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EDITORIAL

Cardiac PDEs and crosstalk between cAMP and cGMP signalling pathways in the regulation of contractility

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Abstract Elucidation of cAMP and cGMP signalling in the heart remains a hot topic, and new regulatory mechanisms continue to appear. Studying the influence of phosphodiesterases on 5-HT_4 receptor signalling in porcine atrium, a paper from this issue of the journal expands findings of a crosstalk between cardiac cGMP and cAMP signalling recently discovered in failing rat ventricle to a different species and cardiac region. The overall data suggest that cGMP, produced following stimulation of the NPR-B receptor for C-type natriuretic peptide (CNP), inhibits cAMP degradation by phosphodiesterase 3 and thereby enhances cAMP-mediated signalling from β-adrenoceptors and 5-HT_4 receptors to inotropic effects. In porcine atrium, this effect can be seen both as an increase in inotropic effect and as a reduced fade of the inotropic effect with time. Thus, accumulating evidence brings together several active fields of research, including cardiac phosphodiesterases, compartmentation of cyclic nucleotide signalling and the field of natriuretic peptides. If present in human hearts, this effect of CNP may have clinical implications.

Introduction

More than 50 years after the discovery of cAMP as a second messenger (Sutherland and Rall 1958), and almost 50 years after its essential role in the inotropic response to catecholamines was proposed (Robison et al. 1965), the fine-tuning of this regulatory principle is still the subject of intense investigation. Although it is now clear that pathways independent of cAMP also play a role in the regulation of cardiac contractility, e.g. through regulation of myosin light chain phosphorylation (Rossmanith et al. 1997; Andersen et al. 2002; Grimm et al. 2005; Qvigstad et al. 2005c; Riise et al. 2008; Hussain et al. 2009), cAMP-dependent pathways are still considered the main regulators of cardiac contractility, and new pieces of the puzzle leading to its understanding are still being added. One important reason for this is the realisation that long-term stimulation of this signalling pathway in patients with chronic heart failure leads to increased mortality and, accordingly, that blocking β-adrenoceptors (β-adrenergic receptors, β-AR), the main receptors that stimulate this pathway, reduces heart failure mortality (Waagstein et al. 1975, 1993; Packer et al. 1996; CIBIS-II Investigators and Committees 1999; MERIT-HF Study Group 1999; Lohse et al. 2003). Much recent attention has been devoted to the compartmentation of cAMP signalling, and although this concept is now more than 30 years old (Corbin et al. 1977; Kaumann and Birnbaumer 1974; Brunton et al. 1981), substantial advances have been seen during the latest few years, brought about by the development of novel technology to measure cAMP at the subcellular level, e.g., by FRET-based cAMP sensors (Zaccolo et al. 2000; Zaccolo and Pozzan 2002; Nikolaev et al. 2004; Mongillo et al. 2004; Ponsioen et al. 2004; Warrier et al. 2005), combined with thorough pharmacological studies where the focus is on interpreting the complex changes observed in cardiac preparations with the combined use of different stimulators and inhibitors. One such study appears in the present issue (Weninger et al. 2013), which, together with a related study by the same authors last year (Weninger et al. 2012), bring together several recent lines of research that have independently and together contributed to the recent understanding of cAMP regulation of cardiac contractility: the discovery and characterisation of 5-HT_4

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receptor-mediated effects in the heart (first in atria, later also in ventricles), the role of different phosphodiesterases in the compartmentation of cAMP and cAMP-mediated effects by limiting diffusion of cAMP, and the recent finding that natriuretic peptides seem to have previously unappreciated effects in the heart by bringing about cGMP-mediated enhancement of cAMP signalling to enhance cardiac contractility (Qvigstad et al. 2010; Afzal et al. 2011b).

