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DRUG-INDUCED DYSKINESIA

—AN ELECTROPHYSIOLOGICAL ANALYSIS OF DYSKINESIA INDUCED BY L-DOPA AND ANTICHOLINERGIC DRUGS—

TADAAKI MANO

1st Department of Internal Medicine Nagoya, University School of Medicine, Nagoya
(Director: Associate Prof. Itsuro Sobne)

INTRODUCTION

The application of L-DOPA (L-3, 4-dihydroxyphenylalanine) to the treatment of extrapyramidal disorders has been extremely beneficial for parkinsonism[1)~8)]. At the same time several side-effects have been recognized. Among them, the appearance of dyskinesia poses an important problem[8)~13)], but causative mechanisms of L-DOPA induced dyskinesia are not yet sufficiently elucidated. Such dyskinesia appears particularly in perioral muscles, the tongue, and less frequently in other facial muscles, neck and extremities. In general there are irregular involuntary movements of the mouth such as chewing, gnawing or mumbling with involuntary protrusions or rotations of the tongue. The same type of dyskinesia has been found in patients treated by major tranquilizers, in particular, phenothiazine derivatives[14)~21)]. This type of involuntary movement was first described by French neurologists as "facio-bucco-linguo-masticatory dyskinesia",[22)] and then written by British authors in terms of "persistent oral dyskinesia"[23)24)]. It has also been reported under the name of "tardive dyskinesia"[25)26)] because of its appearance after an extensive period of neuroleptic medication. But L-DOPA induced dyskinesia is not "tardive" in its character. It would be called as "early dyskinesia", since it appears in general after a short period of L-DOPA administration.

Anticholinergic drugs have been used for a long time in the treatment of parkinsonism. As to their side-effects, clinical symptoms such as blurred vison or dry mouth have been recognized because of their inhibitory effects on the peripheral parasympathetic nervous system. Much less frequently, symptoms of the central nervous system such as hallucination or mental deterioration have been reported as their side-effects, but an appearance of the dyskinesia has never been described. Recently the author has found and already eported that the same types of dyskinesia could be also induced in cases of senile parkinsonism during treatment by synthetic anticholinergic

間 野 忠 明
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drugs[27)28)]. These forms of dyskinesia were confirmed to be induced by anticholinergic drugs because they appeared after anticholinergic medication with an amelioration of parkinsonian symptoms and disappeared after discontinuance with the reappearance of parkinsonism.

Detailed pathophysiological mechanisms of drug-induced dyskinesia are not yet known. On the other hand the similarity between drug-induced dyskinsia and other hyperkinetic syndromes such as chorea or athetosis due to other etiologies can be discussed. Indeed the clinical aspects of various drug-induced dyskinesia strongly resemble those observed in other hyperkinetic syndromes such as Huntington's chorea. Thus drug-induced dyskinesia could serve as a valuable model syndrome of hyperkinetic disorders in man such as chorea or athetosis. Therefore it could be legitimately hoped that an elucidation of pathophysiological mechanism of drug-induced dyskinesia might give an important clue to the basic mechanisms involved in the appearance of hyperkinetic syndromes in man.

Attempts thus far have been made to analyse various involuntary movement disorders and abnormalities of the muscle tonus, applying mainly electrophysiological methods. Some of the results have been previously reported [28)-37)]. The present study sought to investigate electro-clinical characteristics of dyskinesia induced by L-DOPA and anticholinergic drugs in order to analyse abnormalities of the central and peripheral motor controlling systems and to understand their causative mechanisms.

SUBJECTS AND METHODS

The series consisted of 7 cases of dyskinesia induced by L-DOPA and 8 cases of dyskinesia induced by anticholinergic drugs.

The upper row of Table 1 shows a list of 7 subjects who presented L-DOPA induced dyskinesia. Ages of the subjects varied between 32 and 74 years old. L-DOPA was given orally without any other medication for the treatment of parkinsonian symptoms, such as tremor, rigidity or akinesia, at maintenance doses ranging between 2.4 and 4.8 g a day. The dyskinesia appeared in these cases in periods ranging from 2 days to 4 weeks after administration of maintenance doses of L-DOPA. It disappeared within 1-2 weeks after the discontinuance. Older subjects in particular presented dyskinesia of perioral muscles and the tongue, while those younger suffered from dyskinesia of the extremities.

The lower row of Table 1 shows a list of 8 cases with dyskinesia induced by synthetic anticholinergic drugs including trihexyphenidyl hydrochloride (Artane), benztropine methanesulfonate (Cogentin), biperiden hydrochloride (Akineton), procyclidine hydrochloride (Kemadrin) and ethopropazine hydrochloride (Parkin). The dyskinesia appeared in these cases, 1 or 2 weeks after

TABLE 1. A list of 7 cases of L-DOPA induced dyskinesia (upper row) and 8 cases of dyskinesia induced by anticholinergic drugs (lower row)

