Autonomic blocking properties of Wy 21901

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3-[2-(4-Benzamidopiperid-1-yl)ethyl] indole hydrochloride (Wy 21901) is a member of a series of potent hypotensive compounds (Archibald, 1968). Agonist-antagonist studies, made on a number of isolated preparations, have identified several receptor sites of action and can account for its observed cardiovascular actions in intact animals (Alps, Johnson & Wilson, 1970).

On the longitudinal muscle of the guinea-pig isolated ileum, Wy 21901 was found to be a potent, reversible histamine antagonist (pA_2 8·2) fulfilling all the criteria for competitive antagonism (Arunlakshana & Schild, 1959), but was devoid of atropine-like activity even in concentrations as high as 10^{-5}M.

On the guinea-pig vas deferens and aortic strip Wy 21901 was an α-adrenoceptor antagonist (pA_2 7·4), an action reversed on washing continuously for 3 h. β-Adrenoceptor blocking activity was excluded by the failure of Wy 21901 (10^{-4}M) to inhibit relaxation induced by isoprenaline or noradrenaline in the guinea-pig tracheal spiral preparation. Studies with the rat isolated fundus and ileum demonstrated weak anti-5-hydroxytryptamine activity (pA_2 5·9) readily reversible on washing.

Like propranolol, Wy 21901 (10^{-6}–2×10^{-5}M) caused a dose-related reduction of the force and rate of contraction of the rabbit isolated heart. The inotropic and chronotropic actions of isoprenaline were reduced by higher concentrations of Wy 21901, but this effect was nonspecific since the cardiac stimulant actions of aminophylline were also reduced. In view of the known local anaesthetic activity of propranolol (Davis, 1970) the possibility was investigated that the cardio-inhibitory activity of Wy 21901 was caused by a local anaesthetic action. Experiments utilizing the guinea-pig weal test (Bülbring & Wajda, 1945) showed that the compound possessed local anaesthetic potency three times that of procaine.

It is concluded that Wy 21901 has α-adrenoceptor blocking, local anaesthetic and antihistamine properties, the first two of which may be responsible for its hypotensive and anti-arrhythmic actions.

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Changes in the amounts of high-energy phosphate compounds associated with the actions of phenylephrine and isoprenaline on smooth and cardiac muscle

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Changes were measured in the amounts of adenosine triphosphate (ATP) and creatine phosphate (CP) associated with the actions of phenylephrine and isoprenaline on the rabbit aortic strip, the longitudinal muscle strip of rabbit duodenum,

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.