Project title
β₃ adrenergic inhibition of neurogenic responses in murine bladder

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

Supervisory Team
Drs Keith Thornbury & Roddy Large

Brief Project Overview

Background
Overactivity of the detrusor muscle of the urinary bladder is a major cause of incontinence, affecting over 350,000 people over the age of 40 in Ireland. The detrusor is unusual for a smooth muscle tissue, in that it preferentially expresses β₃ adrenergic receptors, rather than β₂ receptors normally found in other smooth muscles. As β receptors are inhibitory in smooth muscle, this provides the opportunity to selectively relax bladder muscle without affecting other smooth muscle tissues, or the heart (that selectively expresses β₁ receptors) and, indeed, several β₃ agonists have been shown to be of clinical benefit in treating overactive bladder (1). However, although these compounds have been shown to inhibit cholinergic contractions in the bladder, they are not as effective as the clinical response would suggest, raising the possibility that they have additional actions (2-3). However, in functionally abnormal bladders, a non-cholinergic activation via the purinergic receptors may occur (4). This project will test the effect of β₃ agonists on the purinergic component of the response to nerve stimulation. This may possibly lead to the identification of new treatment targets for overactive bladder.

Hypothesis
β₃ agonists significantly inhibit the purinergic response to nerve stimulation in murine detrusor smooth muscle.

Methods
Detrusor strips will be isolated from C57BL/6 mice following euthanasia and mounted in organ baths for isometric tension recording. Nerve responses will be evoked by to electrical field stimulation (EFS) and the purinergic component of the response isolated by blocking cholinergic responses with atropine, a broad spectrum muscarinic receptor antagonist. The remaining responses will be subjected to a desensitisation protocol with the P2X receptor agonist, αβ-methylene ATP to confirm that it is purinergic in nature. A series of experiments will be performed to examine the effects of β₃ agonists BRL37344 & CL316243 on the purinergic responses to see if the latter are suppressed. L748,337, a β₃ antagonist will be used to confirm that any such action is mediated by β₃ receptors.

References


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

Disorders of the lower urinary tract is a major focus for the SMRC, who have received major funding in the past from Enterprise Ireland (€2.5M), the National Institutes of health, USA ($1M) and the Wellcome Trust (£300k) in pursuit of this research. This area continues to be a priority for SMRC and the proposed project icomplements two currently active PhD projects within the group.

**Project Objectives**

1. To determine the extent of purinergic versus cholinergic contractile responses following nerve stimulation in murine bladder
2. To determine if β3 agonists BRL37344 & CL316243 cause relaxation of murine bladder
3. To determine the relative effects β3 agonists BRL37344 & CL316243 on purinergic versus cholinergic responses to nerve stimulation in murine bladder.
4. To determine if effects of BRL37344 & CL316243 in bladder are mediated by β3 receptors

**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 characterising the cholinergic and purinergic responses in murine bladder
3. Preliminary data describing the effects of BRL37344 & CL316243 on nerve responses in murine bladder
4. Preliminary data to determine the main target (cholinergic or purinergic) for the inhibitory β3 adrenergic response in murine bladder.

**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