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INVITED EDITORIAL FOCUS: MS# F-125-2017 – Inhibition of smooth muscle contraction and ARF 6 activity by the inhibitor for cytohesin GEFs, secinH3 in the human prostate

TOWARDS BETTER TREATMENT FOR LOWER URINARY TRACT SYMPTOMS ASSOCIATED WITH BENIGN PROSTATIC HYPERPLASIA?

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Abbreviated title: inhibition of prostate contractions by secinH3

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The most effective and fastest acting pharmacotherapeutic relievers of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) are the selective α_{1A}-adrenoceptor antagonists such as tamsulosin, silodosin and alfuzosin (7). This class of drugs relieves symptoms primarily by inhibiting the binding of noradrenaline to α_{1A}-adrenoceptors located on the smooth muscle cells of the urethra and prostate. This antagonism of α_{1A}-adrenoceptors relaxes the urethral and prostatic smooth muscle allowing urine to flow more easily through the urethral obstruction caused by prostate enlargement. Despite this, the α_1-adrenoceptor antagonist class of drugs are only useful in treating mild to moderate symptoms associated with BPH. More severe symptoms require surgical intervention to widen the urethral passage sufficiently to allow smoother flow of urine (8). Another important limitation of α_{1A}-adrenoceptor antagonists is their efficacy, as improvement of urinary symptom scores and flow will generally not exceed 50%.

A major reason why current pharmacotherapies are unable to treat severe LUTS associated with BPH is that noradrenaline is not the only mediator of prostatic smooth muscle contractility. Therefore, future therapies with improved efficacy will most likely only eventuate if non-adrenergic contractions are inhibited in parallel with adrenergic contractions. Several other mediators have been implicated in prostatic smooth muscle contractility and receptors for these mediators including adenosine 5'-triphosphate (ATP), acetylcholine, endothelin, thromboxane A_2 or the tachykinins may also need to be inhibited to produce sufficient prostatic smooth muscle relaxation to relieve severe LUTS (8). This is highlighted by clinical trials reporting that combination therapy of α_1-adrenoceptor antagonists and muscarinic acetylcholine receptor antagonists shows greater improvement in LUTS, than either drug treatment alone (1, 2). Whether or not muscarinic receptor antagonists act by inhibition of bladder detrusor instability or in the prostate to relieve bladder outlet obstruction remains unclear.

Alternative therapeutic strategies to relax prostatic smooth muscle may offer a means of providing a greater amount of prostatic smooth muscle relaxation than can be produced by α_1-adrenoceptor antagonists alone. This would most likely require the use of a combination of drugs. However in this issue of the *American Journal of Physiology – Renal*, researchers from the Department of Urology at Maximilians University in Munich, Germany, investigate the physiological role played by the cytohesin family of guanosine nucleotide exchange factors (GEFs) in human prostatic smooth muscle contractility (6). GEFs are known to play a role in controlling smooth muscle contraction (3) through intracellular pathways that have recently been shown to control prostatic smooth muscle contractility (4, 5, 9).

Unlike many previous studies of prostate contractility, the work described in this issue, employed human rather than laboratory animal prostatic tissue. Tissue was obtained from men undergoing radical prostatectomy for prostate cancer. Importantly, patients who had a history of BPH and had undergone transurethral resection of the prostate were excluded. In addition, following pathological evaluation, any tissue that showed histological signs of neoplasia or cancer were not used. A number of techniques were used to study the role played by the cytohesin family of GEFs in human prostatic smooth muscle contractility and these included: real time reverse transcription polymerase chain reaction (RT-PCR), Western blot analysis, immunofluorescence, isolated tissue tension recording and pull down assays.

Using RT-PCR, mRNA of the cytohesin isoforms 1-4 were detected in all prostate samples with high levels of cytohesin 1 and 2. Western blot analysis supported the RT-PCR by revealing protein expression of both the cytohesin 1 and 2 isoforms. Immunoreactivity to cytohesin 1 and 2 was less convincing as is often the case in tissue localization studies of this nature and is largely due to the non-selectivity of antibodies between different protein isoforms. Nevertheless, immunofluorescence to cytohesin 2 in particular appears to be more

closely localized to the stroma than other structures. Given that the prostatic stroma contains the smooth muscle, it appears likely that cytohesins are associated with a role in contractility rather than another function.

Although, the biochemical and histochemical observations are important as they associate the appropriate cellular mechanisms being investigated with prostatic smooth muscle cells, it is the functional pharmacological studies presented that are the most exciting. The cytohesin GEF inhibitor secinH3 was able to inhibit not only the α_1-adrenoceptor mediated contractions of the isolated human prostate elicited by norepinephrine and phenylephrine, but also non-adrenergic contractions initiated by the thromboxane A_2 analogue U46619 and endothelins 1 and 3. Nerve mediated contractions elicited by electrical field stimulation were also inhibited by secinH3, while combined application of secinH3 and tamsulosin inhibited electrical field stimulation induced contractions by more than either drug alone. Using pull down assays, the authors also showed that secinH3 reduced guanosine triphosphate - ADP ribosylation factor 6 (GTP-ARF6) but not GTP-Rac nor GTP-RhoA in prostate tissues. This suggests that secinH3 induces prostatic smooth muscle relaxation by inhibition of a cytohesin/ARF6 pathway.

The authors conclude that multiple receptors involved in prostate contractility use the secinH3 intracellular pathway to promote contractility or that the secinH3-sensitive pathway is not coupled to receptors but may affect contractility of the prostate in a general way. Either way, the proposition that secinH3 interferes with prostatic smooth muscle contractions mediated by both adrenergic and non-adrenergic pathways is a very attractive one, as it implies that more than one component of contraction can be inhibited by a single molecule. This would avoid the need for combination therapy to block adrenergic and non-adrenergic components of prostatic smooth muscle contraction. Combination therapy is more likely to be associated with greater adverse effects, making monotherapy a more attractive option.

It is yet to be determined whether this mechanism is specific to the prostate gland. If the described pathway were common to other smooth muscles then it may be associated with side effects that make its use intolerable. Tamsulosin for instance, may not be as effective but its uroselectivity gives it a considerable safety advantage. However, since this is the first report of the effects of secinH3 on smooth muscle contractility, conclusions about possible side effects cannot yet be made and it remains to be seen whether this novel pathway may lead to a more effective treatment for LUTS associated with urethral obstruction due to BPH. Definitively, this study shows that the mechanisms of prostate smooth muscle contraction are still not completely understood despite their clinical relevance for the pathophysiology and therapy of LUTS.

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