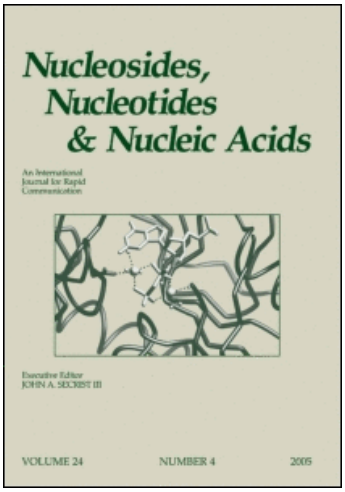

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

P_{2x}-Receptor Characterisation in Rabbit Isolated Ear Artery

S. E. O'connor[a]; B. E. Wood[a]; P. Leff[a]
[a] Department of Pharmacology Fisons plc - Pharmaceutical Division, Leicestershire, UK

To cite this Article O'connor, S. E. , Wood, B. E. and Leff, P.(1991) 'P_{2x}-Receptor Characterisation in Rabbit Isolated Ear Artery', Nucleosides, Nucleotides and Nucleic Acids, 10: 5, 1207 — 1208
To link to this Article: DOI: 10.1080/07328319108047277
URL: http://dx.doi.org/10.1080/07328319108047277

NUCLEOSIDES & NUCLEOTIDES, 10(5), 1207-1208 (1991)

P_{2X}-RECEPTOR CHARACTERISATION IN RABBIT ISOLATED EAR ARTERY

S.E. O'Connor*, B.E. Wood & P. Leff
Department of Pharmacology, Fisons plc - Pharmaceutical Division,
Loughborough, Leicestershire, UK.

Abstract: The P_{2X}-receptor mediating contraction of the rabbit ear artery is characterised by the following agonist potency order: D-αβmethyleneATP > L-βγmethyleneATP > D-βγmethyleneATP ≥ 2-MeSATP > ATP.

Stimulation of P_{2X}-purinoceptors results in contraction of vascular (e.g rabbit ear artery[1]) and visceral smooth muscle (e.g guinea pig bladder[2]). 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-βγmethylene 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_{2X}-agonists with a "classical" sigmoid log. agonist concentration-response curve[1] allowing agonist potency data to be derived with confidence. Also, we have excluded relaxant effects mediated at P_1- or P_{2Y}-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 degradation[4] 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%O_2 / 5%CO_2. All

experiments were performed in the presence of indomethacin (2.8×10^{-6}M) and the selective P_1-purinoceptor antagonist 8-sulphophenyltheophylline (3×10^{-4}M). In each tissue cumulative agonist concentration-effect (E/[A]) curves were constructed to D-αβmethylene 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-αβmethylene ATP (3×10^{-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, $p[A_{50}]$ values (mean ± s.e, n=3-5) are shown in brackets: D-αβmethylene ATP (6.47 ± 0.04) > L-βγmethylene ATP (5.52 ± 0.04) > D-βγmethylene ATP (4.37 ± 0.12) ≥ 2-MeSATP (4.15 ± 0.16) > ATP (3.14 ± 0.14). Responses to the methylene-substituted agonists were effectively abolished by desensitisation with D-αβmethylene 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[5]. However, the Burnstock classification does not distinguish between D-αβmethylene ATP and D-βγmethylene ATP, yet in this tissue they differed in potency by more that 100-fold. Also of interest was the fact that L-βγmethylene ATP is considerably more potent than its D-isomer but 10-fold less potent that D-αβmethylene ATP. This agonist potency order is similar to that reported for rat portal vein[6] but differs from that described for P_{2X}-receptors in the guinea pig bladder where L-βγmethylene ATP is the most potent agent and D-αβmethylene ATP and D-αβmethylene ATP have similar activity[2,4]. 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.

REFERENCES

1. Kennedy, C. & Burnstock, G. (1985) Blood Vessels 22, 145
2. Cusack, N.J. & Hourani, S.M.O. (1984) Br. J. Pharmac. 82, 155
3. Hourani, S.M.O., Loizou, G.D. & Cusack, N.J. (1986) Eur. J. Pharmac. 131, 99
4. Welford, L.A., Cusack, N.J. & Hourani, S.M.O. (1987) Eur. J. Pharmac. 141, 123
5. Burnstock, G. & Kennedy, C. (1985) Gen. Pharmac. 16, 433
6. Reilly, W.M. & Burnstock, G. (1987) Eur. J. Pharmac. 138, 319