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P, -Receptor Characterisation in Rabbit Isolated Ear Artery

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P2x-RECEPTOR CHARACTERISATION IN RABBIT ISOLATED EAR ARTERY

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Abstract: The P2x-receptor mediating contraction of the rabbit ear artery is characterised by the following agonist potency order: D- $\alpha\beta$ methyleneATP > L- $\beta\gamma$ methyleneATP > D- $\beta\gamma$ methyleneATP > 2-MeSATP > ATP.

Stimulation of P_{2X} -purinoceptors results in contraction of vascular (e.g rabbit ear artery¹) and visceral smooth muscle (e.g quinea pig bladder2). We have extended the classification of this receptor sub-type in the rabbit ear artery by examining the relative agonist potencies of a series of ATP analogues. The activity of L-βymethylene ATP was of particular interest since it has been reported to be a stable, selective P_{2x} -agonist in the bladder and the most potent agent of this type tested in this tissue^{2,3}. We have designed our study so as to avoid factors which could limit the validity of an agonist-based receptor classification. Specifically, we have chosen a tissue which responds to $P_{2\chi}$ -agonists with a "classical" sigmoid log. agonist concentration-response curve1 allowing agonist potency data to be derived with confidence. Also, we have excluded relaxant effects mediated at P_1 - or P_2 -receptors which would tend to interfere with interpretation of contractile responses. Selective desensitisation of the P_{2x} -receptor has been employed to establish the specificity of the observed responses. The methylene-substituted analogues are reported to be relatively resistant to ectonucleotidase degradation4 making them more acceptable for receptor classification purposes.

Central ear arteries from male Nz. White rabbits (2.5-3kg) were denuded of endothelium, cut into rings and suspended under 1g resting tension in Krebs solution at 37°C gassed with $95\%0_{2}$ / $5\%\text{CO}_{2}$. All

experiments were performed in the presence of indomethacin (2.8 x 10^{-6}M) and the selective P₁-purinoceptor antagonist 8-sulphophenyl-theophylline (3 x 10^{-4}M). In each tissue cumulative agonist concentration-effect (E/[A]) curves were constructed to D- $\alpha\beta$ methylene ATP as standard and an ATP analogue. The mechanism of the contractions produced was assessed by repeating the E/[A] curve after 15 min exposure to a maximal concentration of D- $\alpha\beta$ methylene ATP (3 x 10^{-5}M) which selectively desensitises P_{2X}-receptors.

All compounds appeared to be full agonists as defined by the standard. Relative potency order was as follows, p[A₆₀] values (mean \pm s.e, n=3-5) are shown in brackets: D- α pmethylene ATP (6.47 \pm 0.04) > L- β pmethylene ATP (5.52 \pm 0.04) > D- β pmethylene ATP (4.37 \pm 0.12) > 2-MeSATP (4.15 \pm 0.16) > ATP (3.14 \pm 0.14). Responses to the methylene-substituted agonists were effectively abolished by desensitisation with D- α pmethylene ATP. However, ATP and 2-MeSATP produced some residual contractions after desensitisation.

The relative order of agonist potencies found in this study is broadly consistent with the order designated as characteristic of P_{2X} -receptors. However, the Burnstock classification does not distinguish between D- α pmethylene ATP and D- β pmethylene ATP, yet in this tissue they differed in potency by more that 100-fold. Also of interest was the fact that L- β pmethylene ATP is considerably more potent than its D-isomer but 10-fold less potent that D- α pmethylene ATP. This agonist potency order is similar to that reported for rat portal vein but differs from that described for P_{2X} -receptors in the guinea pig bladder where L- β pmethylene ATP is the most potent agent and D- α pmethylene ATP and D- α pmethylene ATP have similar activity. The significance of these differences is not easy to assess. However, they do suggest that further quantitative comparisons of P_{2X} -purinoceptors mediating spasmogenic effects are warranted.

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