Exercise Antagonizes Local and Systemic Inflammation via Suppression of NF-κB Activation

Derrick M. Knapik¹, Alisa D. Blazek², Priyangi Perera², Lai-Chu Wu, Ph.D², Wael N. Jarjour, M.D.², Sudha Agarwal, Ph.D².
¹The Ohio State University, Columbus, OH, USA, ²Ohio State University, Columbus, OH, USA.

Disclosures:

Introduction: Inflammation is integral to cartilage damage and bone erosion observed in joints afflicted with osteoarthritis (OA). We have earlier reported that physiologic levels of exercise are anti-inflammatory and suppress local inflammation of joints in experimental models of OA in vivo. The abrogation of pro-inflammatory signals by mechanical signals is mediated by suppression of NF-κB activity. Here we examined whether the observed effects of physiological levels of exercise are mediated via its local or systemic actions on inflammation.

Methods: All protocols were preapproved by the IACUC at The Ohio State University. Transgenic BALBc female mice (12-14 wks old) containing firefly luciferase cDNA in NF-κB response elements (NF-κB-RE-luc mice; Caliper Life Sciences, MA) were used as a tool to study transcriptional regulation of the NF-κB gene, for examining the effects of exercise (treadmill walking at 8 M/min) on inflammation. The inflammation was triggered by injection of LPS (1 µg/gm body weight) or IL-1β (10 -50 ng/30 g body weight) in the right ankle of the mice. Mice received following treatments, (i) no treatment (ii) exercise alone, (iii) LPS injection alone, (iv) pre-exercised for 7 days prior to induction of inflammation, (v) exercised only post induction of inflammation, or (vi) exercised pre and post induction of inflammation. The activation of NF-κB was assessed 2 hrs, 24 hrs, 48 hrs or 5 days post induction of inflammation by examining the luciferase activity by digital imaging (IVIS 100). The induction of proinflammatory cytokines in the serum samples of the same mice was assessed by Multiplex ELISA assays (Biorad Labs).

Results: Control NF-κB-RE-luc mice and those exposed to exercise alone did not exhibit significant NF-κB activation. LPS injection in right ankle provoked a systemic and local inflammatory response that was 6-8 fold greater within 2 hours of LPS administration. Mice exposed to exercise for 7 days prior to LPS injection showed a significant systemic inhibition of LPS-induced NF-κB activation. However, mice exposed to exercise following LPS injection showed more than 90% suppression of NF-κB activation (Fig. 1). These observations indicated that exercise is an important systemic inhibitor of inflammation and its actions are mediated via suppression of NF-κB activity. Further analysis of NF-κB activation revealed that LPS activated NF-κB primarily in axillary and inguinal lymph nodes, spleen and mesentery. Examination of individual lymph nodes showed that exercise was effective in suppressing LPS-induced NF-κB activation in all of these lymph nodes and the site of injection. Further immunofluorescence analysis for the presence of NF-κB in all of these tissue confirmed that exercise inhibited NF-κB nuclear translocation and its synthesis (Fig. 2). To gain molecular insight into the signaling affected by inactivation of NF-κB, we assessed the cytokine levels in the serum levels that follow NF-κB activation. Assessment of major pro-inflammatory cytokines IL-1β, TNF-α, IL-6, IL-17, IL-12 and IL-8 all showed up-regulation by LPS, whereas pre-exercise and post-exercise both effectively suppressed pro-inflammatory cytokine induction. More importantly, the effects of post-exercise were more dramatic than pre-exercise. The above findings prompted us to examine whether the anti-inflammatory effects of exercise are sustained and how long they are sustained. In these experiments mice were either exercised every day or only for one-day post LPS administration. The mice exposed to exercise every day suppressed NF-κB activation in a sustained manner. However, effects of exercise were transient in suppressing NF-κB activation and lasted only 24 h following exercise (Fig. 3).

Discussion:
Significance: The findings suggest that exercise may not only suppress local inflammation of the joints, but its effects may also be systemic by inhibiting NF-κB activation in leukocytes post acute inflammation.

Acknowledgments:
ORS 2014 Annual Meeting
Poster No: 1564