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

G. TEN BRUGGENCATE AND E. WELLER

TUBOCURARINE INDUCED SHIVERING IN CATS: INFLUENCE OF SPINAL CORD LESIONS AND ANTIPARKINSONIAN DRUGS

1. SPINAL MOTOR SYSTEMS IN CURARE SHIVERING

FELDBERG and coworkers (7) first described a tremor state in cats resembling cold shivering, evoked by perfusion of the brain's third ventricle with a tubocurarine solution. Considering the divergent opinions existing on the mechanism of tremor, it seemed worth while to investigate this type of tremor with neurophysiological techniques. The first part of the analysis was carried out some years ago in collaboration with H. D. Henatsch (3, 4, 11, 12). For a better understanding of recent results the main changes in spinal motor systems accompanying curare shivering (CS) will be summarized briefly.

Fig. 1 demonstrates activity in α- and γ-motor systems during CS. A—C show the periodically occuring activity of motor units and muscle spindles during CS. In A and B (triceps surae unstretched) both Ia and II afferents are activated during tremor periods. On the other hand, in C (triceps surae stretched for 1 mm and 10 mm, resp.) the spindle discharges decrease in tremor bursts. In this state, obviously the shortening of motor fibres during the tremor period mainly determines the spindle discharges. Taken together, A and C suggest that the activity of both γ- and α-motoneurones is enhanced during periods of shivering. Coactivation of α- and γ-motor systems under curare is further illustrated in D — F. D shows stretch activated discharges of a single α-motoneurone superimposed on background impulses of γ-motoneurones in the control situation. In E, under curare perfusion, the stretch reflex discharge of α-motoneurones increased. In F, still under curare perfusion, flaxedil was injected to interrupt the γ-spindle loop. Stretch induced activity in α-motoneurones now is less than in E, but still higher than in D. The difference between recordings F and D is attributable to increased α-drive, the difference between E and F to increased γ-drive.

There are indications of a predominant spinal origin of the tremor oscillations in CS (11, 12). On the other hand, there seems to be no

pecemaker-like activity in γ-motoneurones, e. g. no γ-discharge locked to tremor oscillations (3, 12). A way out of this conflict could be a change in receptor sensitivity of muscle spindles induced via the dynamic or static part of the γ-system.

