RESPONSE OF URINARY BLADDER TO CHOLINERGIC AND ADRENERGIC AGENTS*

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ABSTRACT

The pharmacologic response of bladder muscle strip of albino rabbits was studied *in vitro*. The effect of cholinergic and adrenergic agents and their antagonists were demonstrated with a log dose-response curve. Cholinergic receptors were abundant in detrusor muscle. While the excitory alpha adrenergic receptors existed in bladder neck, the inhibitory beta adrenergic receptors were predominant in detrusor muscle. The role of cholinergic and adrenergic receptors in detrusor muscle and bladder neck was discussed.

INTRODUCTION

Despite the morphological evidence of both cholinergic and adrenergic innervation at the mammalian urinary bladder[1)2)3)], the role of adrenergic nerve regarding micturition has been a matter of constant dispute. Parasympathetic pelvic nerve facilitates micturition, elevating bladder tonus and increasing contraction force. Torbey and Leadbetter[4)] could not observe any appreciable change in bladder activity by electrical stimulation of sympathetic hypogastric nerve. Boyarsky *et al.*[5)] noted that stimulation of beta adrenergic receptors impaired the micturition by increasing bladder capacity and lowering the voiding pressure.

Ahlquist[6)] demonstrated in 1948 that adrenergic receptor sites were composed of both alpha and beta receptors. Alpha receptor is associated with excitatory response of the smooth muscle and beta receptor mediates relaxation of smooth muscle, with some exceptions. The aim of the present article is to study the pharmacologic response of the bladder strip to cholinergic and adrenergic agents *in vitro*.

MATERIALS AND METHODS

Twenty albino rabbits were killed by a blow in the neck. The bladder was excised at the level of both ureteral orifices and the proximal portion was used as a detrusor specimen. The mucosa was peeled off with a small scissors. The specimen, 50 mm × 5 mm, was prepared at the random direction and mounted in a small organ bath. The muscle was allowed to equilibrate to Krebs Ringer solution for 30 min warmed at 37°C and aerated with 95 per cent oxygen and 5 per cent carbon dioxide. The activity of the muscle strip was registered with force-displacement transducer (Grass Co., FT-03), then fed to a 4 channel polygraph.

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Norepinephrine and isoproterenol were used as adrenergic stimulant. They work at both alpha and beta receptors. However, the former is generally more potent on alpha receptors and the latter has its main action on beta receptors. Phenoxybenzamine and propranol act as specific blockade of alpha and beta receptors, respectively. Drugs tested are as follows: acetylcholine chloride, hexamethonium bromide, physostigmine, atropine sulfate, L-norepinephrine, DL-isoproterenol hydrochloride, phenoxybenzamine hydrochloride, and propranol.

RESULTS

1. Spontaneous contraction

Regular spontaneous contractions were observed after 30 min equilibration to Krebs Ringer solution; frequency of 4 to 5 per min with amplitude of 1.5 to 2.5 g (Fig. 1). The

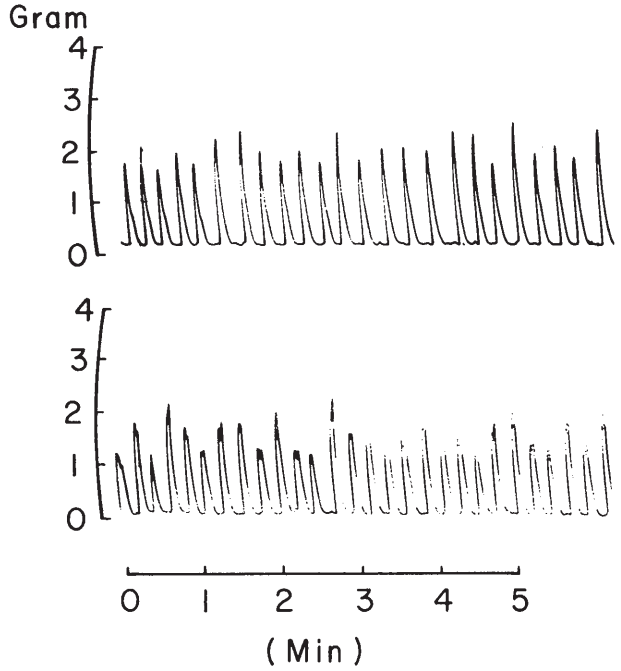

FIG. 1. Spontaneous contraction of rabbit detrusor muscle. Muscle strip resected longitudinally (upper recording) and horizontally (lower recording).

contraction pattern was the same whether the muscle strip was excised longitudinally or horizontally from the detrusor muscle.

2. Response of detrusor muscle to cholinergic agents

The log dose-response curve of acetylcholine and other agents is shown in Fig. 2. The rabbit muscle strip responded to acetylcholine at as low as 1 ng/ml. Muscle tonus was elevated with diminished amplitude and fast contractions (Fig. 3A). Presence of 1 μg/ml atropine, a competitive antagonist at receptor site of smooth muscle, completely inhibited the action of acetylcholine. Physostigmine in a concentration of 1 μg/ml, which inhibited the action of cholinesterase, facilitated the effect of acetylcholine, shifting the dose-response curve to the left. Hexamethonium in a concentration of 1 μg/ml, a ganglion

blockade, did not give any effect on actylcholine.

