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Tremor Induction by Intracaudate Injections of Bretylium, Tetrabenazine, or Mescaline: Functional Deficits in Caudate Dopamine

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Abstract □ Tremor responses were evoked by intracaudate injections of tetrabenazine, bretylium, or mescaline in cats with chronically implanted recording electrodes and microinjection cannulas. The characteristics of the maximal tremors with each agent closely resembled those induced by increased levels of cholinergic activity in the caudate (previously reported). These maximal tremors, like the cholinergic tremors, were suppressed by local injections of catecholamines (dopamine and epinephrine), scopolamine, or hemicholinium but were intensified by intracaudate serotonin. Although local acetylcholine had no effect on established tremor activity, tremors abolished by hemicholinium were reestablished by small doses of acetylcholine. These results suggested that interference with local dopamine inhibitory mechanisms ("functional dopamine deficiency") was the basis for the tremorgenic actions of bretylium, tetrabenazine, and mescaline; the findings also indicated that sustained endogenous acetylcholine activity in the caudate was a necessary condition for the development and maintenance of tremor activity. These data lend support to the hypothesis that an imbalance in the caudate between dopamine inhibition and acetylcholine excitation in favor of the latter results in tremors.

Keyphrases □ *Dopamine*—functional deficiency in caudate tremor mechanisms, role in tetrabenazine-, bretylium-, and mescaline-induced tremor □ Tetrabenazine—tremor evoked by intracaudate injection □ Bretylium—tremor evoked by intracaudate injection □ Mescaline—tremor evoked by intracaudate injection □ Catecholamine—inhibition of tetrabenazine-, bretylium-, and mescaline-induced tremor □ Scopolamine—inhibition of tetrabenazine-, bretylium-, and mescaline-induced tremor □ Hemicholinium—inhibition of tetrabenazine-, bretylium-, and mescaline-induced tremor □ Serotonin—intensification of tetrabenazine-, bretylium-, and mescaline-induced tremor

Resting tremors have been induced consistently by carbachol or anticholinesterases injected directly into the head of the caudate nucleus in unanesthetized cats prepared with permanently implanted recording electrodes and microinjection cannulas. These tremors were inhibited by intracaudate injection of agents that interfere with either postsynaptic receptor actions (atropine and scopolamine) or presynaptic synthesis (hemicholinium-3) of acetylcholine, or they were suppressed by intracaudate injection of catecholamines (epinephrine and dopamine) (1, 2). From these findings and from a consideration of the high concentrations of both acetylcholine and dopamine in the caudate, it has been postulated that the functions of acetylcholine (excitatory) and dopamine (inhibitory) are critically balanced in the caudate so as to comprise a local tremor regulatory mechanism (3–5).

Clinically, the involuntary movement disorders associated with Parkinson's disease have been linked to deficiencies in caudate dopamine (6). Also, the extra-

Table I—Characteristics of Tremor Produced by Intracaudate Injections of Tetrabenazine, Bretylium, and Mescaline

Tremor Parameters[a]	Tremorgenic Agents		
	Tetrabenazine	Bretylium	Mescaline
Effective dose, mcg.[b]	161.2 ± 8.9	112.0 ± 0.5	64.5 ± 5.4
Latency, min.	18.1 ± 1.7	4.0 ± 0.3	6.0 ± 1.2
Maximal tremor characteristics:			
Onset of peak effect, min.	58.6 ± 6.6	13.0 ± 1.7	20.1 ± 3.1
Duration of maximal tremor, hr.	>5[c]	>6[d]	>5
Amplitude, μv.	269.7 ± 32.8	261.3 ± 20.2	311.7 ± 47.1
Amplitude, graded intensity[e]	+++	+++	+++
Tremor bursts per minute	20.7 ± 1.4	23.1 ± 2.0	23.0 ± 2.1
Tremor frequency, c.p.s.	23.6 ± 0.3	24.8 ± 1.1	21.3 ± 0.9
Tremor time, %	59.7 ± 2.8	68.2 ± 3.8	68.2 ± 1.7

[a] Values obtained from no less than six different cats. [b] Mean dose of base (±standard error). [c] Duration of maximal tremor extended beyond 5 hr. in nine of 10 trials. [d] Duration of maximal tremor always extended at least 6 hr.; actual duration beyond this determined in only two trials. [e] Graded against physostigmine tremor (++) as the standard (2).

