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Rifampicin induction of myopathy: lack of a direct effect on rat neuromuscular system

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The effect of acute administration of rifampicin on neuromuscular transmission was tested, in-vivo, in the rat. Rifampicin did not alter the strength of contraction of the muscle indirectly stimulated at various frequencies. Additional isoniazid pretreatment did not alter the absence of effect of rifampicin on neuromuscular action.

Recently a clinical case of severe proximal myopathy caused by rifampicin was reported by Jenkins & Emerson (1981). On the other hand, Kasahara et al (1970) showed that rifampicin at high doses (10^{-5} g ml^{-1} in-vitro and 10 mg kg^{-1} in-vivo) did not modify the contractile parameters of skeletal muscle either in-vitro (frog) or in-vivo (rabbit). In the clinical case reported, the authors (Jenkins & Emerson 1981) hypothesize that the myopathy induced by rifampicin treatment was of immunological nature as are some of the other side effects due to this drug (Poole et al 1971: O'Mahony & Kar 1973). Nevertheless, the authors did not clarify the real nature of the myopathy and they only measured the titre of antibodies six weeks after drug withdrawal. In the present study we analyse in the rat the effects of acute injection of rifampicin on the neuromuscular transmission in-vivo, and we evaluate the possible interference with isoniazid pretreatment.

Methods

Two groups of 12 and 6 male Wistar rats (260–300 g) were used. In the first group, experiments with untreated anaesthetized animals were on the sciatic nerve-gastrocnemius muscle preparation. The mechanical responses of the muscle to single and multiple stimuli applied to the sciatic nerve were recorded before and after injection into the femoral vein of increasing doses of rifampicin (from 10 to 200 mg kg^{-1} in cumulative doses). The single supramaximal impulses were applied at frequency of 1 Hz; multiple stimulation was applied at frequency of 5 Hz and 10 Hz for 30 s. The second group of rats was injected i.m. daily for 12 days with isoniazid (20 mg kg^{-1}) before the acute experiment (as described above). All the procedures used have been described by Renna et al (1981).

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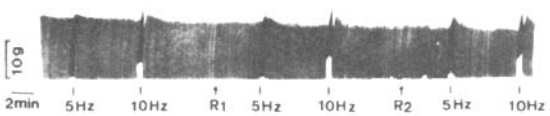

FIG. 1. Typical records of the effect of rifampicin on the strength of contraction of rat gastrocnemius muscle indirectly stimulated at various frequencies (1, 5 10 Hz). At the arrows the rat was injected with rifampicin (R_1 = 50 mg kg^{-1}; R_2 = 100 mg kg^{-1} i.v.) in cumulative doses.

Results

Rifampicin, at the different doses tested, did not influence the strength of contraction of the gastrocnemius muscle stimulated indirectly at various frequencies (Fig. 1). Also, in the rat receiving isoniazid for 12 days before the acute experiment, rifampicin did not affect the contractile parameters of the muscle tested.

Discussion

Several antibiotics are known to interfere with neuromuscular transmission and for most of them the mechanism of this side effect is due to a direct action of the drug on the nerve terminal or on the postjunctional skeletal muscle membrane (Albiero et al 1978; Rubbo et al 1977).

Nevertheless, the clinical case of myopathy reported by Jenkins & Emerson (1981) during rifampicin treatment is the only one imputed to this drug.

Our results indicate that rifampicin does not affect directly neuromuscular transmission in the rat: in fact in the rifampicin injected rats stimulation of the gastrocnemius muscle through the nerve did not demonstrate any alteration in any of the contractile parameters of this muscle. The isoniazid pretreatment of rats did not alter muscle contractility either.

In conclusion, in agreement with the hypothesis of Jenkins & Emerson (1981) it seems likely that the rare rifampicin-induced myopathy, is probably of an immunological nature and not due to any direct effect.

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