

## EXCITATORY $\alpha_1$ -ADRENERGIC RECEPTORS PREDOMINATE OVER INHIBITORY $\beta$ -RECEPTORS IN RABBIT DORSAL DETRUSOR

### Aims of Study

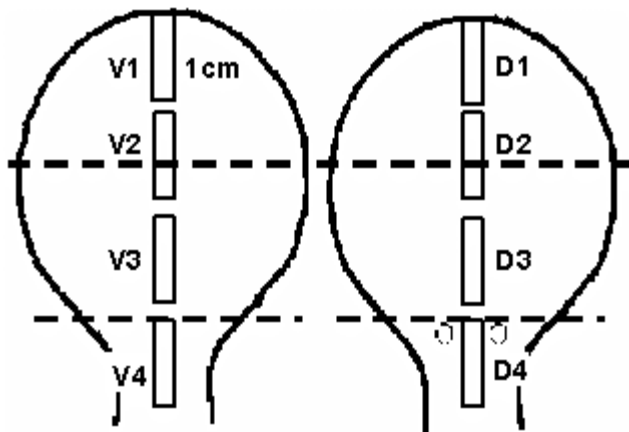
The role of the sympathetic nervous system in detrusor function is still unresolved. By 1940, researchers had established that the detrusor could contract or relax in response to adrenaline, but were unable to explain the mechanism(s) responsible for its dual actions [1]. Using functional and radioligand binding assays, researchers confirmed that the density of excitatory  $\alpha$ -adrenergic receptors (AR) was significantly greater in the bladder base than in the dome, whereas inhibitory  $\beta$ -AR density was significantly greater in the dome [2,3]. More recently, three different subtypes of the  $\alpha_1$ -AR have been identified at the molecular level, the  $\alpha_{1a}$ -,  $\alpha_{1b}$ -, and  $\alpha_{1d}$ -AR. However, there is no good agreement over which subtypes are present in bladder smooth muscles.

A re-examination of the methods of the previous studies indicated that the location of the bladder strips was generally not well defined and the binding studies were done using preparations of the entire bladder dome. Thus, the aims of this study were to map the regional distribution of  $\alpha_1$ - and  $\beta$ -AR in rabbit ventral and dorsal bladder, and characterize the  $\alpha_1$ -AR subtypes responsible for norepinephrine-induced contraction of rabbit dorsal detrusor smooth muscle.

### Methods

Bladders were removed from adult male New Zealand White rabbits. Longitudinal bladder strips were cut from midline locations as shown in fig. 1 and prepared for organ bath studies. To map regional distribution of  $\alpha_1$ - and  $\beta$ -AR, strips were precontracted with KCl (40mM) and  $\text{CaCl}_2$  (4mM), then increasing concentrations of norepinephrine were added cumulatively.

The strips were then incubated with prazosin (10 $\mu\text{M}$ ) for 30 minutes before precontraction with KCl/ $\text{CaCl}_2$  and relaxation with norepinephrine was repeated.

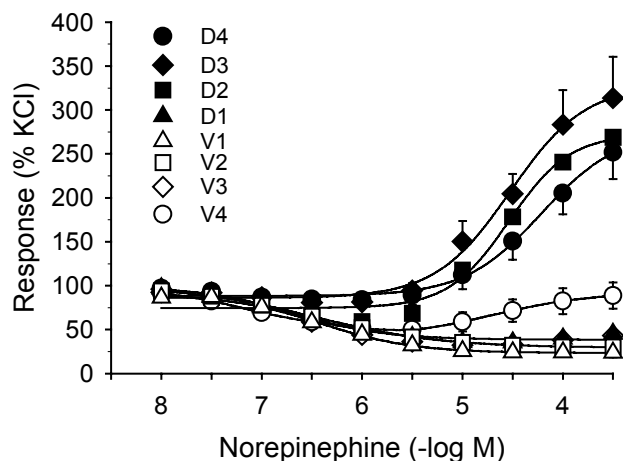


**FIG. 1.** Bars indicate location of strips used to map the relative contribution of  $\alpha_1$ - and  $\beta$ -AR to the response of rabbit bladder to norepinephrine. The dashed lines indicate the bladder equator (half the distance between the tip of the dome and the ureters) and level of the ureters.

To characterize  $\alpha_1$ -AR subtypes, bladder strips were cut from dorsal locations surrounding strips D2 and D3. All strips were incubated in Krebs solution containing indomethacin (10 $\mu\text{M}$ ), corticosterone (3 $\mu\text{M}$ ) to block non-neuronal norepinephrine uptake, desipramine (0.1 $\mu\text{M}$ ) to block neuronal norepinephrine uptake, propranolol (1 $\mu\text{M}$ ) to block  $\beta$ -AR, and yohimbine (0.3 $\mu\text{M}$ ) to block  $\alpha_2$ -AR. Contractile responses to norepinephrine were measured before and after incubation with a single concentration of one of the  $\alpha_1$ -AR antagonists to be studied.

### Results

In the absence of antagonists, ventral strips from the bladder body (V1, V2, V3) relaxed in response to norepinephrine; those from the ventral base (V4) contracted (fig. 2). Dorsal strips from the bladder dome (D1) also relaxed in response to norepinephrine, but dorsal strips from



mid and lower body and base (D2, D3, D4) contracted. All contractile responses were antagonized by incubation with prazosin, indicating that they resulted from  $\alpha$ 1-AR stimulation.

FIG 2. Response of KCl-precontracted bladder strips from 6 rabbits to norepinephrine in the absence of prazosin. Strip locations are shown in fig. 1. All contractile responses were inhibited by incubation with prazosin.

In the presence of indomethacin, corticosterone, desipramine, propranolol, and yohimbine, norepinephrine caused large contractions of dorsal bladder body strips ( $E_{max}$ :  $\sim$  3g;  $pD_2$ :  $\sim$  6.00). The non subtype-selective  $\alpha$ 1-AR antagonist, prazosin, and  $\alpha$ 1A-AR antagonists, 5MU, and WB 4101 all caused concentration-dependent parallel rightward shifts of the norepinephrine concentration-response curves. In contrast, the  $\alpha$ 1D-selective AR antagonist, BMY 7378, was much less potent at inhibiting the response to norepinephrine, and the irreversible  $\alpha$ 1B- and  $\alpha$ 1D-AR antagonist, CEC, was without effect at concentrations up to 10 $\mu$ M.  $pA_2$  values were obtained by Schild regression. Slopes were not significantly different from unity. The rank order of antagonist affinities ( $pA_2$ ) was WB 4101 (8.24)  $\geq$  5MU (8.03)  $\geq$  prazosin(7.95)  $\gg$  BMY 7378 (5.96), suggesting that norepinephrine-induced contraction of rabbit dorsal detrusor is mediated by  $\alpha$ 1A- or  $\alpha$ 1L-AR.

### Conclusions

We have shown that the accepted division of the urinary bladder into two pharmacologically and functionally distinct regions, the bladder base and bladder body, with differences in responsiveness to sympathomimetics and AR distribution does not apply to the rabbit bladder. In contrast, at least 4 distinct regions of the rabbit bladder must be considered; (1) the dorsal and ventral dome, where  $\beta$ -AR predominate, (2) the ventral detrusor, where  $\beta$ -AR predominate, (3) the dorsal detrusor, where  $\alpha$ 1-AR predominate, and (4) the dorsal and ventral bladder neck, where  $\alpha$ 1-AR predominate. The relevance of these findings to human detrusor function remains to be determined.

### References

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