LETTER TO THE EDITOR

The Paracrine Endothelin System: Pathophysiology and Implications in Clinical Medicine


1 Department of Physiology
2 Department of Urology
3 Department of Chemical Pathology & Human Metabolism
Royal Free Hospital & School of Medicine (University of London), London, UK

The review by Hocher et al. (1) is both comprehensive and timely. However, the field of endothelium research is vast and rapidly expanding. It is therefore not surprising that more information can be added.

Human platelet possess endothelin (ET) receptors which appear to be of the ETA subtype (2). Whether endothelin activates platelets was not clear (2, 3). Using the sensitive platelet shape change technique (4) we recently showed that endothelin-1 decreased median platelet volume unlike platelet activators which increase the median platelet volume (unpublished results).

However, endothelin-1 enhanced the effect of two conventional platelet activators, serotonin and ADP. Therefore, in addition to the ‘vacular’ actions of endothelin-1 described by Hocher et al. (1), this peptide can also stimulate platelets.

Endothelin receptors (ETA and ETB) are present in the urinary bladder (5) and prostate (6). These receptors have a ‘regional’ distribution (e.g. higher density in the detrusor compared to the base of the bladder) (5). Furthermore, the normal human prostate has mainly ETA receptors in the stroma whereas ETB receptors predominate in glandular epithelium (6). In contrast, in our studies involving patients with benign prostatic hyperplasia causing bladder outlet obstruction, ETA receptor density was greater than that of the ETB receptors in both the epithelium and stroma (7). These changes may be due to a reduction in epithelial ETB receptor expression, as also observed in metastatic prostatic cancer sites (6).

The clinical significance of these receptor alterations in benign prostatic hyperplasia remains unclear but are certainly provocative.

Endothelin-1 can induce potent, slowly developing, long-lasting contractions in penile smooth muscle (9, 10). Constrictions are also evoked in human corpus cavernosum tissue by endothelin-2 and endothelin-3 but these peptides are less potent than endothelin-1 (9). We recently demonstrated the presence of both ETA and ETB receptors in the cavernosa of healthy control rabbits together with a significant increase in ETB receptor sites in diabetic rabbits (10). This change may enhance local muscle contraction and smooth muscle proliferation. As mentioned above, interactions may also occur with the NO system.

Therefore, endothelin may play a role in the pathogenesis of erectile dysfunction, a common complication of diabetes.

It is likely that more pathophysiological roles for endothelins will be identified thus increasing the number of potential targets for therapeutic intervention.

As a potent smooth muscle constrictor and a mitogen, endothelin-1 may play a role in the pathogenesis of benign prostate hyperplasia, diabetic cysopathy and bladder instability. This hypothesis is supported by evidence showing that plasma endothelin-1 concentrations are raised in diabetics and endothelin-1 and ETB receptor binding sites are significantly increased in the diabetic rabbit urinary bladder (8). Since ET receptors influence nitric oxide (NO) production, NO could play a role in counteracting endothelin-1-induced contractions.

An increase in NO synthase binding sites in the diabetic urinary bladder (8) may therefore be a pathophysiological response to an increase in endothelin receptors and increased plasma endothelin-1 concentrations in diabetics. These observations suggest that endothelins play a role in lower urinary tract function.

References