Testosterone Augments Cerebrovascular Inflammation in Male Rats

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Activation of inflammatory cascades contributes to cerebrovascular disease pathology. Since testosterone and male gender are associated with increased stroke risk, we explored the impact of testosterone on cerebrovascular inflammation using both in vivo and in vitro models of inflammation. We hypothesized that testosterone will augment the expression of two vascular markers of cellular inflammation: cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Using four groups of male rats (intact, orchiectomized (ORX), estrogen treated (ORXE), and testosterone treated (ORXT)), we determined the effects of gonadal steroids on cerebrovascular inflammation after i.p. lipopolysaccharide (LPS) injections. Using Western analysis, the induction of inflammatory markers was decreased in blood vessels from ORXE rats compared to intact or ORX males. In contrast, in cerebral vessels from ORXT rats, there was significant augmentation in LPS-induced COX-2 and iNOS protein levels. Confocal microscopy was used for cellular localization of COX-2 and iNOS. ORXT rats showed increased COX-2 and iNOS immunoreactivity in endothelial and smooth muscle cells after LPS treatment. In vitro incubations with LPS of isolated pial vessels from the same animal groups demonstrated greater COX-2 induction in ORXT rats compared to ORX and ORXE. Increases in PGE2 production, a principal prostaglandin end-product of COX-2 enzymatic activity, were also greater in vessels from ORXT rats. In conclusion, testosterone contributes to increased cerebrovascular inflammation. Thus, this may contribute to differences in stroke morbidity and mortality between men and women. Presently, we are exploring mechanisms by which the gonadal hormones influence the pro-inflammatory signaling nuclear factor kappa-B (NFkB) pathway. Supported by NIH grant HL-50775.