Inhibition of neuromuscular transmission in the intact rat by emetine

Whether the skeletal muscular weakness which often complicates treatment with emetine hydrochloride (Goodman & Gillman, 1965) arises from a direct action on the muscle (Klatskin & Friedman, 1948) or is secondary to an action on the nerve (Brown, 1935) is still uncertain. Young & Tudhope (1926), in experiments on the rat, found no evidence of inflammation in the nerve but observed degenerative changes in muscle; and recently Ng (1966) showed that the drug blocked the indirectly elicited contraction of the rat isolated diaphragm without significantly affecting the directly elicited contraction. This problem has been further investigated by studying the effect of emetine on neuromuscular transmission in the intact rat using the sciatic nerve-gastrocnemius muscle preparation. Emetine is already known to produce morphological as well as *in vitro* functional changes in the neuromuscular system of the rat.

Twelve rats were given subcutaneous injections of emetine, 1 mg/kg (comparable to the human dose), daily for ten days. Twenty-four h after the last injection, a sciatic nerve-gastrocnemius muscle preparation was made. Similar nerve-muscle preparations were also made in 12 untreated rats. The nerve was stimulated supramaximally with square pulses of 100 to 1000 μs duration. Single twitches of the muscles were elicited at a frequency of 8/min, and, at intervals, tetani were elicited by increasing the stimulation rate to 64/s for 15 s.

Nerve stimulation in treated rats produced twitches of the muscle in the usual manner. However, unlike the normal rat preparation, the twitches were often of irregular height, and after 2–5 min there was a progressive fall in twitch height with

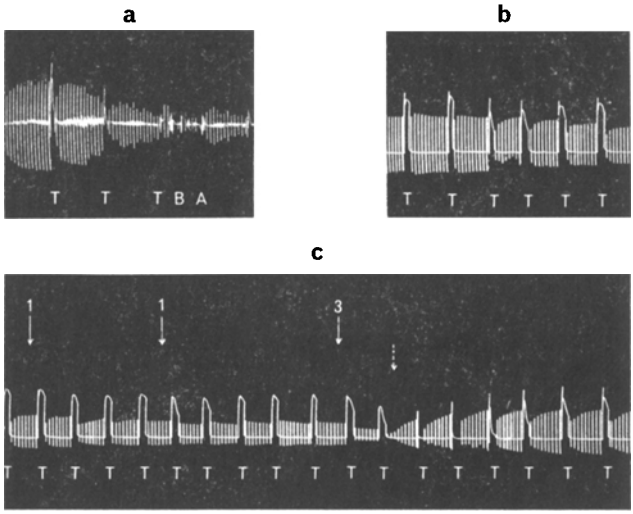

FIG. 1a. Rat 225 g. Treated with emetine hydrochloride 1 mg/kg subcutaneously daily for 10 days. Indirect maximal twitches and tetani (T) of the left gastrocnemius muscle. At B pulse strength was doubled with no effect on twitch. At A, transient recovery of twitch occurred after stopping stimulation for 5 min.

b. Control rat 225 g. Sciatic nerve-gastrocnemius muscle preparation. Indirect maximal single twitches and tetani (T) of the left gastrocnemius muscle. Emetine hydrochloride (1 mg/kg) was given intravenously between the second and third tetani.

c. Control rat 250 g. Indirect maximal twitches and tetani (T) of the left gastrocnemius. At unbroken arrows, emetine hydrochloride was given intravenously. The dose given (in mg/kg) is shown on top of each arrow. At the broken arrow, prostigmine (5 mg) was given intravenously.

complete absence of response after 10–20 min (Fig. 1). Increasing the strength of the impulse did not prevent this abolition of the muscle response, but if nerve stimulation was at this juncture stopped for 5 min or longer, a transient recovery of twitch occurred. Also, in contrast to normal rats, the treated animals failed to maintain muscle tetanus (Fig. 1a).

Intravenous injection of emetine (1 mg/kg) in preparations from untreated rats produced little effect on single twitches, but caused a definite fall in the height of the tetanus with inability to maintain it at a steady height for the duration of the stimuli (Fig. 1b). Onset of the effect as well as recovery from it was rapid, and the effect could be reproduced by repeating the dose of emetine (Fig. 1c). With increasing doses of the drug, single twitches were also inhibited but the effect on tetanus was always greater than that on single twitches. A dose of 3 mg/kg produced complete inhibition of both single twitches and tetanus. The inhibitory effect of the drug was antagonized by prostigmine, the effect on single twitches being more readily antagonized than that on tetanus (Fig. 1c).

The results of these *in situ* studies thus support the *in vitro* findings of Ng (1966) and suggest that emetine has a tubocurarine-like effect on neuromuscular transmission in the rat.

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Treatment of experimental lymphoedema with coumarin

Experimental lymphoedema can be treated with coumarin. Investigations were made in groups of 30 rats, 200 $\pm$ 30 g. Lymphoedema was induced by extensive ligation of cervical lymph nodes, with careful sparing of blood vessels and nerves; the extent of the lymphoedema of the head and of the neck was measured plethysmographically on the 4th postoperative day.

Control animals were treated with 0·9% NaCl solution and the experimental group was injected with 5 mg coumarin per kg daily. The controls showed an increase in the volume of the head and the neck of 21%, the coumarin-treated animals an increase of 10%. The difference between the treated and the untreated group is significant $P < 0{\cdot}02$. The explanation of the therapeutic effect of coumarin remains to be elucidated.

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