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Specific blockade of spasmogens by β-receptor stimulation with nylidrin and isoprenaline

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Nylidrin, a β-adrenoreceptor stimulant drug, blocks the spasmogenic action of acetylcholine, histamine and barium on guinea-pig ileum *in vitro* and bronchial muscles *in vivo*. This action is antagonized by the β-receptor blocking agent, propranolol. It is suggested that the antispasmodic effect of nylidrin is mediated through the activation of β-receptors. Nylidrin seems to be less potent but longer acting in its antispasmodic action than isoprenaline.

Nylidrin is a sympathomimetic agent with a β-adrenoreceptor stimulant action (Goodman & Gilman, 1965); it is used clinically for peripheral vascular disorders (Freedman, 1955; Caliva, Eich & others, 1959).

We have investigated whether nylidrin has an inhibitory action against spasm produced by spasmogens acting through receptors or directly on smooth muscle. We have also sought to explain any inhibition and have compared the effects of the drug with those of isoprenaline.

EXPERIMENTAL

Effect on spasm produced by spasmogens in guinea-pig ileum. Guinea-pigs, 300–400 g, were killed by a blow on the head and bled. A terminal section of ileum was removed, cleaned and set up in a 25 ml bath containing aerated Tyrode solution at 32–34°. Contractions were recorded with a frontal writing lever. The effect of nylidrin ($2{\cdot}4 \times 10^{-8}$ and 8×10^{-7} g/ml) with 1 min contact was studied on spasm produced by histamine, acetylcholine and barium. In other experiments, the effects of nylidrin was studied after blockade of β-adrenoreceptors by propranolol. The inhibitory action of nylidrin against histamine was compared with that of similar doses of isoprenaline.

Effect of bronchoconstriction produced by a histamine aerosol in guinea-pigs. Male guinea-pigs, 400 g, in groups of six, were exposed to a histamine aerosol of 20 mg/ml. When an animal collapsed (dropping of the neck), it was revived by artificial respiration. The time from starting the aerosol to the collapse of the animal was noted. One group acted as control, another group received nylidrin, 5 mg/kg intraperitonally, 15 min before exposure to the aerosol. A third group was treated with propranolol followed at 15 min by the histamine. A fourth group received propranolol followed after 20 min by nylidrin and then 15 min later by the histamine. Cross over tests were made.

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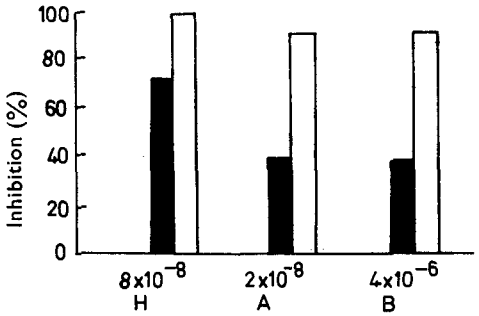

FIG. 1. Inhibitory action of nylidrin against histamine (H), acetylcholine (A) and barium (B). Solid columns represent nylidrin $2{\cdot}4 \times 10^{-8}$ g/ml and open columns nylidrin 8×10^{-7} g/ml.

Drugs used

Nylidrin hydrochloride, histamine acid phosphate, acetylcholine bromide, barium chloride, propranolol hydrochloride, isoprenaline sulphate. Concentrations expressed are of the salts, and are the final concentrations (g/ml) in the bath.

RESULTS

Effect of nylidrin on acetylcholine-, histamine- and barium-induced spasm on guinea-pig ileum. Fig. 1 shows the inhibitory action of nylidrin on the height of contraction produced by histamine (8×10^{-8}), acetylcholine (2×10^{-8}) and barium 4×10^{-6}). Nylidrin was added to the bath followed 1 min later by histamine, acetylcholine or barium. Nylidrin ($2{\cdot}4 \times 10^{-8}$) reduced the contraction of histamine on average by 71% (n = 9) and of acetylcholine on average by 36%. Recovery of the acetylcholine contraction took only 5 min, while for histamine it was incomplete after 60 min. Thus the inhibitory action of nylidrin was more potent and also longer lasting against histamine than acetylcholine.

At a higher concentration (8×10^{-7}) nylidrin completely inhibited the responses to acetylcholine and histamine. Recovery to acetylcholine was complete in 30 min, but for histamine it was not complete 90 min later.

An examination of comparative effect of nylidrin ($2{\cdot}4 \times 10^{-8}$) and isoprenaline ($2{\cdot}4 \times 10^{-8}$) on spasm produced by histamine (8×10^{-8}) showed isoprenaline to be the more potent at equal dosage. It completely blocked the contraction of histamine, while nylidrin reduced the contraction of histamine by 60% (n = 4) on the ileum of one animal. However, recovery of histamine contraction after isoprenaline took only 12 min, and after nylidrin it was 35 min. This showed that although isoprenaline was more potent than nylidrin in identical doses in antagonizing histamine spasm, its effects were shorter lasting.

Effect of β-adrenoreceptor blockade by propranolol. β-Adrenoreceptors were blocked by propranolol (2×10^{-7} mg/ml), a dose having no effect on histamine and acetylcholine. After propranolol, nylidrin ($2{\cdot}4 \times 10^{-8}$ mg/ml) was unable to inhibit the spasm induced by histamine or acetylcholine.

Effect on bronchoconstriction induced by histamine aerosol in guinea-pig. In all control animals, the histamine aerosol (20 ml) produced bronchospasm (as seen by collapse) within 3 min. Nylidrin (5 mg/kg) alone extended the collapse time to 8 min. Propranolol (10 mg/kg) reduced the collapse time to 2 min and caused 50% mortality. Propranolol followed by nylidrin gave a near collapse time of 2·5 min and a 33% (2/6) mortality.

Thus, nylidrin (5 mg/kg) gave significantly protection against histamine induced bronchospasm, which was completely antagonized by propranolol.

DISCUSSION

The results suggest that nylidrin possesses an inhibitory action against histamine-, acetylcholine- and barium-induced spasm of guinea-pig ileum. Further, nylidrin possesses a greater inhibitory action against histamine than against acetylcholine. These results are similar to those obtained for other catecholamines such as isoprenaline, noradrenaline and adrenaline (Wilson, 1964).

The comparative study of the inhibitory action of nylidrin and isoprenaline in similar doses ($2{\cdot}4 \times 10^{-8}$) suggest that isoprenaline is more potent than nylidrin against histamine-induced spasm, but the effects of nylidrin seem to be the longer lasting.

When β-adrenoreceptors are blocked by propranolol, nylidrin fails to antagonize the spasmogenic action of histamine and acetylcholine on ileum, thus suggesting the involvement of β-adrenoreceptors in the inhibitory action of nylidrin. Similar observations have been made by Farmer & Lehrer (1966) with isoprenaline. These authors have also demonstrated that in isolated human myometrium, which contains few or no β-receptors, isoprenaline does not antagonize the action of histamine and acetylcholine.

These observations support the view that the inhibitory action of nylidrin on the spasmogenic drugs is through the activation of β-adrenoreceptors.

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