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Effects of α_1-adrenoceptor Stimulation on Membrane Potential, Twitch Force, Intracellular Na^+, and H^+ Activity in Hyperthyroid Guinea Pig Ventricular Muscle

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ABSTRACT

The roles of β-adrenoceptor were well known in hyperthyroidal heart, but not with α-adrenoceptor. So we studied the effects of phenylephrine on membrane potential, intracellular sodium activity (a^i_{Na}), twitch force, and intracellular pH (pH_i) by continuous intracellular recordings with ion-selective and conventional microelectrodes in the papillary muscles of hyperthyroid guinea pig heart. α_1-Adrenoceptor stimulation by phenylephrine (10^{-5} or 3×10^{-5} M) produced the following changes: variable changes in action potential duration, a hyperpolarization (1.5 ± 0.1 mV) of the diastolic membrane potential, an increase in a^i_{Na} (0.4 ± 0.15 mM), a stronger positive inotropic effect (220 ± 15 %), an increase in pH_i (0.06 ± 0.002 unit). These changes were blocked by prazosin and atenolol. This indicated that the changes in membrane potential, a^i_{Na}, twitch force, and pH_i are mediated by a stimulation of the α_1-adrenoceptor. Ethylisopropylamiloride (10^{-5} M) also blocked the increase in a^i_{Na} and twitch force. On the other hand, strophanthidin, tetrodotoxin, Cs^+, or verapamil did not block the increase in a^i_{Na} and twitch force. Thus, it was suggested that α_1-adrenergic stimulation increased a^i_{Na} and pH_i by stimulation of Na^+-H^+ exchange, thereby allowing intracellular alkalinization and a^i_{Na} increase. These results were very different from euthyroidal heart which showed α_1-adrenoceptor-induced decrease in a^i_{Na} and initial negative inotropic effect. From the above results, it was concluded that α_1-adrenoceptor had a important role in hyperthy-roidal heart.

Key Words: α_1-adrenoceptor, Intracellular sodium activity, Na^+-H^+ exchange, Hyperthyroidism, Heart

INTRODUCTION

α_1-Adrenoceptors are found in mammalian heart muscles (Steinberg and Bilezekian, 1982) and their stimulation by selective agonists causes an increase in contractile force (Bruckner *et al.*, 1985; Benfey, 1987). Some reports demonstrated that α_1-adrenoceptor agonists causes a triphase inotropic response in rat heart muscles (Otani *et al.*, 1990; Tohse *et al.*, 1987) and biphase inotropic response in guinea pig heart muscles (Wang et al., 1990). Recently, Otani *et al.* (1990) reported that α_1-adrenoceptor-mediated positive inotropic response was associated

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with the receptor-linked activation of protein kinase C. This activation was known to stimulate a Na^+-H^+ exchange in a number of different cell or muscle types including heart (Griendling *et al.*, 1988; Vigne *et al.*, 1985). It was also reported that α_1-adrenoceptor agonists were shown to cause an intracellular alkalinization by stimulating the Na^+-H^+ in cardiac Purkinje fibers (Pressler *et al.*, 1989), rat heart muscles (Otani *et al.*, 1990; Iwakura *et al.*, 1990; Terzic and Vogel, 1991), and single isolated ventricular cardiomyocytes (Astarie *et al.*, 1991; Puceat *et al.*, 1993). In addition, this antiporter could increase contractility in cardiac muscle by increasing Ca^{2+} influx through Na^+-Ca^{2+} exchange, following an accumulation of intracellular Na^+ (Ikeda *et al.*, 1988), by increasing the sensitivity of the contractile protein for Ca^{2+} through intracellular alkalinization (Iwakura *et al.*, 1990; Fabiato and Fabiato, 1978). Thus, an increase in intracellular pH produced by receptor activation of Na^+-H^+ exchange was a possible explanation for the increased myofibrillar Ca^{2+} responsiveness attributed to α_1-adrenoceptor agonists. However, whether there was no direct evidence between the ability of α_1-adrenoceptor agonists to stimulate Na^+-H^+ exchange and their ability to elicit a^i_{Na} increase because they did not measure intracellular Na^+ activity (a^i_{Na}) during α_1-adrenoceptor stimulation in beating heart muscles. It was reported that amiloride, Na^+-H^+ exchange inhibitor, abolished the positive inotropic effect of phenylephrine and inhibited the phenylephrine-induced alkalinization in rat heart (Terzic and Vogel, 1990; Otani *et al.*, 1990). Further α_1-adrenoceptor agonists have been reported to decrease a^i_{Na} in euthyroid guinea pig heart and canine Purkinje fibers (Wang *et al.*, 1990; Zaza *et al.*, 1990).

The purpose of the present study was to identify a α_1-adrenoceptor induced Na^+-H^+ exchange stimulation is linked to positive inotropic effect. We measured a^i_{Na}, pH_i, and twitch force with an ion-selective and conventional microelectrodes in isolated hyperthyroid papillary muscles of guinea pig.

MATERIALS AND METHODS

Animals

Guinea pigs (250~350 g) of either sex were randomly assigned to euthyroid or hyperthyroid group. The hyperthyroidism was induced by a daily intraperitoneal with L-thyroxine (T_4), 0.3 mg/kg, for 9~12 days. The injected materials were prepared by dissolving sodium L-thyroxine in 0.1 M NaOH and adjusted to a pH of 8.0 by adding 0.1 M HCl.