Case	Age	Sex	Causative agent	Dose/day	Distribution of dyskinesia
1	74	female	L-DOPA	2.4 g	perioral muscles, tongue, masseter
2	72	female	L-DOPA	3.6 g	perioral muscles, tongue, masseter
3	55	female	L-DOPA	4.8 g	perioral muscles, tongue
4	55	male	L-DOPA	3.0 g	perioral muscles, masseter
5	46	female	L-DOPA	3.0 g	left lower extremity
6	37	female	L-DOPA	2.4 g	upper and lower extremities (right>left)
7	32	male	L-DOPA	4.0 g	right upper extremity
1	77	female	trihexyphenidyl	6 mg	perioral muscles, tongue, masseter
2	74	female	trihexyphenidyl	6 mg	perioral muscles, tongue, masseter
3	71	female	trihexyphenidyl	6 mg	perioral muscles, tongue, masseter
4	64	female	trihexyphenidyl	6 mg	perioral muscles, tongue, masseter
5	67	male	trihexyphenidyl	6 mg	perioral muscles, tongue, masseter
6	64	female	trihexyphenidyl	12 mg	perioral muscles, tongue, masseter
7	72	female	trihexyphenidyl benztropine biperiden	6 mg 4 mg 10 mg	perioral muscles, tongue, masseter face, neck, toes
8	65	female	procyclidine ethopropazine	40 mg} 90 mg}	perioral muscles, tongue, masseter

anticholinergic medication and disappeared after the discontinuance in periods ranging from 1 to 12 weeks. Ages of the subjects were between 64 and 77 years old and all of them presented dyskinesia of perioral muscles, the tongue and the masseter. One of them suffered also from dyskinesia of the toes. A pneumoencephalographic study in one of them revealed a considereble enlargement of the anterior horns of both lateral ventricles.

In these cases electromyograms of affected muscles were recorded from bipolar cutaneous disc electrodes and were amplified by multi-channel polygraph (Nihon-Kohden ME-135) with a time constant at 0.03 seconds, being inscribed on recording paper using an ink-writer. Electromyographic characteristics of involuntary grouping discharges which resulted from the dyskinesia were analysed in regard to their regularities, frequencies, durations and reciprocities between the agonist and the antagonist. Then effects of contractions of other muscles were examined to seek for synkinetic characters, and effects of haloperidol were also investigated to evaluate the action of this drug on the dyskinesia. Then effects of γ-block were observed to analyse the participation of γ-efferent system in the production of drug-induced dyskinesia. By anesthetic infiltration of 0.5% lidocaine hydrochloride on the central portion of the peripheral efferent nerves, which innervate affected muscles, γ-block was performed. Effects of γ-block were estimated by concomitant elevation of

pain threshold, appearances of peripheral vosodilatations and abolition or decrease of the tendon reflex, such being without modification of gross muscle strength, maximum motor or sensory conduction velocity.

In the case with dyskinesia in the extremities, stretch reflex discharges were recorded to evaluate the state of muscle tonus in the affected muscles. During this recording, the angles of passive joint movements were recorded continuously using potentiometer and DC amplifier of the polygraph, being inscribed simultaneously on the recording paper with electromyographic discharges. Moreover evoked electromyograms (M- and H-responses) were elicited by electrical stimulation of peripheral nerves which innervate dyskinetic muscles in order to analyse the excitabilities of α-motoneurons which participate in the production of the dyskinesia. Electrical stimulations, rectangular pulses with intensities between 30 and 50 volts and durations between 0.5 and 1.0 msec were applied on the peripheral nerves transcutaneously using an electronic stimulator (Nihon-Kohden MSE-3). The evoked responses were recorded on a cathode-ray oscilloscope, and their peak-to-peak amplitudes, as well as the recovery cycles of H-responses obtained by double shocks, were analysed.

RESULTS

1. EMG characteristics of dyskinesia induced by L-DOPA

(1) Bucco-linguo-masticatory dyskinesia

In 4 older subjects with bucco-linguo-masticatory dyskinesia induced by L-DOPA, irregular grouping discharges with frequencies between 0.3 and 0.5 cycles per second and durations between 1.0 and 3.0 seconds appeared in perioral muscles during treatment by L-DOPA. Asynchronous irregular ones with longer durations (0.2–0.5 c/s, 1.0–4.0 sec) were manifest in

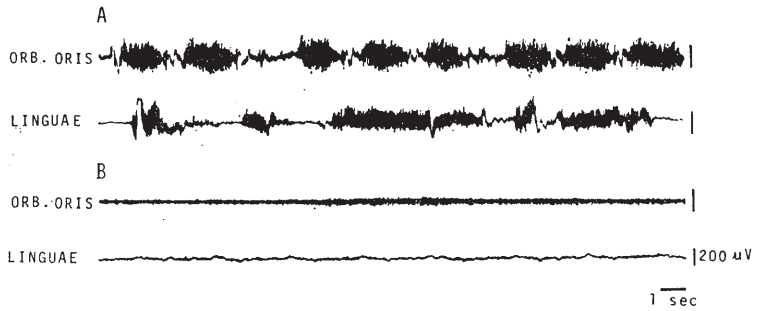

FIG. 1. EMG discharges during treatment by L-DOPA (A) and after administration of haloperidol (B).

Asynchronous irregular grouping discharges in perioral muscles (ORB. ORIS) and the tongue (LINGUAE) observed in (A) disappeared and absent in (B).

