Neurotrophins and their receptors, novel therapeutic targets for pelvic pain in endometriosis, are coordinately regulated by interleukin-1β

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Introduction
Pelvic pain manifested in women with endometriosis is attributed to afferent nociceptors and neuroinflammation in ectopic and eutopic endometrium.

Methods
We tested the hypothesis that nociceptive endometrial nerves were activated by IL-1β, a prominent cytokine in endometriosis, to influence expression of endometrial neurotrophins and their cognate receptors in vivo. Immunofluorescence histochemistry was used to confirm the presence of neurons in human endometrial tissue.

Results
Expression of NGF and BDNF and their receptors in endometrial tissue and cells was validated by immunohistochemistry and Western blotting. Isolated endometrial stromal cells (ESC) were subjected to dose-response and time-course experiments in the absence or presence of IL-1β as an inflammatory stimulus. Specific kinase inhibitors were used to characterize the predominant pathways. In vitro biomarkers were quantified. Several neuronal biomarkers were co-localized in endometrial nerve fibers. NGF, BDNF, and their receptors TrkA, TrkB and p75 NTR were all expressed in primary ESC. IL-1β-stimulated higher TrkA/B expression in ESC derived from endometriosis cases (2.8 ± 0.2-fold) than cells from control subjects (1.5 ± 0.3-fold, t-test, P<0.01).

Conclusions
IL-1β stimulated NGF and BDNF, and also their cognate receptors, TrkA/B and p75NTR in ESC derived from endometriosis cases and controls. TrkA/B levels were greater in endometriosis cells than those from control subjects. The effects were mediated via an intracellular c-Jun N-terminal Kinase (JNK) cascade. Our results support the hypothesis that neurotrophins and their receptors orchestrate innervation of the endometrium, which is augmented by IL-1β. We postulate that JNK inhibitors, like SP600125, could be developed as therapeutic agents to reduce neuroinflammation in women with endometriosis-associated pain.