

ENHANCED BLADDER SENSORY NERVE ACTIVITY FOLLOWING CYCLOPHOSPHAMIDE AND IFOSFAMIDE TREATMENT IN MICE

Hypothesis / aims of study

Cyclophosphamide (CPO) and ifosfamide (IFO) are cytotoxic drugs extensively used in the treatment of various cancers, autoimmune disorders and in bone marrow transplant preconditioning (2). A major limiting factor in the use of CPO and IFO is the resulting bladder toxicity which can lead to ongoing urinary frequency, urgency, feelings of incomplete bladder emptying and dysuria (1). Both drugs have been shown to cause bladder hyperactivity in experimental models suggesting changes in sensory activity may be involved in the bladder dysfunction. The aim of this project was to investigate the hypothesis that the cytotoxic drugs CPO and IFO affect the activity of high and low threshold bladder sensory nerves.

Study design, materials and methods

Male mice (12wks) were administered either CPO (100mg/kg) or IFO (200mg/kg) by i.p. injection and sacrificed for experimentation after 24hrs. Intravesical pressure and bladder afferent nerve activity were then measured during bladder filling and emptying *in vitro*. Intravesical pressure changes in response to electrical field stimulation of the isolated bladder were also measured.

Results

As volume in the bladder increased both intravesical pressure and bladder sensory nerve activity increased. Nerve activity after treatment with CPO or IFO was enhanced throughout bladder filling. At maximum bladder distension the total nerve activity was increased significantly from 182 ± 13 pulses per second (pps) in control animals, to 230 ± 14 pps in CPO treated mice ($p < 0.05$) and 226 ± 17 pps in IFO treated mice ($p < 0.05$) ($n \geq 6$).

Single nerve fibres were identified from each recording and the individual responses of each fibre determined. The number of single fibres located in each treatment group was similar while the firing rate per fibre was enhanced after CPO or IFO treatment compared to control ($p < 0.05$). Each fibre was also characterised as either low threshold (activation at pressures < 15 mmHg) or high threshold (activation at pressures > 15 mmHg). The activity of high threshold nerves was unchanged after treatment with CPO or IFO (Fig 1B), but treatment did cause enhanced activity in the low threshold nerves ($p < 0.05$) (Fig 1A).

Bladder compliance was not affected by systemic CPO or IFO pre-treatment. Similarly, increases in bladder pressure to electrical field stimulation (5s train, 20Hz) were not changed after treatment with CPO or IFO. In addition, the relative contribution of nitric oxide, ACh or adenosine triphosphate to the electrical field stimulation induced responses was not changed after treatment with these cytotoxic drugs.

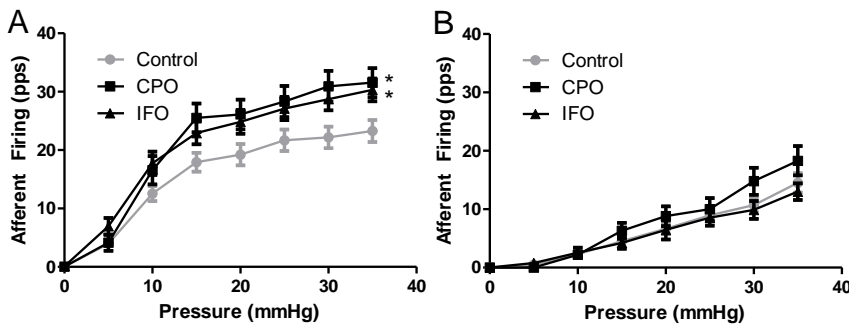


Fig 1: The effect of cyclophosphamide (CPO) (100mg/kg) or ifosfamide (IFO)(200mg/kg) treatment on low threshold (A) and high threshold (B) sensory nerve activity (pulses per second {pps}) in the mouse bladder.

Interpretation of results

Both CPO and IFO enhanced bladder sensory nerve activity. This increased activity was due to increased activity in the low threshold nerves and not the high threshold nerves. Low threshold fibres are considered to be responsible for sensing bladder filling and conveying this information to the central nervous system while the high threshold fibres are responsible for pain sensations (3). However, it has recently been postulated that both low and high threshold stretch-sensitive nerves in hollow organs contribute to pain and discomfort during inflammation (3). Increased afferent sensitivity and firing may explain the pain, urgency and feelings of incomplete bladder emptying experienced by patients after treatment with CPO and IFO and provides a target for treating these adverse effects.

Concluding message

Previous studies into the prevention of CPO and IFO induced bladder dysfunction have revolved around muscle changes and little investigation has been made into a neurogenic source of overactivity. This study will hopefully encourage further work to be done on preventing sensory nerve changes and reducing the long lasting adverse effects of these cytotoxic drugs.

References

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Disclosures

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