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ALPHA-ADRENERGIC RECEPTORS IN HUMAN PROSTATE

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Strips of human prostate showed a contractile response to alpha-adrenergic agonists There was no response to beta-adrenergic and cholinergic agents, prostaglandins, PGE 1 and PGF 2 α or angiotensin Ⅱ. The noradrenaline-induced contraction was inhibited by an alpha-adrenolytic agent. Electrial field stimulation elicited contraction of the prostatic specimens. This stimulation-induced contraction was antagonized by phenoxybenzamine, but not by yohimbine. These results indicate that alpha-1-adrenergic receptors are Preferentially present in the human prostatic tissue.

Key words: Alpha-adrenergic receptor, *in vitro* muscle bath method, Electrical field stimulation, Human prostate

INTRODUCTION

The contraction of the prostatic tissue has been shown in animal experiments[1,2], but the contractile mechanism of the human prostate is not clearly understood.

Histological studies have demonstrated the presence of smooth muscle cells and adrenergic nerves in human prostatic tissue[3~7]. Pharmacological sympathetectomy may lead to the suppression of the contraction of the prostate, resulting in ejaculatory failure[8,9]. Our previous study has demonstrated that noradrenaline causes contraction of human prostatic strips[10]. These findings seem to indicate that a sympathetic nerve mechanism controls the contraction of the human prostate.

In this paper, in order to clarify the contractile effects of the alpha-adrenergic mechanism on human prostatic tissue, a pharmacological experiment was conducted using the *in vitro* muscle bath method and the electrical field stimulation technique.

MATERIALS AND METHODS

Fragments from the enucleated prostatic adenoma were obtained from five patients with benign prostatic hypertrophy, aged 56 to 75 years, and who were undergoing retropubic prostatectomy. Immediately after surgical removal, these specimens were immersed in cold Tyrode's solution and stored in this solution for 30 to 60 minutes before the experiment was started. The prostatic specimens were then carefully dissected into strip preparations approximately 5 mm wide, 3 mm thick, and 15 mm long.

The prostatic strips were mounted vertically in a 50-ml organ bath (Tyrode's medium, 95% O_2 and 5% CO_2, pH 7.3) and were maintained at a resting tension of 0.5 g throughout the experiments. The changes in the tension of these strips were measured isometrically using a strain-gauge transducer and were recorded on a polygraph. The contractile responses of these strips to various drugs were examined. The drugs used were noradrenaline (3×10^{-5}M); phenylephrine (3×10^{-5} M); phentolamine (2 μg/ml); acetylcho-

line (10^{-3}M) ; atropine (10^{-5}M) ; isoproternol (10^{-5}M); propranol (10^{-5}M); prostaglandins PGE 1 (10 μg/ml) and PGF 2α (10 μg/ml) ; angiotensin Ⅱ (10 mg/ml), and tetrodotoxin (10^{-5}M). The drugs were injected into the bath. The above concentrations represent the final drug concentrations in bath.

For electrical field stimulation, the strips were suspended between two platinum wire electrodes and superfused with Tyrode's solution. The electrical stimuli were rectangular pulses of 1.5 msec duration at 60 Hz for 30 s at 55 volts, delivered using an electronic stimulator (Nihon Koden, SEN-7103). These stimulation conditions were fixed throughout the experiments. For the evaluation of the effect of the alpha-adrenergic antagonists, electrical transmural stimulation of the strips was carried out 5, 10, 15 and 30 minutes after superfusing with Tyrodes' solution containing phenoxybenzamine (3×10^{-5}M) or yohimbine ($10^{-6}$to 10^{-5}M) and the change in tension was observed.

RESULTS

After a stabilization period of up to one hour, all specimens showed spontaneous rhythmic contractions (Fig. 1). These spontaneous contractions varied in both rate and amplitude from strip to strip. The contractile tension ranged from 0.05 to 0.2 g above the resting tension of 0.5 g. This spontaneous activity was not inhibited by the treatment with phentolamine, isoproterenol, atropine and tetrodotoxin (Fig. 2).

