National Centre for the Replacement Refinement & Reduction of Animals in Research

NC3Rs/POEMS Network Maths Study Group - Applying mathematics to 3Rs problems

Modelling afferent nerve responses to bladder filling

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Background to the Problem

The bladder stores and eliminates urine from the body via a complex micturition cycle of filling and emptying, involving autonomic and somatic nerves. Alterations in the cycle give rise to clinical conditions such as overactive bladder syndrome (OAB) and urinary incontinence (UI). Until recently, research focussed on the mechanisms which drive bladder contractility and govern smooth muscle function. However it has now become clear that the sensory nerves which detect bladder filling and trigger the micturition cycle may drive the symptoms of these disorders and could even be attractive drug targets. This has led to studies looking at the function of these nerves in animals. However a detailed and integrative understanding of the interactions between the different signalling mechanisms remains elusive. A mathematical model which can describe how sensory nerves respond to bladder filling, and how afferent signals change as a result of disease or ageing would accelerate urology research and potentially reduce our reliance on traditional animal models.

Details of the problem

The bladder is a hollow muscular organ consisting of a number of concentric layers. On the innermost surface is a thin epithelial layer (termed the urothelium) surrounded by the laminar propria and a thick smooth muscle layer (the detrusor) which is covered by an elastin rich serosa. As the bladder fills it undergoes ~40% deformation to accommodate an increase in urine volume without a dramatic increase in intravesical pressure. Sensory nerves innervate, and have terminal endings in, all of the layers of the bladder, and form a plexus of nerves which lie between the urothelium and laminar propria. On filling, intravesical pressure increases with increased volume, triggering mechanosensitive nerve fibres (those responsive to stretch of the tissue or distortion of the nerve terminal endings). These nerves are classified according to their innervation pattern, stimulus-response profile and/or threshold for activation. Studies suggest that there are 5 distinct sub-populations of afferent nerve units innervating the bladder. These include both stretch sensitive and stretch insensitive afferents (i.e. chemosensitive afferents that only respond to chemical mediators).

The urothelium exhibits unique properties in detecting bladder filling and modulating sensory signals and micturition via the release of both excitatory and inhibitory chemical mediators. These mediators act on nearby afferent nerve terminals to modulate or activate nerve activity (mechano and chemosentive nerves). The urothelium also plays a key role in accommodation of the bladder to increasing volumes. It consists of large apical cells termed umbrella cells, intermediate cells and small basal cells. During filling, preformed membrane segments are inserted into the umbrella cell membrane to increase surface area of these cells increasing luminal volume.

Studies suggest that changes in urothelial- afferent signalling may underlie many bladder conditions and bladder sensory nerves could even be future drug targets. Previous studies from our laboratory have been directed at understanding urothelial-afferent pathways. In a recent study we found significant alterations in sensory/urothelial signalling in an aged mouse model. However many questions remain to be answered. As yet there are no reliable models (experimental or otherwise) which allow us to predict how manipulations of the bladder, such as a change in distensibility associated with age, alter sensory nerve function. Moreover measuring the effect of stimulus on a single nerve fibre is incredibly difficult and requires the use of large numbers of animals. A mathematical model would allow us to design a system to study the effect of a stimulus on each type of afferent nerve simultaneously without the need for animals. This model would also allow making predictions on how a particular condition (i.e. ageing or application of a drug) may affect specific populations of afferent nerves.

Ideas and data for informing possible mathematical models

Our lab has developed and characterised an ex vivo mouse model which allows simultaneous recordings of multiple nerve fibres and intravesical pressure. Using this model we can apply various intravesical pressures and intravesical volumes and study the impact on nerve activity. We have conducted a number of studies investigating how various factors such as increased bladder tone/ decreased bladder compliance and chemical removal of the urothelium can alter sensory nerve output. We have also studied the effect of ageing on nerve profiles and urothelial function. We are currently looking at the effect of ageing on nerve density throughout the layers of the bladder wall, collagen thickness and muscle mass to identify what structural features are altered by age. All of these data will be available to inform and build a mathematical model which simulates the sensory nerve response to bladder filling.

Questions you would like to see answered

Our aims are to begin to construct a mathematical model which simulates how subpopulations of sensory nerves respond to normal bladder filling. We would use this model to address the following questions:

1. How do the subpopulations of afferent nerve fibres that terminate in different layers of the bladder wall respond to simulated bladder filling, and how are these signals combined to produce overall sensory input to the micturition circuitry?
2. How do structural changes such as those associated with ageing (i.e. collagen deposition/loss, increased/decreased muscle loss) influence mechanical properties of the bladder and in turn the sensory response to bladder filling?
3. Mechanosensitive ion channels ultimately determine responses to bladder filling but the urothelium has a modulating influence on sensory response? Can these functional interactions be modelled?
4. How would increased or decreased muscle compliance alter overall sensory activity? How might autonomic (parasympathetic and sympathetic) mechanisms that control muscle tone help tune sensory signalling during bladder filling?
5. What further experiments are required to refine the model and make it physiologically relevant?

The potential impact on animal use

Animals have been used in urology research since the 1930s to 1) model human diseases; 2) study normal physiological processes and 3) provide a source of biological material such as tissues and cells for scientific analysis. In the first two of these objectives, rodents have been extremely valuable as they allow an integrative system approach to studying normal and pathological function. Unfortunately replacement of animals entirely in this regard is still not a possibility, however reduction of animal numbers and methodological refinement are being pursued by the scientific community. Currently studying bladder afferent nerve pathways relies exclusively on the use of ex vivo or in vivo animal models (usually rodents), however there are no official estimates on the numbers of animals used for these experiments. A Pubmed search with the keywords "bladder and afferent" but not "human" produced 161 papers from 2008-2013 (all figures exclude reviews). Assuming that each study used about 40-50 animals then the estimated number of animals used each year could exceed 1610. If we were to consider animals used in unpublished academic and pharmaceutical research then the actual numbers used are probably several times higher. As ageing populations are on the increase, there is also scope for considerable growth in this research field over the next couple of years, especially now that ageing research has been prioritised by the research councils UK. Developing a mathematical model to study sensory nerve pathways would significantly reduce the need for animal use and may even in some cases replace the use of in vivo/ex vivo models all together.

Relevance to medicine and healthcare

Functional disorders of the lower urinary tract place a huge burden on global healthcare resources. In the UK, treatment and management of OAB and UI costs the NHS in excess of £233 million per year. Although not life threatening, these conditions severely impair the sufferers' quality of life leading to sleep deprivation, depression, embarrassment and fatigue. The underlying aetiology of these disorders are unknown but there is clear correlation between prevalence of OAB, UI and age. Moreover incontinence has even been cited as the major reason for institutionalisation of the elderly. Given that western populations are demographically ageing there is an urgent need to understand the mechanisms that lead to these conditions and to identify new drug targets for treatment.

The current mainstay for OAB/UI treatment is the use of drugs which inhibit bladder contractility. However these drugs are poorly tolerated, relatively ineffective and can cause bladder retention (i.e. compromised ability to empty the bladder). Moreover the cardinal symptoms OAB: urgency (urgent desire to urinate) and frequent urination, appear to be driven by changes in sensory nerve pathways and it has been suggested that the sensory nerves could be a target for future therapeutic interventions. Developing a model which can be used to look at these pathways will provide an entirely novel tool in the research armoury, facilitating and accelerating research progress and aiding in the screening and development of new pharmaceutical agents.

References

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