Table II—Effects of Locally Injected Dopamine, Epinephrine, or Serotonin on Maximal Tremors Evoked by Intracaudate Tetrabenazine, Bretylium, and Mescaline

Locally Injected Agents	Activity Parameters	Tremors Evoked by		
		Tetrabenazine	Bretylium	Mescaline
Dopamine	Effect on tremor[a]	(−)	(−)	(−)
	Dose, mcg.[b]	81.0 ± 5.2	107.3 ± 7.9	168.0 ± 2.3
	Latency, min.	5.3 ± 0.7	5.0 ± 1.1	6.3 ± 1.4
	Duration, min.	46.2 ± 4.1	60.3 ± 5.1	60.7 ± 8.6
	Activity ratio[c]	6/6	6/6	6/7
Epinephrine	Effect on tremor	(−)	(−)	(−)
	Dose, mcg.	12.3 ± 0.9	4.5 ± 0.4	14.7 ± 1.2
	Latency, min.	6.7 ± 0.4	3.3 ± 0.3	5.7 ± 1.0
	Duration, min.	44.3 ± 3.8	53.2 ± 1.4	54.0 ± 6.9
	Activity ratio	6/6	6/6	6/6
Serotonin	Effect on tremor	(+)	(+)	(+)
	Dose, mcg.	64.5 ± 6.0	44.6 ± 4.6	52.0 ± 7.5
	Latency, min.	8.2 ± 1.6	4.3 ± 1.2	5.8 ± 1.3
	Duration, min.	27.3 ± 2.2	42.0 ± 5.0	45.8 ± 11.3
	Activity ratio	6/6	6/6	6/7

[a] (−) = tremor activity abolished; (+) = tremor activity intensified. [b] Doses of dopamine, epinephrine, or serotonin represent their respective bases (mean ± standard error). [c] Activity ratio = number of tremor inhibitions (or intensifications)/total number of trials.

pyramidal symptoms developing after systemic administration of neuroleptic drugs have been attributed to reduced dopamine functioning (7, 8).

The present investigation was undertaken to explore the relationship between dopamine and acetylcholine in tremor, utilizing tetrabenazine, bretylium, and mescaline as pharmacological tools. The purposes were to ascertain whether interference with caudate dopamine mechanisms was tremorgenic and to determine whether acetylcholine was involved in this tremorgenic process.

EXPERIMENTAL

Thirty-two male cats (3.0–4.5 kg.) were used in these studies. Under pentobarbital anesthesia, permanent bipolar assemblies[1], consisting of microinjection cannulas and recording electrodes, were implanted stereotaxically in both caudate nuclei (R. and L. Caud.) at Horsley-Clarke coordinates A_{15}, R_5, and L_5, D + 5 (9). Bipolar twisted electrodes were also positioned in the cortex and other subcortical recording sites. All electrodes were externalized to a 15-pin plug[2], which was fixed to the skull with acrylic dental cement and hard wax. Details of the assembly and microinjection technique were described previously (2, 10, 11).

After a recovery period of at least 2 weeks, the unanesthetized cat was suspended in a canvas hammock and positioned so that its hindlimbs were extended. Motor and electrographic responses were monitored on an oscilloscope and recorded on an electroencephalograph. Tremor activities were detected by a phonocartridge transducer[3] affixed to the dorsal surface of one hindfoot. Tremor responses were analyzed in terms of amplitude, percent tremor time, tremor frequency, and number of tremor bursts per minute, which provided an accurate assessment of relative tremor intensity (1, 10). The maximal tremor response is characterized in terms of the amplitude of the recorded involuntary movement oscillations (microvolts) for any given dose of drug.

