Phosphodiesterases cleave and, thereby, inactivate the second messengers adenosine cAMP and cGMP. \(^1\) Phosphodiesterases are classified according to their preference for cAMP or cGMP. Phosphodiesterase 2 belongs to a class of phosphodiesterases that hydrolyze cAMP and cGMP with similar kinetics. \(^1\) Several recent studies point to a hitherto underappreciated pathophysiological and therapeutic relevance of phosphodiesterase 2 in cardiovascular diseases. Specifically, phosphodiesterase 2 upregulation in heart failure desensitizes the heart toward stimulation via \(\beta_1\)-adrenergic receptors. \(^2\) In engineered connective tissue, phosphodiesterase 2 enhances the conversion of fibroblasts to myofibroblasts, thereby increasing tissue stiffness. \(^3\) Finally, phosphodiesterase 2 inhibitors induce relaxation of pulmonary arteries and inhibit proliferation of pulmonary arterial smooth muscle cells, indicating that phosphodiesterase 2 inhibitors may constitute an effective strategy for treatment of pulmonary hypertension. \(^4\)

On this background, published in this issue of *Hypertension*, a study by Li et al.\(^5\) adds a new facet to the emerging roles of phosphodiesterase 2 in the pathophysiology of cardiovascular diseases. In sympathetic neurons, depolarization leads to calcium influx via voltage-dependent calcium channels with subsequent release of norepinephrine (Figure). Enhanced norepinephrine release can worsen hypertension, and there is evidence for defective norepinephrine reuptake into sympathetic neurons in hypertensive rats. \(^6\) Li et al.\(^5\) show that brain-derived natriuretic peptide (BNP), via activation of particulate guanylyl cyclase A increases cGMP levels in sympathetic neurons, and subsequently decreases calcium influx and norepinephrine release (Figure). Ultimately, BNP reduces heart rate. These data are in accord with the notion that BNP can exert beneficial effects in cardiovascular diseases, most notably in heart failure. \(^7\)

The study by Li et al.\(^5\) is important for 2 major reasons. First, because of the dual specificity of phosphodiesterase 2 for cAMP and cGMP and the allosteric stimulatory effects of cGMP on phosphodiesterase 2-catalyzed cAMP hydrolysis, phosphodiesterase 2 is, in principle, prone to mediate the cross talk between cAMP and cGMP signaling. \(^1\) But in the study of Li et al.\(^5\), there is no evidence for a cross-regulatory role of phosphodiesterase 2A between cAMP and cGMP. In agreement with the data on rat sympathetic neurons studied by Li et al.\(^5\) in the failing rat heart, phosphodiesterase 2 is the major enzyme responsible for regulation of BNP-induced cGMP increase. \(^8\) An explanation for this high degree of specificity could be that all components of the BNP-particulate guanylyl cyclase A-PKG-phosphodiesterase 2 signaling pathway are localized in a defined cGMP-specific signalosome \(^1\) in sympathetic neurons and the failing ventricle, excluding cross talk with cAMP.

Second, in sympathetic neurons from spontaneously hypertensive rats, the expression of phosphodiesterase 2A is increased by \(\approx 60\%\). \(^5\) Overexpression of phosphodiesterase 2A in sympathetic neurons, mimicked by adrenoviral infection, abrogates the inhibitory effects of BNP on calcium influx and norepinephrine release, and inhibition of this enhanced phosphodiesterase 2A activity with a selective phosphodiesterase 2 inhibitor restores the inhibitory effects of BNP on calcium influx and norepinephrine release. \(^5\) Thus, Li et al.\(^5\) have identified a new molecular mechanism, namely enhanced phosphodiesterase 2A expression, by which beneficial cardiovascular effects of BNP are annihilated.

The study of Li et al.\(^5\) has important implications for future research and therapeutic strategies. The genetic mechanisms underlying the upregulation of phosphodiesterase 2A in sympathetic neurons of spontaneously hypertensive rats are as yet unknown. It will be important to examine the question whether also other phosphodiesterases are dysregulated and which specific mechanisms are involved. Of course, it will be necessary to explore whether phosphodiesterase 2A expression is also altered in specific forms of human systemic hypertension. It should be kept in mind that phosphodiesterase 2 is not a single enzyme, but a family of 3 splice variants that may have slightly different functions. \(^1\) Moreover, in the study of Li et al.\(^5\) on sympathetic neurons, phosphodiesterase 2A exhibited the properties of a cGMP-specific phosphodiesterase (Figure), but in other systems phosphodiesterase 2 regulates both cAMP and cGMP. \(^3,4\) This may reflect differential compartmentalization of proteins involved in cAMP and cGMP signaling.

