Neurokinin 1 Receptor (NK1R) Antagonism Suppresses the Development of Endometriosis

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INTRODUCTION: Substance P (SP), a neurotransmitter peptide secreted by small-diameter, primary, sensory 'pain' fibers, can up-regulate transforming growth factor-β1 (TGF-β1) via neurokinin 1 receptor (NK1R). We hypothesized that NK1R antagonism may hold therapeutic potential. playing a role in intra-abdominal adhesion formation and the development of variant fibrosis. The aim of this study was to investigate the role of SP/NK1R signaling in the development of endometriosis, and further to explore their effect on DIE progression.
MATERIALS AND METHODS: This was a prospective, randomized experimentation. SP and aprepitant, a potent and selective NK1R antagonist, were used to enhance and inhibit the effect of SP/NK1R-induced sensory nervous system. Thirty-two female adult Balb/C mice were randomly divided into 4 groups of equal sizes, control (CTL), SP, Pre-Inhibition, and Post-Inhibition. One day before the induction of endometriosis, mice in CTL, SP, Pre-Inhibition and Post-Inhibition groups were infused with sterile saline, SP and aprepitant, and none, respectively, via Alzet pumps; and two weeks after induction, the Post-Inhibition group was infused with aprepitant via Alzet pumps in the same amount as the Pre-Inhibition group. All mice were sacrificed four weeks after the induction of endometriosis. Bodyweight, hotplate latency and lesion size were measured, and lesion samples were subjected to immunohistochemistry analysis of proliferating cell nuclear antigen (PCNA), vascular endothelial growth factor (VEGF), NK1R and α-smooth muscle actin (α-SMA), and the extent of fibrosis was evaluated by Masson trichrome staining.
RESULTS: Aprepitant treatment nearly completely suppressed the NK1R expression while SP significantly increased its expression. SP treatment resulted in significantly increased lesion weight and exacerbated hyperalgesia, along with significantly elevated extent of fibrosis ($p<0.001$) and the increased immunoreactivity against PCNA ($p<0.05$), NK1R ($p<0.001$) and α-SMA ($p<0.001$), suggesting accelerated development of endometriotic lesions. In contrast NK1R antagonism dramatically retarded the progression of endometriosis development, resulting in an average of reduction in lesion weight by 94% and 54%, respectively, in the Pre- and Post-Inhibition groups, as compared with an average increase by 53% in the SP group. In addition, the Pre- and Post-Inhibition groups had an average reduction by 72% and 51% in the extent of fibrosis, respectively, while SP group had an average increase of 92%.
CONCLUSIONS: These data indicate that SP/NK1R signaling potently promotes the development of endometriosis while NK1R antagonism can significantly hamper its development. These data highlight the interaction between endometriotic lesions and nerve fibers, which form an intimate partnership in promoting endometriosis development and inflicting pains.

Keywords : Substance P; Neurokinin 1 receptor; Nerve fibers; Endometriosis; Fibrosis
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