All microinjections were made into the head of the right or left caudate through the bipolar assemblies[1] by way of a delivery cannula coupled to a calibrated micrometer-driven hypodermic syringe. Only one caudate nucleus was utilized for drug injection in any given experiment. Concentrations (0.1–1.5%) of drug solutions for intracaudate injections were adjusted so that microinjected volumes usually did not exceed 10 μl. Pilot experiments showed that alterations in pH and tonicity of drug solutions over a wide range produced no discernible effect on tremorgenesis or on other drug responses. Solutions of the following compounds prepared in distilled water were employed: bretylium tosylate, mescaline hydrochloride, tetrabenazine methanesulfonate, acetylcholine chloride, physostigmine sulfate, epinephrine bitartrate, dopamine hydrochloride, serotonin creatinine sulfate, hemicholinium-3 hydrobromide, and scopolamine hydrochloride. Drug quantities specified in the text refer to those of their respective bases.

Animals were rested at least 1 week between experiments. At the end of the study, after each brain was fixed in formalin, placements of the electrodes and permanent bipolar assemblies[1] were verified by examination of their tracts and the electrolytic lesions at the electrode tips.

[1] Injectrode.
[2] Amphenol.
[3] Astatic 13TB.

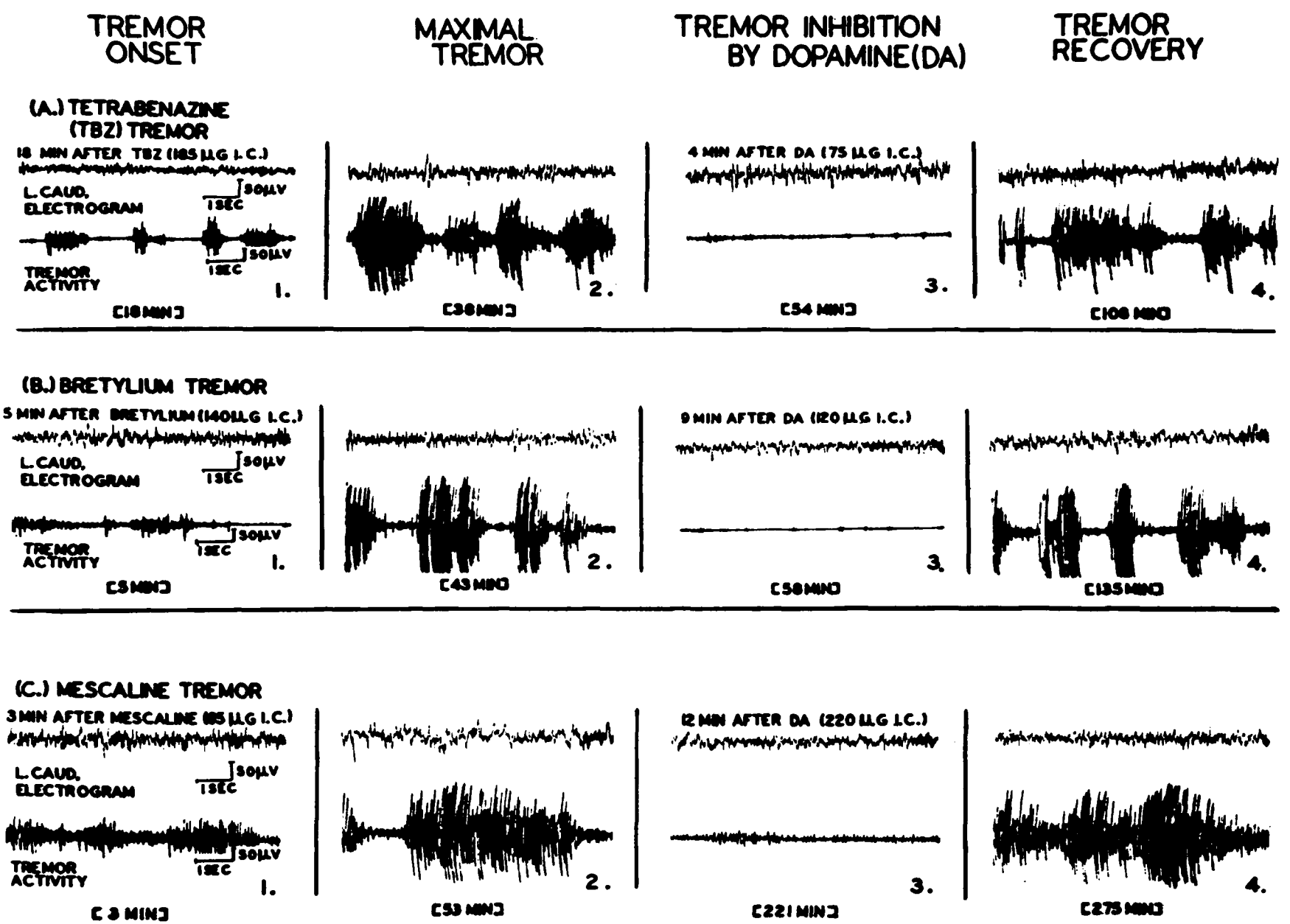

Figure 1—*Suppression of maximal tetrabenazine (TBZ), bretylium, and mescaline tremors by intracaudate injections of dopamine (DA). In each panel, upper tracings are caudate electrograms and lower tracings are tremor recordings. Numbers in brackets indicate the time sequence in minutes, continuous from the injection of each tremorgenic agent. Onset of significant tremor activity after intracaudate injections of tremorgenic agents (column 1) and maximal tremor activities (column 2) are shown. Tremors are abolished after intracaudate injections of DA (column 3) but recover to previous intensities (column 4). Doses of the tremorgenic agents (in parentheses) indicate their respective bases; those of DA represent its hydrochloride salt.*

Table III—Effects of Locally Injected Acetylcholine, Hemicholinium, or Scopolamine on Maximal Tremors Evoked by Intracaudate Tetrabenazine, Bretylium, and Mescaline

Locally Injected Agents	Activity Parameters	Tremors Evoked by—Tetrabenazine	Bretylium	Mescaline
