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Characterization of Increased Prostate Smooth Muscle Reactivity in Middle-aged Rats: Lack of Effect of Testosterone Replacement

Introduction: Benign prostate hyperplasia is one of the most common disorders affecting older men. Previous studies have been shown aging-dependent prostate dysfunctions (1). It is know that aging leads to decreased serum testosterone, which can contribute to prostate alterations (2). In the present study we explored the pathophysiological alterations in prostate smooth muscle (PSM) from middle-aged rats, and evaluated the functional and molecular effects of testosterone replacement.

Methods: Control (3.5-month old) and middle-aged (10-month old) male Wistar rats were used. Rats were divided into three groups: 1) control and 2) middle-aged rats that received peanut oil subcutaneously (s.c.) and 3) middle-aged rats that received daily 0.5 mg/Kg of testosterone cipionate diluted in peanut oil s.c. Concentration-response curves to the contractile agents phenylephrine (□1-adrenoceptor agonist) and α,β-methylene ATP, as well as to the relaxing agents isoproterenol (ISO), sodium nitroprusside (SNP) and Y27632 (Rho kinase inhibitor) were obtained in PSM. Neurogenic contractions produced by electrical-field stimulation (1-32 Hz, 50V, 10 sec), along with measurement of [^{3}H]-noradrenaline release were performed. The levels of cAMP in prostate homogenate and soluble guanylyl cyclase (sGC) protein expression were also determined.

Result: A significant increase ($P<0.05$) in phenylephrine- and α,β-methylene ATP-induced PSM contractions were observed in middle-aged compared with control rats (30% and 32% increase). EFS-induced PSM contractions were 60% higher in middle-aged compared with control group ($P<0.05$). PSM contractions in middle-aged group were accompanied by greater [^{3}H]-noradrenaline release. The PSM-induced relaxations in response to SNP, isoproterenol and Y27632 were lower in middle-aged rats (Emax: 59.4±4%, 48.6±4% and 76.1±3%, respectively; $P<0.05$) in comparison with control rats (76.37±1%, 63.5±3% and 92.3±4%, respectively). The cAMP levels in prostate homogenate were 25% lower ($P<0.05$) in middle-aged compared with control group. The sGC protein expression was reduced in prostate from middle-aged rats compared with control group (4.9- and 2.8-fold reductions to α1 and β1 subunit, respectively). Testosterone replacement restored neither the enhanced PE- and EFS-induced contractions nor the sGC expression in prostate from middle-aged rats.

Conclusion: PSM from middle-aged rats exhibit hypercontractility in response to α1-adrenergic and purinergic P2X1 receptor activation, which is associated with impaired cAMP- and cGMP-mediated relaxations. Furthermore, the failure of testosterone therapy to restore the normal contractile pattern and sGC expression in prostate from middle-aged rats suggests that reduced levels of serum testosterone do not play a key role in the PSM hypercontractility associated with aging.

(1) Rodriguez-Nieves JA et al. (2013). *Nat Rev Urol* **10**: 546-550.

(2) Yassin AA et al. (2008). *World J Urol* **26**: 359-364.