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Reply to: 'The discovery of a new class of synaptic transmitters in smooth muscle fifty years ago and amelioration of coronary artery thrombosis'

M. P. Abbracchio¹, J.-M. Boeynaems², M. Cattaneo³, F. Di Virgilio⁴, P. Illes⁵, K. Inoue⁶, K. A. Jacobson⁷, M. Teresa Miras-Portugal⁸, V. Ralevic⁹, S. C. Robson¹⁰, A. Verkhatsky¹¹, and H. Zimmermann¹²

M. P. Abbracchio: mariapia.abbracchio@unimi.it

¹Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Milano, Italy

²Université Libre de Bruxelles, Bruxelles, Belgium

³Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milano, Italy

⁴Department of Morphology, Surgery and Experimental Medicine, Università di Ferrara, Ferrara, Italy

⁵Department of Pharmacology and Toxicology, University of Leipzig, Leipzig, Germany

⁶Clinical Pharmaceuticals, Kiushu University, Fukuoka, Japan

⁷Molecular Recognition Section, Chief, Laboratory of Bioorganic Chemistry, NIDDK, National Institutes of Health, Bethesda, MD, USA

⁸Department of Biochemistry and Molecular Biology, Universidad Complutense de Madrid, Madrid, Spain

⁹School of Biomedical Sciences, The University of Nottingham, Nottingham, UK

¹⁰Department of Medicine, Harvard University, Boston, MA, USA

¹¹The University of Manchester, Manchester, UK

¹²Institute of Cell Biology and Neuroscience, Biologicum, Goethe University, Frankfurt am Main, Germany

Dear Editor

We have read with interest the article published in your journal and wish to comment as described below:

'The discovery of a new class of synaptic transmitters in smooth muscle fifty years ago and amelioration of coronary artery thrombosis'

by Max R. Bennett, published in *Acta Physiol (Oxf)*.
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The paper deals with the discovery of non-adrenergic, non-cholinergic (NANC) purinergic neurotransmission, some 50 years ago, and the explosion of interest in this new class of transmitters in the subsequent decades. Because of the very high interest of the topic, we felt it important to point out that the paper is a very personal account and, because of this, needs to be considered alongside the evidence provided by a number of excellent reviews and original papers recording the history of the topic. These records identify a number of important errors and omissions in the paper.

1. For example, the key experiments leading to the discovery of non-adrenergic/non-cholinergic (NANC) transmission were possible thanks to the availability of the sucrose gap technique that had been originally applied to guinea pig *taenia coli* by Burnstock & Straub at the University of Oxford and published by them in 1958 (Burnstock & Straub 1958). In the same year, Burnstock (as a single author) published two other papers on this technique (Burnstock 1958a,b). Burnstock brought these methodologies to Australia, and, in 1962 appointed Max Bennett (who was in his final year of his electrical engineering degree), who indeed performed some of the experiments on which the purinergic hypothesis has been built [in this respect, it would also be important to acknowledge the contributions of Edith Bülbring and Mollie Holman, who contributed to understanding of the electrophysiological activity of the *taenia coli* (Bülbring *et al.* 1958)].
2. Many key references are misquoted throughout the text. For example, in the abstract, it is stated that '*In 1968 Graeme Campbell showed that ATP relaxed the taenia coli muscle and in 1969 David Satchell, ... showed that ATP was likely to be released from NANC terminals*'. There is no reference to either Campbell (1968) or Satchell (1969) in the article's reference list, because these papers do not exist. The seminal paper describing this work (on which Prof. Burnstock was a first author and Campbell and Satchell were co-authors) indeed appeared in 1970 (Burnstock *et al.* 1970). Moreover, being the review partially aimed at highlighting the role of P2Y₁₂ receptors in thrombosis, we would have expected a more complete and objective insight into the discovery of this receptor and a more complete appraisal of all the widely used anti-thrombotic agents targeting P2Y₁₂. For example, to quote Bennett's study (1987) for its contribution to the role of P2Y₁₂ receptors in thrombosis is misleading, because the first P2Y receptor was cloned only in 1993 (Webb *et al.* 1993) and the molecular identification of P2Y₁₂ was published in 2001 (Hollopeter *et al.* 2001).
3. Moreover, no mention is made in the article of the major discovery by Burnstock about purinergic neurotransmission, namely that ATP is a cotransmitter with classical transmitters in sympathetic, parasympathetic and enteric nerves (Burnstock 1976). The co-transmission theory has had fundamental consequences in modern basic biology, physiology and medicine and a profound impact on other scientists' activity worldwide.

Finally, the establishment of the purinergic theory has allowed the discovery of a large number of new targets for therapeutic intervention and has had general and immediate translational effects on the drug discovery process for several human diseases. Given the impact that these advancements have had and will have on human health, we believe that Prof. Burnstock's contributions should be fully recognized.

Sincerely,

References

- Bennett, MR. Optimising research & development in Australia: The Role of University based Research Centres. Australian Academy of Science; Canberra: 1987.
- Bülbring E, Burnstock G, Holman ME. Excitation and conduction in the smooth muscle of the isolated taenia coli of the guinea-pig. *J Physiol.* 1958; 142:420–437. [PubMed: 13576445]
- Burnstock G. The action of adrenaline on excitability and membrane potential in the taenia coli of the guineapig and the effect of DNP on this action and on the action of acetylcholine. *J Physiol.* 1958a; 143:183–194. [PubMed: 13576468]

- Burnstock G. The effects of acetylcholine on membrane potential, spike frequency, conduction velocity and excitability in the taenia coli of the guinea-pig. *J Physiol.* 1958b; 143:165–182. [PubMed: 13576467]
- Burnstock G. Do some nerve cells release more than one transmitter? *Neuroscience.* 1976; 1:239–248. [PubMed: 11370511]
- Burnstock G, Straub RW. A method for studying the effects of ions and drugs on the resting and action potentials in smooth muscle with external electrodes. *J Physiol.* 1958; 140:156–167. [PubMed: 13514658]
- Burnstock G, Campbell G, Satchell D, Smythe A. Evidence that adenosine triphosphate or a related nucleotide is the transmitter substance released by non-adrenergic inhibitory nerves in the gut. *Br J Pharmacol.* 1970; 40:668–688. [PubMed: 4322041]
- Hollopeter G, Jantzen HM, Vincent D, Li G, England L, Ramakrishnan V, Yang RB, Nurden P, Nurden A, Julius D, Conley PB. Identification of the platelet ADP receptor targeted by antithrombotic drugs. *Nature.* 2001; 409:202–207. [PubMed: 11196645]
- Webb TE, Simon J, Krishek BJ, Bateson AN, Smart TG, King BF, Burnstock G, Barnard EA. Cloning and functional expression of a brain G-protein-coupled ATP receptor. *FEBS Lett.* 1993; 324:219–225. [PubMed: 8508924]