in initial phase of performance. This means that relearning factor could not be avoided in such design of experiments.

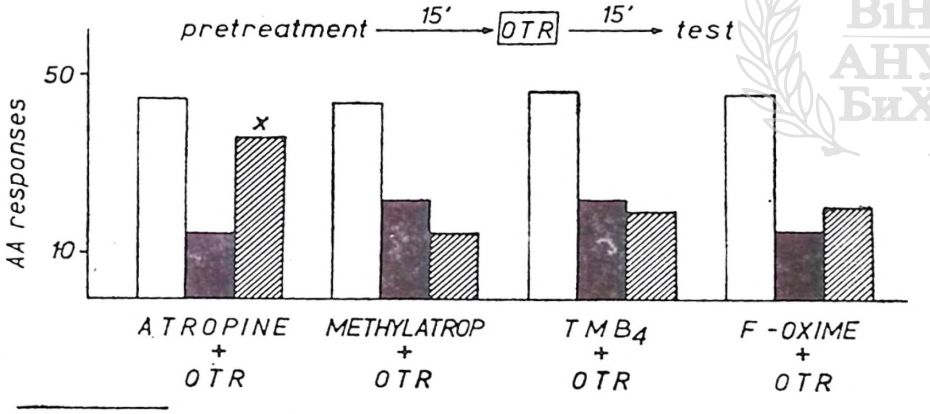
Experiment 2

Experiment 2 deals with the effects of anticholinergic drugs and cholinesterase reactivators on depression of AA behavior induced by 0.075 mg/kg of OTR. The following tested drugs were used: Atropine sulphate (5.0 mg/kg), atropine methyl nitrate (3 mg/kg), N, N'-trimethylenebis (pyridinium-4-aldoxime) dichloride (TMB-4) - 25 mg/kg and l-phenacyloxime-quinolinium chloride (F-oxime) in 12.5 mg/kg.

Experiments were carried out with groups of trained animals assigned at random to drug which has been used in experiments. Effects of tested drugs were studied with cross over experiments. All animals

Fig 3

EFFECTS OF ATROPINE, METHYLATROPINE, TMB4 AND F-OXIME ON DEPRESSION OF AA INDUCED BY OTR



x P<0.001 comparing with results of placebo+OTR experiments

Fig. 3

Effects of atropine, methylatropine, TMB-4 and F-oxime on depression of AA behavior induced by 0.075 mg/kg of OTR. Cross-over experiments. Schedule of test: pretreatment $\overset{15'}{\longrightarrow}$ *OTR* $\overset{15'}{\longrightarrow}$ *test. The columns refer to average numbers of AA responses given:*
— in control test (white columns)
— after placebo+OTR (black columns)
— after pretreatment with tested drugs (shaded columns).

in each group were tested twice. In the first experiment, one half of animals in each group were treated with placebo and OTR, and other half with one of tested drug and OTR. One week later, in second test, two conditions of drugs treatment were exchanged. The results of these experiments have been analyzed by means of »t-test« for paired observations, since each animal contributed scores to each of the two drug--treatment conditions. Animals were pretreated with placebo or with tested drugs 15 minutes before OTR administration, and 15 minutes later, they have been tested in shuttle-boxes. It has to be mentioned that all animals showing less then 30% loss of AA responses during placebo+OTR treatment-were discarded from mathematical analysis, since the conditions of experiments required sufficient amount of AA depression induced by OTR alone.

Results of these experiments are shown in Fig. 3.

Results of experiments show that all animals treated with placebo + OTR exerted behavioral depression amounted to about 60% of the initial values.

When animals were pretreated with atropine, very low degree of AA depression was recorded. These animals performed AA behavior practically with the same rate as it was recorded in control tests.

In all other groups of pretreated animals the degree of AA depression was about the same as it was recorded when they have been treated with placebo + OTR injections.

DISCUSSION

As expected, OTR, like other cholinergic drugs, caused depression of AA behavior in rats. Atropine, but not methylatropine, blocked depressant effects of OTR. Such results indicated cholinergic nature of neurophysiological machanisms underlying this pattern of AA behavior. From behavioral point of view, depressant effects of OTR are in accordance with Carlton's hypothesis (1), which postulated the role of cholinergic brain mechanisms in the control of animal behavior. Namely, stimulation of cholinergic system after administration of OTR, consequently reinforced those psychophysiological mechanisms which are responsible for inhibiting effects in animal behavior.

