and Uro- strips demonstrated a similar decrease in contractile response to EFS and carbachol. Guanethidine failed to normalize the differences in the contractility of Uro- and Uro+ bladder strips. Relaxation responses to the beta adrenergic agonist isoproteronol were significantly reduced in the Uro- strips.

Conclusions: Removal of the urothelium resulted in significant increases in baseline contractile instability and the contractile response of isolated rabbit bladder strips to EFS, carbachol, and methoxamine, while impairing the relaxatory response to isoproteronol. These observations confirm the inhibitory effect of the urothelium on bladder tone. The significant reduction of hypercontractility in Uro- strips in the presence of NDGA suggests a regulatory role for leukotrienes. These agents are known to directly cause smooth muscle contraction. In Uro- tissues, the observed loss of detrusor inhibition normally induced by isoproterenol suggests an important role for the bladder urothelium in adrenergic control over bladder contractility. Urothelial injury may thus be an important mechanism in the development of detrusor instability and other conditions characterized by detrusor overactivity.

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SERIAL CHANGES OF SMOOTH MUSCLE CELL PHENOTYPES IN RAT URINARY BLADDER FOLLOWING PARTIAL OUTFLOW OBSTRUCTION

AIMS OF STUDY

Partial outflow obstruction of the urinary bladder induces the increased bladder weight characterized by a smooth muscle hypertrophy in addition to an increased collagen deposition within the bladder wall. Recently, in several smooth muscle organs such as cardiac artery or gall-bladder, the smooth muscle cells (SMC) can be classified pathomorphologically into three phenotypes; synthetic, contractile, and intermediate. The contractile SMC phenotype is often converted into the synthetic phenotype in response to various pathological conditions. While the function of the contractile SMC is essentially to contract, the synthetic SMC may play an important role in the replication, migration, and the elaboration or degradation of the extracellular matrix proteins. Contrast to the vascular smooth muscle, there has been few reports concerning SMC phenotypes in both normal and obstructed bladder. It is supposed that the conversion of contractile SMC phenotype into synthetic phenotype must be one of the most important clue to elucidate the mechanism of morphological and functional alterations in obstructed bladder dysfunction. The objective of the present study is to investigate the long-term change in bladder SMC phenotype following partial outflow obstruction.

MATERIAL & METHODS

Partial outflow obstruction was created in male Sprague-Dawley rats by tying a ligature around the proximal urethra in the presence of a 0.965 mm polyethylene tube. Urinary bladders were obtained 1, 3, 6, 10, 14, 20 and 30 weeks after obstruction, stained with H-E, Mallory-Azan and classified smooth muscle cells into non-contractile or contractile phenotype in electron-microscopically. And the ratio of non-contractile / contractile phenotype (nC/C ratio) was calculated. The expression amount of contractile protein (calponin) was measured in the remaining resected bladder specimens by the immunoblotting method.

RESULTS AND CONCLUSIONS

The mean weight of the bladder has been increased by 6weeks after outflow obstruction compared as sham operated bladder, and from 10 weeks to 30 weeks after outflow obstruction, kept on plateau. Macroscopically, marked thickening of the bladder wall was observed after outflow obstruction. Fibrosis and muscle-layer thickening were also observed. Sham operated bladder showed a negligible difference in % Fibrosis after surgery. While Obstructed bladder showed a significant decrease in % Fibrosis at 3 weeks, it showed same degree at 14 weeks after obstruction as compared to Sham operated bladder. Sham operated bladder showed a negligible difference in nC/C ratio, Obstructed bladder revealed a tendency to increase, but not statistically significant in proportion to the period of obstruction as compared to Control bladder. The expression amount of contractile protein (calponin) larger for the contractile type than for the synthetic type.

In the present study, we have investigated the morphological changes including bladder weight, % fibrosis, and nC/C ratio phenotype SMC in rat urinary bladders with obstruction.
Our results seem to suggest that bladder outflow obstruction induces a rapid increase in bladder mass characterized by a smooth muscle hypertrophy and hyperplasia followed by an increase in connective tissue elements results from the increase in bladder weight and change in % Fibrosis.
Bladder outflow also causes a conversion of contractile SMC phenotype into synthetic or intermediate phenotype, and this modulation of SMC phenotype may play an important role in bladder contractile dysfunction secondary to outflow obstruction. Much research remains to be done, but our results suggest that synthetic phenotype may secrete some extracellular matrix proteins which leads to a contractile dysfunction of bladder SMC.