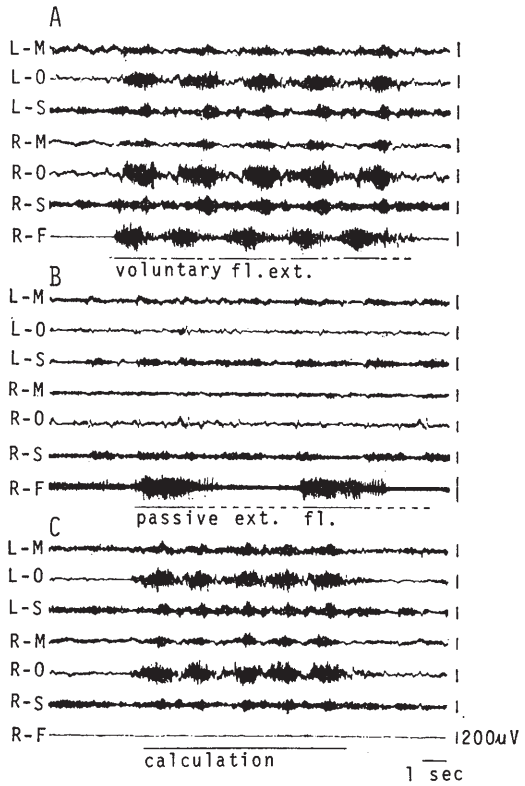

FIG. 2. Characteristics of abnormal EMG discharges induced by L-DOPA.

A: Involuntary grouping discharges appearing synchronously in bilateral (L: left, R: right) Mm. masseter (M), orbicularis oris (O) and suprahyoidei (S). Reinforced bilaterally by voluntary contractions of other muscles, for example the flexor of right hand (R-F).

B: Not influenced by reflex contractions of other muscles induced by their passive joint movements.

C: Also reinforced by mental elaborations, such as calculation.

the tongue (Fig. 1 A). These abnormal discharges disappeared after an administration of haloperidol (Fig. 1 B). The same type of grouping discharges in bilateral masticatory and suprahyoid muscles was found synchronously with those in both perioral muscles. They were markedly reinforced bilaterally by voluntary contractions of other muscles (synkinetic reinforcement), for example by voluntary contractions of the flexor in the right hand (Fig. 2 A). But they were not modified by reflex contractions of other muscles induced by passive joint movements (Fig. 2 B). They were also reinforced considerably by mental elaborations, such as calculations (Fig. 2 C).

(2) Dyskinesia of the extremities

In 3 younger cases, two different types of involuntary grouping discharges became apparent in the extremities during treatment by L-DOPA because of clinical dyskinesia. One consisted of irregular reciprocal grouping discharges

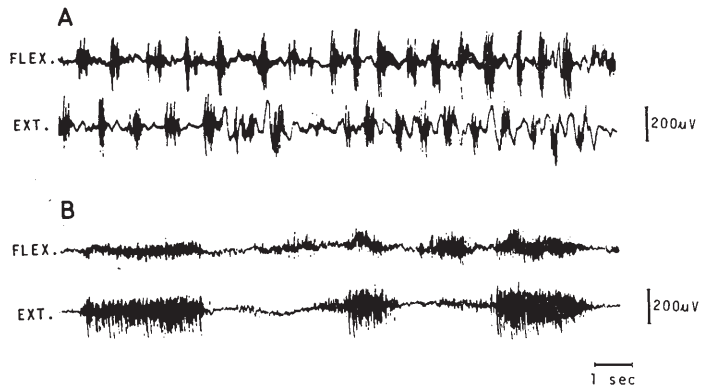

FIG. 3. Two types of abnormal grouping discharges of the extremities induced by L-DOPA.

A: Irregular reciprocal grouping discharges with relatively short durations appearing in the flexor (FLEX.) and extensor (EXT.) of the extremities.

B: Irregular non-reciprocal types with longer durations appearing in the flexor and extensor of the extremities.

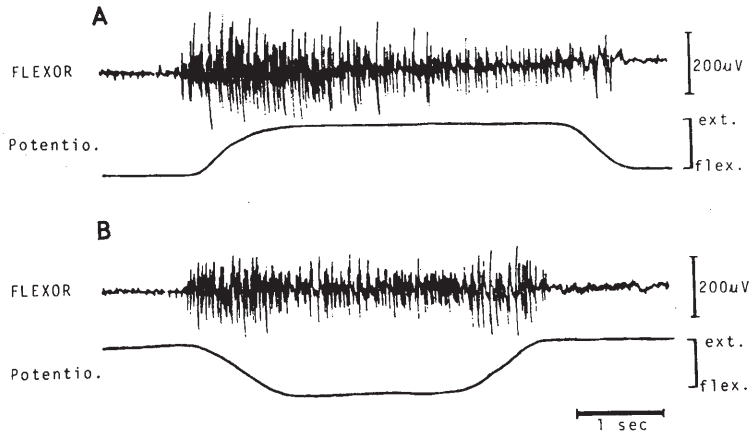

FIG. 4. Reflex discharges before (A) and during (B) treatment by L-DOPA.

Joint angle of the wrist was recorded using potentiometer (Potentio.) simultaneously with EMG of the flexor (FLEXOR) of the hand during its passive extension (ext.) and flexion (flex.). An exaggeration of stretch reflex discharges observed in (A) is absent in (B). Contrary to this, tonic reflex discharges appeared in (B) during passive flexion of the hand (passive shorening of the flexor).

with relatively short durations (0.8–1.5 c/s, 0.2–0.5 sec) which were found in the flexor and the extensor of the affected limb (Fig. 3 A). The other consisted of irregular non-reciprocal grouping discharges with longer durations (0.2–0.3 c/s, 1.0–3.0 sec) in the flexor and the extensor of the dyskinetic extremities (Fig. 3 B).