Cardiac 5-HT$_4$ signalling and the roles of various phosphodiesterases

Weninger et al. (2012, 2013) studied the effects of 5-HT$_4$ receptors in porcine atria, a well-known system for the study of these receptors (Kaumann 1990), which are also present in the atria of human hearts (Kaumann et al. 1990; Kaumann and Levy 2006a). Early studies suggested an apparent lack of such receptors in porcine (Schoemaker et al. 1992; Saxena et al. 1992) and human (Jahnel et al. 1992; Schoemaker et al. 1993) ventricle, but it was later shown that the use of the non-selective phosphodiesterase (PDE) inhibitor 1-isobutyl-methyl-xanthine (IBMX) could reveal 5-HT$_4$-mediated effects also in porcine and human ventricle (Brattelid et al. 2004). Furthermore, studies in rats with heart failure revealed the appearance of functional 5-HT$_4$ receptors in the cardiac ventricle of rats (Qvigstad et al. 2005a), a species where cardioexcitation by serotonin had earlier been thought to be mediated by 5-HT$_2$ receptors (Läer et al. 1998). The increased expression of 5-HT$_4$ receptors in failing rat cardiac ventricle seems to reflect the re-expression of receptors present in the foetal heart (Brattelid et al. 2012). On the basis that the ventricular 5-HT$_4$ receptors showing increased expression in the failing rat and human ventricle signal through cAMP, as do β-AR, it was proposed that treatment with 5-HT$_4$ antagonists could be a useful addition to pharmacological treatment of heart failure (Qvigstad et al. 2005b; Levy et al. 2008). So far, this has been tested in a rat model of heart failure (Birkeland et al. 2007) as well as in a clinical trial on heart failure patients with reduced ejection fraction, receiving the 5-HT$_4$ antagonist piboserod for 6 months (Kjekshus et al. 2009). Both studies showed some results consistent with the hypothesis that 5-HT$_4$ antagonism may be of benefit in heart failure, but further clinical testing will be required to conclude about the potential clinical usefulness of such treatment (Kjekshus et al. 2009).

One of the classical criteria set out by Sutherland that an effect was indeed mediated by cAMP was that the effect should be enhanced by inhibiting the breakdown of cAMP by phosphodiesterases, typically using the classical PDE inhibitor theophylline (Butcher and Sutherland 1962) and later the non-selective PDE inhibitor IBMX. This criterion was indeed also applied to the cardiac 5-HT$_4$ responses, both in porcine atria (De Maeyer et al. 2006) and in porcine, human and rat ventricles (Brattelid et al. 2004; Afzal et al. 2008). Although the initial aim of such studies was to document beyond doubt the involvement of cAMP in the effects of 5-HT, it soon became a question which PDEs could be involved in limiting these responses (Kaumann and Levy 2006b). One important motivation for this was the observation that 5-HT$_4$ receptors, at least in the failing rat heart, appeared to give a robust inotropic effect despite a very modest cAMP production compared to β-AR (Qvigstad et al. 2005a). Further studies were enabled by the developments during the 1990s of the understanding of the multitude of PDE subtypes as well as the availability of PDE subtype-selective inhibitors (see, e.g. Verde et al. 1999) and revealed that 5-HT$_4$-mediated inotropic responses in failing rat and human ventricles were primarily limited by PDE3 (Afzal et al. 2008). However, whereas no effect of the PDE4-selective inhibitor rolipram alone was observed on the 5-HT$_4$-mediated inotropic responses, a further enhancement of the inotropic response by rolipram was observed in the presence of a PDE3 inhibitor (cilostamide), revealing a (secondary) role for PDE4 in limiting the inotropic response both in rat and human failing ventricles (Afzal et al. 2008). Both PDE3 and PDE4 were also found to be involved in the fade of inotropic responses to 5-HT$_4$ receptor stimulation in porcine atria (Galindo-Tovar et al. 2009), the tissue studied by Weninger et al. (2012, 2013), whereas in human atria, PDE3 but not PDE4 was observed to be responsible for fade (Galindo-Tovar et al. 2009). Importantly, Galindo-Tovar et al. (2009) revealed differences between porcine atria and ventricles as well as age-dependent changes in porcine atria, indicating that care must be exercised when extrapolating results not only between species but also between cardiac atria and ventricles and even with age.