3. Response of detrusor muscle to adrenergic agents

Administration of norepinephrine caused relaxation of muscle specimen (Fig. 4).

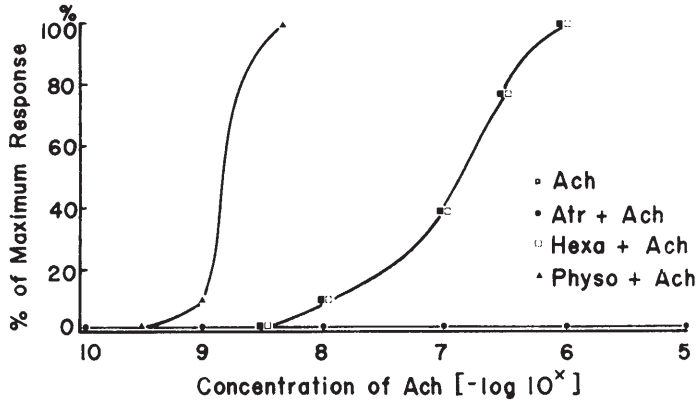

FIG. 2. The effect of acetylcholine and other agents on detrusor muscle is demonstrated with a log dose-response curve. Ach: acetylcholine, Atr: atropine, Hexa: hexamethonium, and Physo: physostigmine.

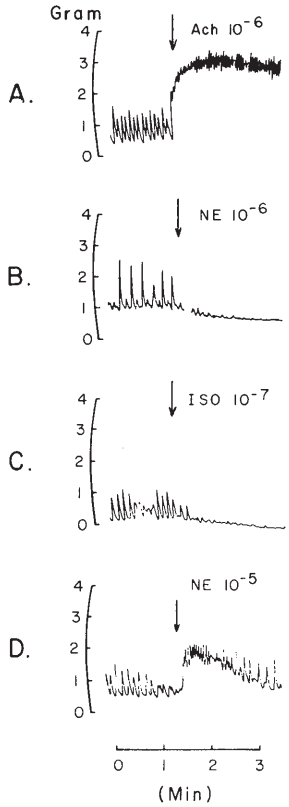

FIG. 3. A, response of detrusor muscle strip to acetylcholine (Ach), 1 μg/ml. B and C, activation of beta adrenergic receptors by norepinephrine (NE), 1 μg/ml and isoproterenol (ISO), 10 μg /ml at detrusor muscle strip. D, activation of alpha adrenergic receptors by norepinephrine (NE), 100 mg/ml at bladder neck.

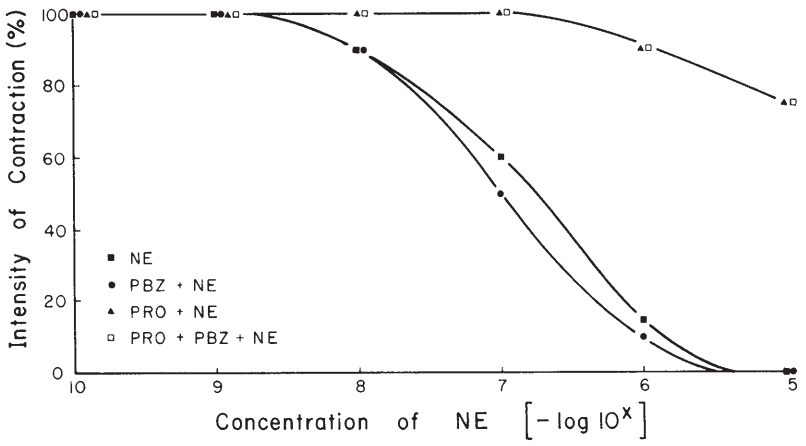

FIG. 4. The effect of norepinephrine and its antagonists on detrusor muscle is shown with a log dose-response curve. NE: norepinephrine, PBZ: phenoxybenzamine, and PRO: propranol.

Frequency and amplitude were the first to be affected, then followed by fall of muscle tonus (Fig. 3B). While phenoxybenzamine in a concentration of 1 μg/ml exerted little change, propranol of the same concentration exerted a strong inhibitory action and shifted the curve to the right. Administration of both phenoxybenzamine and propranol resulted in the same effect as with propranol alone.

Isoproterenol also inhibited muscle contraction in a concentration of 1 ng/ml (Fig. 5). This inhibitory action was prevented by propranol alone and by both propranol and phenoxybenzamine, shifting the curve to the right. Blockade of alpha receptor, phenoxybenzamine slightly facilitated the action of isoproterenol.

