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EVALUATION OF A VITAMIN D3 ANALOGUE IN A RAT MODEL OF BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

Vitamin D3 and an analogue (analogue V) were shown to inhibit BPH cell proliferation and to counteract the mitogenic activity of potent growth factors for BPH cells [1]. Receptors for vitamin D can be demonstrated in rat and human bladder, which makes it conceivable that the bladder may be a target for vitamin D. We hypothesized that analogue V was able to prevent some of the consequences of bladder outlet obstruction, e.g. hypertrophy and loss of contractile function.

Study design, materials and methods

Female Sprague-Dawley rats, weighing 200-250g, were randomly divided into groups as follows: In two thirds bladder outlet obstruction was produced by a standardized method and the animals were divided into 2 groups. One group (n=9) received analogue V (150µg/kg/day) from the day of surgery by oral gavage. The remaining animals (n=11) received vehicle. Twelve sham-operated animals received analogue V (n=6) or vehicle (n=6). Two weeks after BOO a cystometry was performed. Plasma-calcium levels were determined at the end of the experiments. The bladders were then removed and in-vitro contractility studies were performed. The experimental protocol was approved by the Animals Ethics Committee of the University of the performing institution.

Results

There was a significant increase in bladder weight, micturition interval and volume, and bladder capacity in both obstructed groups compared to sham controls, but no difference comparing the 2 obstructed groups. There was a variation in bladder weight within the obstructed groups (drug 160-705mg, vehicle 145-650 mg). Plotting the micturition pressure to bladder weight within the obstructed groups, there was a clear correlation in the vehicle treated group (r^2=0.47), indicating a decrease in contractile function with increasing bladder weight. There was no such correlation in the treatment group.

There was a significant decrease in response to electrical field stimulation (EFS) in both obstructed groups compared to sham, and a significantly greater contractile response at frequencies above 6Hz, comparing bladder strips from treated vs. untreated obstructed animals. There was a strong correlation of increasing bladder weights vs. decrease in in-vitro in response to K+ (r^2=0.46) and EFS (at 32Hz r^2=0.66) in strips from vehicle treated animals, but no correlation in those from drug treated animals (r^2=0.07 and r^2=0.25). No statistically significant differences were found in response to carbachol between the 4 groups. The plasma-calcium level was increased by 12% in the drug-treated animals, compared to vehicle-treated animals.

Interpretation of results

Bladder outlet obstruction in animal models leads, depending on duration and severity of the obstruction, to bladder hypertrophy. In the earliest stages the bladder wall hypertrophy is considered a compensatory mechanism, but it has been found that with further increasing bladder weights, the contractile function in vivo and in vitro decreases as a marker of deterioration of the contractile properties of the smooth muscle. Many attempts have been made to prevent bladder hypertrophy and its negative effects. In this study, a vitamin D3 analogue, which has been shown to inhibit BPH cell proliferation, has been administered, testing the hypothesis that bladder hypertrophy may be prevented. If was found that bladder hypertrophy occurred despite treatment, however, the inverse deterioration of contractile function with increasing bladder weights was not seen in the obstructed treatment group. This effect was seen in vitro and in vivo. These findings suggest that the vitamin D3 analogue may have a protective effect on contractile function of the smooth muscle, even though smooth

muscle hypertrophy occurred. This hypothesis of a strengthening effect on muscle tissue is supported by findings in vitamin D receptor knockout mice, which show a progressive weakness of skeletal muscle [2] and the fact that in humans administration of calcitriol appears to cause an increase in muscle strength, reflected in a decrease of number of falls in elderly subjects [3]. However, whether or not these specific observations also apply to smooth muscle is not yet known.

Concluding message

The vitamin D3 analogue used in this study did not prevent bladder hypertrophy, but appeared to reduce the damage to the bladder smooth muscle, which occurs with increasing bladder weight.

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