Tissue preparation and experimental solutions

Guinea pigs were killed by cervical dislocation, and their heart was rapidly removed through a thoracectomy and transferred to a dissection bath filled with Tyrode's solution oxygenated with 97% O_2-3% CO_2. The papillary muscles were carefully dissected from right ventricle and fixed with an insect pin to the Sylgard bottom of a tissue chamber, and continuously superfused with oxygenated Tyrode's solution prewarmed to 36~37℃ and buffered to pH 7.3~7.4. The muscle next to the insect pin was pressed against the floor by stimulating electrode, which was used to elicit action potential and contraction. The distal end of the muscle was connected to a force transducer (Cambridge Technology, model 405) by a 24 μm silver wire attached to one of the chordae. The twitch force was continuously recorded on a chart recorder (Gould, model 3000). All preparations were stimulated at a rate of 1 Hz and stimulus votage was 20% above threshold voltage.

The composition of the Tyrode's solution (mM/l) was; NaCl 137, KCl 5.4, $MgCl_2$ 1.05, NaH_2PO_4 0.45, $NaHCO_3$ 11.9, $CaCl_2$ 1.8, and dextrose 5. When necessary, we used HEPES buffer solution at buffered of pH 7.4 instead of Tyrode's solution so that the pH-selective electrode could be maintained in a stable state. This solution was oxygenated with 100% O_2.

All drugs were prepared as concentrated stock solutions and diluted to their final concentration with the Tyrode's solution. Phenylephrine hydrochloride, strophanthidin, tetro-

dotoxin, verapamil, cesium hydroxide, atenolol, and prazosin were purchased from Sigma Chemical Co. Ethylisopropylamiloride was purchased from RBI.

Measurement of intracellular Na^+, pH, and membrane potential

All electrodes were calibrated before and after each experiment in standard solutions. Transmembrane action potentials were recorded with conventional KCl microelectrodes.

Single barrel microelectrodes were made from borosilicate glass. And each back-filled with 100 mM NaCl or pH 5 standard solution. The tip of the electrode was then immersed in a resin cocktail containing the neutral carriers (Fluka), and filled by negative pressure. Intracellular Na^+ activity (a^i_{Na}) or H^+ activity (pH_i) were measured with glass micropipettes filled with Na^+-selective or H^+-selective neutral carrier (Fluka AG, Buchs SG, Switzerland) (Lee and Dagostino, 1982, Kaila and Vaughan-Jonse, 1987).

The ion-selective and conventional electrodes were inserted into the beating papillary muscle at constant rate (1 Hz) within 1 mm distance. Intracellular membrane potential (V_M) recorded by the conventional microelectrode and the intracellular potential (V_{NaE} or V_{pHE}) recorded by the ion-selective microelectrodes were referred to the potential of a reference electrode placed in the superfusing solution close to the impaling sites. The potential sensitivity to intracellular sodium (V_{NaE}-V_M) or pH (V_{PHE}-V_M) was converted to a a^i_{Na}(or pH_i) using the individual calibration curve for each electrode. To continu-

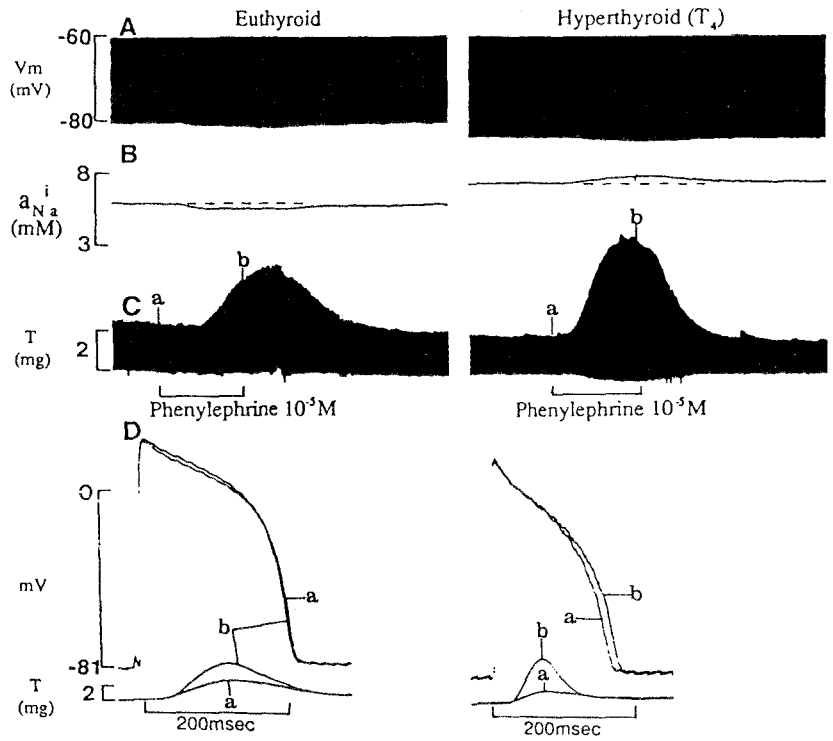

Fig. 1. Effects of 10^{-5} M phenylephrine on membrane potential (Vm), intracellular Na^+ activity (a^i_{Na}), and twitch force (T) in euthyroid and hyperthyroid guinea pig papillary muscles. A, B and C; Recordings of Vm, a^i_{Na} and T respectively. D; Superimposed action potentials (a, b) and twitch forces (a, b) that were recorded at corresponding points marked over C (a; normal Tyrode's solution b; phenylephrine).

ously measure intracellular ion in the beating muscle and to remove the potential fluctuations recorded by conventional and ion-selective microelectrodes, we used two identical low pass filters. The action potential of the muscle was displayed on an oscilloscope (Textronix, model 5113) together with the twitch force. The diastolic membrabe potential of the beating muscles were continuously recorded on a chart recorder (Gould, model 3000) that had a frequency response of 30 Hz.

