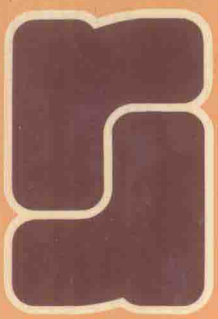

Receptors and Recognition

Series B Volume 12

Purinergic Receptors

Edited by
G. Burnstock

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G. Burnstock

Department of Anatomy and Embryology
University College London

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Receptors and Recognition

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Cellular recognition – the process by which cells interact with, and respond to, molecular signals in their environment – plays a crucial role in virtually all important biological functions. These encompass fertilization, infectious interactions, embryonic development, the activity of the nervous system, the regulation of growth and metabolism by hormones and the immune response to foreign antigens. Although our knowledge if these systems has grown rapidly in recent years, it is clear that a full understanding of cellular recognition phenomena will require an integrated and multidisciplinary approach.

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1 An Introduction to Purinergic Receptors

G. BURNSTOCK and CHRISTINE M. BROWN

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Adenosine 5′-triphosphate (ATP) was primarily considered as an intracellular energy source for many years. However, during the past fifty years purine nucleotides and nucleosides have been shown to have potent extracellular actions on excitable membranes which may be involved in physiological regulatory processes (Berne, 1963; Burnstock, 1972, 1975, 1979; Baer and Drummond, 1979). While knowledge of purinergic receptors is still in its infancy compared to the voluminous work on the classical adrenergic and cholinergic receptors, much progress is being made on their pharmacological characterisation, the ionic basis of their actions and their biochemical identity. The historical aspects of the purinergic receptor field will be briefly summarised below, while details of their distribution, physiological roles and chemistry will be dealt with in the chapters which follow.

1.1 HISTORICAL BACKGROUND

1.1.1 Initial observations of purine sensitivity

The realisation that purine nucleosides and nucleotides had potent extracellular actions on excitable membranes became widespread in the first half of this century (Drury and Szent-Gyorgi, 1929; Gaddum and Holtz, 1933; Green and Stoner, 1950). In a study of the pharmacology of simple extracts from heart muscle, brain, kidney and spleen, Drury and Szent-Gyorgi (1929) found that these crude preparations had potent effetcs upon the mammalian heart. These effects were attributed to the adenylic acid (AMP) content of the extracts. Adenosine, prepared from yeast, was found to have an identical action and, upon intravenous injection into whole animals, it caused a slowing of the heart rate, general lowering of the arterial pressure, dilatation of the coronary vessels and an inhibition of intestinal movements.

Following this report there was considerable activity within the field with particular emphasis being placed on the actions of adenosine and ATP on the cardiovascular system, and their resultant shock inducing properties; the basic aspects of this work was summarised fully by Green and Stoner (1950). During the same period the clinical effects of ATP administration in man were being widely explored, especially in geriatric patients with cardiovascular disorders. An extensive review of the medical literature was published by Boettge *et al.*, (1957), who drew special attention to the physiological significance, pharmacological action and therapeutic use of the adenyl compounds in man.

The potent vasodilatory actions of adenyl compounds led Holton and Holton (1954)

to suggest that ATP might be the vasodilatory substance which was released on antidromic stimulation of sensory nerves. Subsequently, it was shown that antidromic stimulation of the great auricular nerve, which results in vasodilatation of the rabbit ear vessels, was accompanied by ATP release (Holton, 1959).

The sensitivity of the coronary vasculature to these same compounds prompted Berne (1963) to propose that adenosine was the physiological mediator of the coronary vasodilatation associated with myocardial hypoxia. This hypothesis was based on the observation that inosine and hypoxanthine, the degradative products of adenosine, were found in the effluents of the isolated perfused cat heart and in the coronary sinus blood of the dog heart which had been subjected to severe hypoxia (Berne, 1963). It was postulated that, during myocardial hypoxia, intracellular ATP was degraded to adenosine, which crossed the sarcolemma and induced relaxation of the vascular smooth muscle of the resistance vessels. Since ATP is considerably more potent than adenosine in producing vasodilatation of coronary vessels and as increased levels of ATP have now been found in the perfusates from hypoxic hearts, the possibility that ATP makes a more significant contribution to the physiological regulation of coronary blood vessels than adenosine has been considered (Paddle and Burnstock, 1974; Burnstock, 1980a). In addition, the methylxanthines block the vasodilatory effects of adenosine on the coronary vessels (Bünger *et al.*, 1975) but have little affect on hypoxic or ischaemic hyperemia (Eikens and Wilcken, 1973; Giles and Wilcken, 1977; Olsson *et al.*, 1978). Therefore, it is relevant that the vasodilatory action of ATP is also little affected by these drugs (Giles and Wilcken, 1977).

