Pharmacology & Therapeutics

Volume 64, Issue 3, 1994, Pages 445-475

Purinoceptors: Are there families of P2X and P2Y purinoceptors?

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https://doi.org/10.1016/0163-7258(94)00048-4

Abstract

There has been an exponential growth in interest n purinoceptors since the potent effects of purines were first reported in 1929 and purinoceptors defined in 1978. A distinction between P_1 (adenosine) and P_2 (ATP/ADP) purinoceptors was recognized at that time and later, A_1 and A_2, as well as P_{2X} and P_{2Y} subclasses of P_1 and P_2 purinoceptors were also defined. However, in recent years, many new subclasses have been claimed, particularly for the receptors to nucleotides, including P_{2t}, P_{2z}, $P_{2u(n)}$ and P_{2D}, and there is some confusion now about how to incorporate additional discoveries concerning the responses of different tissues to purines. The studies beginning to appear defining the molecular structure of P_2-purinoceptors subtypes are clearly going to be important in resolving this problem, as well as the introduction of new compounds that can discriminate pharmacologically between subtypes. Thus, in this review, on the basis of this new data and after a detailed analysis of the literature, we propose that:

1. (1) P2X(ligand-gated) and P2Y(G-protein-coupled) puriceptor families are established:

established.

2. (2) four subclasses of P2X-purinoceptor can be identified ($P2X_1$-$P2X_4$) to date;

3. (3) the variously named P_2-purinoceptors that are G-protein-coupled should be incorporated into numbered subclasses of the P2Y family. Thus:

1. $P2Y_1$ represents the recently cloned P2Y receptor (clone 803) from chick brain;

2. $P2Y_2$ represents the recently cloned P_{2u} (or P_{2n}) receptor from neuroblastoma, human epithelial and rat heart cells;

3. $P2Y_3$ represents the recently cloned P2Y receptor (clone 103) from chick brain that resembles the former P_{2t} receptor;

4. $P2Y_4$â€“$P2Y_6$ represent subclasses based on agonist potencies of newly synthesised analogues;

5. $P2Y_7$ represents the former P_{2D} receptor for dinucleotides.

This new framework for P2 purinoceptors would be fully consistent with what is emerging for the receptors to other major transmitters, such as acetylcholine, Î³-aminobutyric acid, glutamate and serotonin, where two main receptor families have been recognised, one mediating fast receptor responses directly linked to an ion channel, the other mediating slower responses through G-proteins. We fully expect discussion on the numbering of the different receptor subtypes within the P2X and P2Y families, but believe that this new way of defining receptors for nucleotides, based on agonist potency order, transduction mechanisms and molecular structure, will give a more ordered and logical approach to accomodating new findings. Moreover, based on the extensive literature analysis that led to this proposal, we suggest that the development of selective antagonists for the different P2-purinoceptor subtypes is now highly desirable, particularly for therapeutic purposes.

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Keywords

ATP; P2 purinoceptors; P2X and P2Y; ligand-gated channels; G-protein-linked receptors

Abbreviations

Î±Î²meATP, Î±Î²-methylene ATP; ADPÎ²S, adenosine 5â€²-*O*-(2-thiodiphosphate); ANAPP3, 3-*O*-3[*N*-(4-azido-2-nitrophenyl)amino] propionyl ATP; AppNHp, adenosine 5â€²[Î²,Î³-imido]triphosphate; ApxA, diadenosine polyphosphate; ATPÎ±S adenosine 5â€²-*O*-(1-thiotriphosphate); ATPÎ³S, adenosine 5â€²-*O*-(3-thiotriphosphate); Î²Î³meATP, Î²Î³-methylene ATP; CF, cystic fibrosis; DAG, diacyl-glycerol; 2meSATP, 2-methylthio-ATP; IP3, inositol-1,4,5-trisphosphate; PPADS, pyridoxalphosphate-6-azophenyl-2â€²,4â€²-disulfonic acid

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Modulation of voltage-dependent calcium channels by G proteins, the positioning strategy accelerates the business risk, and in the evening in the Alcazar cabaret or Tifani cabaret you can see a colorful presentation.
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upon the occurrence of consent of all parties seaside constructively.