British Journal of Pharmacology (2005) 144, 1–2
www.nature.com/bjp

COMMENTARY

Two for the price of one?

*,[1]Mike Wyllie

[1]Urodoc Ltd, Maryland Ridgeway Road, Herne, Kent CT6 7LN

British Journal of Pharmacology (2005) **144,** 1–2. doi:10.1038/sj.bjp.0706038
Keywords: Benign prostatic hyperplasia; mitogenesis; apoptosis

In the increasingly cost-conscious healthcare environment we live in, potential bargains are particularly welcome. A recent paper in the *British Journal of Pharmacology* (Wennemuth & Aumuller, 2004) raises the prospect that an existing family of drugs, angiotensin type 1 (AT1) receptor antagonists, could be used to treat and prevent one of the most common complaints in the ageing male, benign prostatic hyperplasia (BPH). At present, recommended treatment is heading towards a two-drug approach (McConnell *et al*., 2003).

It is estimated that up to 80% of males will experience BPH with varying degrees of severity (ouch!). It results from an enlargement of the prostate gland that subsequently restricts the flow of urine from the bladder. The resultant symptoms include urinary urgency and frequency and nocturia. Apart from causing personal distress BPH has a significant economic impact, which may be linked to the 'greying' of the population.

Traditionally, the disorder was treated by surgical removal of the prostate gland but there was some degree of 'mortality and morbidity', which has improved with new surgical techniques. Two types of drugs were also developed, aimed at shrinking the size of the prostate or reducing acute lower urinary tract symptoms by blocking smooth muscle contraction. Today, the majority of sufferers are treated with drug monotherapy. However, this may be about to change again and we could be entering the era of treating BPH with two different approaches. So let us review the evidence for a potential breakthrough in both therapy (and treatment cost).

A recent large-scale clinical trial, the Medical Therapy Of Prostatic Symptoms (MTOPS), has shown that ideal therapy for managing patients with BPH could involve combination therapy (McConnell *et al*., 2003). This approach would involve the use of one drug to alleviate the acute lower urinary tract symptoms and a 'prostate shrinker' to reduce the size of the gland and thereby reduce the symptomatology. Traditionally, in the context of the former, alpha-adrenoceptor antagonists, for example, alfuzosin, doxazosin, tamsulosin and terazosin, are most widely used and have become the mainstay of therapy for BPH patients. It has been hypothesised that at least two of these drugs, doxazosin and terazosin, have an additional proapoptotic action, which is not a 'class effect' and may involve a 'quinazoline receptor' (Kyprianou, 2003). However, the contribution of this to the overall clinical benefit observed with these drugs is unknown.

*Author for correspondence; E-mail: mike@urodoc.co.uk
Advance online publication: 6 December 2004

With respect to reducing gland size and/or the rate of glandular progression, in theory either a proapoptotic (or apoptosis-inducing action) or antimitogenic action could be exploited. In practice only the former has been achieved with strategies based on inhibition of the enzyme 5-alpha-reductase. Two such agents are marketed; finasteride, an inhibitor of the 5-alpha-reductase2 isozyme, and dutasteride, which inhibits 5-alpha reductase 1 and 2 isoforms with more or less equal affinity. However, the benefit of stopping glandular progression may not become apparent for 9–15 months, and indeed meta-analysis shows that the clinical benefit is only modest (Boyle *et al*., 1996).

The development of the 5-alpha-reductase inhibitors was based on the fact that androgens were known to be promoters of prostatic growth and the assumption that reduction in the major androgenic influence (dihydrotestosterone) would cause stromal and epithelial regression. However, little consideration appears to have been given to the compensatory increase in testosterone and aromatisation to oestrogens, which are also potent prostatic growth factors. With hindsight it could be argued that the effect of 5-alpha-reductase inhibitors was always likely to be self-limiting!

Could other proapoptotic drugs be used and, if so, how would we recognise them? In the development of novel 'prostate shrinker' agents, the major problem is the complete lack of relevant animal models of BPH. Only two animal species, the dog and African lion, are known to develop spontaneous BPH. The dog, however, is not relevant to man as the prostate growth is almost entirely oestrogen dependent.

The study of Wennemuth & Aumuller (2004) suggests that the most reasonable initial approach is to analyse the balance between proliferation and apoptosis in a relevant cell culture system. Such as the human prostate stromal cell line hPCPs. However, there could be some debate as to the most relevant one and indeed a coculture system involving both stromal and epithelial elements might be of further value (Bayne *et al*., 1998).

Wennemuth & Aumuller (2004) demonstrate very elegantly that in this *in vitro* system angiotensin II (AII) is a mitogen acting *via* the AT1 receptor. It raises the question of whether the corollary will apply, that is, would the use of an AT1 receptor antagonist necessarily produce any clinical benefit in BPH? Indeed, if any clinical benefit was apparent, one would have expected it to have been reported by urologists and primary care physicians treating BPH patients including those who are also receiving AII antagonists. However, no prospective clinical trial has been carried out, so absence of

evidence should not be confused with evidence of absence (of such a link).

This study provides some insight into the pharmacology of angiotensin-induced prostatic proliferation; however, since angiotensin is only one of the many factors involved in the regulation of normal and abnormal cellular proliferation, it also indicates the potential value of investigating other proapoptic factors in similar cell culture systems. However, if one drug can have an immediate effect on symptoms and reduce the size of the prostate, the impact on both patient and the healthcare purse is obvious. Only time will tell whether an approach based on AT1 receptor modulation has this potential.

M.G. Wyllie is Associate Editor, BJU Int.

References

BAYNE, C.W., ROSS, M., DONNELLY, F., CHAPMAN, K., BUCK, C., BOLLINA, P. & HABIB, F. (1998). Selective interactions between prostate fibroblast and epithelial cells in co-culture maintain the BPH phenotype. *Urol. Int.,* **61,** 1–7.

BOYLE, P., GOULD, A.L. & ROEHRBORN, C.G. (1996). Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. *Urology,* **48,** 398–405.

KYPRIANOU, N. (2003). Doxazosin and terazosin suppress prostate growth by inducing apoptosis: clinical significance. *J. Urol.,* **169,** 1520–1525.

MCCONNELL, J.D., ROEHRBORN, C.G., BAUTISTA, O.M., ANDRIOLE JR, G.L., DIXON, C.M., KUSEK, J.W., LEPOR, H., MCVARY, K.T., NYBERG JR, L.M., CLARKE, H.S., CRAWFORD, E.D., DIOKNO, A., FOLEY, J.P., FOSTER, H.E., JACOBS, S.C., KAPLAN, S.A., KREDER, K.J., LIEBER, M.M., LUCIA, M.S., MILLER, G.J., MENON, M., MILAM, D.F., RAMSDELL, J.W., SCHENKMAN, N.S., SLAWIN, K.M., SMITH, J.A. & Medical Therapy of Prostatic Symptoms (MTOPS) Research Group (2003). The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N. Engl. J. Med.,* **349,** 2387–2398.

WENNEMUTH, G. & AUMULLER, A. (2004). Angiotensin II-mediated calcium signals and mitogenesis in human prostate stromal cell line hPCPs. *Br. J. Pharmacol.,* (in press).

(Received September 13, 2004
Accepted October 1, 2004)