EFFECT OF VARIOUS PHARMACOLOGICAL AGONISTS ON THE RAT CAECUM-APPENDIX PREPARATION : *A PRELIMINARY STUDY*

ASHOK K. MEHTA, S. K. KULKARNI* AND M. SINGH

Pharmacology Division, Department of Pharmaceutical Sciences, Panjab University, Chandigarh

(Received on April 14, 1982)

Summary : A preliminary study with various pharmacological agents revealed the presence of contractile muscarinic and H_1-histamine receptors as well as inhibitory α- and β-adrenoceptors and purinoceptors in rat caecum-appendix. Histamine also produced indirect actions mediated through the release of catecholamines 5-Hydroxytrptamine produced variable response, the contractile response was mediated through 5-HT receptors and the relaxant response through the release of catecholamines

Key words : Caecum-appendix purinoceptors α, β-adrenoceptors 5-hydroxytryptamine

INTRODUCTION

Although no physiological function has been attributed to human appendix the presence of functionally active muscarinic, histamine, 5-hydroxytryptamine (5-HT) and inhibitory adrenoceptors has been reported in this organ (1). The fowl and mouse caecum also are reported to possess β-adrenoceptors and 5-HT receptors (3,6), though the latter is completely devoid of α-adrenoceptors and is insensitive to histamine (6). The present investigation was undertaken to demonstrate the effects of various pharmacological agonists on rat caecum-appendix.

MATERIALS AND METHODS

The appendix, an extension from caecum, is fused in the case of the rat and as such this organ cannot be anatomically distinguished in this species (4). Therefore, the whole tissue was taken up for study and was referred to as caecum-appendix preparation.

*Corresponding author

Adult albino Wistar rats of either sex were sacrificed by a blow on the head and by carotid bleeding. The caecum-appendix was isolated from ileocaecal junction and was mounted in a 10 *ml* bath containing Krebs solution (pH 7.4±0.2) maintained at 35°C and was bubbled with air. The tissue was allowed to equilibrate for fortyfive min under a tension of 0.5 g during which period it was washed every five min. The tone of the rat caecum-appendix was recorded using a frontal writing isotonic lever.

Testing procedure :

The responses to various agonists were recorded for two min or until it was maximal. Antagonists were added to the bath fluid and allowed to act for twenty min.

In order to deplete catecholamine stores, the animals were reserpinized (5 *mg/kg*, ip). Twentyfour hr after reserpine administration, the animals were sacrificed and the tissues were used as described above. For chemical sympathectomy, 6-hydroxydopamine (100 *mg/kg*) was iniected (ip) and the same dose was repeated after 5 hr. The animals were sacrificed 24 hr after the first injection and tissues were used as described before.

Student 't' test was used for statistical analysis of the data.

Agonists and antagonists :

Acetylcholine chloride (BDH), (—)-adrenaline tartrate (Burroughs Wellcome) (±)-isoprenaline sulphate (Burroughs Wellcome), (—)-noradrenaline bitartrate (Unichem), histamine base (Sigma), 5-hydroxytryptamine creatinine sulphate (C.H. Boehringer Sohn) and adenosine triphosphate disodium salt (Sisco) were used as agonists. Atropine sulphate, phenoxybenzamine (SKF), DL-propranolol HCl (Sigma), mepyramine maleate (May and Baker), metiamide (SKF), cyproheptadine HCl (MSD) and caffeine base (C. H. Boeringer Sohn) were used as antagonists and prepared freshly in normal saline. The solutions of nor-adrenaline and isoprenaline contained ascorbic acid as anti-oxidant.

RESULTS

Muscarinic receptors :

Acetylcholine (5.505×10^{-8} M to 5.768×10^{-2} M) induced a dose-dependent contraction of the rat caecum-appendix. Dose-response curve for acetylcholine was shifted to right and in parallel fashion in the presence of atropine (1.439×10^{-6} M, n=5), the dose ratio being 16±0.5.

