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ODJELJENJE MEDICINSKIH NAUKA
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MEĐUNARODNI SIMPOZIJUM

O EKSPERIMENTALNOM TREMORU

1 — 3. APRIL 1971. GODINE

Urednik
PAVEL ŠTERN,
redovni član Akademije nauka i umjetnosti
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P. STERN

METHODS FOR CAUSING DISEASES OF THE EXTRAPYRAMIDAL SYSTEM

Six years ago in a paper at the symposium »Methods in drug evaluation«, I presented in a short form, methods of examining antitremogenic substances (AT) (51). Even that analysis showed that there are good possibilities for different forms of tremor (T), rest-tremor (RT), parkinsonic type, non-parkinsonic type and intentional tremor (IT) caused by different drugs, to occur. Besides this we draw attention to spontaneous tremor in animals as well as to the possibility of examination of AT in man. In that paper I was limited to examination of AT, but not to the arrest of symptoms connected with diseases of the striatum, like rigor, and other forms of akinesis, e. g. hyperkinesia of a choriatic character or other kind. As we have developed new methods in the meantime e. g. causing IT Wilson's type (56, 57, 31), and chorea minor (55) and as in our Institute we work intensily on the problem of models of rigor and certain metabolic processes connected with rigor (43, 40, 60), we think that it would be necessary to return again to this theme and to extend it to specific areas. Besides this many other authors have in the meantime published new methods for causing tremor or akinesis. In this paper we shall take into consideration the central causes of T but not to secondary ones e. g. shaking due to the cold etc.

We make a division based on clinical criteria. The methods of causing ST parkinsonic type and ST non-parkinsonic type i. e. those that do not react to known anti-parkinsonics, are shown. Only the methods of causing ST parkinsonic type where the action of oxotremorine (OT) is increased are shown. In this paper in contrast to the one published six years ago (51), we have also presented methods for causing parkinsonic and non-parkinsonic type rigor as well as of forced movements which are similar to chorea and therefore also a disease of the striatium. According to our experiments up to now it seems that the most suitable criteria for parkinsonic type rigor is if it reacts to gamma-hydroxidebutyrate (43, 60). With this we could limit the kind of rigor to parkinsonic or non-parkinsonic type.

We will also present methods for causing IT Wilson's type e. g. those which do not react to penicillamine or alfa-methyl dopa and non-Wilson's type (56).

As is seen from the table it is possible to cause forced movements similar to choreatic.

Besides this as in the past paper, the spontaneous tremors which appear in experimental animals and some experimental surgical methods for causing T, are enumerated. Accordingly all the characteristic diseases of the striatum as we find them in human pathology are included in this paper.

TABLES

As we see the possibility of causing tremor or akinesis by pharmacological methods is very large, and so it is necessary to know that the drugs were given i. p., i. m., i. v., or directly into the CNS in cistern or in a certain region, using steriotactic methods. This can be seen from the added tables with reference to different laboratory animals: mouse, rat, rabbit, cat, dog, chicken and monkey.

In experimental medicine it is important to mention the methods caused experimental tremor or rigor in laboratory animals spontaneously or by means of infection. As we have already seen described in dogs, cats, mice and chickens.

The attempts of Rinaldi and Himwich (41) who tried to examine AC in animals by means of EEG, are interesting.

In connection with our presentation it is necessary to mention the collective paper of Jenden (29) which has many useful suggestions as does Friedmane (22).

Finally it is necessary to mention some neuro-surgical methods of causing tremor or rigor but it is immediatly necessary to say that opinions for the success of such methods are not of one accord. Jenden (29) explicittly emphasises in his review article that such methods do not always produce the same results. We should like however, to mention the often used method of Vernier and Unna with monkeys, as also the reference article of Aronson et al (4). The surgical method of Carpenter et al. (13) is interesting, where the nuclei of the cerebelum are damaged, and rigor caused by damaging the back hypothalmus.

CONCLUSION

This survey shows that today it is possible to imitate many neurological diseases of the striatum with pharmacological methods. Models like this can surely be used for the discovery of new drugs. For a brilliant example for the investigation of new therapeutic agents on models in laboratory animals we suggest the therapy of Wilson's disease with alfa-methyl dopa, or chorea with reserpine which we found earlier only on models that we alone constructed.

