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Oral presentation

Cyclic nucleotide phosphodiesterases – 40 years of progress

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In this lecture I will discuss some of the relevant history of cGMP-selective and cGMP-regulated phosphodiesterases. Emphasis will be put largely on those experiments carried out in our own laboratories over the last 40 years. Short vignettes or anecdotes on the discoveries of the "cGMP-stimulated" (PDE2s) and "cGMP-inhibited" (PDE3s) phosphodiesterases as well as on the original cloning of PDEs 5,6, 9, and 11 will be mentioned. I will then spend a bit more time discussing a recent series of experiments on the opposing roles of PDE2s and PDE3s in endothelial barrier function. These experiments provide data to suggest that both of these PDEs can subserve one or more pools of cGMP that can functionally regulate endothelial permeability, but in opposite directions depending on the cGMP concentration. Finally, I will describe a series of experiments that strongly suggest treatment of whole animals with selective PDE5 antagonists may provide effective functional improvement in the cardiac dysfunction that occurs in muscular dystrophy. These studies utilize two different models of muscular dystrophy in the mouse. When given chronically in the drinking water, sildenafil appears not only to stop the decline in cardiac function that occurs with age, but also may reverse existing dysfunction after it has developed, at least as assessed by echocardiography.