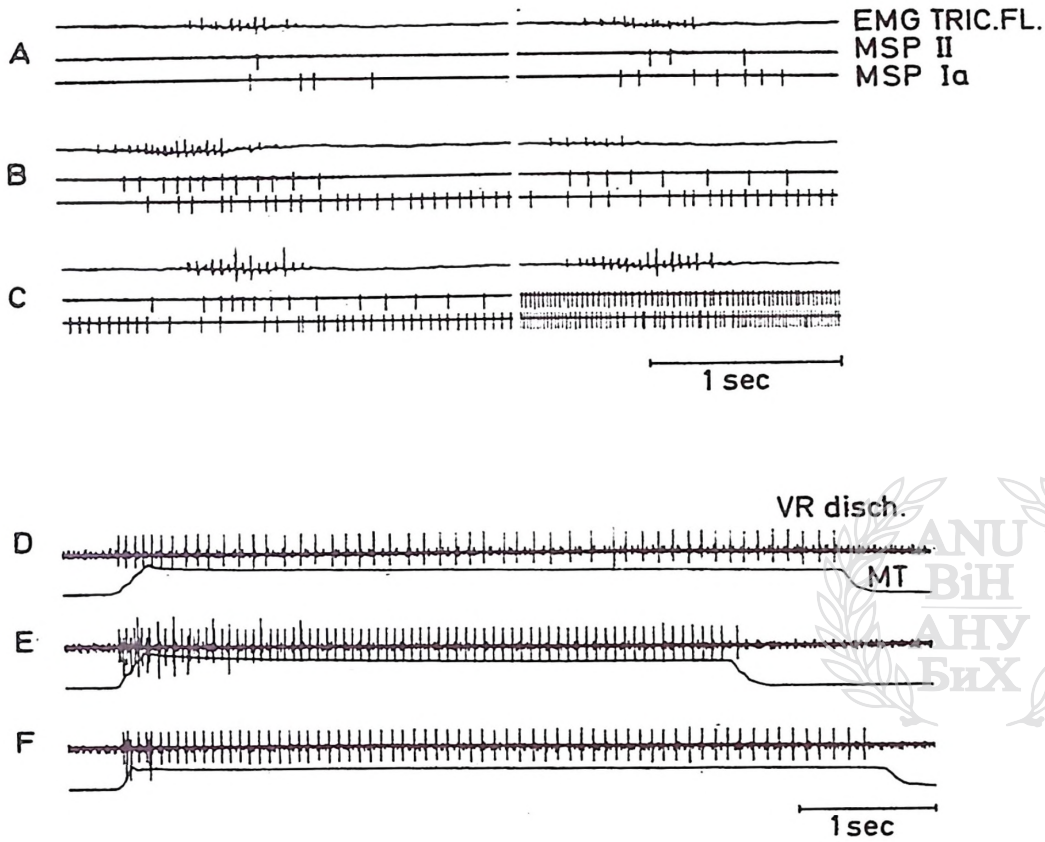

Fig. 1

Coactivation of α- and γ-systems during CS.

A—C: Records of EMG in forelimb extensor, and discharges of secondary and primary muscle spindle endings from triceps surae. Specimen taken during tremor periods and successively after the end of a previous stretch of triceps surae, with slack muscle (A, B) and stretched muscle (C, 1 mm on the left, 10 mm on the right).

D—F: Discharges of α- and γ-motoneurones recorded from a small ventral root filament (roots otherwise intact). D: Activation of a single α-motoneurone on muscle stretch before curare perfusion. E: Activation of several α-units during curare. F: Activity after interruption of the γ-loop (Flaxedil 20 mg/kg). Lower trace: muscle tension (MT) (length of muscle extension identical in D, E, and F).

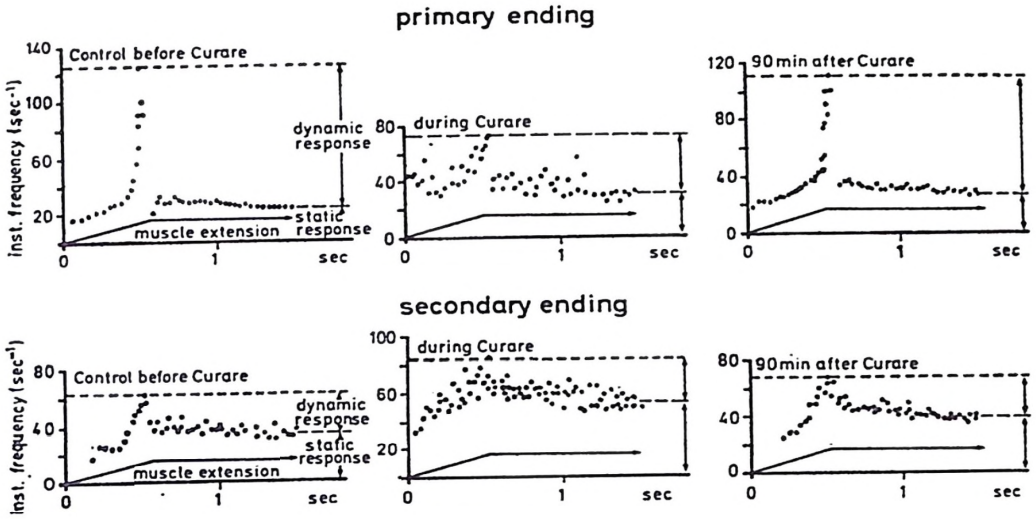

Fig. 2

Decrease of dynamic, and increase of static responses of muscle spindle endings during CS.