As to the stretch reflex of the dyskinetic muscles in the extremities, an exaggeration of tonic stretch reflex caused by clinical rigidity before treatment disappeared generally during administration of L-DOPA. Contrary to this, reflex discharges became frequently apparent in the dyskinetic muscles during their passive shortenings (Fig. 4).

2. EMG characteristics of dyskinesia induced by anticholinergic drugs

(1) Bucco-linguo-masticatory dyskinesia

In all of 8 aged cases with bucco-linguo-masticatory dyskinesia induced by anticholinergic drugs, synchronous irregular grouping discharges (0.5–1.5 c/s, 0.2–1.5 sec) in bilateral perioral and masticatory muscles, as well as asynchronous ones with longer durations (0.2–0.5 c/s, 0.5–2.0 sec) in the tongue appeared during treatment by anticholinergic drugs (Fig. 5 A). After discontinuance of anticholinergic medication, they disappeared, and only normal tonic discharges persisted (Fig. 5 B).

The dyskinetic grouping discharges in both perioral muscles were reinforced by voluntary movements of the foot (synkinetic reinforcement) (Fig. 6 A). These discharges, as well as their synkinetic reinforcement, were completely inhibited by administration of haloperidol, but rhythmic grouping discharges (4–5 c/s) appeared in both perioral muscles during opening of the mouth (Fig. 6 B).

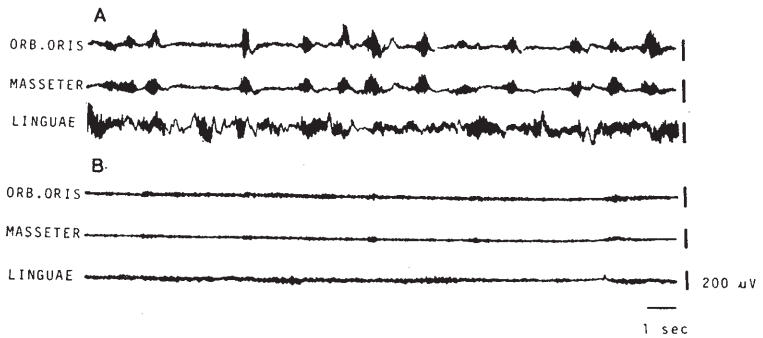

FIG. 5. EMG discharges during administration (A) and after discontinuance (B) of anticholinergic drug.

Synchronous irregular grouping discharges in perioral (ORB. ORIS) and masticatory (MASSETER) muscles, as well as asynchronous ones with longer durations in the tongue (LINGUAE) observed in (A) disappeared in (B).

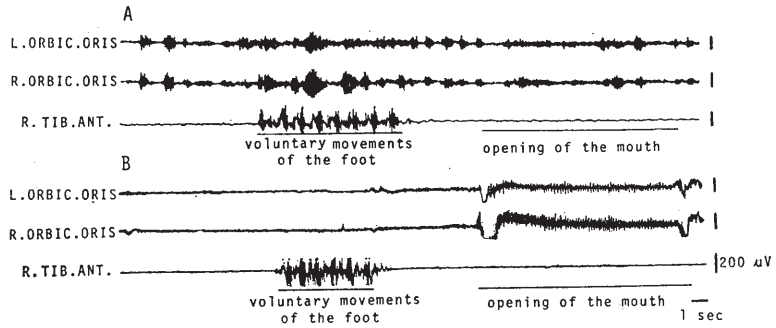

FIG. 6. EMG discharges during treatment by anticholinergic drug (A) and after administration of haloperidol (B).

Irregular grouping discharges in bilateral perioral muscles (L. and R. ORBIC. ORIS) and their reinforcements by voluntary contractions of right anterior tibial muscle (R. TIB. ANT.) observed in (A) and absent in (B) with an appearance of rhythmic grouping discharges (4-5 c/s) in both perioral muscles during opening of the mouth.

(2) *Dyskinesia of the extremities*

In a case with dyskinesia of the toes, irregular non-reciprocal grouping discharges with relatively long durations (0.2-1.0 c/s, 0.5-3.0 sec) were manifest in the extensor and the flexor of the toes (Fig. 7 A). In the dyskinetic muscles, reflex discharges became apparent during their passive shortening. For example, tonic reflex discharges appeared in the anterior tibial muscle during passive dorsi-flexion of the foot (Fig. 7 B).

The dyskinetic grouping discharges in the extensor and the flexor of the toes were markedly reinforced by voluntary contractions of other muscles (synkinetic reinforcement) (Fig. 8 A), but were not modified by reflex contractions of other muscles evoked by their passive joint movements (Fig. 8 B). These discharges, as well as their synkinetic reinforcements, were not significantly influenced by γ-block of the dyskinetic muscles (Fig. 8 C).

As to evoked electromyographic responses of the dyskinetic muscles, amplitudes of direct motor M-responses were almost constant, while those of reflex H-responses changed noticeably with their increases during appearances of the dyskinetic grouping discharges (Figs. 9 A and B). Recovery cycles of H-responses obtained by double shocks showed a remarkable shortening of the silent period and noteworthy supernormalities at the intervals around 200 and 400 msec (Fig. 9 C).