Acetylcholine	Effect on tremor[a]	(0)	(0)	(0)
	Dose, mcg.[b]	32.2	32.2	32.2
	Activity ratio[c]	0/6	0/6	0/6
Hemicholinium	Effect on tremor	(−)	(−)	(−)
	Dose, mcg.	124.3 ± 4.3	140.0 ± 10.0	120.0
	Latency, min.	43.4 ± 1.1	35.0 ± 1.7	42.4 ± 2.0
	Activity ratio	7/7	6/6	7/7
	Duration[d]			
Scopolamine	Effect on tremor	(−)	(−)	(−)
	Dose, mcg.	78.1 ± 4.2	102.2 ± 9.2	178.8 ± 29.9
	Latency, min.	25.7 ± 3.4	19.0 ± 3.8	19.0 ± 3.9
	Activity ratio	6/6	6/6	7/7
	Duration[e]			

[a] (−) = tremor activity abolished; (0) = no effect on tremor activity. [b] Doses of acetylcholine or scopolamine represent their respective bases (mean ± standard error). [c] Activity ratio = number of tremor inhibitions/total number of trials. [d] Duration not followed; tremors reestablished by intracaudate injection of acetylcholine chloride (15–30 mcg.). [e] Duration of inhibition not followed; higher doses of scopolamine, after initially blocking tremors, evoked behavioral effects and involuntary movements, distinguishable from the test tremors elicited by tetrabenazine, bretylium, or mescaline.

RESULTS

Tremor Characteristics—Tetrabenazine, bretylium, and mescaline were tremorgenic over a range of doses (50–175 mcg.); the intensity and duration of tremor responses were proportional to the dose. Only the tremor responses to the higher doses of each drug were quantified; only in these higher doses was maximal tremor maintained throughout the entire experimental period of 5–6 hr.

As indicated in Table I, the tremors generated by these agents were more intense and of longer duration than the cholinergic tremors evoked by 150 mcg. intracaudate physostigmine (2). Bretylium had the most rapid onset of action, mescaline was intermediate, and tetrabenazine exhibited the longest latencies for onset and development of maximal tremor. The mean intracaudate doses required for comparable maximal tremor responses and duration were: tetrabenazine, 161 mcg.; bretylium, 112 mcg.; and mescaline, 64 mcg. Tremor characteristics (bursts per minute, tremor frequency, and percent tremor time) were similar for these three compounds and did not differ appreciably from those recorded during physostigmine (cholinergic) tremors. Neither autonomic nor behavioral changes were observed with any of the drugs while the animals were tremoring.