Absence of antagonism between oximes and OTR does not exclude the evidence of weak anticholinergic action of these drugs. There are many other factors which have to be investigated in order to detect anticholinergic actions of oximes in behavioral studies. Some of these factors are: lower sensitivity of AA behavior, necessity of large scale experimentation on dose levels and timing using different oximes, etc.

Finally, observed effects of OTR were obtained by using rather small dose range. It would be interesting, from pharmacological point of view, to consider a possible mechanism of above mentioned effects. Holmstedt (4) reported that doses of 0.5 mg/kg and higher, must be administered to rats in order to obtain evident rise of Ach in brain.

Accordingly, there is small probability that depressant effects of OTR on AA behavior, obtained in these experiments, could be ascribed to the action of OTR by mobilizing Ach.

CONCLUSIONS

The effects of subtremorogenic doses (0.025, 0.05 and 0.075 mg/kg) of OTR on active avoidance behavior in rats were investigated. Except dose of 0.025 mg/kg, the other doses produced a marked depression of active avoidance behavior in rats. Depression occured early after administration of OTR, reaching the maximum between 15 and 20 minutes. The effects dissappeared 50 minutes after injection of OTR.

Depressant effects of OTR could be prevented by atropine, but not by methylatropine, TMB-4 and F-oxime, respectively.

N. ROSIĆ, B. BOŠKOVIĆ I V. VOJVODIĆ

DEPRESIJA »PONAŠANJA IZBJEGAVANJA« KOD ŠTAKORA SA NISKIM DOZAMA OKSOTREMORINA

KRATAK SADRŽAJ

Ispitivani su kod štakora efekti suptremorogenih doza (0.025, 0.05 i 0.075 mg/kg) OTR na aktivno »ponašanje izbjegavanja» (avoidance behavior).

Osim doze 0.025 mg/kg, druge doze su izazivale izrazitu depresiju aktivnog »ponašanja izbjegavanja« kod štakora.

Depresija se javljala ubrzo poslije davanja OTR, postižući maksimum između 15 i 20 minuta. Efekti iščezavaju 50 minuta poslije injekcije OTR. Depresivni efekti OTR mogu biti spriječeni atropinom, ali ne metilatropinom, TMB-4, odnosno F-oximom.

REFERENCES

1. Carlton, P. L.: Cholinergic mechanisms in the control of behavior. In D. H. Efron, J. O. Cole, J. Levine and J. R. Wittenborn (Eds.): Psychopharmacology, a Review of Progress 1957—1967. Proc. 6th Annual Meeting of the American College of Neuro-Psycho-Pharmacology, San Juan (Puerto Rico) 1967, pp. 125—135. Washington D. C.: Superintendent of Documents, U. S. Goverment Printing Office.
2. Chalmers, R. K. and Erickson, C. K.: Central cholinergic blockade of the conditioned avoidance responses in rats. Psychopharmacologia (Berlin) 5: 31—41, 1964.

3. Firemark, H., Barlow, C. F. and Roth, L. J.: The penetration of PAM-Cl^{14} into brain and the effect of cholinesterase inhibitors on its transport. J. Pharmacol. 145: 252—257, 1964.

4. Holmstedt, B.: Mobilization of Acetylcholine by Cholinergic Agents. Ann. N. Y. Acad. Sci. 144, 433—458, 1967.

5. Longo, V., Nachmansohn, D. and Bovet, D.: Aspect electroencephalografiques de l'antagonisme entre le iodmethylate de 2-pyridine aldoxime (PAM) et le methyl-fluoro-phosphate d'isopropyle (Sarin). Arch. int. Pharmacodyn. 123: 282—290, 1960.

6. Milošević, M. P. and Anđelković, D.: Reactivation of Paraoxon-inactivated cholinesterase in the rat cerebral cortex by pralidoxime chloride. Nature 210: 206, 1966.

7. Pfeiffer, C. C. and Jenney, E. H.: The inhibition of the conditioned response and the counteraction of schizophrenia by muscarinic stimulation of the brain. Ann. N. Y. Acad. Sci. 66: 653—764, 1957.

8. Rosić, N.: Partial antagonism by Cholinesterase Reactivators of the Effects of Organophosphate Compounds on Shuttle-Box Avoidance. Arch. int. Pharmacodyn. 183: 139—147, 1970.