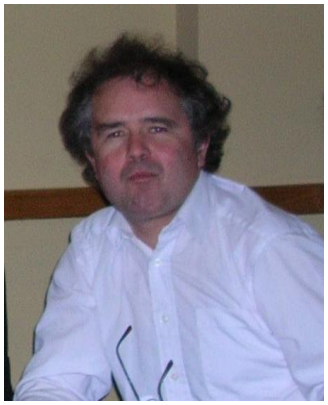
BHF 4 Year PhD Programme in Cardiovascular Research

Principal Investigator Details



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Title

Interactions between cAMP and Ca^{2+} signals in human aortic smooth muscle cells

Abstract

Increases in cytoplasmic Ca^{2+} concentration regulate many aspects of vascular smooth muscle behaviour, most notably contraction and thereby vascular tone [1, 2]}. In many tissues, including vascular smooth muscle, interactions between signalling pathways involving Ca^{2+} and cyclic nucleotides (cGMP and cAMP) are important because they allow integration of information from different cell-surface receptors [3]. We recently demonstrated that in human aortic smooth muscle cells, the Ca^{2+} signals evoked by histamine are attenuated by prostaglandin E_2 (PGE_2), but the mechanism is unresolved. The responses to histamine are mediated by IP_3 produced by phospholipase C. PGE_2 stimulates formation of cAMP, and 8-Br-cAMP (a membrane-permeant form of cAMP) mimics the effects of PGE_2 on histamine-evoked Ca^{2+} signals. But the effects of PGE_2 appear not to be affected by inhibition of cAMP-dependent protein kinase. In cells loaded with caged IP_3, flash-photolysis evokes Ca^{2+} release via IP_3 receptors, but these responses are unaffected by PGE_2, suggested that the effects of cAMP are unlikely to be mediated by direct inhibition of IP_3 receptors. Preliminary evidence also suggests that the inhibition of histamine-evoked Ca^{2+} signals may involve cAMP signalling junctions, wherein cAMP is locally delivered at high concentrations to its target. This project, which will measure both Ca^{2+} and cAMP in human aortic smooth muscle cells, will address two questions:

1. What is the molecular target to which the cAMP binds?
2. Where within the sequence from histamine to IP_3R, does cAMP cause inhibition?

Key references

1 Govindan, S., Taylor, E. J. A. and Taylor, C. W. (2010) Ca^{2+} signalling by P2Y receptors in cultured rat aortic smooth muscle cells. Br. J. Pharmacol. **160**, 1953-1962
2 Pantazaka, E., Taylor, E. J. A., Bernard, W. and Taylor, C. W. (2013) Ca^{2+} signals evoked by histamine H_1 receptors are attenuated by activation of prostaglandin EP_2 and EP_4 receptors in human aortic smooth muscle cells. Br. J. Pharmacol. **169**, 1624-1634
3 Tovey, S. C., Dedos, S. G., Taylor, E. J. A., Church, J. E. and Taylor, C. W. (2008) Selective coupling of type 6 adenylyl cyclase with type 2 IP_3 receptors mediates a direct sensitization of IP_3 receptors by cAMP. J. Cell Biol. **183**, 297-311