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Title (type in CAPITAL LETTERS): CARDIOVASCULAR EFFECTS OF α_1-ADRENOCEPTOR ANTAGONISTS AT DOSES WHICH INHIBIT NON-MICTURITION BLADDER CONTRACTIONS IN CONSCIOUS, CHRONICALLY-OBSTRUCTED RATS

Aims of Study

The non-selective α_1-adrenoceptor (AR) antagonist prazosin and the selective α_{1D}-AR antagonist BMY 7378, but not the selective α_{1A}-AR antagonist SNAP 6201+, have been shown to inhibit non-micturition bladder contractions (NMBCs) in conscious rats with chronically obstructed urethras (1). It was concluded that α_{1D}-ARs are involved in NMBCs resulting from chronic obstruction. The aims of the present study were: A) to confirm the effect of α_1-AR antagonists on NMBCs, using Ro110-0329 (2) as a selective α_{1A}-AR antagonist, and B) to determine the cardiovascular effects of α_1-AR antagonists at doses used in cystometry studies.

Methods

Cystometry Studies: Female Sprague-Dawley rats (200-350g) were anesthetized with isoflurane. The urethra was partially obstructed with a ligature using a metal rod (≈1mm diameter) to standardize the degree of obstruction. Two days prior to the study (4-6 weeks post obstruction), the ligature was removed and the bladder dome and femoral vein were cannulated. Cannulas were exited and secured in the scapular region. On the study day, each rat was placed in a metabolic cage and the bladder infused with saline (20ml/h, 18°C). Bladder pressure and void volumes were monitored. After 60-90 minutes, a single intravenous dose of vehicle (saline, 0.5ml/kg), prazosin (300µg/kg), BMY 7378 (300µg/kg) or Ro110-0329 (30µg/kg) was given to rats exhibiting consistent NMBCs. Rats with decompensated bladders (no pressure rise with void) were not studied. At the end of the experiment, rats were euthanized and the bladder was removed and weighed.

Cardiovascular Studies: A femoral artery and vein of female Sprague-Dawley rats (280-380g) were cannulated under ether anesthesia and then placed in Bollman restraint cages. One hour later a single intravenous dose of antagonist was administered and blood pressure and heart rate were monitored. Rats were euthanized at the end of the study.

Results:

Cystometry Studies: Representative traces demonstrating the effect of intravenously administered vehicle, prazosin, BMY 7378 and Ro110-0329 on NMBCs in conscious, chronically-obstructed rats are shown below. Qualitative assessment of

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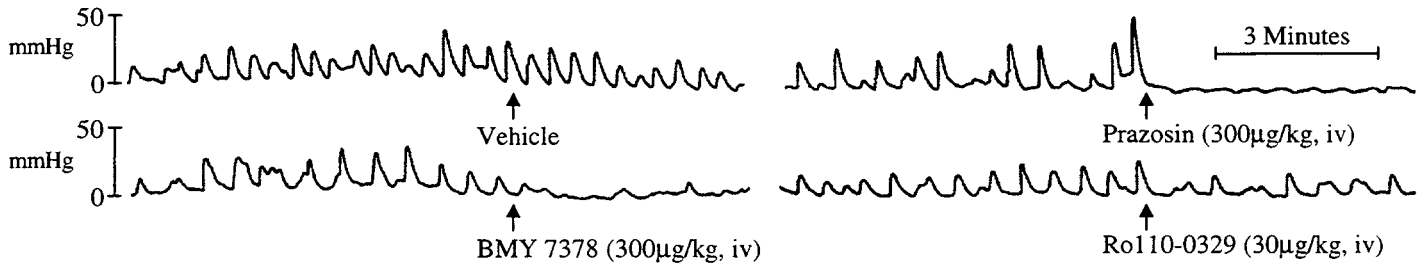
the effect of test compounds on the amplitude and frequency of NMBCs was obtained from multiple experiments: vehicle (n=8), prazosin (n=8), BMY 7378 (n=5) and Ro110-0329 (n=5).



Vehicle and Ro110-0329 had little or no effect on NMBCs. In contrast, prazosin and BMY 7378 inhibited the amplitude and frequency of NMBCs. Prazosin consistently decreased both parameters to a greater extent than BMY 7378, often completely abolishing NMBCs. The effect of prazosin was longer in duration than that seen with BMY 7378. It is important to note that none of the antagonists affected the micturition pressure associated with normal voids.

Cardiovascular Studies: Baseline blood pressure and heart rate (n=4) were as follows: vehicle (120±2mmHg & 375±20bpm), prazosin (121±2mmHg & 354±17bpm), BMY 7378 (120±1mmHg & 385±13bpm) and Ro110-0329 (127±2mmHg & 400±9bpm). Relative to vehicle, Ro110-0329 failed to decrease blood pressure (-6±3mmHg) but did evoke a transient tachycardia (56±10bpm). In contrast, BMY 7378 and prazosin produced significant hypotensive effects of -16±1mmHg and -26±5mmHg, respectively. The duration of the hypotensive effect produced by prazosin was approximately twice that of BMY 7378 (60 versus 30 min). BMY 7378 was without effect on heart rate (-27±12bpm) whereas prazosin produced a sustained tachycardia (133±7bpm)

Conclusions:

The present study confirms the effect of both non-selective and subtype-selective (α_{1A}- and α_{1D}-AR) α_1-AR antagonists on NMBCs in conscious, chronically obstructed rats as previously reported (1). We have extended these observations by evaluating the cardiovascular effects of these antagonists at the doses used in cystometry studies. The present study demonstrated a striking similarity between the magnitude and duration of the effect of these antagonists on NMBCs and cardiovascular parameters. This observation, coupled with the fact that these antagonists did not affect normal micturition pressures, suggests that the effect of these antagonists on NMBCs may result from their vasodilatory effects.

References:

1) FASEB Journal (1998)12:A445.
2) In vitro α_1-adrenoceptor pharmacology of Ro70-0004 and RS-100329, novel α_{1A}-adrenoceptor selective antagonists. British Journal of Pharmacology (1999) in press.