Plots of instantaneous frequency versus time for identical muscle extensions before, during, and after curare perfusion. Each dot represents a spike of a primary and secondary ending, respectively. The increase of the static response during curare is paralleled by an increase in the variability of discharge intervalls (scatter of dots). (After 2).

Fig. 2 shows the discharge patterns of a primary and a secondary ending simultaneously recorded before, during, and after perfusion. The insets show the afferents' discharge rate during muscle extension (indicated below). Each dot represents an action potential, its distance from the zeroaxis indicating the instantaneous discharge frequency. Obviously, the dynamic sensitivity of the primary ending decreases considerably whilst the static discharge rate during extension increases, particularly in case of the secondary ending. In terms of feedback control in the stretch reflex arch, decreased dynamic sensitivity and increased static sensitivity should lead to instability of the system (c. f. 16).

Thus, in our opinion curare perfusion evokes a steady, primarily arrhythmic, descending drive to spinal motoneurones. The influence impressed upon the fusimotor system leads to changes in receptor sensitivity which should at least contribute to the development of tremor oscillations at a spinal level.

2. EFFECTS OF SPINAL CORD LESIONS ON SPINAL MOTOR SYSTEMS DURING CS

It was our general experience that small circumscribed lesions, differently located in the spinal cord, did not entirely abolish CS below the level of the lesion in question. However, there was always a diminuation of CS in varying degrees. The relatively clearest effects were

observed with rather superficial lesions of the dorsolateral funiculus (DLF) which sometimes reduced shivering on the side contralateral to the lesions also.

Recording from ventral root filaments disclosed that shivering reduction caused by lesions in the DLF usually was accompanied by a reduction in the discharges of α-units. Fig. 3 shows an experiment with

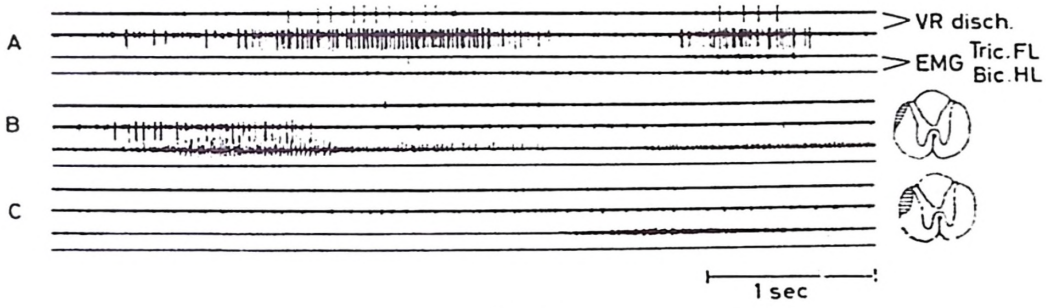

Fig. 3

Decrease of curare-induced discharges of α-units by lesions in the DLF. A: Background discharges of γ-units (small) and periodically occurring α-discharges during CS. EMG from forelimb and hindlimb muscles in the lower beams. B and C: Reduction of α-discharges and tremor in the hindlimb after lesions in the ipsilateral DLF, as indicated on the right. No significant change in γ-discharges. Increase of shivering EMG-discharges in the forelimb.

marked effects on CS. In A, during curare perfusion, shivering occurred periodically in fore- and hindlimb muscles, simultaneously with α- and γ-discharges. A superficial lesion in DLF (B) dramatically reduces electromyographic activity in the hindlimb muscle, parallel to a corresponding effect on discharges of α-units, while γ-impulses seem rather unchanged. The effects are somewhat accentuated in C with an enlarged lesion. Typically, after the lesion shivering intensity in the forelimb increased.

Discharge rates of γ-units, enhanced during curare perfusion were »normalized« only after hemisection of the cord. Recording from muscle spindle afferents gave results confirming this notion. Fig. 4 shows the response of a primary ending to muscle extension. During CS the dynamic response is reduced, the static enhanced (4B, cf. fig. 2), the discharges being more scattered than in the control. A lesion of the DLF only temporarily reduces the curare effects (C) the behavior of the receptor in D (9 min after lesion) being rather similar to B. A discharge pattern like the one in the control situation results only after extension of the lesion to include most of the VLF (E, F).

