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SCH 23390 can enhance field stimulation-induced contractions of longitudinal smooth muscle from guinea-pig stomach

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Field stimulation-induced contractions of guinea-pig stomach longitudinal muscle strips were enhanced by metoclopramide (a D-2 receptor antagonist) and SCH 23390 (a D-1 receptor antagonist) but not by *cis*-flupenthixol (a D-1 and D-2 receptor antagonist) or sulpiride (a D-2 receptor antagonist). SCH 23390 is the first non-benzamide neuroleptic drug shown to enhance cholinergic mediated contraction responses of gastric smooth muscle, but the response does not appear to reflect a D-1 receptor antagonism.

The cerebral D-2 dopamine receptor antagonists metoclopramide and clebopride are both able to facilitate contractions of stomach smooth muscle, but this property is not shared by other agents of similar antagonist profile (Costall et al 1984). The indication of a dissociation between action on gastric smooth muscle and dopamine antagonist properties is extended in an analysis of the actions of a highly selective D-1 dopamine receptor antagonist, SCH 23390 [(*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine] (Iorio et al 1981, 1983; Hyttel 1983).

Male Dunkin-Hartley guinea-pigs were killed by cervical dislocation, the stomachs removed and body longitudinal muscle strips (20 mm long, 5 mm wide) taken and placed in organ baths containing oxygenated (95% O_2, 5% CO_2) Krebs-Henseleit solution at 37 °C. 1 g tension was applied to the tissues which were allowed to equilibrate for 45 min before electrical stimulation, achieved through platinum electrodes placed approximately 5 mm apart (supramaximal voltage, 0·1 ms pulse width). Tissues were stimulated for 30 s every 5 min. Tension changes were detected by Grass tension transducers and displayed on a Grass recorder. A frequency-response curve (0·125–10 Hz) was initially constructed in the absence of drug and then in the presence of the potential interacting drug (40 min pretreatment); the second curve was related to the first to assess the degree of change.

Field stimulation (FS) of the stomach strips caused repeatable frequency-related contraction responses which could be reversed to relaxations by atropine (5×10^{-8} M). Metoclopramide and SCH 23390 both enhanced the contraction responses without significant effect on resting tension (both active at 10^{-7}–10^{-5} M, Fig. 1). (−)Sulpiride and *cis*-flupenthixol (10^{-7}–10^{-5} M) failed to modify the FS-induced contractions or (at 10^{-6} M) the enhancement of these by metoclopramide or SCH 23390. Prazosin, propranolol and yohimbine (5×10^{-7} M) also failed to modify the enhanced contractions

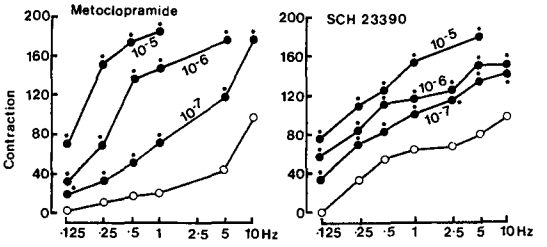

FIG. 1. Enhancement of field stimulation (0·125–10 Hz)–induced contractions of longitudinal smooth muscle, taken from the body of guinea-pig stomach, by SCH 23390 and metoclopramide (●—● M concentrations indicated); ○—○ control values. All values are expressed as a percentage of the control contractions occurring at 10 Hz. n = 6–8, s.e.m.s on original data <13%. Significant increase above control values indicated as $^*P < 0{\cdot}01$–$P < 0{\cdot}001$ (Mann Whitney U test).

caused by metoclopramide or SCH 23390 although these were abolished by atropine (5×10^{-8} M). Metoclopramide and SCH 23390 (10^{-6}–10^{-5} M) failed to modify the relaxation responses obtained to FS in the presence of atropine (5×10^{-8} M), and failed (at 10^{-5} M) to modify the contractions to exogenous acetylcholine (10^{-8}–4×10^{-8} M).

SCH 23390 is the first non-benzamide neuroleptic agent shown to enhance cholinergic-mediated contraction responses of gastric smooth muscle preparations. That this action is not mimicked by *cis*-flupenthixol (an effective D-1 dopamine receptor antagonist) (Hyttel 1983), and that the facilitatory actions of metoclopramide and clebopride are not shared by sulpiride (D-2 dopamine receptor antagonist) (Hyttel 1983), is forwarded as evidence of an independence between neuroleptic properties to antagonize at D-1 and D-2 dopamine receptors and ability to facilitate cholinergic contraction responses of the stomach musculature.

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