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Scientists on the spot: Phosphodiesterases and heart failure

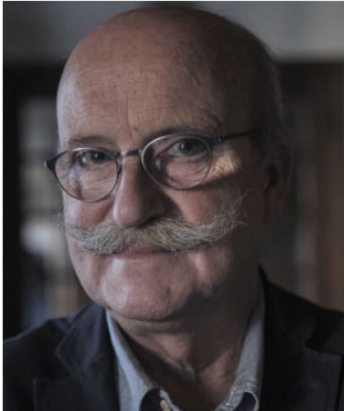
Albano C. Meli and **Rodolphe Fischmeister***

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Keywords

Cyclic nucleotides Phosphodiesterases Heart pathophysiology Calcium channels

Watch the interview here: https://youtu.be/_cScyj775Ug.



Highlight: In this *Onlife* interview, Dr Rodolphe Fischmeister speaks about his interest and findings on phosphodiesterases regulating cyclic nucleotides in the heart and potential future therapeutics for patients with heart failure.

Biography: Dr Rodolphe Fischmeister is a Director of Research of Exceptional Class (DRCE) at the French Institute of Health, called INSERM. He is an eminent French scientist known worldwide for his interest in cyclic nucleotide phosphodiesterases (PDE) regulating some major ion channels in the heart. He received training as an Engineer at the 'Ecole supérieure d'électricité' commonly known as Centrale Supélec of Gif sur Yvette (France). He then received his PhD in Physiology and Biophysics at the University of Paris-Sud in 1980. He worked as a postdoctoral research fellow at the Department of Physiology and Biophysics in the Dalhousie University of Halifax (Canada) until 1982. He joined the Department of Anatomy of Emory University in Atlanta (Georgia, USA) for 2 years. Back to France, he obtained in 1983 a tenure position as INSERM Research Associate at the University of Paris-Sud in Orsay (France). In 1989, he became Director of Research at INSERM and in 2011, he became Director

of Research of 'Classe Exceptionnelle' at INSERM. Dr Fischmeister has published over 160 original peer-reviewed research articles. He is currently Deputy Director of INSERM UMR-S 1180 at Châtenay-Malabry (France) and Head of the Laboratory of Excellence in Research on Medication and Innovative Therapeutics (LabEx LERMIT) that combines 15 different research laboratories. He is also Deputy Vice-President of Research of the new University Paris-Saclay.

Summary of interview

Dr Fischmeister has always been interested in the cardiac fight or flight response and its regulation by the sympathetic and parasympathetic stimulation. He considered one of his main finding to be the antagonism of cyclic nucleotides—namely, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) on cardiac function regulation. Hence, 30 years ago, when he performed patch-clamp experiments on frog cardiomyocytes with cAMP, he found that adding cGMP strongly affected the regulation of cardiac calcium voltage-dependent channels. Therefore, he observed that cardiomyocytes exhibit dynamic and efficient regulation in order to quickly hydrolyze cAMP close to some calcium channels. These experiments were the very beginning steps of his interests around the role of phosphodiesterases (PDEs).

Thereafter, Dr Fischmeister talks about the large family of PDEs in cardiomyocytes. There are different genes coding for splice variants and isoforms of PDEs. They regulate both cAMP and cGMP. PDE3 is the most well known in the human heart and has been targeted pharmacologically. The initial therapeutic concept with PDEs was to inhibit them in order to increase cAMP and cardiac function in chronic cardiac diseases. However, quickly, it was figured out that such approaches rather contribute towards worsening of a patient's heart, similarly to the initial idea that beta-adrenergic receptors should be stimulated (using agonists) rather than inhibited in heart failure.



CARDIOVASCULAR
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— Dr. Albano C. Meli

INSERM Montpellier, France



— Dr. Rodolphe Fischmeister

INSERM Paris, France

Dr Albano C. Meli from INSERM Montpellier (France), interviews Dr Rodolphe Fischmeister, Director of Research of Exceptional Class (DRCE) at INSERM Paris (France).

So, the current concept is to activate PDEs, but the key question is which enzymes should be specifically targeted. In this way, PDE2 and 4 are investigated in Dr Fischmeister's lab. PDE2 is likely a good candidate to activate, as it has an allosteric stimulatory domain and binds cAMP when it reaches high concentration. Therefore, activating PDE2 may be a good approach to protect the heart from cAMP overflow in cardiomyocytes. PDE4 works at a much lower concentration of cAMP, and it is decreased in heart failure. Dr Fischmeister and his lab propose that PDE4 activation may be useful to control cAMP level in specific domains in cardiomyocytes. One key question raised through his research is to further understand the compartmentalization of cAMP in cardiomyocytes.

Lastly, Dr Fischmeister gave some advice for young scientists hoping to do research. First is to understand that research is a quest that should be animated by passion, curiosity, and humility. Another wise piece of advice is to systematically challenge ideas found in papers but also those proposed by seniors (i.e. your boss). It is important to develop your own ideas, opinions, and ways of thinking. Moreover, it is important to look around and in other disciplines. In fact, multidisciplinary research is essential to push the limits of knowledge.

Conflict of interest: none declared.