Regulation of cerebral blood flow by adenosine has also been proposed, since this nucleoside is rapidly produced in ischaemic brain (Berne *et al.*, 1974) and is a potent dilator of cerebral arterioles when applied topically to the pial vessels (Berne *et al.*, 1974). Furthermore, a significant increase in brain adenosine levels is produced by electrical stimulation of the brain, reduction of arterial pressure, hypoxaemia and hypocapnia (Rubio *et al.*, 1975). The possibility of a vasodilatory function of adenosine and adenine nucleotides in skeletal muscle was initially considered to be unlikely, due to the rapid enzymatic deamination of adenosine to inosine (Haddy and Scott, 1968). However, increased concentrations of ATP and adenosine have been observed in the venous effluent of skeletal muscle during sustained exercise (Forrester and Lind, 1969), indicating a possible pathophysiological function for these compounds in skeletal muscle. This concept has also been extended by Haddy and Scott (1968) to include the regulation of blood flow through the renal vascular bed.

1.1.2 Purinergic nerve hypothesis

A component in the autonomic nervous system, which was neither adrenergic nor cholinergic was recognised in the early 1960's (Burnstock, 1969, 1972 and 1975; Burnstock *et al.*, 1964; Campbell, 1970; Furness and Costa, 1973). These

Table 1.1 Effects of purine nucleotides and nucleosides on visceral muscle and accessory organs

				References
(a) *Alimentary canal*				
Oesophagus	Opposum	ATP	Stimulation or inhibition	Decarle and Christensen, 1976
Oesophagus	Chicken	AD/ATP	Contraction	Bartlett, 1974
Stomach	Toad	ATP	Relaxation or contraction	Burnstock *et al.*, 1972b
cardia	Pig	ATP	Relaxation then contraction	Ohga and Taneike, 1977
fundus (l.m.*)	Guinea pig	ATP	Relaxation	Okwuasaba *et al.*, 1977a; Small and Weston, 1979
fundus (l.m.)	Guinea pig	ATP	Contraction	Baer and Frew, 1979
fundus (l.m.)	Guinea pig	ATP	Hyperpolarisation	Shuba and Vladimirova, 1980
fundus (c.m.†)	Guinea pig	ATP	Relaxation	Burnstock *et al.*, 1970
fundus (c.m.)	Rabbit	ATP	Relaxation then contraction	Burnstock *et al.*, 1970
fundus (c.m.)	Rat	ATP	Relaxation then contraction	Burnstock *et al.*, 1970
corpus	Guinea pig	ATP	Relaxation	Burnstock *et al.*, 1972b
corpus	Rat	ATP	Relaxation then contraction	Hunt *et al.*, 1978
Small intestine	Rabbit	ATP	Relaxation then contraction	Gillespie, 1934
Duodenum	Rabbit	AD/ATP	Inhibition	Ally and Nakatsu, 1976
Duodenum	Rat Mouse	ATP	Relaxation then contraction	Burnstock *et al.*, 1972b

* l.m = longitudinal muscle
† c.m. = circular muscle

(*continued on the next page*)

Table 1.1 Effects of purine nucleotides and nucleosides on visceral muscle and accessory organs (*continued*)

				References
(a) *Alimentary canal*				
Duodenum	Toad Lizard	ATP	Contraction	Sneddon *et al.*, 1973
Ileum	Cat	AD	Inhibition	Drury and Szent-Györgyi, 1929
Ileum	Guinea pig	AD	Inhibition	Ewing *et al.*, 1949; Moulton *et al.*, 1957
Ileum	Guinea pig	AD/ATP	Inhibition	Gintzler and Musacchio, 1975; Okwuasaba *et al.*, 1977b; Van Neuten *et al.*, 1977; Moritoki *et al.*, 1978; Small and Weston, 1979
Ileum	Guinea pig	ATP	Contraction	Buchthal and Kahlson, 1944; Naess and Schanche, 1957; Iso, 1974; Kazic and Milosvaljevic, 1977
Ileum	Guinea pig	ATP	Relaxation then contraction	Burnstock *et al.*, 1970
Ileum	Rabbit	AD/ATP	Inhibition	McKenzie *et al.*, 1977
Ileum	Rat	ATP	Relaxation then contraction	Burnstock *et al.*, 1972b
Ileum	Mouse	ATP	Relaxation	Burnstock *et al.*, 1972b
Colon	Fish	ATP	Contraction	Burnstock *et al.*, 1972b