3. EFFECTS OF ANTIPARKINSON DRUGS.

CS seems a useful model to study changes of spinal motor functions occurring in a tremor-like state. However, the question remains, as to what extent this model is similar to clinically relevant tremor states. One point, which seemed worth being tested, is the effect of drugs used clinically to reduce parkinsonian tremor. Furthermore, we wanted to know if any eventual effect was due to a selective mechanism

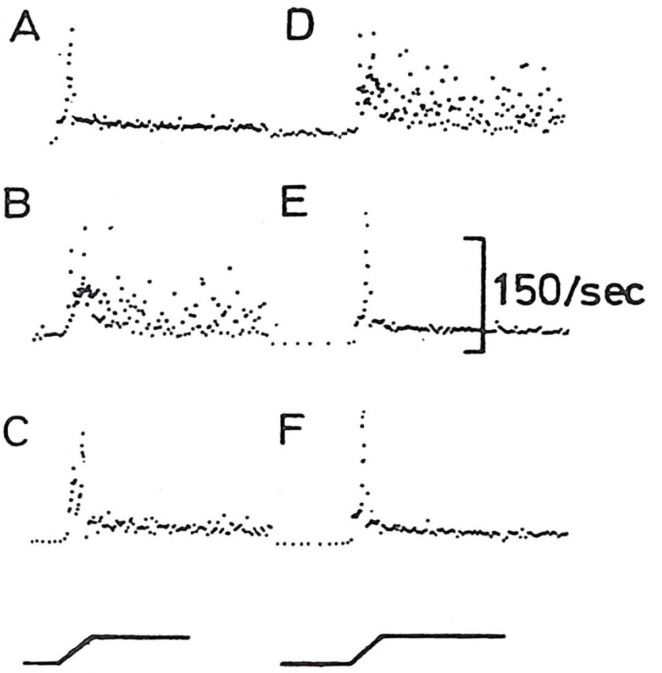

Fig. 4

Reversal of curare-induced changes in muscle spindle sensitivity by spinal cord lesions.

Plots of instantaneous frequencies of a primary ending versus time for identical muscle extensions, as in fig. 2. A: Control. B: Curare-induced decrease of dynamic and increase of static sensitivity. C: 1 min, D: 9 min after a DLF lesion as in fig. 3C. E, F: 1 min and 10 min after an additional lesion in VLF.

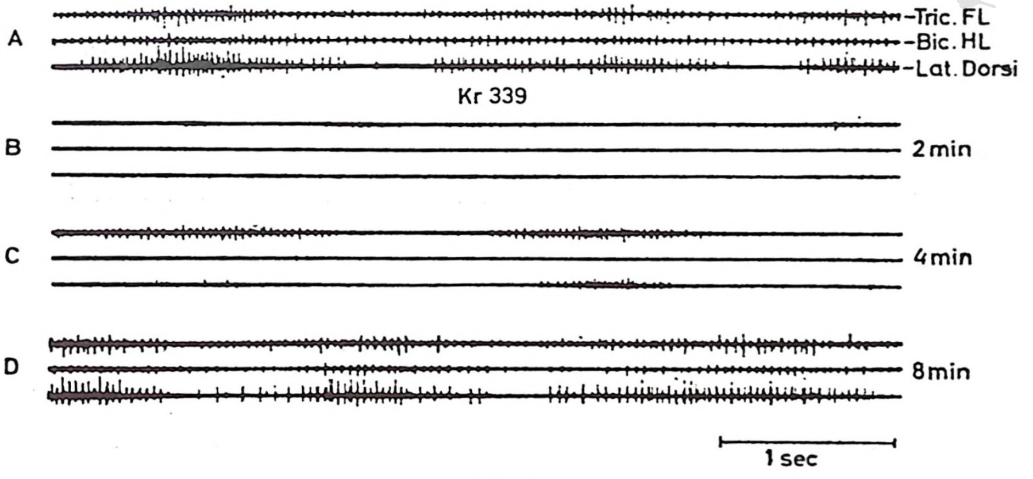

Fig. 5.