Adrenoceptors :

Noradrendline (2.96×10^{-9} M to 1.22×10^{-5}M) induced a dose-dependent relaxation which was blocked by phenoxybenzamine (2.94×10^{-6} M, n=5). Isoprenaline (2.80×10^{-9} M to 4.60×10^{-5} M) also caused a dose-dependent relaxation of the preparation which was blocked by propranolol (3.48×10^{-6} M, n= 6)

Histamine receptors :

Rat caecum-appendix was relatively insensitive to histamine but doses as high as 2.605×10^{-4} M to 6.680×10^{-2} M (n=5) caused a relaxation of the tissue in a dose-

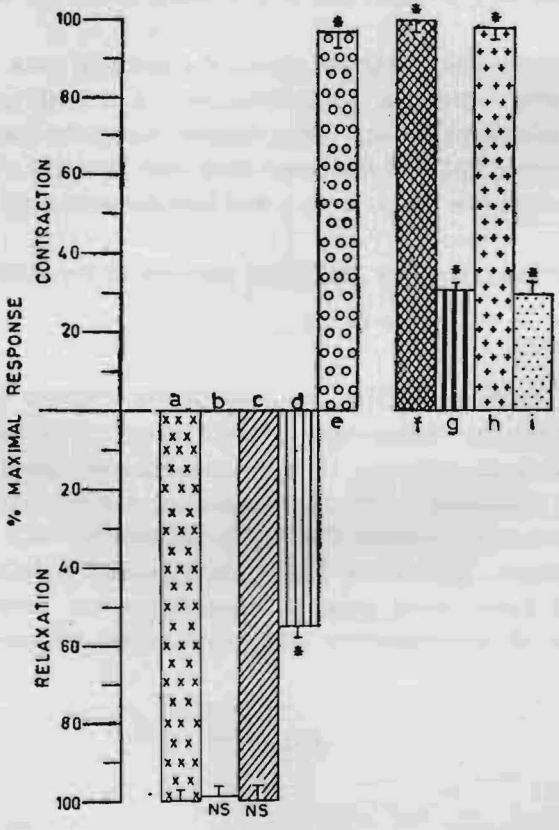

Fig. 1 : Histogram showing the influence of various agents on the effect of histamine (1.67×10^{-2}M) on rat caecum-appendix. Each bar represent mean±S.E. (n=5). (a) Control relaxant effect with histamine ; (b) mepyramine+histamine ; (c) metiamide+histamine : (d) phenoxybenzamine+histamine ; (e) propranolol+histamine ; (f) histamine in 6-OHDA treated animals ; (g) mepyramine+histamine in 6-OHDA treated animals ; (h) histamine in reserpined animals and (i) mepyramine+histamine in reserpinised animals. Value differs significantly from control (*$P < 0.01$): NS, no significant difference.

dependent manner, the pD_2 value being 2.68 ± 0.05. The histamine-induced relaxation was neither blocked by mepyramine (2.491×10^{-6} M, n=5) nor by metiamide (8.18×10^{-6} M, n=5). However, it was partially blocked by phenoxybenzamine (2.4×10^{-6}M, n=6). On the other hand, the effect of propranolol was such that in tissues exposed to propranolol (6.76×10^{-6} M, n=5), histamine produced a contraction of rat caecum-appendix instead of relaxation. Following catecholamine depletion with reserpine (n=5) or sympathectomy with 6-hydroxydopamine (n=5), histamine (9.0×10^{-3} M) induced a contraction of the tissue and this effect was antagonized by mepyramine (2.49×10^{-4} M).

Fig. 1 summarizes the observations pertaining to histamine.

