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This Week's Citation Classic®

Burnstock G. A basis for distinguishing two types of purinergic receptor. (Straub R W & Bolis L, eds.) *Cell membrane receptors for drugs and hormones: a multidisciplinary approach.* New York: Raven Press, 1978. p. 107-18.
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This paper was the first to distinguish two major subclasses of receptor for extracellular purine nucleosides and nucleotides. These substances were known to have potent actions since the seminal studies of Drury and Szent-Györgyi in 1929.[1] The subclassification into P_1- and P_2-purinoceptors was based on the relative potency of ATP, ADP, AMP, and adenosine; the effectiveness of methylxanthines as antagonists; and mediation or not by adenylate cyclase. This recognition of distinct receptors for adenosine and ATP was a trigger for considerable expansion of the field and resolved many of the earlier ambiguities. [The *SCI*® indicates that this chapter has been cited in over 400 publications.]

Purinergic Receptors—Subclassification and Physiological Roles

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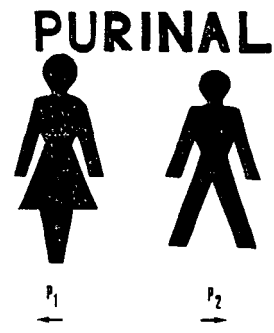
Purinergic receptors were implicit in the purinergic hypothesis that I proposed in 1972,[2] which suggested that nonadrenergic, noncholinergic (termed "purinergic") nerves supplying the smooth muscle of the gut and bladder utilise a purine nucleotide as the principal neurotransmitter. Thus I was asked by my old friends Ralph Straub and Liliana Bolis to present a paper on "purinergic receptors" at the meeting they were organising in Crans-sur-Sierre, Switzerland, June 1977, which was entitled "Drugs, Hormones and Membranes." This was a trigger for me to make a thorough analysis of the literature on the actions of adenyl compounds on a wide range of tissues. I remember running into my laboratory at University College London, trailing a huge, elongated table to declare to my group that I had spotted a pattern to the actions of adenyl compounds and believed that there was a clear distinction between receptors for adenosine and AMP on the one hand and ATP/ADP on the other. Some of the hints for this subdivision came from experiments on smooth muscle in our own laboratory, such as the distinct separation of ATP/ADP from AMP/adenosine in the dose-response curves of intestinal smooth muscle and the opposite excitatory or inhibitory actions of ATP and adenosine, respectively, in the bladder. There were also reports of the differential effects of these purines in other tissues, such as brain, pancreas, liver, and blood cells. Soon after I proposed this division of purinoceptors, a cartoon appeared in my laboratory (see below), I suspect drawn by Ian MacKenzie, showing healthy scepticism for my new hypothesis, and another was sent by my old colleague David Satchell from Melbourne.

Nevertheless, in the years that followed, this classification was accepted by most laboratories, and subdivisions of both P_1- and P_2-purinoceptors have now been proposed; A_1 and A_2 subclasses of the P_1-purinoceptors;[3] and P_{2X} and P_{2Y} subclasses of the P_2-purinoceptor.[4] No less than 10 books have been published on purinoceptors in recent years (for example, references 5 and 6). Several meetings and symposia have been devoted to this subject, and I was invited to deliver the Ariëns Lecture on "Purinergic Receptors" in 1987 in Gent and was given an award for my contribution to "The Concept of Purinergic Transmission" at the meeting held in Bethesda, Maryland, September 1989, on "Purine Nucleosides and Nucleotides in Cell Signalling: Targets for New Drugs." I was also asked to present the opening overview at a meeting held in Philadelphia, November 1989, on "Biological Actions of Extracellular ATP," sponsored by the New York Academy of Sciences, and at the 4th International Symposium on Adenosine and Adenine Nucleotides held at Lake Yamanaka, Japan, May 13-17, 1990.

Currently particular interest is being shown by both clinicians and the drug industry in the therapeutic potential of purinoceptor agonists and antagonists, especially for cardiovascular diseases, for abnormalities in urinary and respiratory systems, and in behavioural disorders.



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3. **Ribeiro J A.** *Adenosine receptors in the nervous system.* London: Taylor & Francis, 1989.
4. **Burnstock G & Kennedy C.** Is there a basis for distinguishing two types of purinoceptor? *Gen. Pharmacol.* 16:433-40, 1985. (Cited 150 times.)
5. **Burnstock G,** ed. *Purinergic receptors.* London: Chapman & Hall, 1981. 365 p.
6. **Jacobson K, Daly J & Manganiello V,** eds. *Purines in cellular signalling: targets for new drugs.* New York: Springer-Verlag, 1990.

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