Cyclic nucleotide coupled phosphodiesterase signalling in cardiac sympathetic neurons in heart disease: novel therapeutic targets

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Natriuretic peptides (NP) and the gaseous messenger nitric oxide (NO) are powerful regulators of cyclic nucleotides (cAMP & cGMP). Disruption of these pathways is thought to be important in the aetiology of both vascular and neuropsychiatric disease. Moreover, emerging evidence now suggests that impairment of cyclic nucleotide signalling, coupled to abnormal regulation of phosphodiesterases (PDE), is linked to enhanced intracellular calcium transients and exocytosis in sympathetic neurons (Li *et al.*, 2015; Lu *et al.*, 2015). This pathway has been implicated in cardiac dysautonomia associated with hypertension, heart failure and arrhythmia (*e.g.* LQT syndrome and catecholaminergic polymorphic ventricular tachycardia –CPVT). Phosphodiesterases cleave and therefore inactivate the second messengers cAMP and cGMP and are classified according to their preference for cAMP or cGMP. Phosphodiesterase 2A (PDE2A) belongs to a class of PDEs that hydrolyze both cAMP and cGMP with similar kinetics. Several recent studies point to a hitherto underappreciated pathophysiological and therapeutic relevance of PDE2A in neurological and cardiovascular diseases. Specifically, PDE2A upregulation in heart failure desensitizes the heart toward stimulation via β1-adrenergic receptors and enhances the conversion of fibroblasts to myofibroblasts, thereby increasing tissue stiffness. Inhibition of PDE2A is anti-hypertrophic and induces relaxation of pulmonary arteries and proliferation of pulmonary arterial smooth muscle cells, indicating it may constitute an effective strategy for treatment of pulmonary hypertension.

Our recent work suggests that abnormal regulation of PDE2A could be central to the efficacy of cyclic nucleotide function in cardiac sympathetic neurons when activated by either NO (Li *et al.*, 2015) or NP (Lu *et al.*, 2015). Failure to regulate this pathway in cardiac disease leads to enhanced neurotransmission and abnormal post-synaptic excitability and may be responsible for the clinical failure of iv brain natriuretic peptide (BNP) (Seifert, 2015). Up-regulation of NP production is seen as a compensatory mechanism affording beneficial haemodynamic and myocardial effects, reflected in their ability to slow the progression of heart failure and also inhibit cardiac sympathetic responsiveness. However, the paracrine action of NP on the sympathetic nervous system is controversial. We have recently established that the beneficial inhibitory action of BNP on the calcium current/intracellular calcium transient and neurotransmission is prevented by overexpression of PDE2A. This was associated with ~60% reduction in cGMP, suggesting that PDE2A plays a key role in modulating the efficacy of BNP. Furthermore, blockade of overexpressed PDE2A re-established the action of BNP. Our data suggest a possible site of regulation on PDE2A signalling where BNP might fail in hypertension/heart failure, resulting in excessive sympathetic activity. Unpublished pilot data shows neurons from pre-hypertensive rats are unresponsive to BNP, although dominant negative neuronal PDE2A gene transfer can rescue this. NO generated from neuronal nitric oxide synthase (nNOS) and its adaptor protein (CAPON) behave in a similar manner to BNP in regulating cGMP. Interestingly, genetic models of hypertension have a pre-disease neuronal phenotype that is coupled to metabolic stress impairing NP/NO activated cGMP resulting in impaired intracellular calcium handling. Gene transfer of CAPON or nNOS can rescue this cellular phenotype, whereas gene transfer of PDE2A abrogates the inhibitory effects of BNP on calcium influx and noradrenaline release. Whether this is directly influenced by dysregulation of PDE to its molecular partners is not known.

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Seifert R. (2015) Emerging role of phosphodiesterase 2A in hypertension. *Hypertension* **66:** 13-14.