Statistical comparisons were made using Student's *t* test, and all results were expressed as mean±standard deviation.

RESULTS

Determination of thyroid status

T_4-treated animals were more active and excitable than the controls. Also, evaluation of thyroid state was determined after and before each experiment by the serum T_3 and T_4, and ratio of heart weight to body weight. T_4 values of 10 euthyroid guinea pigs was of 2.5 μg/dl and that of hyperthyroid was higher than 258 μg/dl. The increased heart weight and ratio of heart weight to body weight in the thyroxine-treated animals were consistent with cardic muscle hypertrophy which had been described (Morkin and Flink, 1983).

Effects of phenylephrine on diastolic membrane potential (Vm), intracellular sodium activity (a^i_{Na}), twitch force, and action potential duration (APD) in euthyroid and hyperthyroid guinea pig papillary muscles

The effects of phenylephrine on Vm, a^i_{Na}, twitch force, and APD on euthyroid and hyperthyroid ventricular papillary muscle are

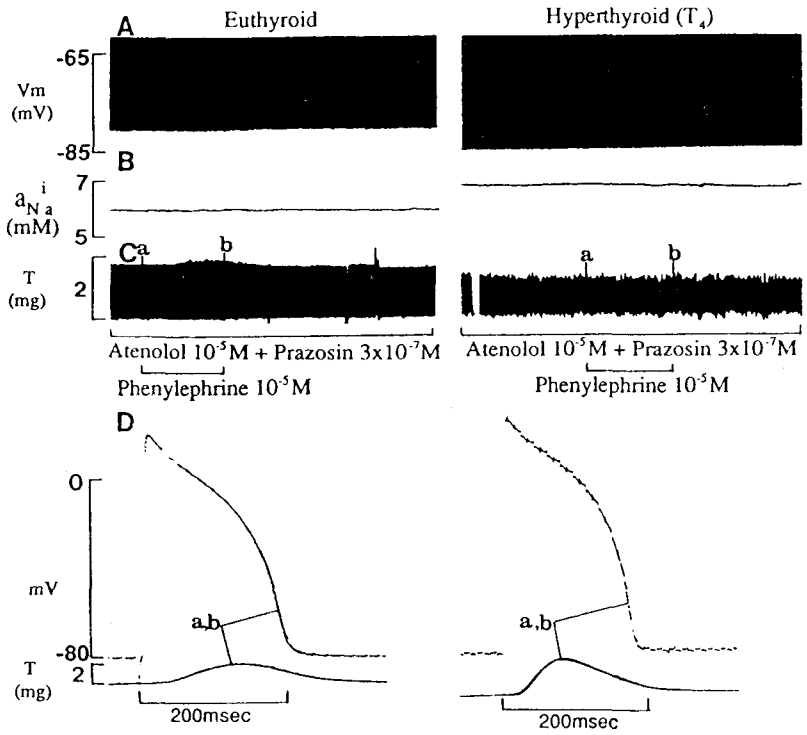

Fig. 2. Effects of phenylephrine on membrane potential (Vm), intracellular Na^+ activity (a^i_{Na}), and twitch force (T) in the presence of atenolol and prazosin in euthyroid and hyperthyroid guinea pig papillary muscles. Other legends are the same as in Fig. 1.

shown (Fig. 1, panel left). Diastolic membrane potentials in both euthyroid and hyperthyroid preparation were slightly hyperpolarized (1.5±0.1 mV). 10^{-5} M Phenylephrine decreased a^i_{Na} from 4.8±0.8 to 4.4±1.0 mM (n=24) in euthyroid preparations. This result observed were similar to those described by Zaza *et al.* (1990) on canine Purkinje fibers and by Wang *et al.* (1990) on guinea pig ventricular muscles. However, 10^{-5} M phenylephrine produced increase a^i_{Na} from 5.1±0.9 to 5.6±1.1 mM (n=21) in hyperthyroid ones. Phenylephrine-induced contractility was stronger in hyperthyroid papillary muscle than the euthyroid ones. The action potential from the hyperthyroid animal shortened clearly. Althrough phenylephrine produced a variable changes in APD, it decreased the a^i_{Na} in euthyroid papillary muscle and increased the the a^i_{Na} in hyperthyroid ones constantly. Re-exposure to normal Tyrode's solution produced the Vm, a^i_{Na}, twitch force, and APD return to control levels. In the presence of atenolol, β-adrenergic antagonist, these changes were similar to those described by Fig. 1 in all muscles (not shown). However, these changes were blocked by prazosin, α_1-adrenergic antagonist (Fig. 2). Therefore, the these changes were seemed as results of stimulation of α_1-adrenoceptor.