In this context, it is interesting to relate these findings with the 5-HT$_4$ receptor to the large and increasing body of knowledge concerning its better-known relatives, the β_1- and β_2-adrenoceptors or adrenergic receptors (β-AR). It has become clear recently that there are marked differences between β_1- and β_2-AR-mediated signalling, e.g. in terms of localization of the cAMP produced (Nikolaev et al. 2006), the effects of PDE subtypes on the cAMP produced (Rochais et al. 2006) and the localisation of the receptors (Nikolaev et al. 2010).

These groundbreaking molecular studies, combined with studies on the PDEs regulating the functional effects of β_1- and β_2-AR-mediated effects in different species and cardiac regions, such as human atrium (Christ et al. 2006; Kaumann et al. 2007), rat ventricle (Vargas et al. 2006; Christ et al. 2009; Afzal et al. 2011a), mouse atrium and ventricle (Galindo-Tovar and Kaumann 2008) and human ventricle (Molenaar et al. 2013), are now providing a much better understanding than we had just a few years ago concerning

the mechanisms by which different stimuli, through the same second messenger—cAMP—can produce different cellular and physiological effects. Although there is still a long way to go because of the complexity of the information obtained, some common patterns seem to emerge: β_1-AR produce a large cAMP signal which reaches large parts of the cell (Nikolaev et al. 2006). When measured as whole-cell cAMP or with sensors that are widely distributed, this cAMP signal is mainly limited by PDE4. However, β_1-AR-mediated inotropic effects are still primarily limited by PDE3, indicating the co-localisation of certain isoforms of PDE3 with the cAMP regulating the phosphorylations relevant to increase contractility, e.g. PLB and TnI phosphorylation. The results tend to diverge to some extent regarding whether PDE4 achieves an important role once PDE3 is inhibited, a question which may well be of clinical importance in patients using PDE inhibitors. Two main patterns seem to be important in this regard: (1) PDE4 seems to play a relatively smaller role in human compared to rat atrium (Christ et al. 2006 and Kaumann et al. 2007 vs. Christ et al. 2009) and (2) the functional role of PDE4 in the cardiac ventricle seems to be reduced in heart failure, at least in rats (Afzal et al. 2011a). But for the 5-HT_4-mediated inotropic response, PDE3 inhibition seems to demask a role of PDE4, both in rat and human failing ventricles (Afzal et al. 2008).

Atrial natriuretic peptides and crosstalk with cAMP-mediated signalling

The other main line of research addressed by the study of Weninger et al. (2012, 2013) is the interference of signalling through natriuretic peptides (ANP, BNP, CNP) and their receptors NPR-A and NPR-B (also known as particulate or membrane-bound guanylyl cyclase GC-A and GC-B) with cAMP-mediated signalling. It was shown by Qvigstad et al. (2010) that CNP, acting through NPR-B, but not ANP or BNP, acting through NPR-A, enhances β_1-AR-mediated signalling in failing rat ventricles through cGMP-mediated (competitive) inhibition of PDE3. This effect is also seen on 5-HT_4-mediated inotropic effects in the failing rat ventricle (Afzal et al. 2011b). These findings are now followed up in a different species and cardiac region by studies of CNP effects in the porcine atrium by Weninger et al. (2012 and this issue). In failing rat ventricles, this crosstalk was shown to result in increased inotropic effects of β_1-AR and 5-HT_4 receptor stimulation (Qvigstad et al. 2010; Afzal et al. 2011b), and CNP also promoted β_1-AR-stimulated cardiomyocyte apoptosis similar to the inhibition of PDE3 by cilostamide (Qvigstad et al. 2010). In porcine atrium, the functional effect of CNP was observed both as an increased inotropic response to 5-HT_4 receptor stimulation and as a reduced fade of the inotropic response with time (Weninger et al. 2012, 2013). Whereas the first study of Weninger et al. (2012) could seem to imply a need for PDE2 inhibition to observe the effect of CNP, this apparent discrepancy with the rat ventricular data was resolved in the second study, where there is clearly no additional role of the PDE2 inhibitor EHNA (Weninger et al. 2013). Whilst the study of Afzal et al. (2011b) found apparently opposite effects of cGMP generated by soluble guanylyl cyclase (sGC) and NPR-B receptor stimulation on the 5-HT_4-mediated inotropic response in rat failing ventricles, this result could not be confirmed by Weninger et al. (2012, 2013) in porcine atrium, who found that sGC stimulation rather seemed to attenuate responses to 5-HT. Whether this apparent controversy reflects a species or tissue difference or may be explained by methodological differences remains to be determined.