About therapeutic interventions, 1 evident strategy based on the results of Li et al.\(^5\) is to enhance the clinical effects of BNP derivatives such as nesiritide \(^2\) with phosphodiesterase 2 inhibitors. On the basis of different mechanisms of action, we may expect synergistic beneficial cardiovascular effects. A dual therapy with a particulate guanylyl cyclase A agonist and a phosphodiesterase 2 inhibitor entails, of course, the risk of increased side effects, specifically in cells that express both particulate guanylyl cyclase A and phosphodiesterase 2A. But it is certainly worthwhile to pursue this avenue of drug research.
Role of phosphodiesterase 2 (PDE2) in the modulation of sympathetic neuron function by brain-derived natriuretic peptide (BNP). Depolarization of sympathetic neurons leads to activation of voltage-dependent calcium channels (VOCC). The calcium influx results in the release of norepinephrine (NE), which via β₁-adrenergic receptors increases heart rate and, via α₁-adrenergic receptors, increases vascular resistance. As a result, blood pressure increases. This pathway is functionally antagonized by BNP, which activates the particulate guanylyl cyclase A (pGC-A). pGC-A catalyzes the cyclization of GTP to the second messenger guanosine cGMP, which in turn activates protein kinase G (PKG, also referred to as cGMP-dependent protein kinase). As a result, calcium influx, NE release, and heart rate are decreased. cGMP is inactivated by PDE2. Overexpression of PDE2 in spontaneously hypertensive rats (SHR) or adenoviral overexpression of PDE2 in sympathetic neurons abrogates the inhibitory effects of BNP on calcium influx and norepinephrine release. In contrast, the selective PDE2 inhibitor BAY 60-7550 restores the inhibitory actions of BNP. As a control, the selective PDE3 inhibitor milrinone is ineffective. BAY 60-7550 indicates a prototypical selective PDE2 inhibitor; Isatin, a compound with pleiotropic pharmacological effects including blockade of pGC-A activation by BNP; Milrinone, a prototypical selective PDE3 inhibitor; and Rp-8-BR-PET-cGMP, a selective and membrane-permeable inhibitor of PKG.

A recent study provided proof-of-concept that phosphodiesterase 2A inhibition exerts beneficial effects in several preclinical models of pulmonary hypertension. As a next step, similar studies should be conducted with respect to systemic arterial hypertension. Several potent and selective phosphodiesterase 2 inhibitors have been developed based on the crystal structure of phosphodiesterase 2A and systematic structure–activity relationship studies of compound series. Currently, the focus of clinical phosphodiesterase 2 inhibitor research is on the treatment of neuropsychiatric diseases associated with cognitive impairment, such as Alzheimer disease, schizophrenia, and depression. Given the high prevalence of Alzheimer disease, depression, and hypertension, phosphodiesterase 2A inhibitors may perhaps become the first class of drugs to simultaneously treat both cardiovascular and neuropsychiatric diseases. Phosphodiesterase 2 inhibitors that do not penetrate the blood–brain barrier are available, as well. In view of the fact that phosphodiesterase 2A hydrolyzes both cAMP and cGMP and is stimulated by cGMP, it may be important to target just specific cell types to minimize side effects.

In conclusion, the present study of Li et al. together with other reports, most notably the study by Bubb et al. on pulmonary hypertension, have placed the concept of phosphodiesterase 2 inhibition in a prominent position for future pathophysiological and pharmacological research. The study of Li et al. is an excellent example how substantial progress can be obtained through wise application of pharmacological and molecular biology methods in appropriate (patho)physiological models.

Acknowledgments

I thank Annette Stanke for preparation of the Figure and critical reading of the article.

Disclosures

None.

References

Emerging Role of Phosphodiesterase 2A in Hypertension
Roland Seifert

Hypertension. 2015;66:13-14; originally published online April 27, 2015;
doi: 10.1161/HYPERTENSIONAHA.115.05170

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/66/1/13