Effects of strophanthidin, tetrodotoxin (TTX), cesium hydroxide (Cs^-), verapamil, or ethylisopropylamiloride (EIPA) on phenylephrine-induced Vm, a^i_{Na}, and twitch force in hyperthyroid ventricular papillary muscles

In cardiac cells or Purkinje fibers, a^i_{Na} could be changed by Na^+ efflux *via* the Na-K pump, Na^+ influx through the Na^+ and Ca^{2+} channels, and *via* pacemaker current (in Purkinje fibers), or the Na^+-H^+ exchange. To estimate the mechanism of the increase in a^i_{Na} by α_1-adrenergic stimulation in the hyperthyroid heart, we tested

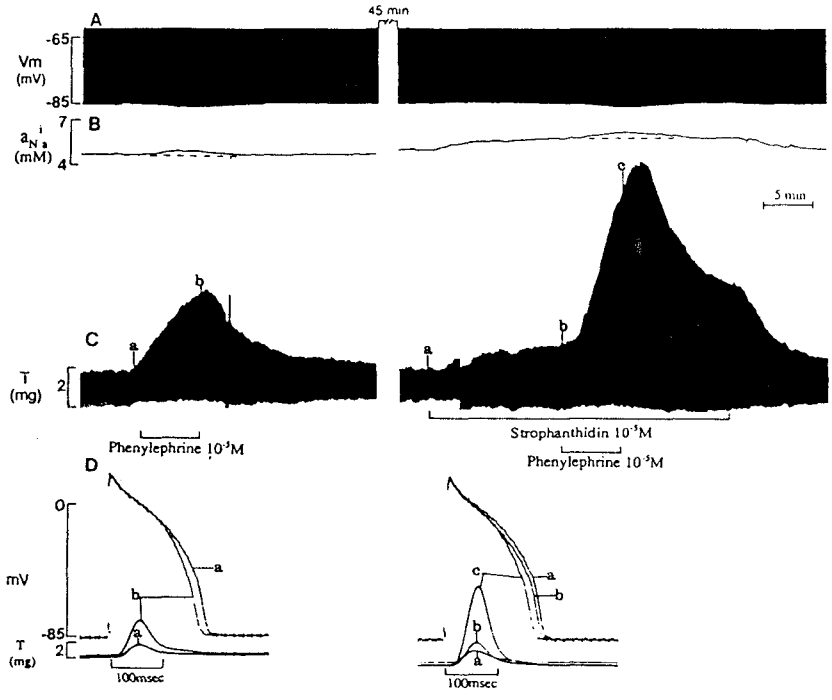

Fig. 3. Effects of phenylephrine on membrane potential (Vm), intracellular Na^+ activity (a^i_{Na}), and twitch force (T) in the absence (panel left) or presence (panel right) of strophanthidin in hyperthyroid guinea pig papillary muscles. Other legends are the same as in Fig. 1.

the effects of strophanthidin (Na^+-K^+ pump inhibitor), tetrodotoxin (Na^+ channel blocker), Cs^+ (pacemaker current inhibitor), verapamil (Ca^{2+} channel blocker), or EIPA (Na^+-H^+ exchange inhibitor) on phenylephrine-induced a^i_{Na} increase in beating ventricular muscles.

Fig. 3 shows the effect of 10^{-5} M strophanthidin on phenylephrine-induced Vm, a^i_{Na}, twitch force, and APD changes. Phenylephrine produced a hyperpolarization of the diastolic membrane potential (trace A), an increase in a^i_{Na} (trace B), an increase in twitch force (trace C), and a shortening of APD (trace D). Then the preparation was exposed to strophathidin, which substantially increased a^i_{Na} and twitch force (panel right). In the presence of strophanthidin, phenylephrine still hyperpolarized the diastolic membrane potential, increased a^i_{Na} and twitch force, and shortened the APD (panel right). This result indicates that the increase in a^i_{Na} and twitch force by phenylephrine are not due to an inhibition of the Na^+-K^+ pump.

Fig. 4 and 5 shows the effect of 10^{-5} M TTX or Cs^+ on phenylephrine-induced Vm, a^i_{Na}, twitch force, and APD changes. After control experiments, the preparations were exposed to TTX, Cs or TTX decreased a^i_{Na} and twitch force (Fig. 4., panel right) but Cs^+ did not. In the presence of TTX or Cs^+, the effects phenylephrine on Vm, a^i_{Na}, and twitch force had similar to the control experiment (Fig. 4, 5). These results indicate that the increase in a^i_{Na} by α_1-adrenergic stimulation is not related to the opening of the Na^+ channels or the stimulation of the pacemaker current.