Possible clinical relevance of modulatory roles of cGMP

The field of cGMP-mediated effects in the heart and the potential benefits of enhancing cGMP signalling in heart failure has received some recent attention, the clinical culmination of one line of this research being the disappointing results of the RELAX Study of the PDE5 inhibitor sildenafil in heart failure patients with preserved ejection fraction (a.k.a. diastolic heart failure; Redfield et al. 2013). The story of natriuretic peptides in the heart has many aspects. Clearly, different variants of these peptides or their precursors serve as very useful biomarkers of heart failure based on the increased levels of ANP and BNP and their derivatives in heart failure (Omland et al. 1996). From the assumption that their natriuretic and haemodynamic properties would be beneficial in heart failure, BNP, in the form of nesiritide, has also been used in the treatment of heart failure, initially with promising results (Colucci et al. 2000). But with increasing evidence that the long-term effect of this treatment might not be so beneficial (Yancy 2004; Sackner-Bernstein et al. 2005), the era of their use in heart failure treatment may be reaching an end after the conclusion of the ASCEND-HF trial, showing that treatment of acute decompensated heart failure with nesiritide does not provide any survival benefit (O'Connor et al. 2011). In this context, recent results, including those of Weninger et al. concerning the effects of CNP in the heart, may be of clinical interest. Although nesiritide primarily activates the NPR-A receptor and CNP primarily activates the NPR-B receptor, this distinction may not be absolute, also not in a clinical setting. In light of the beneficial effects of beta-blockers in heart failure and the deleterious effects of enhancing cardiac cAMP-mediated effects in heart failure patients by PDE inhibition (Packer et al. 1991; Cohn et al. 1998), or even by only partial β-AR stimulation (The Xamoterol in Severe Heart Failure Study Group 1990), the enhancement of cAMP-mediated inotropic effects of β_1-AR (Qvigstad et al. 2010)

and 5-HT_4 receptor stimulation (Afzal et al. 2011b; Weninger et al. 2012; Weninger et al. 2013) by CNP may prove to be critically relevant for the absence of the expected beneficial effects of using BNP in heart failure treatment.

Perspectives

It remains to be seen whether the cGMP-mediated inhibition of PDE3 so far reported in rat ventricle and porcine atrium is also present and of significance in the human heart. If so, it could be of interest to determine whether blocking this effect of CNP will be of benefit in heart failure treatment. Perhaps treatment with a natriuretic peptide, like nesiritide, could be combined with a selective NPR-B receptor antagonist to eliminate these newly reported cardiac effects of natriuretic peptides whilst preserving their presumably beneficial NPR-A-mediated effects, including natriuretic, haemodynamic and possibly cardiac relaxant and anti-hypertrophic properties. However, as long as no such selective NPR-B receptor antagonist is available for clinical use (the closest candidate would seem to be the peptide P-19, reported by Deschênes et al. 2005), there is still a way to go to resolve this issue.

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