Effect of Intracaudate Monoamines on Tremors—The effects of microinjected dopamine, epinephrine, or serotonin when superimposed on ongoing maximal tremors induced by intracaudate tetrabenazine, bretylium, or mescaline are summarized in Table II. Intracaudate injections of the catecholamines (dopamine and epinephrine) temporarily abolished all three types of maximally developed tremors. Figure 1 illustrates the progressive changes in the development of tremors to maximal intensities, their subsequent inhibition by dopamine, and recovery with the return of tremor activity. Based on the doses required for maximal tremor suppression, epinephrine was six to seven times more potent than dopamine, but their respective latencies and durations of tremor inhibition were comparable. Mescaline tremors required appreciably higher doses of the catecholamines than the other two tremorgenic agents for complete suppression. Tetrabenazine tremors, although the most susceptible to suppression with dopamine, recovered to maximal intensities more rapidly than those of bretylium or mescaline.

In contrast to the catecholamines, intracaudate injection of serotonin, even at relatively low doses, intensified all three types of tremors, as evidenced by significant increases in essentially all tremor parameters (*i.e.*, amplitude, percent tremor time, and duration of tremor). However, these tremor intensities declined steadily to preserotonin levels within 25–60 min.

Intracaudate Cholinergic Agents on Tremors—Intracaudate acetylcholine, at a dose of 32 mcg., produced no discernible changes in tremor activity or electrograph patterns when injected during periods of maximal tremors induced by each of the three tremorgenic agents (Table III); this dose of acetylcholine is substantially below that (>500 mcg.) shown to be tremorgenic in the caudate (10). Comparable small doses of acetylcholine injected during the declining phases of these tremors also failed to alter existing tremor intensities. By contrast, local injections of hemicholinium, an agent known to interfere with acetylcholine synthesis, abolished all three types of tremors within 33–45 min., with no evidence of spontaneous recovery with the reestablishing of tremor activity during the experimental period. This inhibition of tremor was accompanied by bilateral synchronous slow waves in the caudate nuclei and postcruciate (frontal) cortex (Fig. 2). Parallel changes in behavior, autonomic functioning, or respiration were not evident. In all experiments, tremor suppressed by hemicholinium was readily restored (within 8–20 min.) by minimal supplemental doses (12–24 mcg.) of acetylcholine. This reestablished tremor activity usually persisted for less than 30 min. before declining. Nontremorgenic doses (6–13 mcg.) of physostigmine, when added to the acetylcholine injection, extended the duration of the reestablished tremor well beyond 1 hr.

Scopolamine, when microinjected into the caudate, also abolished the maximal tremors evoked by each of the three tremorgenic agents within 13–30 min. (Table III). The relatively high doses of scopolamine (>120 mcg.) required in the present study to suppress tremor (contrasting with scopolamine doses of less than 25 mcg. that suppress cholinergic tremors) produced another type of involuntary motor activity. These movements were slower (10–20 c.p.s.) rotational excursions of the hindlimb and were readily distinguished from the characteristic maximal tremor (21–25 c.p.s.).The involuntary movements generated by large doses of scopolamine were accompanied by pronounced autonomic (mydriasis), behavioral (apparent disorientation and distress), and electrographic (caudate-localized and projected synchronous slow waves) changes. In contrast to the inhibitory action of hemicholinium, tremor suppression by scopolamine was not reversed by intracaudate acetylcholine.

