

DEPRESSED EFFECT OF AGING ON CONTRACTILE RESPONSE OF PORCINE DISTAL URETER TO 5-HYDROXYTRYPTAMINE VIA 5-HT_{2A} RECEPTOR SUBTYPE

Hypothesis / aims of study

Aging has been reported to increase the risk of ureteral calculus development [1]. This condition is frequently accompanied with ureteral colic which is understood to be caused by constriction of the ureteric tube, initiated by smooth muscle contractions. The aim of this study was to investigate the effects of age on 5-hydroxytryptamine(5-HT)-mediated contractile responses of the porcine distal ureter and to pharmacologically characterise the subtype/s of 5-HT receptor mediating these responses in young and old animals.

Study design, materials and methods

Urinary bladders with attached ureters, from young (20 weeks) and old (56 weeks) female pigs were obtained from a local abattoir and transported to the laboratory in Krebs's-bicarbonate solution (4°C). Distal ureteral strips were dissected longitudinally and tissues were set up under 1g tension in Krebs-bicarbonate solution at 37°C. Contractile responses of isolated smooth muscle strips to 5-HT were examined. In experiments involving 5-HT receptor antagonists, adjacent tissue preparations were prepared where one strip was incubated with an antagonist for 30 minutes and the other, without antagonist, followed by measurements of 5-HT contractile responses. The antagonists used in this study include 5-HT_{2A} receptor antagonist ketanserin (10nM, 30nM, 100nM), 5-HT₂ and 5-HT₁ antagonist methiothepin (10nM), 5-HT_{2C} antagonist RS 102221 (30nM), 5-HT₃ antagonist ondansetron (30nM), and 5-HT₄ antagonist GR 113808 (100nM). Tissues developed spontaneous phasic contractile activity and responses to 5-HT were expressed as area under the curve (gs) and frequency normalized to tissues weight.

Results

The potency (pEC_{50}) of 5-HT in distal ureteral tissues from young and old pigs were similar (5.16 ± 0.10 vs 5.43 ± 0.20 , $p > 0.05$). However, distal ureteral strips from the younger animals produced a greater maximum contraction in comparison to the older animals ($p < 0.0001$, unpaired t -test, $n = 8$) (Fig. 1).

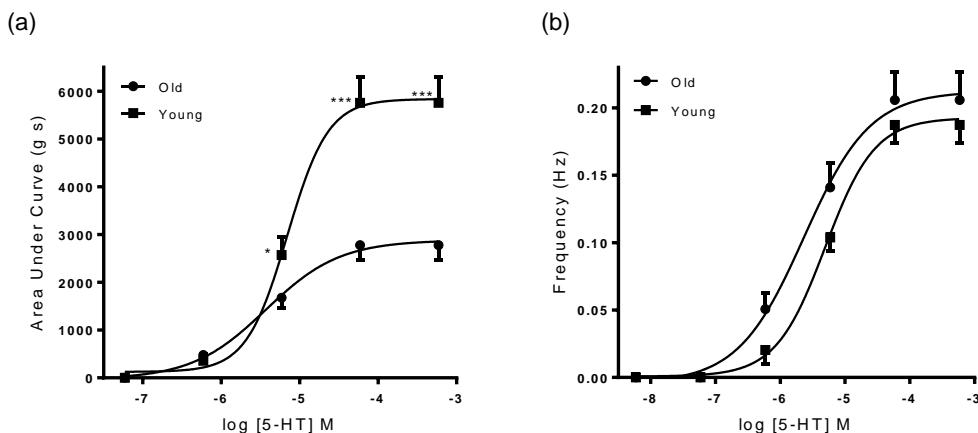


Fig. 1. Concentration-response curves to 5-HT in distal ureteral strips from old and young pigs. Mean (\pm SEM) responses are expressed as (a) area under the curve and (b) frequency of phasic contractions (* $P < 0.05$, ** $P < 0.005$, *** $P < 0.001$, $n=8$).

Treatment of ureteral strips with the 5-HT_{2A} antagonist ketanserin (10nM, 30nM, 100nM) produced a rightward shift of 5-HT concentration-response curves in animals of both age groups. Maximum responses to 5-HT could not be obtained in the presence of antagonist but the Hill slopes of the curves with and without the antagonist were similar (suggesting a competitive antagonism) and this was found in both age groups ($P > 0.05$) (Fig. 2). Using EC₄₀ values for 5-HT in the presence of ketanserin, the affinity estimates (pK_b) were 8.67 and 8.19 in younger and older tissues respectively. The Schild plots had slopes of 0.79 ± 0.07 and 1.25 ± 0.18 in younger and older animals which were both not significantly different from unity.

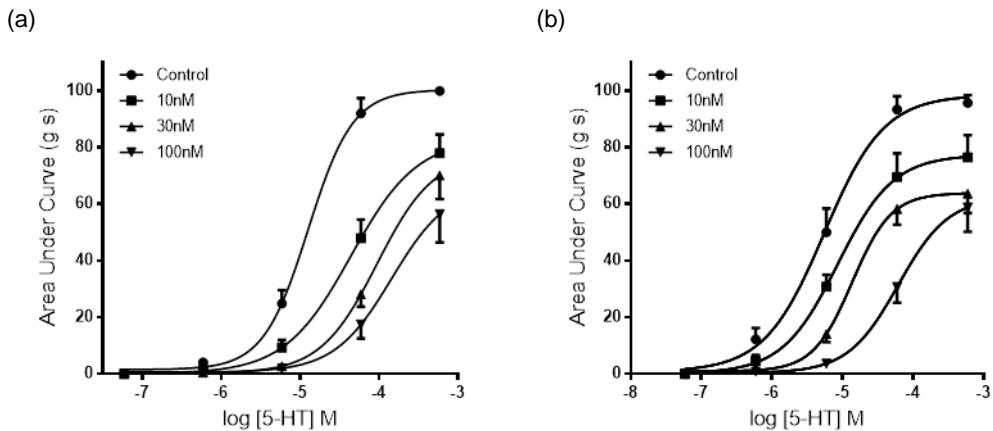


Fig. 2. Concentration-response curves to 5-HT in distal ureter from (a) young and (b) old pigs in the absence and presence of ketanserin (10 – 100nM). Values are represented as mean \pm SEM ($n=8$).

In contrast, the 5-HT antagonists GR-113808, methiothepin, ondansetron and RS 102221 failed to cause any significant shift of 5-HT concentration-response curves in tissues from both age groups although, methiothepin caused a significant reduction in the maximum response to 5-HT ($P<0.0001$) in the younger animals.

Interpretation of results

Affinity estimates for ketanserin were comparable to those reported in the literature (8.9) at 5-HT_{2A} subtype [2]. Our findings indicate that the 5-HT-induced contractile response of the pig distal ureter is mediated by the 5-HT_{2A} receptor subtype in both young and old animals.

Concluding message

Contraction of porcine distal ureter to 5-HT are depressed in older animals. Despite the differences in contractile responses to 5-HT between the young and old ureteral tissues, our study suggests that these responses in the porcine distal ureter are mediated by the same receptor subtype, 5-HT_{2A} and this is not affected by age.

References

1. Costa-Bauza et al (2007) World J Urol 25:415-421.
2. Bonhaus et al (1997) Neuropharmacology 36:621-629.

Disclosures

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