DISCUSSION

Abnormal grouping discharges observed in the foregoing cases due to dyskinesia induced by L-DOPA or anticholinergic drugs are classified as choreic

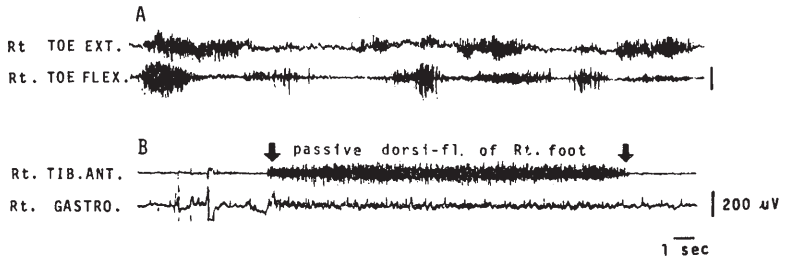

FIG. 7. Spontaneous (A) and reflex (B) EMG discharges in muscles with dyskinesia induced by anticholinergic drug.

A: Irregular non-reciprocal grouping discharges appearing in the extensor (Rt. TOE EXT.) and the flexor (Rt. TOE FLEX.) of right toe.

B: Tonic reflex discharges appearing in right anterior tibial muscle (Rt. TIB. ANT.) during passive dorsi-flexion of right foot.

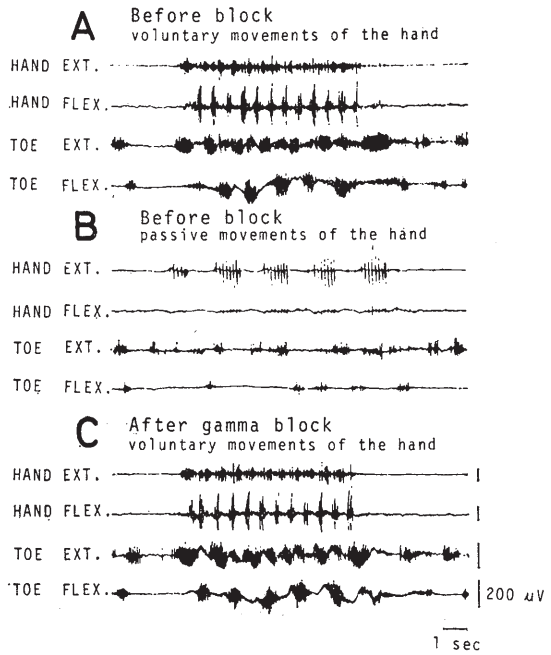

FIG. 8. Characteristics of EMG discharges induced during treatment by anticholinergic drug.

A: Involuntary grouping discharges in the extensor (TOE EXT.) and the flexor (TOE ELEX.) of the toe were reinforced by voluntary contractions of the extensor (HAND EXT.) and the flexor (HAND FLEX.) of the hand.

B: Not modified by reflex contractions of the extensor and the flexor of the hand induced by its passive joint movements.

C: Dyskinetic grouping discharges, as well as their reinforcements by voluntary movements of the hand, as not influenced by γ-block.

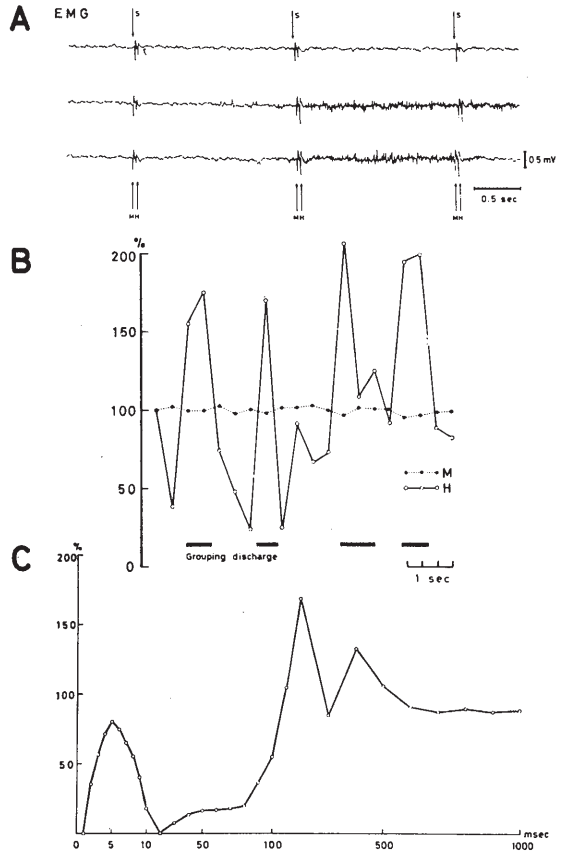

FIG. 9. H-reflex in muscles with dyskinesia induced by anticholinergic drug.

A: Continuous recordings of spontaneous and evoked EMG in the dyskinetic muscles; amplitudes of direct moter M-responses (M) were almost constant, while those of reflex H-responses (H) increased during appearances of the dyskinetic grouping discharges.

