Project title
Role of Kv7 Channels in Mediating Contractions in Murine Airway

Research Centre/Group
The Smooth Muscle Research Centre (SMRC)

Supervisory Team
Drs Keith Thornbury & Eamonn Bradley

Brief Project Overview

Background
The SMRC have developed a series of novel potassium channel openers, designated GoSlo-SR compounds (e.g. GoSlo-SR-5-6, GoSlo-SR-5-130; for references see 1-X). These compounds were originally believed to selectively activate larges conductance Ca$^{2+}$-activated K’ channels (BK channels, Refs 1-6), but recently we have found that they are also the most potent known activators of voltage-dependent K+ channels (Kv7.1-7.5), homologously expressed in HEK293 cells (S Dudem, unpublished data). Recently, Kv7 channels have also been shown to be expressed in airway smooth muscle, where they have the potential to modulate contractile function (7).

Hypothesis
GoSlo-SR compounds will relax airway smooth muscle due to activation of Kv7 and/or BK channels.

Methods
Bronchial rings will be isolated from C57BL/6 mice following euthanasia and mounted in organ baths for isometric tension recording. A variety of GoSlo-SR compounds will be tested on tension responses due to cholinergic stimulation with carbachol and in response to electrical field stimulation (EFS). GoSo-SR effects will be repeated in the presence of a BK blocker (e.g. iberiotoxin), in the presence of a Kv7 blocker (e.g. XE991) and in a combination of both compounds. In this way, it will be possible to determine if relaxations induced by GoSo-SR are due to activation of Kv7, BK, or both. Other known BK channel openers (e.g. NS 1619) and Kv7 openers (e.g. flupirtine) will be examined for comparison.

References


**Strategic Relevance of project to centre/group's research agenda**

Under the EI Applied Research Enhancement Scheme (£2M), SMRC developed a library of biologically active GoSlo-SR compounds, shown to be potent activators of BK channels. These are currently under patent application (WO/2012/035122). Work on these compounds continues to be a major focus of SMRC, who further seek to determine the biological targets on which they act and the functional effects they induce in a range of body tissues and organ systems. Of these, airway smooth muscle is a major focus, as evidenced by BREATHE, a major new project funded by the Special EU Programmes Body, where DkIT was awarded €7.7M in partnership with QUB and UWS. The currently applied project ties in with both of these areas, in combining the study of GoSlo-SR and airway smooth muscle and is therefore at the centre of our research agenda.

**Project Objectives**

1. To determine if GoSlo-SR compounds cause relaxation of murine airway
2. To determine if Kv7 channels regulate contraction in murine airway
3. To determine if BK channels regulate contraction in murine airway
4. To determine if GoSlo-SR compounds act via either BK channels of Kv7 channels in murine airway.

**Measurable Outcomes / deliverables**

This project will deliver

1. A 6 week training programme in research methods to a 3rd undergraduate year student
2. Preliminary data to support or refute the role of BK channels in regulating murine airway contraction
3. Preliminary data describing the effects of GoSlo-SR compounds in modulating murine airway contraction
4. Preliminary data to support understanding of the possible mechanisms of GoSlo-SR action in murine airway smooth muscle (namely, via Kv7, BK or both).
Profile of Undergraduate Candidate sought
I am seeking a high performing 3rd year student, who may choose to do their BSc project with me and eventually, perhaps, a PhD. Ideally, they will have demonstrated competence and imagination in scientific writing, as evidenced by their 3rd Year project. If this has not yet been completed, a recommendation from their current 3rd Year project supervisor will be sought.

Current Targeted Undergraduate course
Applied Bioscience
Biopharmaceutical science