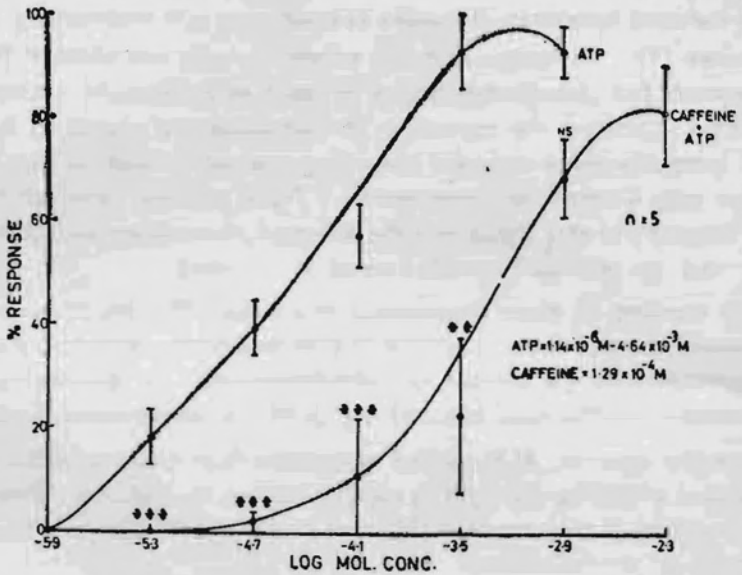

Fig. 2 : Dose response curve for the relaxant effect of ATP in the absence and in the presence of caffeine (1.29×10^{-4} M). Each point represents the mean ± S.E. (n=5). Value significantly differs from control : $^{**}P<0.025$, $^{***}P<0.01$; NS. no significant difference.

5-HT receptors :

5-HT produced inconsistent response in the rat caecum-appendix preparation. It induced relaxation in some experiments (n=12) and contraction in others (n=5). 5-HT (6.32×10^{-6} M, n=5) induced contraction was blocked by cyproheptadine (2.85×10^{-6} M). Relaxant effect of 5-HT (6.32×10^{-5} M, n=6) was blocked by propranolol (6.76×10^{-6} M). After phenoxybenzamine (5.88×10^{-6} M n=6) treatment, 5-HT (6.32×10^{-5} M) induced a contraction of tissue. In reserpinized rats, however, 5-HT

(2.47×10^{-7} M to 6.32×10^{-5} M), always induced contractions in all the preparations (n=10) and this effect was blocked by cyproheptadine (2.85×10^{-6} M).

Purine receptors :

Adenosine triphosphate (1.14×10^{-6} M to 4.64×10^{-3} M) caused relaxation in a dose dependent manner. The dose-response curve was shifted to the right by caffeine (1.29×10^{-4} M, n=5) as shown in Fig. 2.

DISCUSSION

The present study has demonstrated the presence of muscarinic receptors and inhibitory α–and β–adrenoceptors in the rat caecum-appendix as the specific antagonists of these receptors blocked the responses to their agonists. Unlike these observations, catecholamine-induced responses of human appendix are not reversed by α–or β–adrenoceptor antagonists (1). Histamine-induced relaxation was not blocked by H_1– and H_2 receptor antagonists but phenoxybenzamine as well as propranolol prevented histamine-induced relaxation indicating the mediation of catecholamine release in its action. Reserpinization or sympathectomy reversed histamine-induced relaxation into contraction and this contraction was blocked by mepyramine. These studies suggest the presence of H_1-histamine receptors in this tissue but the effect of H_1-receptor activation is not evident till relaxation due to released catecholamine is blocked.

5- HT is reported to show inconsistent responses (5) ; the stimulant effects being mediated through postsynaptic (cyproheptadine-sensitive) receptor and the relaxant effect being mediated by the release of catecholamines. In accordance with this, we observed consistent contractions induced by 5- HT in reserpinised tissues.

Purinoceptor agonist, ATP caused dose-depedent relaxant effect and the dose-response curve was shifted to the right in parallel fashion by caffeine. Phenoxybenzamine, yet another antagonist of purinoceptor (2), also blocked ATP effects. These observations suggest presence of purinoceptors.

REFERENCES

1. Antanackovic, D., M.A. Becassy, M. Dzoljic and K. Svajcer. Pharmacology of the human appendix. *Arch. Int. Pharmacodyn.*, **173** : 327–331, 1968.
2. Burnstock, G. A. Basis for Distinguishing Two Types of Purinergic Receptors. In : 'Cell Membrane Receptors for Drugs and Hormones : A multi-disciplinary approach' by Straub, R.W. and L. Bolis. Raven Press, New York, pp 107–118, 1978.
3. Cleugh, J., J. H Gaddum. P. Holton and E. Leach. Assay of substance P on the fowl rectal caecum. *Br. J. Pharmac.*, **17** : 144–158, 1961
4. Dhami, P.S. and J.K. Dhami. In : 'Fundamental Anatomy of the Rat" R. Chand and Co., Delhi, pp 53–5, 1975.
5. Garattini, S. and L. Valzelli. In : 'Serotonin'. Elsevier Pub. Co., Amsterdam, pp. 1–25, 1965.
6. Kaul, P.N. and S.J. Whittle. Mouse caecum as a selective β-adrenoceptor tissue. *J. Pharm. Pharmac.*, **24** : 609–614, 1972.