EFFECT OF NIFEDIPINE ON THE CONTRACTILE RESPONSES OF HUMAN COLONIC MUSCLE

In recent years calcium antagonists have gained popularity for use in certain cardiovascular abnormalities, the therapeutic objective being a controlled inhibition of cardiovascular tone and contractility. Since these drugs are believed to act by inhibiting the calcium influx into smooth muscle, it seems reasonable to expect that calcium antagonists would exert a depressant effect on the contractile responses of gastrointestinal smooth muscle. To the best of our knowledge the influence of these drugs on the contractile responses of mammalian colonic muscle has not been reported before. We give here an account of preliminary investigations on the effect of nifedipine on the contractile responses of human colonic muscle.

All experiments were performed on *in vitro* preparations, dissected from superficially healthy human colonic muscle removed during operations on seven patients for carcinoma of the large intestine or for ulcerative colitis. Strips of longitudinal muscle and of circular muscle, about 3 cm long and 3 mm wide, were prepared and suspended at 36°C at a resting tension of 1.5 g in Krebs-Henseleit solution: (mM: NaCl,

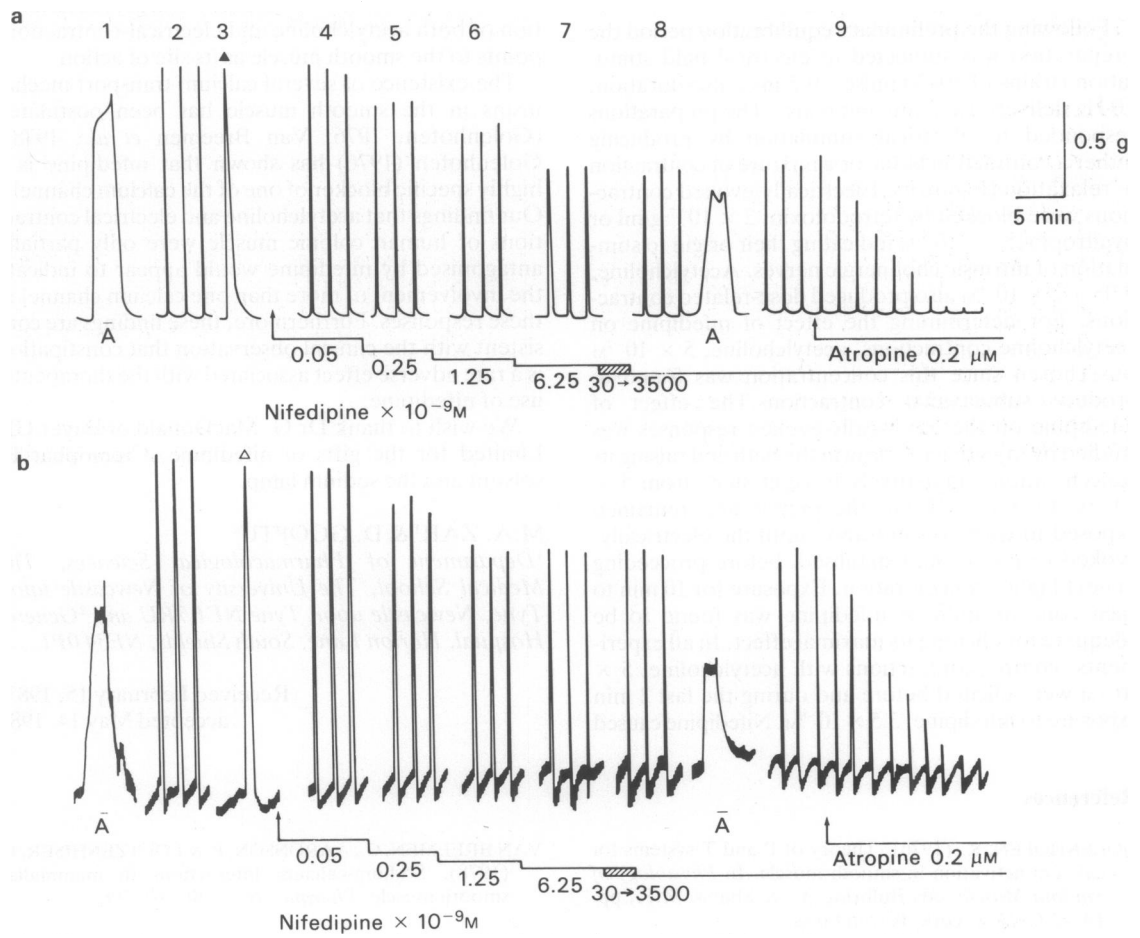

Figure 1 Effect of nifedipine and atropine on the responses of longitudinal muscle (a) and circular muscle (b) preparations of colonic muscle from a 62 year old female patient. The contractile responses (a) were evoked by exposure to acetylcholine, 0.5 μM. All other contractile (and relaxant) responses were evoked by electrical stimulation (trains of 20 pulses, 0.5 ms pulse duration, 10 Hz delivered at 2 min intervals). The responses in panel 3 (▲ △) were recorded at five times normal chart speed. From panel 4 onwards, the preparations were exposed to cumulatively rising concentrations of nifedipine and each panel shows the last 3 min of 10 min exposure to each concentration. Panel 8 also shows the effect of nifedipine on acetylcholine contraction. Note the partial block of electrically evoked contractions by nifedipine but their virtual total extinction by atropine.

13; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25; glucose, 11.5), bubbled with 95% O_2–5% CO_2 in 10 ml organ baths with built-in platinum electrodes. The preparation was allowed to equilibrate in the bathing medium for 2 h and was washed repeatedly with fresh Krebs solution at intervals of 10–15 min; during this period it gradually acquired tone, necessitating adjustments of resting tension to keep it at 1.5 g. Smooth muscle tone was monitored continuously using an isometric transducer and pen-recorder. Since nifedipine is extremely unstable in natural light, all experiments were conducted in a blacked out laboratory using a sodium lamp for illumination. Nifedipine was dissolved in Cremophor El solvent to make 3×10^{-2}M solution and further dilutions were prepared with saline.