10^{-5} M Verapamil decreased a^i_{Na} and twitch force, and shortened the duration of the action potential (Fig. 6, panel right). In the presence of verapamil, phenylephrine-induced changes still occurred in all muscles tested, although a

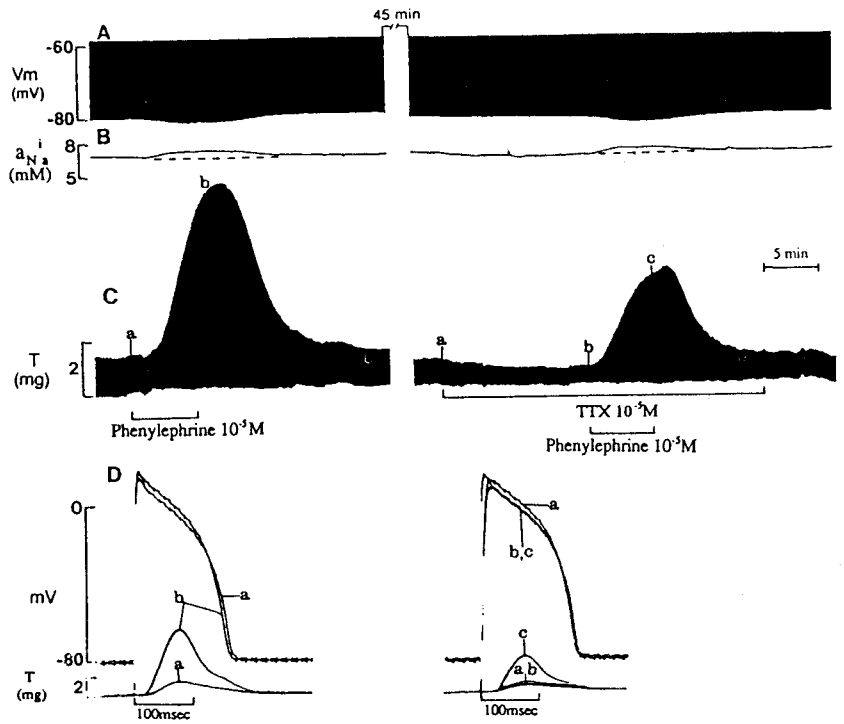

Fig. 4. Effects of phenylephrine on membrane potential (Vm), intracellular Na^+ activity (a^i_{Na}), and twitch force (T) in the absence (panel left) or presence (panel right) of tetrodotoxin in hyperthyroid guinea pig papillary muscles. Other legends are the same as in Fig. 1.

slight inhibition of twitch force were shown. This result indicate that the increase in a^i_{Na} by α_1-adrenergic stimulation is not related to an influx through the Ca^{2-} channel.

Stimulation of Na^+-H^+ exchange could be operated to increase Na^+ influx, which increased intracellular Ca^{2+} via Na^+-Ca^{2+} exchange (Frelin *et al.*, 1984; Ikeda *et al.*, 1988). Further, alkalinization could be a mechanism for α_1-adrenoceptor-mediated sustained positive inotropic effect (Otani *et al.*, 1990). But until now, there was no report of a^i_{Na} increase during α_1-adrenoceptor stimulation on heart muscle. However, we show that the a^i_{Na} increase in a^i_{Na} was observed in the hyperthyroid guinea pig papillary muscle, indicating that the stimulation of α_1-adrenoceptor could be activation of Na^+-H^+ exchange. To determine whether a^i_{Na} increase was associated with activation of Na^+-H^- exchange, we measured the effect of phenylephrine in the presence of EIPA (5 μM), (Fig. 7). EIPA produced no change in a diastolic membrane potential, a^i_{Na}, twitch force, and APD. In the presence of EIPA, a^i_{Na} and twitch force were completly blocked. But, phenylephrine still caused a hyperpolarization of diastolic membrane potential and a shortening APD (Fig. 7, panel right). This result suggested that the a^i_{Na} increase and twitch force increase by phenylephrine was due to the increase Na^+ influx *via* Na^+-H^- exchange.

Effects of phenylephrine on Vm, intracellular pH (pH$_i$), and twitch force in driven and quiescent ventricular papillary muscle of hyperthyroid guinea pig

To elucidate the mechanism of α_1-adrenergic stimulation on Na^+-H^+ exchange in the hyperthyroid animal, we tested the effects of phenylephrine on pH$_i$ of 1Hz driven (Fig. 8, trace B) and quiescent (Fig. 8, trace E) papillary muscle. As show in Fig. 8, in a driven and quiescent preparation, phenylephrine increased pH$_i$ from 7.17±0.02 to 7.23±0.03 (n=6, P<0.01).

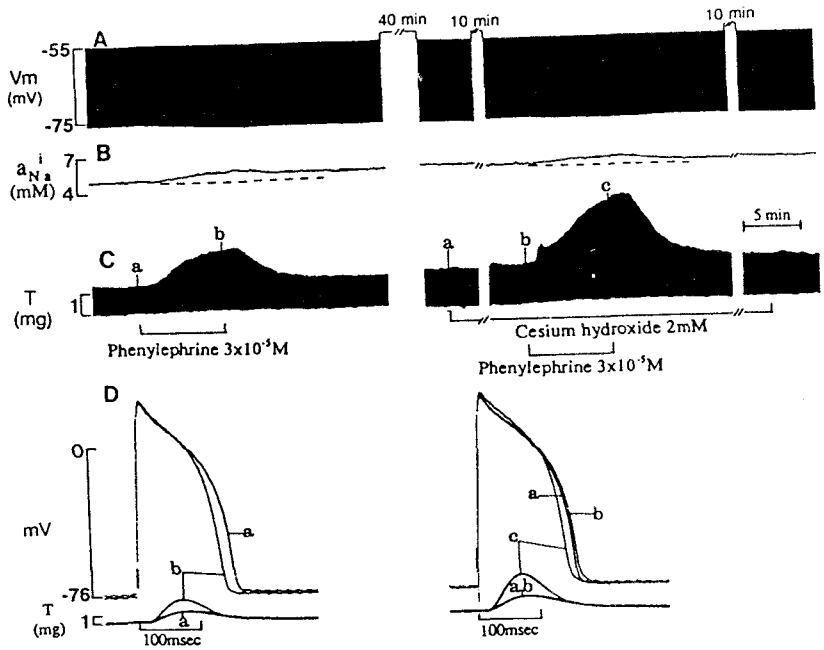

Fig. 5. Effects of phenylephrine on membrane potential (Vm), intracellular Na^+ activity (a^i_{Na}), and twitch force (T) in the absence (panel left) or presence (panel right) of cesium hydroxide in hyperthyroid guinea pig papillary muscles. Other legends are the same as in Fig. 1.

