INVESTIGATION OF THE MECHANISMS OF URIDINE 5' TRIPHOSPHATE INDUCED CONTRACTION OF RAT MESENTERIC ARTERY SMOOTH MUSCLE

Thesis submitted for the degree of

Doctor of Philosophy

at the University of Leicester

by

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July 2011

ABSTRACT

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Investigation of the mechanisms of uridine 5' triphosphate induced contraction of rat mesenteric artery smooth muscle.

Uridine 5' triphosphate (UTP) is a pyrimidine nucleotide which is released from a variety of cells including platelets and endothelial cells. The release of UTP can lead to vasoconstriction if there is damage to the endothelial layer and hence its actions on the vasculature are important areas of investigation.

The research presented in this thesis describes the measurement of isometric contractile responses of rat mesenteric arteries to UTP and of the electrophysiological measurements of ionic currents of smooth muscle cells isolated from these arteries.

UTP induced contractions were recorded using various pharmacological tools to investigate the possible signaling mechanisms leading to the contractile response. Particular attention was given to the identification of the ion channels involved in generating the UTP induced contraction. It was clear that the contraction was dependent on Ca^{2+} influx and my results indicated that this influx was only partly due to an increased activity of voltage-gated Ca^{2+} channels and that non-selective cation channels were also important. The involvement of PLC is likely as using U73122, a PLC blocker, significantly reduced the UTP induced response. However, the potential involvement of PKC is less convincing as several PKC isoform peptide inhibitors, linked to the carrier peptide Tat(47-57) to render them membrane permeable, failed to affect the contraction.

The ionic basis of the UTP induced contraction was studied by measuring the effect of UTP on various ionic currents measured in enzymatically isolated mesenteric artery smooth muscle cells using the whole-cell patch-clamp technique. UTP was found to inhibit both Kv and K_{ATP} currents, though in parallel to the contraction results, the UTP induced inhibition of these currents remained even in the presence of PKC block, suggesting a lack of involvement of PKC. Finally, application of UTP resulted in the activation of a non-selective current. An inhibition of K^+ currents and the activation of a non-selective cation current would lead to membrane depolarization, the activation of voltage-gated Ca^{2+} channels and, dependent on the permeability of the non-selective channels, an additional route for Ca^{2+} influx and hence contraction.

Acknowledgements

I would like to thank my Mum Fatima Panhwar and Dad Faiz Muhammad Panhwar for their motivation and prayers. A very special thanks and love to my husband Aqeel Ahmed Qureshi, and children Safia, Manzoor and Ramsha, without their cooperation, love, and encouragement I could never achieved my goal.

I would like to thank my supervisor, Dr. Noel Davies for all his help and support over the last four years especially in electrophysiology, data analyses and during writing up my thesis. I also extend my thanks to Dr Bob Norman for the Tat-PKC inhibitor peptides. I am thankful to Mrs Diane Everitt for all her technical support from learning dissection of rat mesenteric arteries to myography technique. I would like to thank Dr Nina Storey and all my lab fellows Jenny Brignell, Yusuf Bhagatte, Helen Turrell, Carl Nelson, Richard Rainbow, and Sadaf Afreen for having a fantastic time together.

I would like to thank my employer, University of Sindh and my sponsor, Islamic development Bank for providing me opportunity and financial support for the entire course of study.