DISCUSSION

Although significant differences exist in their neuropharmacological actions (12), several lines of evidence support the position that tetrabenazine, bretylium, and mescaline share a common basis for their local tremorgenic actions in the caudate, namely interference with the level of dopamine functioning. The characteristics of their tremor responses (frequencies, bursts per minute, and tremor time) were strikingly similar; however, there were appreciable differences in their tremorgenic potencies (mescaline > bretylium > tetrabenazine) and in their onset and time sequences for reaching peak activity. It is significant that their tremor activities were quite comparable to the tremor type characterized previously during increased cholinergic activity in the caudate (10) and also that the catecholamines (dopamine and epinephrine) and hemicholinium were highly effective in suppressing cholinergic tremor (1, 2) as well as "dopamine-deficiency" tremors described in the current investigation. Because of its putative neurotransmitter role (13), attention

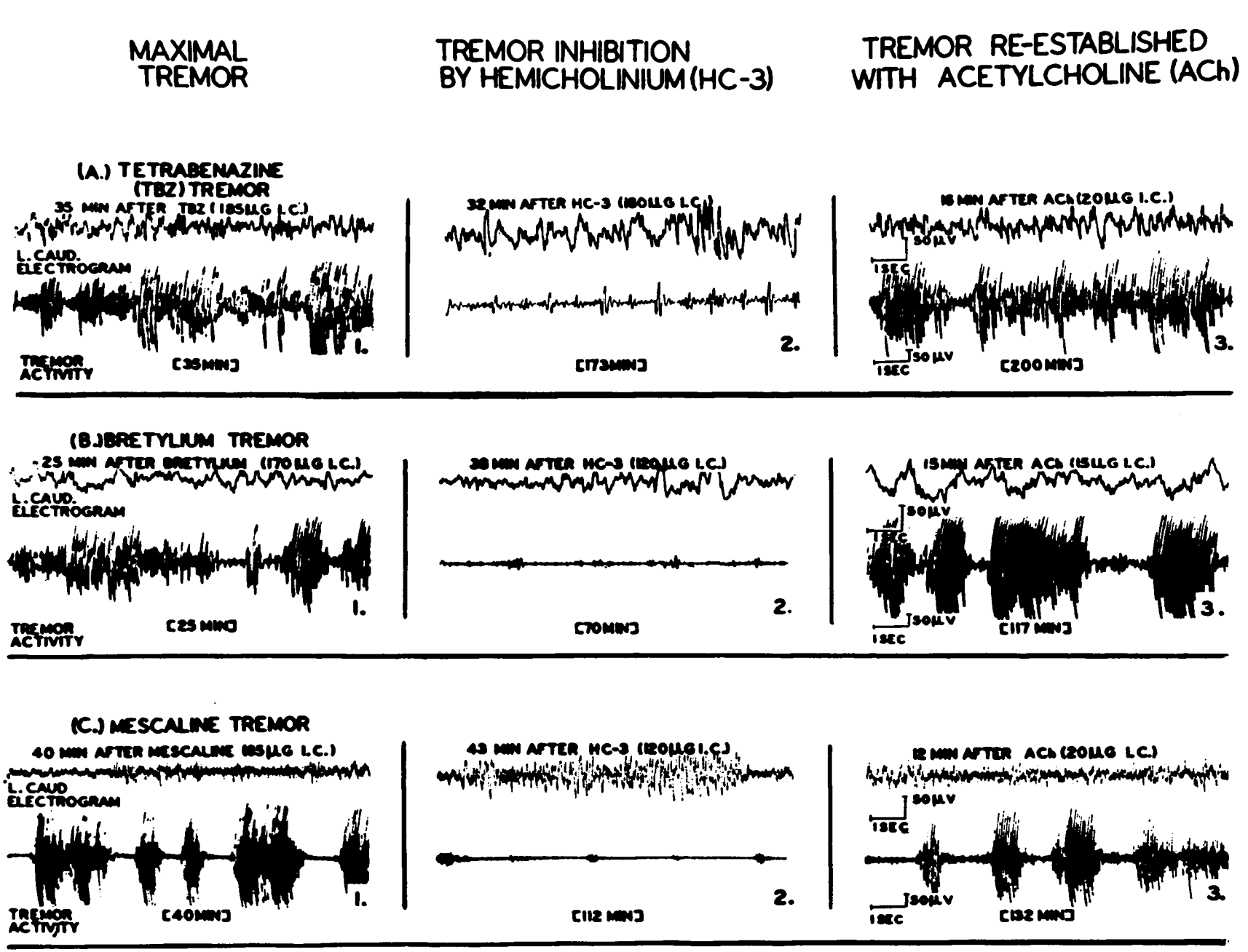

Figure 2—*Inhibition of maximal tetrabenazine (TBZ), bretylium, and mescaline tremors by intracaudate injections of hemicholinium-3 (HC-3). Tremors were reestablished temporarily by intracaudate supplemental injections of acetylcholine (ACh). Doses of acetylcholine represent its chloride salt.*

