COMPARISON OF NEWLY SYNTHESIZED β-ADRENERGIC BLOCKERS, OPC 1085 AND SQ 11725, WITH PINDOLOL AND PROPRANOLOL IN THE BLOOD-PERFUSED CANINE SA NODE AND PAPILLARY MUSCLE PREPARATIONS

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In previous studies (1, 2, 3), we assessed the β-adrenergic blocking activity of 11 compounds against the positive chronotropic and inotropic effect of norepinephrine in the isolated and blood-perfused canine sino-atrial (SA) node and papillary muscle preparations with donor animals. The blocking potencies of these compounds on the β-adrenergic effects on the cardiac functions were roughly divided in those of propranolol and of pindolol, and also in two groups on the difference of presence or absence of sympathomimetic effect. In this paper, two newly synthesized compounds were compared with the potencies of pindolol and propranolol.

The isolated SA node and papillary muscle preparations were perfused at 100 mm Hg with the arterial blood conducted from the carotid artery of a heparinized donor dog by the aid of a peristaltic pump. The experimental setup of these preparations have been described in detail in previous papers (4, 5). Drugs used were as follows: l-norepinephrine, dl-propranolol hydrochloride, dl-pindolol, dl-5(3-tert-butylamino-2-hydroxy) propoxy-3,4 dihydrocarbostyril hydrochloride (OPC 1085, Otstika) (6) and dl-2,3-cis-1,2,3,4-tetrahydro...
FIG. 1. Dose-effect curves for 4 β-adrenergic blocking agents on the positive chronotropic response caused by norepinephrine in the blood-perfused SA node preparation. These values were calculated from the data obtained 1 min after the administration of antagonists. Each point indicates the mean of 5 to 7 observations and vertical bars represent S.E.

FIG. 2. Dose-effect curves for 4 β-adrenergic blocking agents on the positive inotropic response caused by norepinephrine in the blood-perfused papillary muscle preparation. These values were calculated from the data obtained 1 min after the administration of antagonists. Each point indicates the mean of 5 to 7 observations and vertical bars represent S.E.

5-(2-hydroxy-3-tert-butylamino)propoxy-2,3-naphthalendiol (SQ 11725, Squibb) (7). All drugs were injected i.a. with microsyringes in volumes of 10–30 µl for 4 sec.

Norepinephrine was used as an agonist in doses of 0.1 to 1 nmol. Norepinephrine was given 1 min after the administration of the antagonist and every 10 min successively until complete recovery from the β-adrenergic blocking effect. OPC 1085 showed a sympathomimetic response like pindolol, but its β-adrenergic blocking effect was more long-lasting and in doses sufficient to block completely the chronotropic and inotropic responses to 0.3–1 nmol of norepinephrine, its effect persisted over 2 hours. SQ 11725 had practically no sympathomimetic effect, and its blocking effect disappeared within a period of one hour even in doses for inducing a complete blocking activity to 0.3–1 nmol of norepinephrine, which was shorter than that of propranolol. Dose-effect curves for these compounds to block the effect of norepinephrine in the SA node preparation are shown in Fig. 1 and those in the papillary muscle preparation in Fig. 2. The potencies of these compounds at the peak effect were as follows: OPC 1085 > pindolol = SQ 11725 > propranolol.

REFERENCES


INFLUENCE OF AMYLOPECTINE SULFATE ON GASTRIC MUCOSA IN NORMAL OR WATER-IMMERSION STRESSED RATS

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While amylopectine sulfate (APS) has been confirmed to be a potent anti-peptic and anti-ulcer agent (1, 2), in recent studies the ability of APS to induce ulcerative changes in the colon in laboratory animals was evident (3, 4). We have also found that APS has noxious effects on the stomach in water-immersion stressed rats with pylorus ligation (5). The following experiments were done to determine whether or not, 1) APS induces any damage to the stomach of rats in normal conditions, 2) APS has any influence on stress ulcers developed in rats with an intact pylorus, and 3) the APS-induced gastric ulcers are prevented by pharmacological agents.

Male Donryu strain rats, 220-250 g, were deprived of food for 24 hr. In most of the animals, the pylorus was ligated under ether anesthesia. Rats with or without pylorus ligation were given APS derived from potato starch p.o. and then placed in either normal or stressful situations in which the animals were immersed in a water bath (23°C) up to the xiphoïd process for 7 hr (6). After such stressing, the animals were sacrificed by a blow on the head and the stomach of each was removed. In the case of pylorus-ligated rats, the gastric contents were collected through the esophagus and analyzed for volume and acidity; the acidity was determined by titration of the gastric juice with 0.1 N NaOH to pH 7.0. The peptic activity was determined by Anson’s method (7), and was expressed as mg tyrosine per ml. The stomach was then subjected to the 1% formalin treatment and examined for mucosal ulcers which had developed in the corpus and antrum. The sum of the length (mm) of each ulcer was used as an ulcer index. The gastric specimens were put in 10% formalin solution for histological examination. Either sodium bicarbonate, L-glutamine suspended in 1% carboxymethylcellulose (CMC) solution, or atropine sulfate in saline solution was given to the rats p.o. or s.c. concomitantly with APS 10 min prior to stressing,