EMG records of curare-induced shivering, and its reduction by intravenous injection of an antitremor drug.

Recordings as indicated from forelimb triceps, hindlimb biceps and latissimus dorsi. (After 20).

or rather to an unspecific, general action. Fig. 5 illustrates the effect of Kr 339* on electromyographically recorded CS. Shivering was abolished by 1,6 mg/kg kr 339 for about 2 min and definitely reduced for 7 min. The behaviour of α- and γ-motoneurones was also investigated.

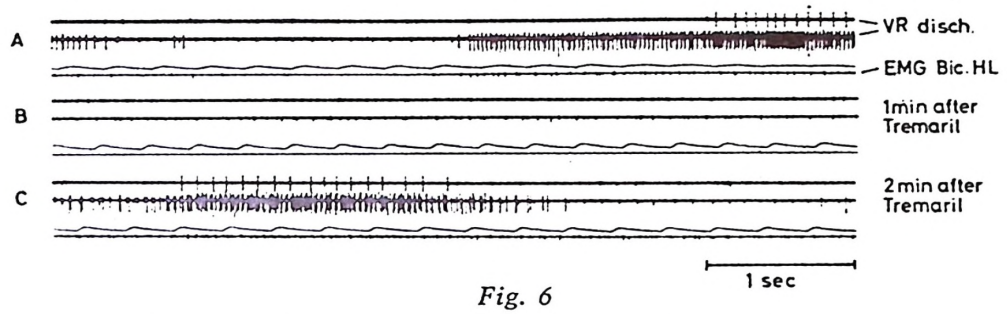

Fig. 6

Temporary reduction of curare-induced periodical α-discharges by an antitremor drug. (After 20).

Fig. 6 shows a reduction of α motoneurone discharges after a dose of tremaril* which abolished the shivering.

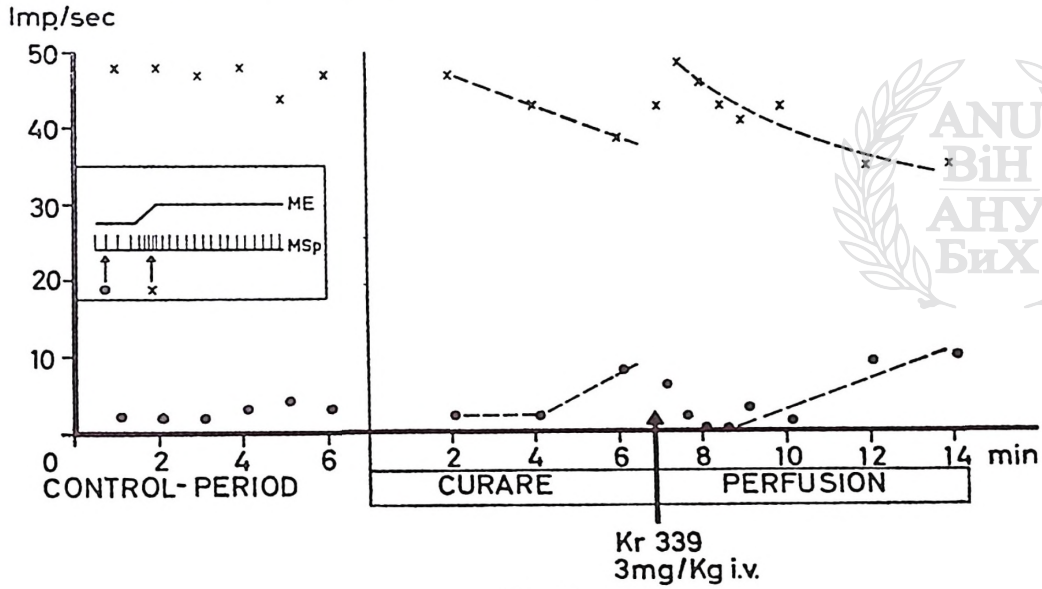

Fig. 7

Curare-induced changes in muscle spindle sensitivity, and the effect of an antitremor drug.
Plots of dynamic peak frequency (crosses) and spontaneous discharges (points) as indicated. Reduction of dynamics, increase of static sinsitivity during curare. Temporary reversal of these effects by injection of antitremor drug.