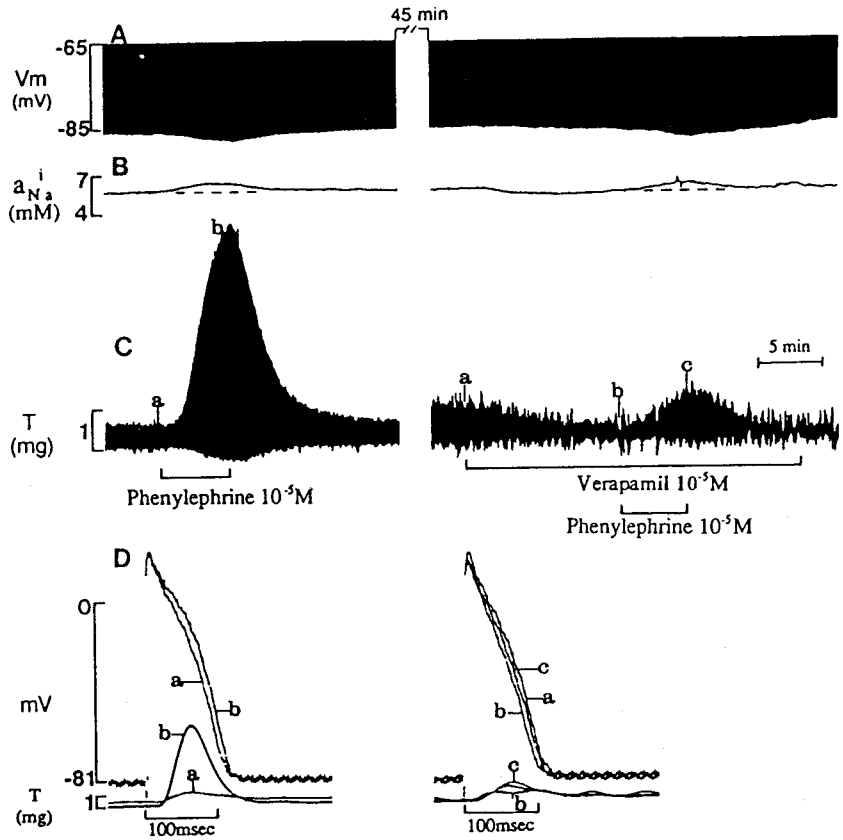

Fig. 6. Effects of phenylephrine on membrane potential (Vm), intracellular Na^+ activity (a^i_{Na}), and twitch force (T) in the absence (panel left) or presence (panel right) of verapamil in hyperthyroid guinea pig papillary muscles. Other legends are the same as in Fig. 1.

Even though there was a^i_{Na} decrease, the alkalinization were also observed in the preparations of euthyroid guinea pig, and these changes were blocked by prazosin, α_1-adrenoceptor antagonist, or amiloride, Na^+-H^+ exchange inhibitor (not shown). Therefore, we suggest that the increase in a^i_{Na} produced by stimulation of α_1-adrenoceptor of hyperthyroid heart muscle might be related to the increase in Na^+ influx *via* Na^+-H^+ exchange.

DISCUSSION

We observed that α_1-adrenergic stimulation produced a decrease in a^i_{Na} and initial negative inotropic effect in euthyroid preparations, but in hyperthyroid ones, increased a^i_{Na}, and positive inotropic effect, this suggested that thyroid hormone may affect on function of cardiac muscle by altering of intracellular sodium handling. Previous studies have demonstrated that the thyroid hormones have profound effect on cardiac electrophysiolgical characteristics (Arnsdorf and Childers, 1970: Jaeger *et al.*, 1981). The major findings were that chronic hyperthyroidism, and hypothyroidism are associated with a decrease and an increase in action potential duration, respectively (Felzen *et al.*, 1987; Binah *et al.*, 1987). Furthermore, the electrophysiolgical effects of thyroid hormone are ① the modulation of membrane currents (Binah *et al.* 1987; Rabinstein and Binah, 1989), ② the in-

