A nerve-blocking action of MJ-1999

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The local anaesthetic action of propranolol is a disadvantage when the drug is used to investigate the possible β-receptor activity of a neurotransmitter. MJ-1999 (4'-(2-isopropylamino-1-hydroxyethyl) methanesulphonanilide hydrochloride), is reported to be a β-receptor blocking drug without local anaesthetic action (Lish, Weikel & Dungan, 1965). We have compared the β-receptor and nerve-blocking actions of these drugs on isolated organs bathed in Krebs solution.

Both drugs antagonized isoprenaline on chick rectum, propranolol (4 ng/ml.) and MJ-1999 (2·2 μg/ml.), giving a dose ratio of 100. Contractions of guinea-pig vas deferens to hypogastric nerve stimulation (0·1 msec, 30 Hz, submaximal) for 5 sec in every 5 min were antagonized, 20 min exposure to propranolol (4 μg/ml.) or MJ-1999 (108 μg/ml.) producing a 50% block (Fig. 1). Although propranolol was 27 times as potent as MJ-1999 in its nerve-blocking action, it was 550 times as potent in antagonizing isoprenaline. Thus propranolol was the more potent and specific β-receptor blocking drug.

The nerve-blocking action of these drugs was studied further. MJ-1999 (10% w/v) did not anaesthetize the rabbit cornea but propranolol (0·2% w/v) did. MJ-1999 (200 μg/ml.) antagonized contractions of the vas deferens to stimulation through the hypogastric nerve but not to transmural stimulation. Propranolol (10 μg/ml.) antagonized contractions of the vas deferens to both hypogastric and transmural

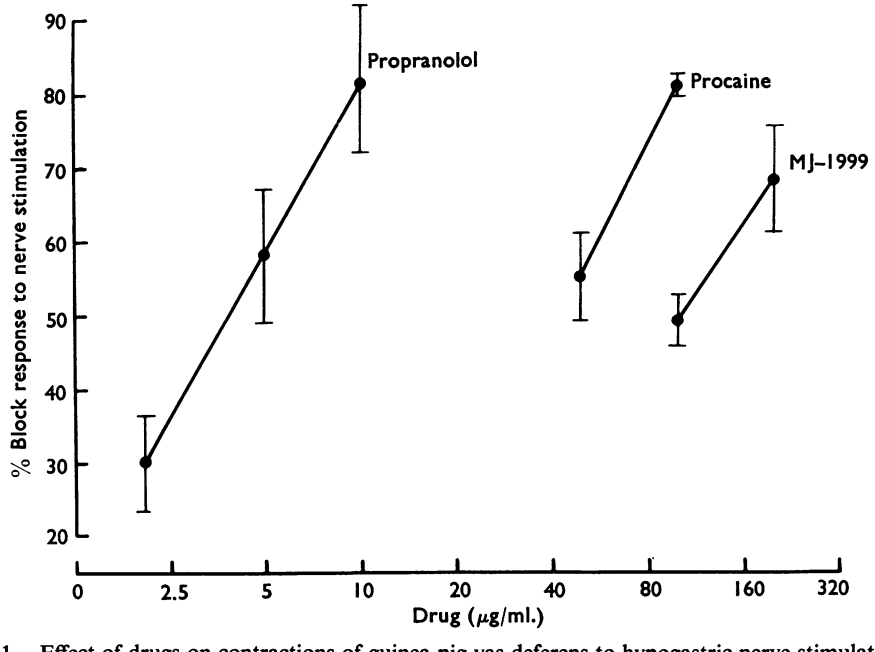

FIG. 1. Effect of drugs on contractions of guinea-pig vas deferens to hypogastric nerve stimulation. Ordinate, % reduction in height of contraction after 20 min exposure to drug; abscissa, drug concentration (μg/ml.) on a log scale. Each point represents the mean value obtained from four experiments, the vertical bars depicting the standard errors of the means.

stimulation, but did not antagonize noradrenaline. The guinea-pig oesophagus responded to vagal stimulation with a twitch followed by a contracture; MJ-1999 (200 μg/ml.) antagonized the contracture but not the twitch, whereas propranolol (10 μg/ml.) antagonized both. The effects of MJ-1999 on the guinea-pig vas deferens and oesophagus resemble those of hexamethonium (Birmingham & Wilson, 1963; Bartlet, 1968) and confirm its lack of local anaesthetic action.

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Comparison of propranolol and I.C.I. 50,172 on isoprenaline-induced increase in skin temperature in man

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Propranolol and I.C.I. 50,172 both block adrenoceptive β-receptors in the heart, whereas only propranolol blocks those in the smooth muscle of peripheral blood vessels (Dunlop & Shanks, 1968). These compounds have been compared, therefore, for their effects on isoprenaline-induced increase of skin temperature in man.

Six normal subjects aged 21–48 years were given propranolol 80 mg, I.C.I. 50,172 200 mg and placebo by oral administration at weekly intervals. The drugs and the placebo were given in random order based on a latin square design, under double blind conditions. Two hours later the skin temperature responses to isoprenaline inhalation from " Medihaler IsoForte " aerosols were recorded by means of copper-constantan thermocouples (voltage output 40 μV/° C). These were attached to the cheek, over the sterno-clavicular joint, to the volar surface of the forearm and to the dorsum of the hand. They were connected to Grass polygraph Model 7P1-preamplifiers calibrated within a range of 24°–40° C. The number of " puffs " of isoprenaline necessary to obtain a consistent temperature increase over cheek or sternum or both had previously been determined for each subject. Temperatures were recorded before and for 10 min after inhalation. Heart rate was monitored simultaneously by electrocardiographic recording on the same Grass polygraph.

The results demonstrated a significant rise of mean skin temperature over the cheek (0·5° C, S.E.M. 0·14, $t=3{\cdot}57$, $P<0{\cdot}02$) when isoprenaline was inhaled following placebo administration, but changes in temperature in the other areas were not significant. Propranolol abolished the increase in mean cheek temperature after isoprenaline inhalation (0·18° C, S.E.M. 0·09, $t=2{\cdot}0$) but I.C.I. 50,172 did not (0·65° C, S.E.M. 0·15, $t=4.33$, $P<0{\cdot}01$). The differences in response between placebo and propranolol, and between I.C.I. 50,172 and propranolol were significant ($P<0{\cdot}01$ and $<0{\cdot}05$ respectively).