---

* 2-phenyl-biciclo-(2, 2, 1)-heptane-2-carbonic acid (γ-diethyl-aminopropyl) -ester, Knoll AG, Ludwigshafen/Rhein.

* 9-(N - methyl - 3 - piperidyl)-methyl-thioxanthen - hydrochloride, Wander GmbH, Frankfurt.

On the other hand, discharges of γ-motoneurones definitely are not reduced. In fact, temporary increases were seen in several experiments shortly after injection of the drug. If there was a reduction of γ-impulses (always less clear than the effect on impulses of α-motoneurones), it occurred at a later time after injection.

Fig. 7 graphically demonstrates the behavior of 1) spontaneous discharges (muscle unstretched) and 2) dynamic peak frequency of a primary muscle spindle ending. Curare perfusion lead to a decrease of dynamic peak frequency and an increase of the tonic background discharges. Injection of the antitremor drug temporarily reversed the curare-induced changes in muscle spindle impulse pattern.

4. DISCUSSION

Tubocurarine applied to the surroundings of the third ventricle leads to a shivering tremor which obviously is accompanied by a complex change in reactivity of spinal motor systems. Taking into consideration the striking similarity with cold shivering, it is of interest that B i r z i s and H e m i n g w a y (1) were able to record in descending »shivering pathways« only arrhythmic discharges, asynchronous with the shivering ascillations. We also failed so deffect a clear synchronization of discharges of α-motoneurones in paralyzed animals, whilst γ-discharges never showed any synchronization even in unparalyzed cats. Our conclusion is, therefore, that in CS the shivering rhythm originates at a spinal level, and that in CS proprioceptive contribution plays a dominating role. There is evidence which suggests that the first conclusion is also valid for cold shivering (8, 19). However, the importance of the proprioceptive contribution compared to the interneuronal contribution is probably less in cold shivering (8, 20), as well as in animals with locally cooled spinal cord (17).

With local cooling of the spinal cord, shivering can be produced even in chronically deafferented animals (17). This suggests that spinal interneurons, perhaps, together with changes of the motoneuronal membrane properties (18), are correlates of tremorgenesis in this case. However, as to the spinal mechanisms responsible for the origin of shivering, the experimental approach with local cooling within the vertebral channel seems hardly comparable to a pharmacological model acting on centrencephalic structures.

Our results with limited lesions within the spinal cord agree with the previous notion that there is a rather diffuse, general descending influence, acting on α- and γ-motor systems and even on presynaptic inhibition (5). Motor activity may depend on coactivation of α- and γ-motoneurones (α-γ-linkage, 9, 10); reduction of shivering amplitude by spinal cord lesions with a variety of localizations would then be understood as a threshold effect, reducing the final input to α-motoneurones (either running directly and/or via the γ-loop) below firing level.

The finding, that superficial lesions within the DLF often had a relatively great effect, has yet to be explained. Since neither acute

pyramidotomy nor chronic lesions of the red nuclei abolish CS (ten Bruggencate and Weller, in preparation), a contribution of reticulospinal systems or of ascending paths must be considered.