B: Percent amplitude of M-(dotted line) and H-(straight line) responses to the amplitude of the first ones in the dyskinetic muscles; In contrast to the stability of amplitudes of M-responses, those of H-responses fluctuated remarkably with their increases during appearances of the grouping discharges.

C: Recovery cycle of H-response in the dyskinetic muscles. Abscissa represents intervals (msec) between conditioned and test shocks; ordinate indicates percent amplitudes of the responses evoked by test shocks to those by conditioned ones. A remarkable shortening of the silent period and noteworthy supernormalities were recognized.

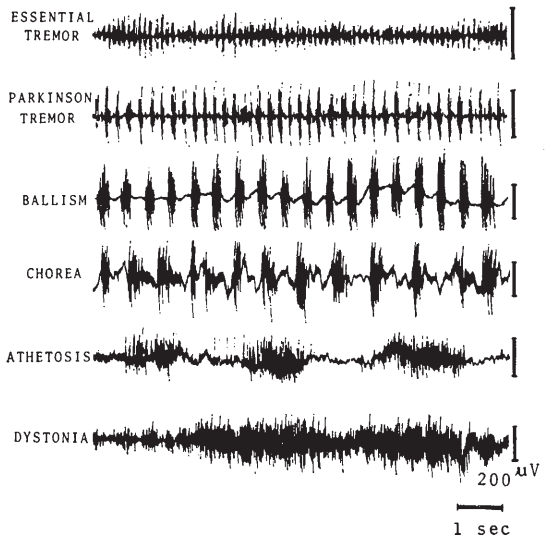

FIG. 10. Tentative EMG classification of involuntary movement disorders*.

Various involuntary movements are classified by characteristics (regularities, reciprocities, frequencies and durations) of abnormal EMG grouping discharges which appear in the affected muscles as follows; 1. Essential tremor: rhythmic reciprocal grouping discharges with frequencies around 8 and 9 c/s; 2. Parkinsonian tremor: rhythmic reciprocal grouping discharges with frequencies around 4 and 5 c/s; 3. Ballism: relatively regular and reciprocal grouping discharges with frequencies between 0.5 and 2 c/s and durations between 0.2 and 0.8 sec; 4. Chorea: irregular, mainly reciprocal grouping discharges with frequencies between 0.4 and 1.5 c/s and durations between 0.2 and 1.0 sec; 5. Athetosis: irregular, mainly non-reciprocal grouping discharges with frequencies between 0.1 and 0.3 c/s and durations between 1.0 and 3.0 sec; 6. Dystonia: non-reciprocal grouping discharges with durations longer than 3.0 sec.

(* reproduced from Clinical Electroencephalography 14: 253–261, 1972)

or athetosic discharges according the author's electromyographic classification of involuntary movement disorders (Fig. 10) described elsewhere in detail[35]. Namely, irregular grouping discharges observed in the said cases with frequencies between 0.4 and 1.5 c/s and durations between 0.2 and 1.0 sec, would be classified as choreic, and those with frequencies between 0.2 and 0.3 c/s and durations between 1.0 and 3.0 sec would be classified as athetosic discharges. Moreover electrophysiological characteristics of the dyskinetic discharges in these cases, in particular, the synkinetic reinforcement by voluntary contraction of other muscles, immutabilities by γ-block, inhibitions

by haloperidol and associations with facilitations of H-reflex, correspond well to those observed in choreic or athetosic discharges due to other etiologies such as Huntington's chorea[30]. Therefore it would be postulated that the dyskinesia in the cases involved here were produced by basic pathophysiological mechanisms almost identical to those of the chorea or athetosis due to other etiologies.

Chorea and athetosis are considered to be produced by cerebral lesions situated mainly in the striatum[38)~40)]. Thus the dyskinesia in the present cases would result from the striatal lesions. An enlargement of the anterior horns of bilateral lateral ventricles revealed by a pneumoencephalographic study in one of the cases suggests also possible atrophic lesion in the striatum. The striatum is considered to play an important role as one of the extrapyramidal centers for the performance of normal movements and the maintenance of normal muscle tonus. In the striatum there exist many cholinergic neurons[41)42)] in addition to the dopaminergic neurons which form synaptic terminals of the nigro-striatal dopaminergic pathways[43)~48)]. Experimental studies in animals show that cholinergic neurons in the striatum are functionally antagonistic to dopaminergic neurons in this structure[49)50)]. Normal motor functions in man would be based on cholinergic-dopaminergic functional balances in the striatum. Many authors have described the hypothesis that an imbalance of the cholinergic-dopaminergic balances in favor of cholinergic systems produces parkinsonism[51)~54)]. According to this hypothesis, an administration of L-DOPA or anticholinergic drugs normalizes this shift of cholinergic-dopaminergic balances and relieves parkinsonism. The appearance of the dyskinesia in the cases under study, during administrations of L-DOPA or anticholinergic drugs, suggest that an excess activation of the dopaminergic system due to L-DOPA medication or an excess inactivation of the cholinergic system due to anticholinergic treatment would induce a shift of cholinergic-dopaminergic balances in the striatum in favor of dopaminergic systems and thus produce dyskinesia. This suggestion would be supported by the fact that haloperidol, a possible blocking agent in central dopaminergic transmissions[55)~57)], has been shown to inhibit not only L-DOPA induced dyskinesia but also dyskinesia induced by anticholinergic drugs. A schematic representation of the mechanisms above-mentioned is shown in Fig. 11. This schema may be far too simple an attempt to depict the causative mechanisms of dyskinesia. In addition to the role of the cholinergic and dopaminergic systems in the striatum, which would be involved in the production of dyskinesia, that of histamine, 5-hydroxytryptamine (serotonin) or γ-aminobutyric acid (GABA) in the central structures should not be excluded. But in the present stage of knowledge, where information is still insufficient about central neurotransmitters which figure in the origin of basal ganglia disorders, it is, nevertheless, useful to approach the cause of complex extrapyramidal symptoms