The difference between contractile type and synthetic type in morphology

	contractile type	synthetic type
Size and shape	Spindle	Round or/and oval
Background	Collagen, elastin	Glycosaminoglycan
Myofilament	↑ ↑	↓
Rough ER	↓(+)	↑ ↑(+)
Golgi apparatus	↓(±)	↑ ↑(±)
Free ribosome	↓(+)	↑ ↑(+)
Mitosis	↓(+)	↑(−)
Lysosome	(±)	(++)
Dense body	(±)	(++)

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Title (type in CAPITAL LETTERS, leave one blank line before the text):
ROLE OF TYROSINE KINASE IN MEDIATING NORADRENALINE-INDUCED CONTRACTIONS IN BENIGN PROSTATIC HYPERPLASIA

Aims of study: Alpha-adrenoceptors have been characterised into 3 subtypes (α1A, α1B and α1D). All appears to be G-protein linked receptors coupled to calcium mobilisation via the activation of phospholipase C. It has recently become apparent that many G-protein linked receptors can also activate the tyrosine kinase/MAP kinase signalling pathway(1). The present study was performed to determine if activation of the tyrosine kinase/MAP kinase pathway plays a role in the α-adrenoceptor induced contraction of the human prostate.
Methods: Samples of human prostate were obtained from patients (aged 60-75 years) undergoing transurethral resection of the prostate for benign prostatic hyperplasia. Muscle strips were suspended under 1g tension in gassed Krebs solution. Cumulative concentration-response curves (CRCs) to noradrenaline were obtained in the presence of corticosterone (10μM), cocaine(10μM) and propranolol (1μM). Following the initial CRC, tissues were washed for 1hr and a second noradrenaline curve constructed in the presence of genistein (tyrosine kinase inhibitor), nifedipine, PD98059 (MAP kinase inhibitor), Wortmannin (phosphatidyl inositol kinase inhibitor), Cyclopiazonic acid and/or ryanodine. In some tissues KCl (100mM) was added after the completion of the CRCs to noradrenaline.
Results: Noradrenaline produced a slowly developing tonic contraction without the phasic component reported for some other tissues. Nifedipine (1μM) reduced significantly ($p<0.05$) the maximal response to noradrenaline to 57.4±7.4% of the initial control maximum (n=14). Genistein (30μM) also significantly ($p<0.05$) reduced the maximal response to noradrenaline to 56.2±3.5% (n=12). Nifedipine and genistein together caused a reduction in the maximal response to noradrenaline to 34.7±7.4% (n=7), which was a significantly ($p<0.05$) greater reduction than either agent alone. Ryanodine (n=8) or Cyclopiazonic acid (n=12), which can both deplete calcium from intracellular stores significantly ($p<0.05$ and $p<0.01$, respectively) reduced the maximal response to noradrenaline to 49.0± 8.0%and 45.5±4.4%, respectively. Ryanodine (30μM) plus genistein (30μM) almost completely abolished the maximal response to noradrenaline (n=6). However the MAP kinase inhibitor PD98059 (50μM) (n=6) or 100nM Wortmannin (n=10) did not significantly reduce the maximal response to noradrenaline (83.5±3.5% and 84.7±3.54% of the initial maximum, respectively). The maximal response to noradrenaline was only 48.3±7.6% of that to KCL, suggesting that extracellular calcium is not fully activated following stimulation by noradrenaline.
Conclusions: The tyrosine kinase activation would appear to be involved in the α-adrenoceptor mediated smooth muscle contraction of benign prostatic hyperplasia. However the MAP kinase pathway does not appear to be involved. The source of calcium used to cause contraction following tyrosine kinase activation appears to come from internal stores.
Reference: 1. Nature 380:541-544, 1996.