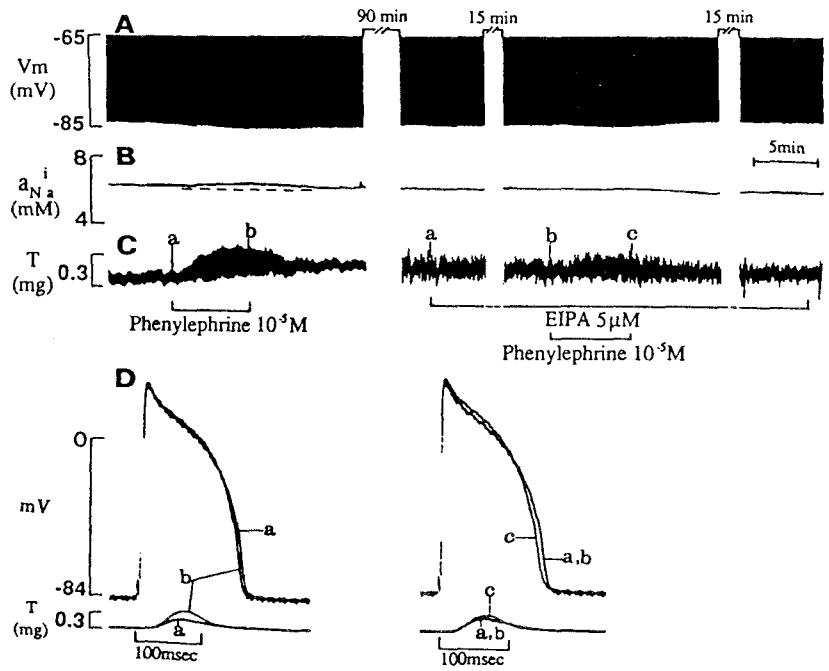

Fig. 7. Effects of phenylephrine on membrane potential (Vm), intracellular Na^+ activity (a^i_{Na}), and twitch force (T) in the absence (panel left) or presence (panel right) of ethylisopropylamilolide(EIPA) in hyperthyroid guinea pig papillary muscles. Other legends are the same as in Fig. 1.

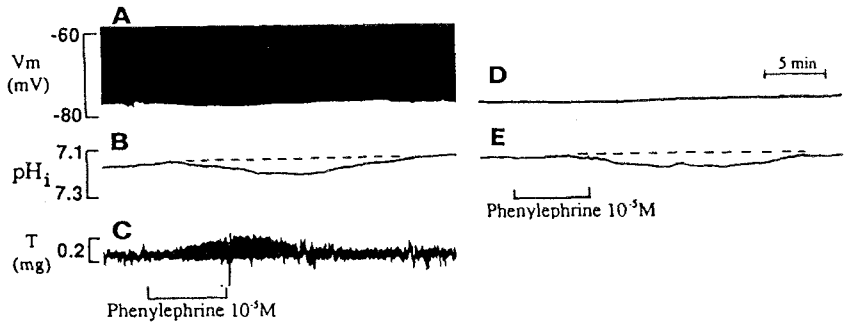

Fig. 8. Effects of phenylephrine on membrane potential (Vm), intracellular hydrogen activity (pH_i), and twitch force (T) in driven and quiescent papillary muscles of hyperthyroid guinea pig. D and F; Resting membrane potential and pH_i respectively.

flux of Ca^{2+} *via* Ca^{2+} channel and Na^+-Ca^{2+} exchange (Kim and Smith, 1985), ③ the decrease in intracellular Na^+ resulting in an activation of Na^+-K^+ pump in skeletal myotubes (Brodie and Sampson, 1988), ④ the Na^+ channel synthesis in skeletal myotubes (Brodie and Sampson, 1989). Among the important electrophysiological effects of α_1-adrenergic ago-

nists are ① the negative chronotropic effect resulting in an activation of Na^+-K^+ pump (Zaza *et al.*, 1990), ② the modulation of K^+ channels (Fedida and Bouchard, 1992), ③ the increase in cytosolic Ca^{2+} resulting in an activation of protein kinase C (Capogrossi *et al* ., 1991), ④ the modulation of the action potential duration (Dirksen and Sheu, 1990; Miura and Inui, 1984), ⑤ the cytosolic alkalinization via activation of the Na^+-H^+ exchange (Terzic *et al.*, 1992). These alteraions in α_1-adrenoceptor effects could produce the changes in the positive inotropic response and intracellular Na^+ and Ca^{2+} concentration. There is a large amount of evidence for an α_1-adrenoceptor agonists induced positive inotropic effect in cardiac tissue (for review see Terzic *et al.*, 1993). In the presence of verapamil, phenylephrine-induced increase in a^i_{Na} and twitch force still occurred in hyperthyroid preparations (Fig. 6). This result indicates that the increase in a^i_{Na} by α_1-adrenoceptor stimulation is not related to an influx through the Ca^{2+} channel.

In addition, activation of protein kinase C was known to stimulate a Na^+-H^+ exchange system in cardiac cell (for discussion see Iwakura *et al.*, 1990). This exchange system could increase contractility in cardiac muscle increasing Ca^{2+} (Blinks and Endoh., 1986) influx through Na^+-Ca^{2+} exchange, however, an increase in the Ca^{2+} sensitivity of myofilaments also contributes to positive inotropic effect (Blinks and Endoh, 1986). Since the Ca^{2+} sensitivity of myofilaments increases in alkalinized condition (Fabiato and Fabiato, 1978), the intracellular alkalinization through Na^+-H^+ exchange may also agument the α_1-adrenoceptor-mediated positive inotropic effect. In addition to producing an intracellular alkalinization, the activation of Na^+-H^+ exchange by α_1-adrenoceptor agonists could be expected to increase intracellular Na^+. However, α_1-adrenoceptor was reported to stimulate Na^+-K^+ pump activity (Zaza *et al.*, 1990). But, we observed an increase in a^i_{Na} in papillary muscle of the hyperthyroidism animals contrary to euthyroid animals. In our study, an inhibitor of Na^+-K^+ pump, strophanthidin, also did not block the phenylephrine-induced a increase in a^i_{Na} activity (Fig. 3), suggesting that the α_1-adrenoceptor is not associated with an inhibition of the Na^+-K^+ pump. During action potential, Na^+ influx through the fast Na^+ channel may be cause of α_1-adrenoceptor induced a^i_{Na} increase. Thus we tested a opening of the Na^+ channel by use of tetrodotoxin. Tetrodotoxin did not block the increase in a^i_{Na} and twitch force (Fig. 4). This result indicates that the increase in a^i_{Na} by α_1-adrenergic stimulaion is not related to the opening of the Na^+ channels.

