Participation of the Ventral Root in Drug-Induced Tremor (Tremorine)*

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Numerous investigators have described the synchronous electromyographic discharges in various types of tremor, experimental and pathological. Synchronous unit discharges have been recorded in the thalamus of patients with parkinsonism, and in the cerebral cortex of animals with experimental tremor. Decima, et al., have reported synchronous bursts in muscle nerves in the cat after administration of tremorine. Whereas a synchronous alpha motoneuron discharge in time with tremor is the obvious explanation for the phenomenon of tremor, there does not appear to be a report of a direct demonstration of its occurrence. The present study shows that for one type of tremor at least, that induced in rats by tremorine, such synchronous firing does indeed occur in the ventral root fibers and appears to result solely from the central descending influences on the alpha motoneuron.

Tremorine (1,4-dipyrrrolidino-2-butyne)† is oxidized in the liver to oxotremorine (1-(2-oxopyrrrolidino)-4-pyrrolidino-2-butyne), which induces among other effects tremor, rigidity, and akinesia in birds and mammals. The 10–15 cps tremor occurs at rest but also during action; is asynchronous in the four limbs; is inhibited by antiparkinsonian drugs and by proprioneptive stimuli, and is also associated with certain alterations in brain stem bio-

amines. Previous studies in this and other laboratories strongly suggest that in the rat the tremor is induced by direct action on the midbrain reticular formation, in the region where Siminoff demonstrated the only reticular neurons whose stimulation altered the firing of inter- and motoneurons. Thus the tremor is independent of cerebellar hemispheres and structures rostral to subthalamus, including the cerebral hemispheres. The tremorigenic effect is conducted bilaterally in the brain stem and cord. True tremorine tremor does not occur below the level of cord section. Moreover, the fact that it is not affected by dorsal rhizotomy indicates that it can occur independent of the muscle spindle mechanism.

Method

Tracheotomies and lumbar laminectomies were performed on 100 albino rats (weighing 500 gm each) under nembutal anesthesia (60 mg/kg) and 1% lidocaine hydrochloride infiltration. Following curarization (d-tubocurarine 0.16 mg/kg), animals were suspended rigidly with vertebral clamps and maintained on the Harvard pump (45 cycles per min, 65 cc tidal volume). Ventral roots, and in some cases dorsal roots, were identified and teased to small fibers under paraffin oil at 37°C with the help of a ×16 dissecting microscope. After extensive dorsal rhizotomy, the nembutal anesthesia was allowed to wear off over 3 to 4 hours. Root action potentials were led off through monopolar or biopolar 30-gauge stainless steel wire electrodes to a Grass P5 preamplifier and Tektronix RM565 dual beam oscilloscope. After control records were recorded, 10 mg/kg Tremorine was injected intraperitoneally and the action potentials were followed.

Results

Ventral root action potentials were virtually absent in curarized control animals except for occasional bursts similar in timing to the spontaneous motor activity seen in suspended intact rats. These could also be initiated by disturbing the animal.

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Approximately 5 min after tremorine injection, the first change in ventral root activity occurred with random firing of low voltage units (10 to 30 μV) similar to that induced by squeezing the ear in the control state. After 5 to 7 min, this activity became synchronized at 10 to 15 cps (Fig. 1a), slightly before the expected time of visible tremor in the intact animal. After 7 to 10 min at precisely the expected time of appearance of visible tremor in the noncurarized rat, high voltage (100 to 125 μV) potentials appeared for the first time, synchronized from the outset at 10 to 15 cps (usually 12 to 15). Progressively more units participated in these bursts, which became more regular up to 15 min after Tremorine injection (Fig. 1b). This activity could be inhibited by the same proprioceptive stimuli that suppressed visible tremor in the intact rat (Fig. 1c). Following release of such sensory inhibition, the same accentuation of synchronous bursts occurred as had been seen with visible tremor in the intact rat. About 15 min after

Fig. 1. Activity of a whole left lumbar ventral root after Tremorine. Time scale: each small division equals 1 msec. Slow wave activity equals that of EKG. a) Rat F29/IV/65, 7 min after Tremorine: bursts of low voltage activity at 12 cps. b) Rat F11/V/65, 15 min after Tremorine: high voltage potentials in synchronous bursts at 12 cps. c) Rat F11/V/65, consecutive trace from left to right. Base of tail compressed lightly between the arrows inhibited tremor.