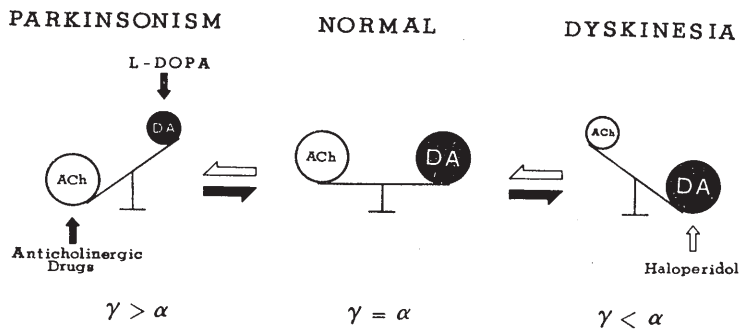

FIG. 11. Schematic representation of possible mechanism of dyskinesia induced by L-DOPA and anticholinergic drugs.

In normal state functional balances between cholinergic (ACh) and dopaminergic (DA) systems may be maintained in the striatum and equilibriums between peripheral α-and γ-motor systems may exist in order to perform normal movements and to keep normal muscle tonus. A shift of these balances in favor of ACh system would produce parkinsonism where hyperfunctions of γ-system predominate to induce clinical symptoms like rigidigy. An administration of L-DOPA or anticholinergic drug would correct these imblances and relieve parkinsonism. However an excess activation of DA system due to L-DOPA administration or an excess inactivation of ACh system due to anticholinergic medication would tend to shift these balances in favor of DA system and elicit hyperfunctions of α-motor system which would be responsible for appearance of the dyskinesia. Haloperidol would have reverse effects on these balances because of its inhibitory action on central dopaminergic transmission.

such as dyskinesia, employing this simplified schematic representation.

Besides these central disturbances, the dyskinesia in the cases here studied are thought to be related to fnnctional abnormalities of peripheral motor controlling systems, in particular α- and γ-motor systems. In previous studies conducted here, parkinsonian rigidity was concluded to be related to hyperfunctions of γ-system, because it disappeared after γ-block[34)36)]. In the present study an exaggerated tonic stretch reflex existing before treatment was found to disappear or be markedly reduced after administration of L-DOPA or anticholinergic drugs. But again, reflex discharges became apparent in dyskinetic muscles during their passive shortenings. This type of reflex discharges has already been described by Rondot *et al.*[58)59)] and by the author[35)36)] in dystonia, athetosis or in chorea, but the exact pathophysiological mechanism of this reflex is not yet known. These discharges are not influenced by γ-block[36)] and are frequently associated with clinical hypotonia. Therefore they are not caused by hyperfunctions of γ-system. Inversely the frequent association of an exaggeration of H-reflex with such discharges would suggest that they were produced by hyperfunctions of α-system.

The dyskinetic grouping discharges themselves are not considered to be

produced by hyperfunctions of γ-system, because they are not modified by γ-block and are not associated with an exaggeration of tonic stretch reflex. They would be produced by hyperfunctions of α-motor system, since they are accompanied by remarkable facilitations of H-reflex which reflect excitabilities of α-motoneurons. Synkinetic reinforcements of dyskinetic discharges observed in the present cases would also result in hyperexcitabilities of α-motor system rather than γ-system, because they are not influenced by γ-block. They would not be produced by afferent impulses which originate from muscle spindles of other muscles; because they are manifest only during voluntary contractions, such are not in evidence during reflex contractions of other muscles induced by their passive joint movements. Reinforcements of dyskinetic discharges found also during mental elaborations, such as calculation, would indicate that the synkinetic reinforcements would be produced by direct descending facilitations from the central structures on α-motoneurons which innervate dyskinetic muscles. On account of all of these electrophysiological characteristics, it may be concluded that the dyskinesia in evidence was produced on the basis of hyperfunctions of α-motor system rather than γ-system.