(*continued on the next page*)

Table 1.1 Effects of purine nucleotides and nucleosides on visceral muscle and accessory organs (*continued*)

				References
(a) *Alimentary canal*				
Colon	Guinea pig Mouse Human	ATP	Relaxation then contraction	Burnstock *et al.*, 1972b
Colon	Rabbit	ATP	Relaxation or contraction	McKirdy, 1972
Taenia coli	Guinea pig	AD/ATP	Relaxation	Axelsson *et al.*, 1965; Burnstock *et al.*, 1970; Satchell and Burnstock, 1975; Spedding and Weetman, 1976
Taenia coli	Guinea pig	ATP	Relaxation then contraction	Satchell and Burnstock, 1975; Maas and Den Hertog, 1980
Taenia coli	Guinea pig	ATP	Increased K^+ conductance	Tomita and Watanabe, 1973; Jager, 1974
Rectum	Mouse Rat	ATP	Relaxation then contraction	Burnstock *et al.*, 1972b
Rectum	Rabbit	ATP	Inhibition	McKay and McKirdy, 1972
Rectum	Chicken	AD/AMP	Relaxation	Bartlett, 1974

(*continued on the next page*)

Table 1.1 Effects of purine nucleotides and nucleosides on visceral muscle and accessory organs (*continued*)

				References
(a) *Alimentary canal*				
Rectum	Chicken	ADP/ATP	Contraction	Bartlett, 1974
Anococcygeus	Rabbit	ATP	Relaxation	Creed *et al.*, 1977
Anococcygeus	Cat	ATP	Relaxation	Gillespie and McGrath, 1974
Anococcygeus	Rat	ATP	Contraction	Gillespie, 1972
Anococcygeus	Rat	ATP	Relaxation	Burnstock *et al.*, 1978
Rectococcygeus	Rabbit	ATP	Contraction	McKirdy, 1972
Rectococcygeus	Rabbit	ATP	Relaxation	Cocks *et al.*, 1979
(b) *Respiratory system*				
Trachea	Guinea pig	AD/ATP	Relaxation	Coleman, 1976
Trachea	Guinea pig	AD/ATP	Contraction then relaxation	Kamikawa and Shimo, 1976; Farmer and Farrar, 1976
Trachea	Monkey	AD/ATP	Relaxation	Doidge and Satchell (personal communication) Bennett and Drury, 1931; Bianchi *et al.*, 1973
Bronchioles	Human	AD/ATP	Relaxation	Doidge and Satchell (personal communication)
Lung	Frog	ATP	Relaxation	Meves, 1953

(*continued on the next page*)

Table 1.1 Effects of purine nucleotides and nucleosides on visceral muscle and accessory organs (*continued*)

				References
(c) *Urino-genital system*				
Bladder				
Detrusor muscle	Rat	AD/AMP	Relaxation	Ambache and Zar, 1970
Detrusor muscle	Rat	ADP/ATP	Contraction	Ambache and Zar, 1970
Detrusor muscle	Guinea pig	AD/AMP	Relaxation	Burnstock *et al.*, 1972a
Detrusor muscle	Guinea pig	ADP/ATP	Contraction	Burnstock *et al.*, 1972a; Weetman and Turner, 1977
Detrusor muscle	Rabbit	ATP	Contraction	Dean and Downie, 1978
Detrusor muscle	Monkey	ATP	Contraction	Johns and Paton, 1977
Uterus	Guinea pig	AD	Contraction	Bennett and Drury, 1931; Deuticke, 1932; Mihich *et al.*, 1954; Stafford, 1966
Uterus	Guinea pig	AD/ATP	Contraction	Gillespie, 1934; Moritoki *et al.*, 1979
Uterus	Rat	AD	Relaxation	Barsoum and Gaddum, 1935
Uterus	Rat	ADP/ATP	Contraction	Watts, 1953; Bunday *et al.*, 1961; Daniel and Irwin, 1965
Retractor penis	Dog	AD/ATP	Contraction	Luduena and Grigas, 1972

(*continued on the next page*)