4. Response of bladder neck strip

Spontaneous rhythmic contraction was observed in Krebs Ringer solution. The

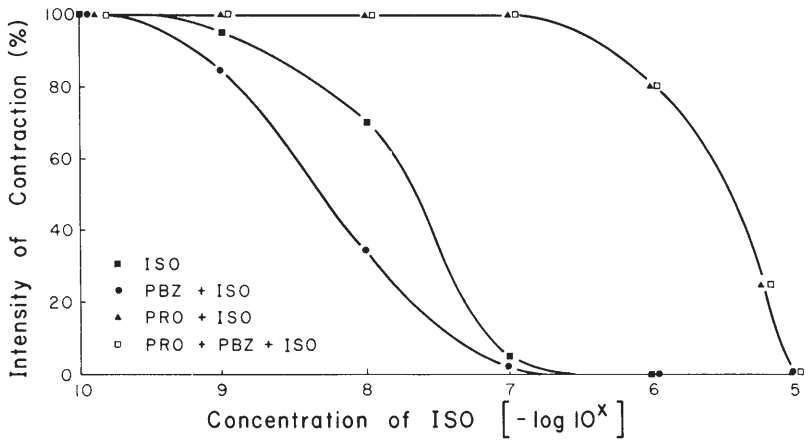

FIG. 5. The effect of isoproterenol and its antagonists on detrusor muscle is demonstrated with a log dose-response curve. ISO: isoproterenol, PBZ: phenoxybenzamine, and PRO: propranol.

excitatory response of specimen to acetylcholine was weak and irregular. The effect of norepinephrine and isoproterenol was excitatory (Fig. 3D), quite different from that observed in detrusor muscle. This action could be inhibited by phenoxybenzamine but not by propranol, indicating the predominance of alpha adrenergic receptors in this portion.

DISCUSSION

Since excitatory action of detrusor muscle is solely mediated through parasympathetic nerve, the acetylcholine derivative which possesses the least side effect on other organs should be chosen for the hypotonic or atonic bladder dysfunction[7)8)]. Atropine derivatives such as methantheline (Banthine)[9)] and propantheline (Pro-Banthine) have been successfully used for the treatment of uninhibited and reflex type of neurogenic bladder dysfunction. Physostigmine has a great affinity for cholinesterase, ten thousand times more than that of acetylcholine, which, in turn, augumented the actylcholine action. Hexamethonium, ganglion blockade, was of no effect at the post synapse in the detrusor muscle.

Figures 4 and 5 obviously demonstrated that inhibitory beta adrenergic receptors are predominant but the excitatory alpha adrenergic receptors are very few in the detrusor muscle. At the bladder neck, on the contrary, the alpha adrenergic receptors are abundantly present (Fig. 3D). Naturally, one can not substitute alpha adrenergic stimulant for cholinergic drug. Distribution of alpha and beta receptors and cholinergic receptors in urinary bladder can be schematically demonstrated as in Fig. 6.

What role do these cholinergic and adrenergic receptors play upon the function of the bladder from the clinical point of view?

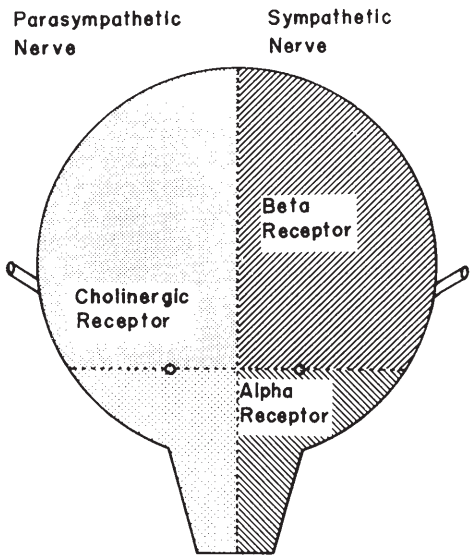

FIG. 6. The schematic presentation of cholinergic and adrenergic receptors found in detrusor muscle and bladder neck in vitro.

URINE ACCUMULATION PHASE: The intrinsic characteristic, which the bladder muscle possesses, allows to accumulate urine without an appreciable increase in intravesical pressure[10]. Besides, the detrusor muscle would be allowed to relax and its tonus to fall due to the effect of beta receptors[5]. It is probable that the alpha receptors would close the bladder outlet tight and be involved in the mechanism of urinary continence.

MICTURITION PHASE: Contraction of detrusor muscle and resultant elevation of intravesical pressure are the most important factors to initiate the micturition. Subsequently, the opening of the inner urethral orifice and relaxation of voluntary muscle of the external urethral sphincter are to be followed. Activation of cholinergic receptors via pelvic nerve yields a strong contraction throughout the detrusor muscle, which would easily overcome the antagonistic effect of beta receptors. The transformation of so-called flat base plate into a funnel shape at bladder neck is achieved by the contraction of Bell's muscle, and inner and outer longitudinal detrusor muscles[11]. Since the burst of electric discharge is recorded from hypogastric nerve before and during micturition[12], it is possible that the alpha adrenergic receptors would more or less take part in opening the inner urethral orifice by increasing muscle tonicity. Recently Krane and Olsson[13] have reported the clinical trial of phenoxybenzamine, an alpha adrenergic blocking agent. The micturition disturbance owing to bladder neck dysfunction was successfully treated by the oral administration of this agent in 52 paraplegics.

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