Finally, if one considers these disturbances of peripheral motor controlling systems in relation to the abnormalities of central neurohumoral mechanisms, the following may be postulated: Parkinsonism, which would result from a shift of striatal cholinergic-dopaminergic functional balances in favor of cholinergic systems, would be associated with a state where hyperfunctions of γ-motor system predominate so as to manifest clinical symptoms as rigidity. A shift of these cholinergic-dopaminergic balances in favor of dopaminergic systems would elicit hyperfunctions of peripheral α-motor system which would be responsible for appearances of dyskinesia (Fig. 11). This conclusion contradicts Steg's hypothesis[60] that rigidity of tail muscles in a reserpinized rat depends on hyperfunctions of α-system and hypofunctions of γ-system. It also would stand in opposition to the results of an experimental study on the rat by Arvidsson *et al.*[61], who insist that an administration of L-DOPA or anticholinergic drugs facilitates γ-system and inhibits α-system, while haloperidol would have a reverse effect. These contradictory findings might result from disparity of mode and dose of drug administration and possibly from the difference between man and rat. Indeed, many studies in man indicate the importance of hyperfunctions of γ-system in human parkinsonian rigidity[62)-67)]. Meanwhile the conclusion itself of Arvidsson *et al. i.e.*, that cholinergic and dopaminergic agents manifest reciprocal effects on α- and γ-motor systems, would correspond to the author's conclusion. But recent studies have classified the γ-motor system into two functionally different components (dynamic and static)[68)69)]. Experimental studies with animals suggest that dopaminergic drugs, for example L-DOPA, show different, even reciprocal effects on these different components of γ-system[70)]. Therefore further studies could be

expected to elucidate more accurately the pathophysiological mechanisms of drug-induced extrapyramidal symptoms in man. At the present stage, when no method exists to record directly the activities of α- and γ-systems in man, it would be proper to discuss the disturbances of these motor controlling systems on the basis of electromyographic recordings as presented in this study, as related to functional abnormalities of central neurohumoral mechanisms. More advanced investigation of extrapyramidal disorders would very much depend on the exploration of newer neurophysiological methodologies in man.

SUMMARY

Electrophysiological characteristics of drug-induced dyskinesia were analysed, mainly employing electromyographic methods. The subjects consisted of 7 cases of dyskinesia induced by L-DOPA and 8 cases of dyskinesia induced by synthetic anticholinergic drug including trihexyphenidyl hydrochloride (Artane), benztropine methanesulfonate (Cogentin), biperiden hydrochloride (Akineton), procyclidine hydrochloride (Kemadrin) and ethopropazine hydrochloride (Parkin). These drugs were given orally against parkinsonian symptoms such as rigidity, tremor and akinesia. Electromyograms were recorded using bipolar cutaneous disc electrodes. Characteristics of abnormal EMG grouping discharges which appeared because of clinical dyskinesia and those of stretch reflex discharges, as well as H-reflexes, were analysed in the dyskinetic muscles.

1. Synchronous irregular grouping discharges (0.3-0.5 c/s, 1.0-3.0 sec) in bilateral perioral, masticatory and suprahyoid muscles as well as asynchronous ones with longer durations (0.2-0.5 c/s, 1.0-4.0 sec) in the tongue appeared due to clinical bucco-linguo-masticatory dyskinesia induced by L-DOPA. They were inhibited by an administration of haloperidol and notably reinforced by voluntary contractions of other muscles (synkinetic reinforcement), and also by mental calculation; but no influence by reflex contractions of other muscles induced by their passive joint movements was found.

2. Irregular reciprocal grouping discharges (0.8-1.5 c/s, 0.2-0.5 sec) or irregular non-reciprocal types with longer durations (0.2-0.3 c/s, 1.0-3.0 sec) were manifest in the flexor and the extensor of the extremities because of clinical dyskinesia induced by L-DOPA. Stretch reflex discharges decreased in dyskinetic musles of the extremities. Contrary to this, tonic reflex discharges became apparent in the affected muscles during their passive shortenings.

3. Synchronous irregular grouping discharges (0.5-1.5 c/s, 0.2-1.5 sec) in bilateral perioral and masticatory muscles as well as asynchronous ones with longer durations (0.2-0.5 c/s, 0.5-2.0 sec) appeared, owing to clinical bucco-linguo-masticaory dyskinesia, and irregular non-reciprocal grouping discharges

(0.2-1.0 c/s, 0.5-3.0 sec) were manifest in the flexor and the extensor of the extremities because of the dyskinesia induced by anticholinergic drugs. Such discharges were reinforced by voluntary contractions of other muscles (synkinetic reinforcement) but were not modified by reflex contractions of other muscles induced by their passive joint movements. Both these diskinetic discharges and their synkinetic reinforcements were not influenced by γ-block and were inhibited by haloperidol.

4. Tonic reflex discharges became apparent in affected muscles of the extremities by dyskinesia induced by anticholinergic drugs during their passive shortenings. H-reflexes of the dyskinetic muscles were remarkably facilitated during abnormal grouping discharge manifestations. In recovery cycles, a remarkable shortening of the silent period and noteworthy supernormalities were recognized.

Based on these electrophysiological characteristics, the dyskinesia, as found in these cases, was concluded to be produced by hyperfunctions of α-motor system rather than γ-system. The dyskinesia with almost identical electrophysiological characteristics was induced by L-DOPA and anticholinergic drugs, and they were inhibited by haloperidol. Moreover the same type of abnormal grouping discharges have been observed in chorea or athetosis associated mainly with striatal lesions due to other etiologies. On the basis of all of these findings, the following hypothesis concerning the origin of the dyskinesia under study here was presented: An excess activation of central dopaminergic systems induced by an administration of L-DOPA or an excess inactivation of central cholinergic systems induced by anticholinergic medications in parkinsonism would produce a shift of possible functional balances between cholinergic and dopaminergic systems in the striatum in favor of the latter, and elicit hyperfunctions of peripheral α-motor system such as would be responsible for the appearence of dyskinesia.

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