The Onuf's nucleus, serotonin and spinal cord injury

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Nerve fibres innervating the urethral and anal striated sphincters play an important role in the regulation of urinary and defaecatory continence. These fibres are derived from a group of neurons in the sacral spinal cord known as the Onuf's nucleus. Different neuron groups innervate the anal and urethral sphincter, and the nucleus uniquely demonstrates sexual dimorphism across different species. The densely packed small-sized neurons in the Onuf's nucleus share features between somatic and autonomic neurons, and intriguingly are vulnerable to neurodegenerative changes in conditions affecting the autonomic nervous system such a Multiple System Atrophy, whereas they are relatively preserved in Motor Neuron Disease (1) (2).

The neurotransmitter glutamate activates neurons in the Onuf's nucleus resulting in contraction of the sphincters. Serotonin and noradrenaline modulate the effects of glutamate (3) (figure 1) and, in general, serotonergic receptor agonists exert a pro-continence effect by suppressing parasympathetic activity and increasing sympathetic and somatic activity in the lower urinary tract (LUT) (3). Serotonin is released from the brainstem raphe nuclei and binds to different receptors (5-HT_{1A}, 5-$HT_{2A,}$ 5-HT_{2C}, 5-HT_3 and 5-HT_7), and in experimental studies this is associated with an increase in activity in electromyographic (EMG) recordings from the urethral sphincter (3). Duloxetine, which is licensed for use in women with moderate to severe stress incontinence, is a potent inhibitor of the neuronal uptake of serotonin and noradrenaline, thereby resulting in increased serotonin levels in the synapses of neurons. Experimental studies have demonstrated increased urethral sphincter EMG activity following the administration of duloxetine, which is possibly mediated by the 5-HT_2 receptor and an α_1-adrenoceptor (4).

Following spinal cord injury (SCI), serotonergic nerve fibres degenerate below the level of injury. Ni et al. have demonstrated a

significant increase in the number of 5-HT_7 receptors in the Onuf's nucleus in a rat model (5). Cystometry in healthy rats demonstrates a finding known as high frequency oscillations (HFOs) during micturition, and these occur due to the rhythmic opening and closing of the urethra (known as bursting activity of the external urethral sphincter), and is essential for the bladder to empty efficiently. Following SCI however, the number of HFOs diminishes and voiding efficiency reduces (6). Ni et al. demonstrated that injecting a selective 5-HT_7 receptor agonist known as LP44 into the spinal fluid had no effects in healthy rats, whereas in SCI rats changes in several urodynamic voiding parameters were observed including an increase in the number of HFOs, greater voiding efficiency and reduced residual volume (5). The 5-HT_7 receptor is likely to contribute to LUT dysfunction following SCI, and further studies are required to investigate the functional consequences of the increased number of 5-HT_7 receptors that appear after injury, and its relationship with bursting activity of the sphincter. Moreover, Ni et al. also showed that the number of inefficient non-voiding contractions reduced, and whether 5-HT_7 receptors play a role in regulating detrusor contractions needs to be further investigated.

What is the relevance of these findings in humans? Detrusor sphincter dyssynergia (DSD) is an important cause for voiding dysfunction following SCI, and is a risk factor for developing upper urinary tract damage (7). Currently, treatments for ameliorating DSD are limited, and there is a need to design studies translating results from basic science studies into preclinical development and early clinical trials in humans. The findings of this study suggest that targeting the serotonergic system may be a novel therapeutic strategy in the future.

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Figure 1.

The Onuf ‘s nucleus is located in the anterior horn of the spinal cord and is distinct from other anterior horn cells. In the storage phase, serotonin and noradrenaline potentiate the effects of glutamate at the Onuf’s nucleus resulting in enhanced release of acetylcholine at the Pudendal nerve free endings and contraction of the striated urethral sphincter.

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