was directed to the functional status of dopamine (rather than epinephrine) in the caudate. The interpretation that seems most consistent with the present data and previous findings with cholinergic tremor is that interference with local dopamine functioning results in a relative increase (or imbalance) in favor of acetylcholine activity, which then causes tremors. In keeping with this is the proposal that the effects of acetylcholine in the caudate are excitatory and that, under stable conditions, these effects are offset by the local inhibitory action of dopamine (3, 14).

Since levels of dopamine in the caudate were not determined chemically, evidence is lacking to substantiate this interpretation directly. However, a consideration of the neuropharmacology of the three agents may establish a relationship to their ability to impair the functioning of endogenous dopamine. Bretylium, by virtue of its quaternary structure, is limited in its access to the brain; but when administered systemically, bretylium is taken up by tissues having a relatively high concentration of dopamine (15). Thus, it would be reasonable to expect that microinjected bretylium might be localized in dopamine-containing axon terminals of the caudate nucleus and, by analogy with its peripheral antiadrenergic actions (16), that it may elicit tremors by interfering with the release of intracaudate dopamine. Along parallel lines, tetrabenazine, like reserpine, depletes catecholamines (as well as serotonin) in the CNS by blocking ATP-dependent uptake of monoamines into storage granules (17). Of the monoamines in question, a deficiency of serotonin is ruled out as the basis for the tremors in these studies, since supplemental microinjected serotonin intensified tetrabenazine tremor responses whereas dopamine suppressed them. It thus appears that tetrabenazine tremor can be linked more appropriately to a deficiency of dopamine.

Mescaline and other *O*-methylated derivatives of dopamine were reported (18, 19) to produce tremors experimentally. Tremorgenic effects of intracaudate mescaline in cats demonstrated in this study essentially parallel the findings by Little and Dill (19) of dyskinesias after injection of mescaline into the caudate–putamen complex in rats. Dill (14) attributed mescaline dyskinesias in part to blockade of adrenergic inhibitory receptors, which in turn upsets a hypothesized local acetylcholine–dopamine balance. Results of the present studies tend to support this general proposition. Apparently, mescaline also exerts an "intrinsic," nonadrenergic, tremorgenic action since various other adrenergic receptor blocking agents (chlorpromazine and propranolol) neither suppress the dyskinetic excitatory effects of mescaline (14) nor are themselves tremorgenic when injected into the caudate (1). Significantly, on brainstem neurons, microinjected mescaline blocked only the inhibitory actions of the catecholamines without affecting the excitatory ones (20). The higher doses of dopamine required to suppress mescaline tremors, in comparison to doses that suppressed bretylium or tetrabenazine tremors, might be explained by the effective dopamine receptor blocking action of mescaline.

The data also underscore the key role of local acetylcholine in the development and maintenance of tremor activities with all three agents. This is evidenced not only by hemicholinium suppression of tremor and by restoration of this activity with acetylcholine but also by antagonism with scopolamine. However, since neither tetrabenazine nor bretylium nor mescaline had an apparent anticholinesterase action (no potentiation of low doses of microinjected acetylcholine), the involvement of acetylcholine as a necessary condition for these tremors may be attributed to a resulting predominance of endogenous cholinergic mechanisms. This appears to have a bearing on the increased cholinergic hyperactivity secondary to decreased dopamine functioning noted in clinical Parkinsonism (21).

It is concluded that tetrabenazine, bretylium, and mescaline are tremorgenic because they each produce, by somewhat different mechanisms, a functional dopamine deficiency in the caudate. Yet, for the development and maintenance of these tremors, a sustained endogenous acetylcholine activity in the caudate is essential. The data thus add support to the hypothesis that the excitatory effects of acetylcholine and the inhibitory actions of dopamine in the caudate are critically balanced and, as such, represent an important local system for regulating motor activity.

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