Activation of protein kinase C was known to stimulate a Na^+-H^+ exchange system in cardiac cell (for discussion see Iwakura *et al.*, 1990), several reports indicate that the activity of the Na^+-H^+ exchange could participate in the positive inotropic effects of α_1-adrenergic agonists. First, inhibition of Na^+-H^+ exchange by selective blockers inhibits the increase in contractile force produced by phenylephrine in multicellular cardiac preparations (Gambassi *et al.*, 1992). Similarly, ionic substitution of Na^+ with other ions blocks the positive inotropic effect of phenylephrine (Terzic and Vogel, 1991). Second, the time course and magnitude of the α_1-adrenoceptor-mediated alkalinization closely correlates to that of the positive inotropic effect (Terzic *et al.*, 1991,1992; Gambass *et al.*, 1992). Third, the degree (0.1 pH unit) of alkalinization caused by α_1-adrenoceptor agonists (Terzic *et al.*, 1992) is known to increase contractile force by several-fold in cardiac tissue (Bountra and Vaughan-Jones, 1989; Lagadic-Gossmann and Feuvray, 1990). In previous results, however, the change of the a^i_{Na} by α_1-adrenergic stimulation had not been well analysed. If alkalinization by α_1-adrenergic stimulation is due to an activation of Na^+-H^+ exchange, phenylephrine should increase the a^i_{Na} and pH_i. However, a^i_{Na} was shown to be reduced rather than elevated by α_1-adrenoceptor agonists in the normmal canine Pukinje fibers and guinea pig papillary muscles. So α_1-adrenoceptor has dual effects on intracellular sodium activity. One is a^i_{Na} increase by Na^+-H^+ exchange, another is a^i_{Na} decrease by Na^+-K^+ pump stimulation, which fast sodium channel inhibitor but later two mechanism are not clear.

α_1-Adrenoceptor stimulation does not have a^i_{Na} decreasing effect in hyperthyroid heart which take 9 to 12 days after thyroid hormone treat-

ment. In euthyroid heart, a^{i}_{Na} decreasing effect is more stronger than increasing effect. The a^{i}_{Na} decreasing effect is seemed to be linked with protein kinase C because after phorbol dibutyrate treatment, α_1-adrenoceptor stimulation shows only a^{i}_{Na} increasing effect in eutyroid heart (data is not show). Until now, the importance of β-adrenoceptor is known in hyperthyriod heart. But neurotransmitter norepinephrine and epinephrine have also strong α-adrenergic stimulation effect. So roles of α-adrenoceptor of hyperthyroidal heart need to reevaluation.

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=국문초록=

갑상선 기능 항진 기니픽 심근에서 α_1-Adrenergic 수용체 자극이 막전위, 수축력 및 세포내 Na^+과 H^+ 활성도에 미치는 영향

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갑상선 기능 항진증 심장에서의 β-adrenoceptor의 역할은 잘 알려져 있으나 α-adrenoceptor에 대해서는 알려져 있지 않은 바, 저자 등은 갑상선 기능 항진증 기니픽 심장의 유두근에서 일반 미세 전극과 이온-선택적 미세 전극을 이용하여 세포내 Na^+과 H^+ 활성도에 대한 phenylephrine의 영향을 연구하였다.

Phenylephrine (10^{-5} 또는 3×10^{-5} M)에 의한 α_1-adrenoceptor 자극은 다양한 활동전위의 변동, 수축기 막전위의 과분극 (1.5±0.1 mM), 세포내 활성도 증가 (0.4±0.15 mM), 현저한 수축력 증가 (220±15%) 그리고 세포내 pH의 증가 (0.06±0.002 unit)를 일으켰고, 이와 같은 변동이 prazosin과 atenolol에 의해 차단되었다. 그래서 이들 효과가 α_1-adrenoceptor를 경유함을 알 수 있었고, 역시, 세포내 Na^+ 활성도와 수축력 증가 효과가 Na^+-H^+ 교환기 억제제인 ethyl-isopropylamiloride로 차단됨으로 보아 α_1-adrenoceptor 자극은 Na^+-H^+ 교환기를 자극하여 세포내 a^i_{Na}와 pH를 증가시킴을 시사한다. 이는 α_1-adrenoceptor 자극에 의한 세포내 Na^+감소와 초기 수축력 감소 효과를 나타내는 정상 기니픽 심장과는 매우 다른 결과로 갑상선 기능 항진증 심장에서 α_1-adrenoceptor는 매우 중요한 기능을 갖고 있음을 의미한다.