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Letter to the Editor

Particulate guanylyl cyclase and cholinergic control of cardiac excitability is site specific

Neil Herring, Junaid A.B. Zaman, David J. Paterson*

University Laboratory of Physiology, Oxford University, Parks Road, Oxford OX1 3PT, UK

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We read with interest the recent study by Imai et al. [7] who provide evidence that muscarinic inhibition of pre-stimulated L-type calcium current (I_{CaL}) may involve an increase in cGMP levels via particulate guanylyl cyclase. This mechanism is apparent when cAMP has been raised by inhibition of phosphodiesterase. The role of the cGMP pathway in the cholinergic modulation of cardiac excitability is controversial. Han et al. [3] first proposed that stimulation of muscarinic receptors in sinoatrial node cells increases nitric oxide (NO) production via endothelial NO synthase (eNOS). Stimulation of soluble guanylyl cyclase was essential for cholinergic inhibition of L-type calcium current (I_{CaL}) following adrenergic pre-stimulation, although others fail to confirm this result (e.g. Refs. [2,8,9]).

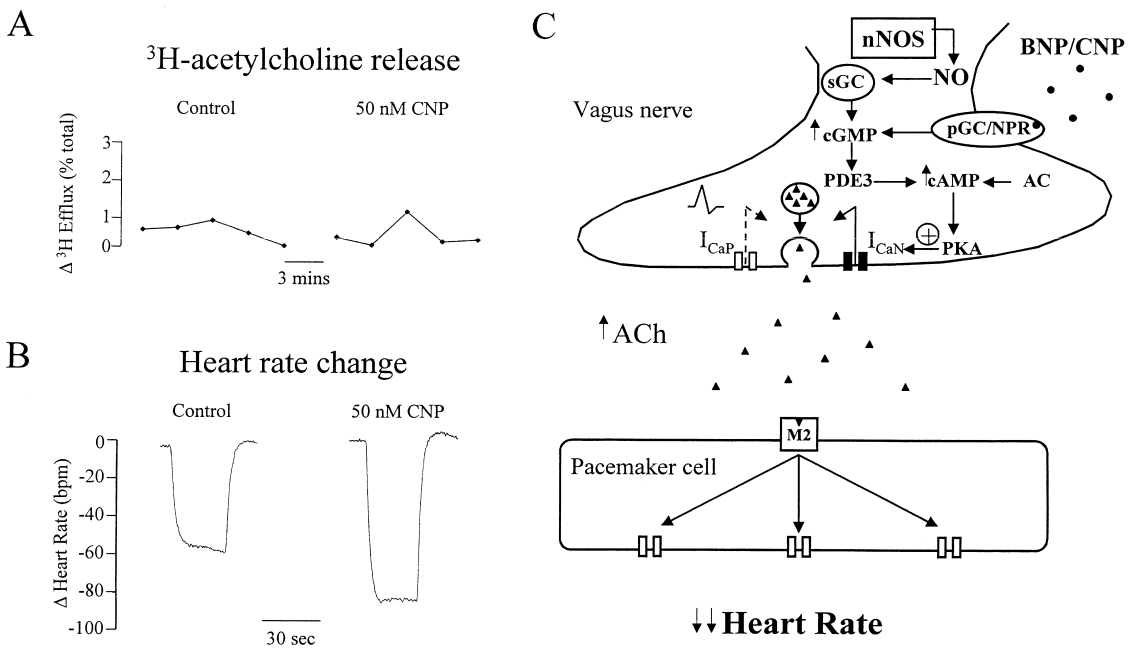

Fig. 1. NO and natriuretic peptides facilitate vagal bradycardia and acetylcholine release. Brain derived (BNP) and C-type natriuretic peptide (CNP) like NO generated by neuronal nitric oxide synthase (nNOS) increase the release of ^{3}H-acetylcholine to field stimulation (A) and the heart rate response to vagal nerve stimulation (B). This is thought to be due to stimulation of the particulate guanylyl cyclase coupled natriuretic peptide receptor (pGC/NPR) and soluble guanylyl cyclase respectively. Both increase cGMP which may inhibit phosphodiesterase 3 (PDE3) to increaase cAMP-protein kinase A (PKA) dependent phosphorylation of N-type calcium channels (I_{CaN}) (adapted from [6]).

*Corresponding author. Tel.: +44-1865-272-518; fax: +44-1865-282-170.
E-mail address: david.paterson@physiol.ox.ac.uk (D.J. Paterson).

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The paper by Imai et al. adds weight to a mounting body of evidence that suggests I_{CaL} is differentially regulated by complex multi-pathway signalling from the muscarinic receptor and that no one pathway is obligatory for control of function. Imai et al. also find that in the presence of beta-adrenergic stimulation, inhibition of neither soluble nor particulate guanylyl cyclase prevents muscarinic control of I_{CaL} implying that the functional significance of the cGMP pathway may not be as important as first proposed.

However, recent work suggests that both particulate [6] and soluble [5] guanylyl cyclase play a more significant role in the cholinergic control of cardiac excitability via the pre-synaptic control of acetylcholine release. Although natriuretic peptides and NO generated by neuronal NOS [1,4] do not affect the bradycardia to bath-applied acetylcholine, both augment the heart rate response to direct stimulation of the vagus nerve. This is due to an increase in the release of acetylcholine itself subsequent to pre-synaptic phosphorylation of N-type calcium channels (as we illustrate in Fig. 1). The notion that soluble guanylyl cyclase has no role in the cholinergic modulation of cardiac function and the finding that muscarinic receptor stimulation is also coupled to particulate guanylyl cyclase activity [7] must, therefore, be viewed with caution. The functional role of cGMP in the cholinergic control of cardiac excitability is clearly site specific.

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