The prostatic strips showed a contractile response only to noradrenaline and phenylephrine, and these brugs produced contraction even when tetrodotoxin treatment was carried out. There was no response to isoproterenol, propanol, acetylcholine, prostaglandins (PGE 1 and PGF 2α), or angiotensin Ⅱ. The increase in resting tension induced by noradrenaline was dependent on the dose added to the bath. Noradrenaline was added to the bath in increasing concentration (3×10^{-7} to 3×10^{-5}M), so that a cumulative dose

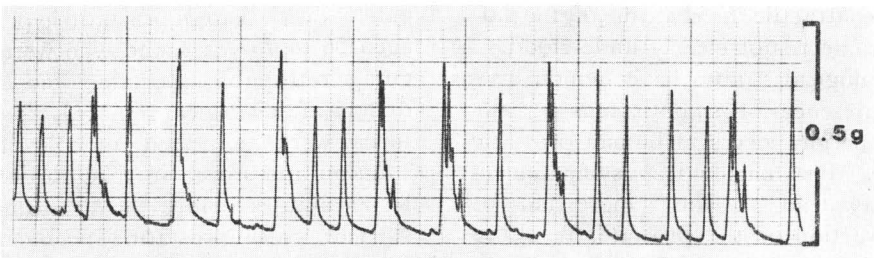

Fig. 1. Spontaneous contractions of tissue strips of the human prostate

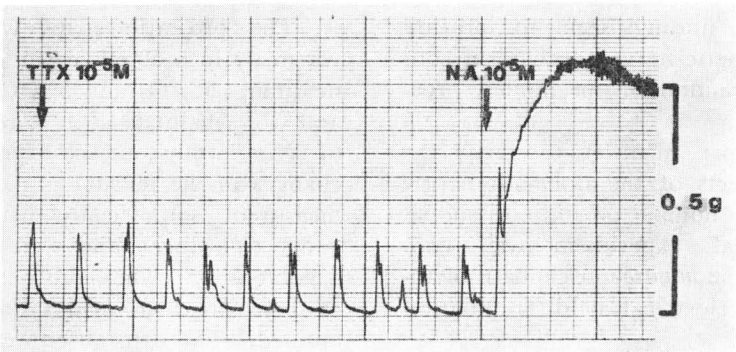

Fig. 2. Effect of tetrodotoxin on spontaneous contractions, and the contractile effect of noradrenaline in the presence of tetrodotoxin

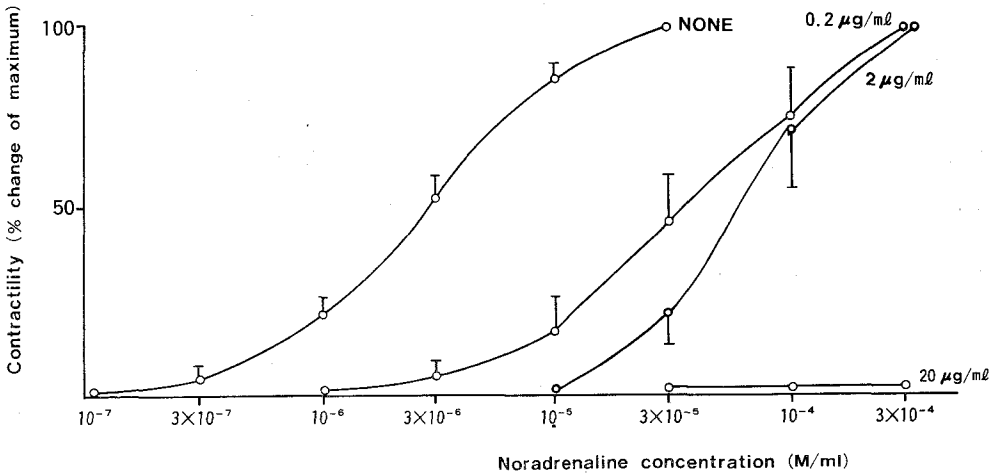

Fig. 3. Effect of phentolamine on the dose-response curve to noradrenaline. Each point and bar represents the mean and standard error of five experiments

