



Baština Akademije nauka i umjetnosti Bosne i Hercegovine

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

Stern, Pavao

1972

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Preuzeto s Baštine Akademije nauka i umjetnosti Bosne i Hercegovine

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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 STERN,
redovni član Akademije nauka i umjetnosti
Bosne i Hercegovine



SARAJEVO
1972

G. M. EVERETT

CHOLINERGIC AND BIOGENIC AMINE SYSTEMS IN THE ORGANIZATION OF MOTOR ACTIVITY

It is with deep regret that I cannot attend the symposium on Experimental Tremor and we wish it all success.

Our interest in this field goes back to our discovery of Tremorine in 1955. Since that time the number of papers in which this drug and its metabolite oxotremorine have been used as tools in Neuropharmacology has grown to a literature of hundreds of studies. We among others have long proposed the idea that the normal function of the motor system is dependent on a balance of cholinergic and biogenic amine systems. Tremorine and oxotremorine imbalance these systems by causing marked increases in acetylcholine (Holsted) and by causing decreases in either norepinephrine or dopamine (Everett, Friedman). Further, Gessa et al have shown oxotremorine causes a compensatory increase in dopamine turnover in the caudate. In our most recent studies we have shown that the tremor, rigidity and decreases in motor activity produced by oxotremorine (0.5 mg/kg i. p.) are antagonized by L-DOPA in doses of 200 to 400 mg/kg i. p. Likewise methamphetamine also antagonizes these motor deficits as does apomorphine. These findings support the thesis of rebalancing neuro-modulator system by increasing the levels of dopamine directly with L-DOPA or by giving dopaminemimetic drugs.

Thus tremorine and oxotremorine remain useful tools in preparing animal models on which to experiment and search for still more effective drugs against the various motor disorders in man.

Of equal importance in this field has been the use of rauwolfia alkaloids, which deplete the biogenic amines, resulting in a cholinergic dominant system and again producing a neuromuscular state resembling parkinsonism in animals and man. Our studies on the reversal of these abnormalities in mice and especially in monkeys by giving a MAOI and dl-DOPA (1957) and more recently with L-DOPA alone again supports the thesis of balanced systems involved in normal motor functions. Recently we have prepared the »Ultimate Parkinsonian Mouse«, or »Double Parkinsonian Mouse« if you prefer. The mice are first given a dose of 100 mg/kg deserpidine i. p. and four hours later, when full symptoms are present, a dose of oxotremorine (0.05 mg/kg i. p.) is given. These mice show decreased motor activity, tremor, abnormal posture

and ptosis. In these mice atropine only blocks tremor but not the other signs. However, L-DOPA is highly effective as its methamphetamine in reversing or decreasing these symptoms. Apomorphine (in high doses of 25 and 50 mg/kg i. p.) is surprisingly ineffective in this preparation. This model is also worthy of further study.

We should also point out the many unexplored compounds which will produce sustained tremor without signs of cholinergic stimulation. These remain for future experimentation. Finally, we should consider the good fortune we have had to find drugs which affect some of the basic biochemical modulators of the brain and thus offer us much closer models of neurological diseases than one might rightly have hoped for.

G. M. EVERETT

HOLINERGIČNI I BIOGENI AMINI U POSTANKU MOTORNE AKTIVNOSTI

KRATAK SADRŽAJ

Autor je 1955. godine otkrio tremorin. To je dalo povoda za nastanak jednog ogromnog broja radova i omogućilo je bolji studij statičkog tremora parkinsonskog tipa. Tremorin i oxotremorin uzrokuju porast acetilholina i pad dopamina i norepinefrina u mozgu. Kompenzatorno dolazi do porasta metabolizma dopamina u caudatusu. Sve se to može antagonizirati pomoću L-DOPE. To upućuje na zaključak da je tremorin idealna supstanca za izazivanje Parkinsonove bolesti na životinjama. Autor upozorava i važnost Rauwolfija-alkaloida za ovu vrstu ispitivanja, kao i inhibitora mono-amino-oksidade, kao i na uticaj amfetamina na inhibiciju raznih simptoma uzrokovanih tremorinom ili oxotremorinom.