the guinea-pig taenia coli and the rat perfused heart. These tissues provide examples of α-adrenoceptor-mediated excitation and inhibition and β-adrenoceptor-mediated inhibition and excitation.

First the ED20 and ED80 for each agonist on each tissue was determined, using isometric recording. Concentrations of phentolamine (pA_{10} to pA_{50}) or propranolol (pA_{10} to pA_{100}) were selected which would reduce to 20% the response to an ED80 of agonist. These concentrations were then used in the metabolic study.

ATP and CP were assayed fluorimetrically by the method of Lowry, Passonneau, Hasselberger & Schulz (1964). The action of phenylephrine on the aortic strip and on the rabbit longitudinal intestinal muscle and guinea-pig taenia coli in the presence of a pA_{100} of propranolol was associated with no significant changes in the amounts of ATP and CP. These measurements were made at three times chosen to precede and include the time of the maximum tension effect of the agonist.

In contrast, the action of isoprenaline on the rat heart and on the rabbit longitudinal intestinal muscle and guinea-pig taenia coli in the presence of a pA_{100} of phentolamine was associated with significant, dose-dependent changes in the amounts of ATP and CP. These measurements were made at a minimum of three times chosen to precede and include the time of maximum tension effect of the agonist. The action of phenylephrine was similarly examined on the rat heart and the ED80 produced significant changes in the amounts of ATP and CP.

The presence of phentolamine and propranolol was not associated with significant changes in the resting amounts of ATP or CP in any of the tissues.

When the physiological response was excitatory (rat heart; both phenylephrine and isoprenaline), the amounts of ATP and CP were reduced. When the response was inhibitory (rabbit duodenum and taenia coli; isoprenaline), the amounts of ATP and CP were increased. Both the decrements in ATP and CP in the rat heart and their increments in intestinal muscle associated with an ED80 of isoprenaline were reduced by the selected dose of propranolol.

These results are consistent with current views that the effects mediated by α- and β-adrenoceptors are associated with different biochemical mechanisms.

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Interaction of isoprenaline and β-adrenoceptor blocking drugs on intestinal smooth muscle

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The interaction between catecholamines and β-adrenoceptor blocking drugs at β-adrenoceptors in tissues such as heart, trachea and uterus is competitive and compatible with a simple bimolecular drug-receptor reaction (Black, Duncan & Shanks, 1965; Patil, 1967; Blinks, 1967). The present paper is concerned with the interaction between β-stimulants and β-adrenoceptor blocking drugs in smooth muscle of the alimentary tract.

Isoprenaline relaxed the longitudinal muscle of guinea-pig colon bathed with Krebs solution at 32° C. Reproducible dose-response curves were obtained for isoprenaline in the dose-range 0·3–300 ng/ml. Propranolol was added to the bathing fluid for a contact period of 45 min. With low concentrations (1–10 ng/ml) of propranolol the dose-response curve for isoprenaline was shifted to the right by up to 30-fold, but these shifts were not always dose-dependent. Moreover, higher concentrations (10–125 ng/ml) of propranolol had little further blocking effect. Similar results were obtained using coaxially-stimulated ileum or longitudinal strips of oesophageal muscle from the guinea pig, or when the β-adrenoceptor blocking drugs sotalol or practolol were used instead of propranolol.

Ahlquist & Levy (1959) showed that inhibitory effects of catecholamines in intestine are mediated *via* both α- and β-adrenoceptors. Therefore, the interaction of isoprenaline with the irreversible α-adrenoceptor blocking drug dibenamine was investigated. In guinea-pig colon exposed to dibenamine (10 μg/ml) for 30 min, the response to isoprenaline was either completely abolished or the dose-response curve was shifted to the right and the maximum relaxation attainable was greatly reduced. In only two of seven dibenamine-treated preparations was the residual response to isoprenaline large enough for the interaction with propranolol to be examined. In these preparations responses to isoprenaline were progressively blocked by propranolol (5, 25, 125 ng/ml).

Bartlet & Hassan (1969) showed that chick rectum contained β- but not α-receptors. Isoprenaline relaxed this preparation in the dose-range 0·3–30 ng/ml. The dose-response curve for isoprenaline was progressively shifted to the right by increasing concentrations of propranolol (5, 25 and 125 ng/ml). This interaction clearly differed from that in guinea-pig colon.

The results, which confirm those of Farmer & Levy (1969), show that in guinea-pig colon the relaxation induced by isoprenaline is mediated mainly through stimulation of α-adrenoceptors. Consequently, propranolol and other β-blocking drugs have little blocking action. In chick rectum, where isoprenaline-induced relaxation is mediated *via* β-adrenoceptors, propranolol exerts its normal blocking action.

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Relative affinities of some α-adrenoceptor blocking drugs in isolated human smooth muscle

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Information on new drugs is often derived only from studies in animal tissues.