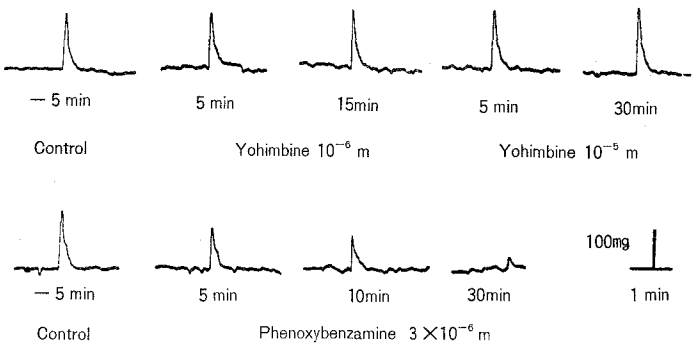

Fig. 4. Effect of phenoxybenzamine and yohimbine on contraction of prostatic strips induced by electrical field stimulation

response curve was obtained. After treatment of the tissue strips with phentolamine (0.5 to 20 μg) for 15 min, the addition of increasing concentrations of noradrenaline was repeated, and the dose response curves in the presence of the antagonists were obtained (Fig. 3). Phentolamine caused a parallel shift to the right in the dose response curve to noradrenaline. Almost full antagonism was obtained with phentolamine at 20 μg.

Transmural electrical stimulation elicited contraction of the prostatic specimens. The contractile tension was approximately 0.2 g. This contbactile response was inhibited by treatment with phenoxybenzamine. Yohimbine had no effect on the contraction of the prostatic strips at concentrations between 10^{-4} and 10^{-5}M (Fig. 4).

DISCUSSION

Our results have demonstrated that two alpha-adrenergic agonists (nor-adrenaline and phenylephrine) caused dose-dependent contractions, and that an alpha-adrenolytic agent (phentolamine) inhibited the noradrenaline-induced contractions in human prastatic strip. These findings support a previous study in which alpha-adrenergic receptors were found in rat and human prostatic tissues[11,12]. On the other hand, because beta-adrenergic and cholinergic agents did not have any effect on the contractile response, beta-adrenergic receptors and cholinergic receptors may not be present in human prostatic tissue. Histochemical studies have revealed the

presence of cholinergic nerves in human prostatic tissue[6,7]. Our experimental results indicate that these cholinergic nerves are not involved in the contraction of the prostate. Rather, we surmise that the function of these nerves relates to the secretion of the prostate gland.

Neither angiotensin II nor the prostaglandins, PGE 1 and PGF 2α, were found to cause either contraction or relaxation of human prostatic strips. With regard to the effects of these drugs on the smooth muscle of the human urinary tract, it has been reported that angiotensin II brings about contraction of isolated muscle strips from the human urinary bladder[13]. PGF 2α and PGE 1 cause contraction of the bladder muscle. It has also been reported that PGF 2α causes contraction of both ureteral smooth muscle and urethral smooth muscle, and PGE 1 brings about the relaxation of these muscle tissues[14~16]. Accordingly, our results show a clear qualitative difference in the effects of these drugs on human prostatic smooth muscle and urinary tract smooth muscle.

We observed that the human prostatic strips contracted in response to electrical field stimulation. The stimulation conditions we employed were similar to those in another report[17] : Stimulation of the taenia strips isolated from the caecum of the guinea pig, caused release of noradrenaline and the tissue strips to relax. This stimulation-induced contraction of human prostatic strips was antagonized by phenoxybenzamine (alpha-1-blocker). This result suggests that alpha-1-receptors are present in the human prostatic tissue. On the other hand, our observation that yohimbine (alpha-2-blocker) did not bring about an increase in the electrical stimulation-induced contraction indicates that there are no alpha-2-receptors in human prostatic tissue. It has been reported that during transmural electrical stimulation of strips of rabbit main pulmonary artery which had been preincubated in [^{3}H]-noradrenaline, yohimbine enhanced the overflow of tritium and smooth muscle contraction[18]. This is due to yohimbine's activity to block the alpha-2-receptors of the arterial tissue. Therefore, in order to prove that there are no alpha-2-receptors in human prostatic tissue, it may be necessary to measure the noradrenaline concentration in the incubation medium when applying electrical field stimulation in the presence of yohimbine.

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和文抄録

ヒト前立腺のアルファ受容体

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