ADRENOCEPTORS IN THE GUINEA PIG'S GALLBLADDER*

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Since Ahlquist and Levy (1) proposed that intestinal inhibitory actions of sympathomimetic amines could be a result of stimulation either of $\alpha$ or $\beta$ receptor, considerable effort has been directed to the study of drug receptors on the smooth muscle of digestive tract. The nature of adrenoceptor in the biliary system relaxed by the amines remains to be clarified (2). A previous report (3) has indicated that the Oddi sphincter in rabbits has both $\alpha$ and $\beta$ receptors, the former being responsible for contraction and the latter for relaxation. Therefore, the present experiments were undertaken to determine the nature of adrenoceptors in the isolated gallbladder of guinea pigs. Isolated Oddi sphincter preparation was used as reference.

Methods: Male and female guinea pigs, weighing 250 to 450 g, were used. The animals were killed by a blow on the head. The entire gallbladder was removed and the terminal tract of the bile duct was isolated from the duodenum. They were suspended vertically in two separate 25-ml organ baths containing Tyrode solution gassed with 95 % O$_2$ and 5 % CO$_2$ and maintained at 35 $\pm$ 0.5 $^\circ$C. The composition of Tyrode solution in gram per liter was: NaCl 8.0, KCl 0.2, CaCl$_2$ 0.2, MgCl$_2$ 0.1, NaH$_2$PO$_4$ 0.05, NaHCO$_3$ 1.0 and dextrose 1.0. Tension changes were recorded isometrically by means of a force-displacement transducer (Nihon Kohden, SB-IT) coupled to an ink-writing oscillograph (Sanei biophysiograph 180 system and ink-writing recorder RA-101). One gram tension was loaded to the tissues. The preparation was allowed to equilibrate for one hr before the experimental procedure was initiated. The concentration of drugs is expressed as final concentration on a molar basis of salt in the organ bath.

Results and discussion: Phenylephrine ($5 \times 10^{-6}$ M) produced contractions of both gallbladder and Oddi sphincter (Fig. 1A). In both preparations, the onset of contraction began 5 to 10 sec after application of phenylephrine. Excitatory response to phenylephrine was completely blocked by a ten-min pretreatment with phentolamine ($1.3 \times 10^{-5}$ M) (Fig. 1B) or by tolazoline ($10^{-4}$ M). Propranolol ($4 \times 10^{-6}$ M) did not affect the response to phenylephrine.

Norepinephrine ($5 \times 10^{-6}$ M) caused contractions in four of the six preparations of gallbladder, but in only two of six preparations of Oddi sphincter. Contractile response to norepinephrine of both gallbladder and Oddi sphincter was remarkably inhibited by a

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ten-min pretreatment with phentolamine ($1.3 \times 10^{-5}$ M), but not by propranolol ($4 \times 10^{-6}$ M). Relaxation due to norepinephrine was reversed to a slight contraction by pretreatment with propranolol. After treatment with a combination of phentolamine ($1.3 \times 10^{-5}$ M) and propranolol ($4 \times 10^{-6}$ M), both epinephrine and norepinephrine failed to cause contraction or relaxation with either preparation.

Isoproterenol ($4 \times 10^{-6}$ M) caused relaxations of both gallbladder and Oddi sphincter (Fig. 2A). Pretreatment with phentolamine ($1.3 \times 10^{-5}$ M) or tolazoline ($10^{-4}$ M) did not modify the relaxing response to isoproterenol, however, relaxation produced by isoproterenol was completely inhibited by a ten-min pretreatment with propranolol ($4 \times 10^{-6}$ M) (Fig. 2B).
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The present results show that excitation of $\alpha$ receptor by phenylephrine induces contractions of both gallbladder and Oddi sphincter. Furthermore, excitation of $\beta$ receptor by isoproterenol consistently causes relaxations of both gallbladder and Oddi sphincter. The fact that dual responses are obtained by norepinephrine in the Oddi sphincter may be explained by mixed $\alpha$ and $\beta$ adrenoceptor stimulating property of this agent. It has been indicated that the gallbladder of the guinea pig has $\alpha$ adrenoceptor which mediates contraction and $\beta$ adrenoceptor mediating relaxation.

REFERENCES

DIFFERENCES IN CHRONOTROPIC AND DROMOTROPIC RESPONSES OF THE SA AND AV NODES TO ADENOSINE AND ACETYLCHOLINE

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It is well known that adenosine produces a deceleration of sinus rate though not so prominent while a high grade AV block is seen in the guinea-pig. In the dog the sinus rate is so considerably retarded by adenosine that the action upon the AV conduction is not appreciated on rough examination (Drury and Szent-Györgyi 1929) (1). In the present study, selective perfusion systems of the sinus and AV node arteries were arranged (2). The double perfusion method has been described in a previous paper (3). Effects of adenoine on the AV conductivity in comparison with those on the automaticity of the SA or AV node were examined.

Five mongrel dogs weighing 10 to 14 kg were used. When a relatively small dose of acetylcholine (ACh), 0.1 to 0.3 $\mu$g, was injected into the sinus node artery, a sinus deceleration was usually induced. Adenosine at doses of 1 to 10 $\mu$g induced almost the same degree of a sinus deceleration when injected into the sinus node artery. Table 1 shows effects of ACh and adenosine on the SA pacemaker activity.

On AV conductivity, 3 $\mu$g of ACh regularly induced complete AV block when injected into the AV node artery. On the other hand, adenosine even at a dose of 100 $\mu$g did not produce any type of AV block in the ECG recordings. A larger dose of 1 mg of adenosine induced PQ prolongation (1 degree AV block) but did not induce complete AV block in all