Our experiments with injection of antiparkinsonian drugs show that these drugs are to some extent also effective in CS, »normalizing« all motor symptoms induced by curare perfusion. Concerning the effect on α- and γ-discharges, the reduction of activity of α- and γ-units showed the reversed order to the activity increase during curare perfusion: curare tends to activate γ-motoneurones earlier than α-units; whereas antitremor drugs depress α-units first, high amplitude units more strongly and earlier than low amplitude α-units or even γ-units. This fact suggests that both curare and antitremor drugs influence spinal motoneurones in a rather unspecific manner, seemingly largely dependent on cell size and, therefore, probably on general properties of cell membranes (6, 13). Again, this supports the view that curare sets free an elementary system which activates mechanisms inherent to the spinal cord. Biologically, the ideas expressed by v. Holst (quoted in 14) and Jung (14) still hold, i. e. that shivering tremor might be the sign of phylogenetically old mechanisms related to flapper movements.

G. TEN BRUGGENCATE

EFEKTI LEZIJA KIČMENOG STUBA I ANTIPARKINSONSKIH LIJEKOVA NA TREMOR MAČAKA IZAZVAN KURAREOM

KRATAK SADRŽAJ

Već ranije je analiziran tremor izazvan tubokurarinskom perfuzijom moždanih ventrikula s obzirom na kičmene alfa i gama motorne sisteme.

Glavni rezultati su bili: a) povećanje rasterećenja fuzimotornih neurona tokom kurare perfuzije, bez ikakvog znaka uspostavljanja ritmičke aktivnosti; b) ritmička rasterećenja alfa-jedinica, uništenih interupcijom vretenastih spojnica, koja indiciraju da ritam tremora potiče iz nivoa kičme; c) promjene osjetljivosti vretenastih završetaka mišića koje mogu biti važne za pretlıodne zaključke.

Izneseni eksperimenti opisuju efekte različito lociranih lezija kičmenog stuba na ponašanje alfa i gama motornih sistema u toku kurare tremora (KT). Da se unište svi neurofiziološki simptomi koji prate KT, bile su potrebne velike lezije. Ova činjenica potkrepljuje ideju da silazne aktivnosti u toku kurare tremora olakšavaju kičmene motorneurone na nespecifičan način i da se one ne prenose samo preko dobro uhodanih (određenih) ekstrapiramidalnih puteva.

Sasvim drugo pitanje se postavlja: da li KT može da bude model za istraživanje kliničkih supstanci koje su primijenjene kao antiparkin-

sonski lijekovi? Pokazano je da ovi lijekovi »normalizuju« neurofiziološke KT-simptome, premda je poznato da se moraju primjenjivati visoke doze. Čini se da KT može da bude upotrijebljen kao eksperimentalni model u neurofarmakološkim ispitivanjima.

REFERENCES

1. Birzis, L. & A. Hemingway: Efferent brain discharge during shivering.
   J. Neurophysiol. **20.** 156 (1957).
2. Bossmann, H. D.: Dynamische und statische Empfindlichkeit der Muskelspindeln beim Zittern der Katze infolge intracerebraler Curare — Wirkung.
   Dissertation, Universität Göttingen, 1965.
3. Bruggencate, H. G., ten, H. -D. Henatsch & H. Bossmann: Reduction of dynamic sensitivity of primary muscle spindle endings in experimental tremor.
   Experientia **20.** 554 (1964).
4. Bruggencate, H. G., ten, H. -D. Henatsch & H. Bossmann: Tremor und spinalmotorische α- und γ-Systeme der Katze bei Curareperfusion der Hirnventrikel.
   Pflüg. Arch. **282.** 102 — 118 (1965).
5. Bruggencate, H. G., ten & K. Schulze: Erregbarkeit primärer Afferenzen beim Curarezittern der Katze.
   Pflüg. Arch. **291.** 3 (1966).
6. Burke, R. E.: Group Ia synaptic input to fast and slow twitch motor units of cat triceps surae.
   J. Physiol. **196.** 605 — 630 (1968).
7. Carmichael, E. A., W. Feldberg & K. Fleischhauer: The site of origin of the tremor produced by tubocurarine acting from the cerebral ventricles.
   J. Physiol. **162,** 539—554 (1962).
8. Eldred, E., K. Ott, K. Ishikawa & D. Stuart: Proprioceptive contributions to the shivering tremor.
   Nobel Symp. I. Muscular afferents and motor control. Almquist & Wiksell/Stockholm 151 — 163.
9. Granit, R.: The functional role of the muscle spindle's primary end organs.
   Roy. Soc. Med. **61.** 69 — 78 (1968).
10. Hagbarth, K. E. & A. B. Vallbo: Discharge characteristics of human muscle afferents during muscle stretch and contraction.
    Exptl. Neurol. **22.** 674 — 694 (1968).
11. Henatsch, H.-D.: Spinal motor systems and dynamic/static properties of muscle spindles in experimental tremor states of the cat.
    In: Muscular afferents and motor control by: R. GRANIT, Almquist & Wiksell, Stockholm 1966, 165 — 176.
12. Henatsch, H.-D., H. G. ten Bruggencate & H. Bossmann: Bedeutung der Proprioceptoren und der γ-Muskelspindel-Schleife für das »Curarezittern« der Katze.
    Pflüg. Arch. **292.** 356 — 373 (1966).