Following the preliminary equilibration period the preparation was subjected to electrical field stimulation (trains of 10–30 pulses, 0.5 ms pulse-duration, 10 Hz delivered at 2 min intervals). The preparations responded to electrical stimulation by producing either a contraction alone or a mixture of contraction + relaxation (Figure 1). Electrically-evoked contractions were blocked by tetrodotoxin, 2×10^{-7} g/ml or by atropine, 2×10^{-7}M indicating their origin to stimulation of intrinsic cholinergic nerves. Acetylcholine, $0.05 - 2 \times 10^{-6}$M also produced dose-related contractions. For determining the effect of nifedipine on acetylcholine contractions, acetylcholine, 5×10^{-7}M was chosen since this concentration was found to produce submaximal contractions. The effect of nifedipine on the electrically-evoked responses was studied by injecting the drug in the bath and raising its concentration cumulatively in eight steps from 5×10^{-11}M to 3.5×10^{-6}M; the preparation remained exposed to each concentration until the electrically-evoked responses had stabilised, before proceeding to next higher concentration. Exposure for 10 min to each concentration of nifedipine was found to be adequate for eliciting its maximal effect. In all experiments, control contractions with acetylcholine, 5×10^{-7}M were elicited before and during the last 2 min exposure to nifedipine, 3.5×10^{-6}M. Nifedipine caused partial inhibition of electrical and acetylcholine-contractions both in longitudinal and circular muscle preparations (Figure 1). The contractile responses of control preparations, in which comparable volumes of saline containing equivalent quantities of Cremophor El solvent were added, remained unchanged during this period. The threshold concentration of nifedipine for inhibition of electrical contractions ranged between $0.5–2.5 \times 10^{-10}$M. Although the mean values of maximum % inhibition of contractions ± s.e. mean were modest (longitudinal muscle: electrical 36.17 ± 10.68, acetylcholine 41.7 ± 5.2; circular muscle: electrical 40.02 ± 4.85, acetylcholine 38.65 ± 8.6), these were achieved by a relatively low concentration of nifedipine (3×10^{-8}M). The finding that nifedipine exerted comparable degrees of inhibition of both acetylcholine and electrical-contractions points to the smooth muscle as its site of action.

The existence of several calcium transport mechanisms in the smooth muscle has been postulated (Golenhofen, 1976; Van Breemen *et al.*, 1978). Golenhofen (1976) has shown that nifedipine is a highly specific blocker of one of the calcium channels. Our findings that acetylcholine and electrical contractions of human colonic muscle were only partially antagonised by nifedipine would appear to indicate the involvement of more than one calcium channel in these responses. Furthermore, these findings are consistent with the clinical observation that constipation is a rare adverse effect associated with the therapeutic use of nifedipine.

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References

GOLENHOFEN, K. (1976). Theory of P and T systems for calcium activation in smooth muscle. In *Physiology of Smooth Muscle*, eds Bulbring, E. & Shuba, M.F., pp. 197–202. New York: Raven Press.

VAN BREEMEN, C., AARONSON, P. & LOUTZENHISER, R. (1978). Sodium-calcium interactions in mammalian smooth muscle. *Pharmac. Rev.*, **30**, 167–208.