Table I

EXPERIMENTAL METHODS FOR PRODUCING DISEASES OF STRIATUM

I. Pharmacological methods to produce tremor < parenteral / intracranial

II. Pharmacological methods to produce rigor < parenteral / intracranial

III. Pharmacological methods to produce choreatic movements

IV. Spontaneus tremor

V. Surgical methods

VI. Experimentes on humans

Table II

TREMOROGENIC SUBSTANCES OF PARKINSONIC TYPE INJECTED PARENTERALLY

	Dosis mg/kg	Animals	References
Tremorine	5—30 i. p.	Mo, d, r, c, m, ch	21
Oxotremorine	0,1—1 i. p. i. v.	Mo, d, r, c, m, ch	14
Acedicline	25 s. c.	r, m	34
Acetylene-dicarbonic acid-dipyrrolidid	30—40 i. v.	r	15
Arecoline	20 i. p.	r, m.	28
Reserpine	10 i. v.	r, m.	63
Physostigmine	0,2 i. v.	r, m.	63
α-methyl dopa	100 i. p.	r, m.	58
Tetrabenizine	5—20 i. p.	c	12
Chlorpromazine	300 s. c. few days	c	30
p-methoxy-dopamine	100 i. p.	m	48
Chloreathylamine	75 i. p.	r	42
R S - 86	5 i. p.	m, r.	29

TREMOROGENIC SUBSTANCES OF PARKINSONIC TYPE WHICH INCREASE THE ACTIVITY OF OXOTREMORINE

Oxotremorine + $CuCl_2$	10 i. p.	r, m.	50
Oxotremorine + 5-HTP	100 i. p.	r, m.	50
Oxotremorine + CS_2	50 i. p.	r, m.	54
Oxotremorine + Chlorpromazine	5 i. p.	r, m.	50
Oxotremorine + Natriumazid	3 i. p.	r, m.	54

Table IV

TREMOROGENIC SUBSTANCES OF NON-PARKINSONIC TYPE WHICH CAUSE REST TREMOR

	Dosis mg/kg	Animals	References
Veratramine	10 i. p.	r, m.	46
LSD	1 i. p.	m	2
5-hydroxytryptophane	100—200 i. p.	m	7
Amino-triphenylpropane	30 i. p.	m	2
Nicotine	50 i. p.	rb	9
Cyclopium toxin	0,5 i. v.	r, m.	52
2-imino-3-(2', 6''-dichlorphenyl)-thiasolidine	10 i. p.	r, m.	3
Acrylamid	r 100 per os 2 x weacky c 40—50 i. v. 3—6 days	r, c.	23, 5, 32
Prenderol (2,2-diethyl, 1, 3-propanediol)	0,2 i. v.	r	6
Phencyclidine	10 i. p.	m	35
3, 4-dimethylphenethylamine (3, 4-DM)	40—60 i. p.	r	47
Ibogaine	10—20 s. c.	m	67
Adipiodone	2,0—2,5 i. v.	m	19
Harmine	15 i. p.	m	65
Harmiline	10—30 i. p.	r, m.	10
Hydralasine	40 i. p.	m	58
β, β' iminodipropionitrile	100 s. c. 3x	mo	23a

SUBSTANCES WHICH CAUSE NON-PARKINSONIC TYPE RIGOR

Ryanodine	0,150 i. p.	r	61

Table III

SUBSTANCES WHICH CAUSE OF REST TREMOR AFTER APLICATION INTO THE CNS

	Dosis mg/kg	Animals	References
Deferoxamine G. P.	10 γ	r	55
Carbachol G. P.	2—10 γ	r	43, 18, 16
3, 4-dimethoxyphenylethylamine St.	1—5 γ	r	33
5-HT N. N.	0,2—2 γ	r	24
5-HTP N. N.	0,2—2γ	r	24
Mescaline St.	1—5 γ	r	33
α, α″-dipyridyl N. N.	1—5γ	r	53a
Zinc-acetate i. c.	1—16γ	r, m.	8
Oxotremorine	2—4γ/m	r	40
Continuase infusion of ACH in G. P.	1γ/m	r	44
SUBSTANCES WHICH CAUSE PARKINSONIC TYPE RIGOR			
Trifluoperazine	10 i. p.	r	43, 60
Fluphenasine	10 i. p.	r	40
Perfenazine	5 i. p.	r	36
Reserpine	Mo 0,25 per os 3 x r 7,5 i. p.	Mo, r.	40, 37, 49
Bulbocapnine	7 i. p.	r. m.	66, 40
2, 4-dichlorophenoxyacetic (2, 4-D)	100 i. p.	r	11
Derivatives methoxyphenylethyl-amine (so called Ernst's subst.)	—	r, m.	20
p-methoxidopamine	100 i. p.	m	48
Centaurea repens L.	Food in 10—20 days	horse	64
MnO_2	200 s. c. 2 x in 40 days	Mo	38