13. Henneman, E., G. Somjen & D. O. Carpenter: Excitability and inhibility of motoneurones of different sizes. J. Neurophysiol. **28.** 599 — 620 (1965).

14. Jung, R.: Physiologische Untersuchungen über den Parkinsontremor und andere Zitterformen beim Menschen. Z. ges. Neurol. Psychiat. **173**, 263—332 (1941).

15. Klussmann, F. W. & H.-D. Henatsch: Der Einfluss der Temperatur auf die afferente und efferente motorische Innervation des Rückenmarks. II. Temperaturabhängigkeit der Muskelspindelfunktion. Pflüg. Arch. **305.** 316 — 339 (1969).

16. Matthews, P. B. C.: Muscle spindles and their motor control. Physiol. Rev. **44.** 219 — 288 (1964).

17. Meurer, K. A., C. Jessen & M. Iriki: Kältezittern während isolierter Kühlung des Rückenmarks nach Durchschneidung der Hinterwurzeln. Pflüg. Arch. **293**: 236—255 (1967).

18. Pierau, F. K., M. R. Klee & F. W. Klussmann: Effects of local hypo- and hyperthermia on mammalian spinal motoneurones. Fed. Proc. **28.** 1006—1010 (1969).

19. Simon, E., F. W. Klussmann, W. Rautenberg & M. Kosaka: Kältezittern bei narkotisierten spinalen Hunden. Pflüg. Arch. **291.** 187 — 204 (1966).

20. Stuart, D., K. Ott, K. Ishikawa & E. Eldred: The rhythm of shivering: II. Passive proprioceptive contributions. Amer. J. physic. Med. **45.** 75 — 90 (1966).

21. Weller, E. & H. G. ten Bruggencate: Wirkungen von Antiparkinsonmitteln auf das Curarezittern der Katze. Dtsch. Z. f. Nervenhlk. **192.** 275 — 289 (1968).

The excellent technical assistance of Miss U. Catoir and Mr. K. H. Brehm is gratefully acknowledged. The work was supported by the Deutsche Forschungsgemeinschaft (Br. 242/3).

DISCUSSION

Stern: Have you tried to act upon tremor which you have developed in cat by atropin and methyl-atropin? In thet way we could investigation of antiparkinsonics. If this tremor can be inhibited by methyl-atropin, it means that it is of peripheral nature.

Bruggencate: I am sorry, we didn't test atropine or methylatropine. Thank you so much for your waluable suggestion.

Schnieden: Did you monitor the temperature of your preparation and did the antiparkinsonian agents, effective in modifyng E. M. G. picture, also affect temperature of your preparations.

Bruggencate: We measured rectal temperature and kept it constant by a heating device. However, we have not done recordings of temperature and did not try to correlate it with curare perfusion. We did not pay attention to short time temperature drops, eventually related to injection of antitremor drugs. Therefore, any effect of these drugs on rectal temperature has probably escaped our observation.