Table V

SUBSTANCES WHICH CAUSE INTENTIONAL WILSON TYPE TREMOR WHEN GIVEN PARENTERALLY

	Dosis mg/kg	Animals	References
Diethylcysteamine	50 s. c.	r, m.	59
CCl_4	700 s. c.	m	56
Guanetidine	25—50 i. p.	m	17
Catapresan (rest tremor)	50 i. p.	m	31
SUBSTANCES WHICH CAUSE PARKINSONIC TYPE RIGOR WHEN GIVEN INTO CNS			
Carbachole (n. niger)	5—10 γ	r	43
Oxotremorine (n. niger)	5	r	43
/(4-(1-naphtylvinyl)-pyridine/HCl) (G. P.)	10 γ	r	53
SUBSTANCES WHICH CAUSE INTENTIONAL TREMOR OF NON-WILSON TYPE			
Thioacetamide	170 s. c.	r	56
SPONTANEOUS TREMOR IN LABORITARY ANIMALS			
The dog			1, 62
The cat			39
The mouse			45
The chicken			26
SUBSTANCES WHICH GIVE CHOREATIC-LIKE MOVEMENTS			
2, 2', 2''-tripyridine	0,25 i. p.	r, m.	55,25
3-acetylpyridine	100 i. p.	r, m.	27

Mo = monkey, c = cat, rb = rabit, d = dog, m = mouse, ch = chicken
N. N. = nucleus niger, St = striatum, G. P. = globus pallidus, i. c. = intra cranial.

P. ŠTERN

METODE ZA IZAZIVANJE BOLESTI EKSTRAPIRAMIDALNOG SISTEMA

KRATAK SADRŽAJ

Autor je pokazao da se mogu izazvati praktično sve tipične bolesti ekstrapiramidalnog sistema, kao što su Parkinsonova bolest, Wilsonova bolest, horeatički pokreti. Osim toga, opisane su i druge vrste tremora statičkog, ali ne parkinsonskog tipa, intencionog tremora, koji nije Wilsonovog tipa itd. Zatim su opisane metode izazivanja eksperimentalnog rigora. Nabrojane su i takve eksperimentalne manifestacije tremora koje reagiraju samo na inhibitore polisinaptičkih puteva ili samo na glicin. Skupljene su na jednom mjestu sve dosada poznate metode za izazivanje ekstrapiramidalnih oboljenja, i to na različitim životinjama, i upozoreno je koje od njih najviše se približuju po svojim biokemijskim osobinama sličnim bolestima u humanoj patologiji.

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DISCUSSION

Barbeau: Another explantation for guanethidine and catapressan action: it may be trough feedback information from peripheral nerve system. In the striatum we find a marked change in the turnover of dopamine to HVA, after small doses of guanethidine or catapressan. Thus, somehow, the striatum is informed of what is taking place at the periphery or even in the brain stem and reacts by modifying the dopamine content and thereafter changing the delicate balance between other important amines. This feedback control mechanism may be an important function of the striatum.

Štern: Thank you dr Barbeau for your interesting informations.

Cox: Please could you tell me more about the tremor produced by p-methoxidopamin with respect to 1) Time course of tremor, 2) Nature of tremor, 3) Is it antagonised by L-dopa, 4) Mode of action.

Štern: Tremor caused by methoxidopamin is a very good model because it simultaneously causes both tremor and rigor in mice and rats. In doun't know if it can be antagonised by L-DOPA. The mechanism of acting is explained by Ernst theory.

Vizi: I wonder hov can you explain the effect of guanethidine on inducing Wilson-type tremor. There is a great discussion in literature wheather guanethidine is capable of passing the blood-brain barrier. It has been found that guanethidine reduces the NR-content of the brain (Pfeifer, Vizi), however, by others it was not confirmed. Do you not think, that the effect of guanethidine on adrenergic system may play some role in causing this type of tremor. And what about catapressan? How does it work?

Štern: Catapressan as well as guanethidin passes the haemoencephalbarrier in lave amounts. Thus the increasa of Cu occurs in brain and liver. It is probable that the small doses wich do not generate tremor do not pass the barrier niether. These sorts of tremors resemble very much to Wilson tremor, because thay can be impeded by penicilamin. It is interesting that catapressan produces the clinical picture of a rest-tremor and yet it can be inhibited by penicilamin and not by atropin.

Schnieden: I wonder if you would like to give your views on how carbon tetrachlorid produces tremor and why penicillamine inhibits form of tremor?

Štern: CCl_4 probably produces tremor by demaging liver and brain which leads to gathering of Cu. Penicillamin acts by linking Cu to itself.

Bernard: 1) How long after an experimental virus infection in the chicken does tremor manifest itself? 2) Have specific lesions been found in the chicken brain after this type of virus infection?

Štern: The infection of chicken with that virus causes strong tremor which lasts 3 or 4 days when chicken day. Mephenesin doesn't prolong the life of infected chicken.

Bruggencate: I would like to ask two questions to Prof. Stern: 1) As to the chicken-tremor you described, I would like to know what kinde of virus has to be applied, and how it acts; e. g. does it cause degeneration in cerebellum or somewhere else? 2) Are the tremor types being not influenced by glycine?

Štern: 1) It is a virus which is applicated intracranially. I know neither mechanism of acting nor whether it damages cerebellum.

2) Many types do not react on glycin, but tremor developed by cyclopium toxin reacts well.

György: Do not you think that atropine methylbromide in high doses can penetrate the blood-brain barrier of the cat?

Štern: I agree with you.