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Calcium and Sodium Channel Blockers and Gastrointestinal Motility

Emine Koç

Department of Physiology, Near East University School of Medicine, Nicosia, Cyprus

ORCID iD of the author: E.K. 0000-0001-8804-4937.

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BACKGROUND/AIMS
Calcium and sodium channels are necessary in all excitable cells to maintain their functions. Calciumchannel blockers are generally used clinically to treat various pathological conditions such as cardiovascular diseases. Moreover, sodium channel blockers are widely used clinically, such as in dentistry. Given their widespread use, these blockers may have effects on gastrointestinal motility.

MATERIAL and METHODS
This study used healthy adult Wistar rats for the experiments. The ileal segments were isolated and suspended in tissuebath. Contractile responses induced by acetylcholine (ACh) were recorded. To study the effects of calciumchannel blocker nifedipine (l,4-dihidropyridine calcium channel blocker) and sodiumchannel blocker prilocaine [2-(propylamino)-o-propionotoluidide], ileal segments were incubated with these agents, and ACh-induced contractions were then recorded.

RESULTS
All doses of calcium and sodium channel blockers significantly decreased the ACh-induced contractions in isolated ileal segments.

CONCLUSION
Calcium and sodium channel blockers have significantly decreasedgastrointestinal motility.

Keywords: Calcium channel blocker, sodium channel blocker, gastrointestinal motility

INTRODUCTION

Calcium channels are essentialfor many functions in excitablebody cells, such asin transmitter release, hormone secretion, excitation, and excitation–contraction coupling. L-type calcium channels play a key role in muscles that need extracellular calcium for contraction. Calcium channel blockers are generally used to treat cardiovascular diseasesas well as hypertension.As such, L-type calcium channel blockers are used in many clinical situations, such asin the treatment of hyperinsulinemichypoglycemia (l), respiratory system diseases (2), cardiac disorders, Parkinson's disease (3), and hypertension. Moreover, nifedipine may have a partially protective effect on noise-induced hearing loss (4). For many years, calciumchannel blockers have been used in the treatment of hypertension, and their side effectshave been well studied. Calcium blockers hypothetically exhibit relaxation effects not only on vascular smooth muscles but also on gastrointestinal smooth muscles. Although studies have focused on the effect of calcium channel blockers on vascular smooth muscle, only a few have investigated gastrointestinal motility.

Local anesthetics that have sodium channel blocking potentials are agents that reversibly block action potentials in excitable membranes. The exact mechanism of the effects of local anesthetics on various cellular physiological functions remains unknown. Thus, this study was carried out to investigate the effects of calcium channel blocker nifedipine andsodium channel blockerprilocaine on the amplitude of acetylcholine (Ach)-induced contractions on isolated rat ileum. As channel blockers are used commonly and systematically, specifically, this study aimed to investigate the possible effects of these blockers on gastrointestinal motility.

MATERIAL and METHODS

Healthy adult Wistar rats (n=l0) weighing an average 0f l50–250 g were used in theexperiments. This study was approved by the local ethics committee of Near East University (reference no. 2019/06). The animals were anesthetized lightly with

Corresponding Author: Emine Koç
E-mail: ekoc@medicine.ankara.edu.tr

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pentobarbital (35 mg/kg i.p.) and were slain by decapitation and exsanguination. Ileal segments were suspended in an isolated tissue bath containing Tyrode's solution (mM: NaCl 137, KCl 2.68, $MgCl_2$ 1.05, $CaCl_2$ 1.8, NaH_2PO_4 0.42, $NaHCO_3$ 11.9, and 5.5 glucose) and on bubbles with 95% O_2, 5% CO_2 mixture at 37°Cat pH 7.4. Tissue segments were brought into equilibrium for 60 minunder the optimal resting tension of 0.3 g. Contraction of ileal segments were then induced by adding ACh (6.7×10^{-5} M) which is accepted as maximal contractions in the control group. The amplitude of ACh-induced contraction was measured in millimeters from the recorded traces and was calibrated as 1g per 10 mm. When ileal segments were contracted with ACh (6.7×10^{-5} M),these parameters were accepted as ACh-induced control group. Local anesthetic prilocaine were used in two doses at 4.7×10^{-5}M and 9.4×10^{-5} M. After the addition of one of the prilocaine doses, Ach was added after 3 minutes a few minutes into the medium, and the results were recorded. Calcium channel blocker nifedipine was used in four different doses: 3.6×10^{-6}M, 7.2×10^{-6}M, 1.4×10^{-5}M, and 7.2×10^{-5}M. The ileal segments were washed several times and left for 60 minbefore each agent was added into the bath solution. Calcium channel blockerswere added first, followed by the addition of prilocaine and AChinto the medium, and the results were recorded.

RESULTS

The effects of calcium channel blocker nifedipine and sodium channel blocker prilocaine on ACh-induced contraction of isolated rat ileal segments were examined. The average peak amplitudes of ACh-induced contractions bytwo doses of prilocaine have decreased significantlycompared with those of the control groups (without prilocaine) (Figure 1).

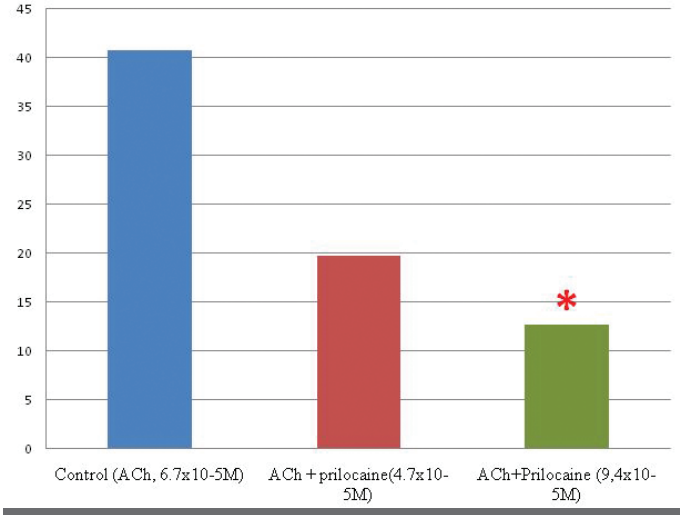

FIGURE 1. TheACh-inducedcontractionbydifferentdoses of Prilocaine

Main Points:

- Calcium and sodium Channel blockers have decreased the isolated ileal contractility.
- Local anaesthetic prilocaine significantly reduced ACh-induced contraction.
- Prilocaine has decreased calcium and sodium entry to the gastrointestinal smooth muscle.

In Figure 2, the average peak amplitude of ACh-induced contractions were significantly lower in all doses of nifedipine in the Tyrode group than in the control (without nifedipine) group.

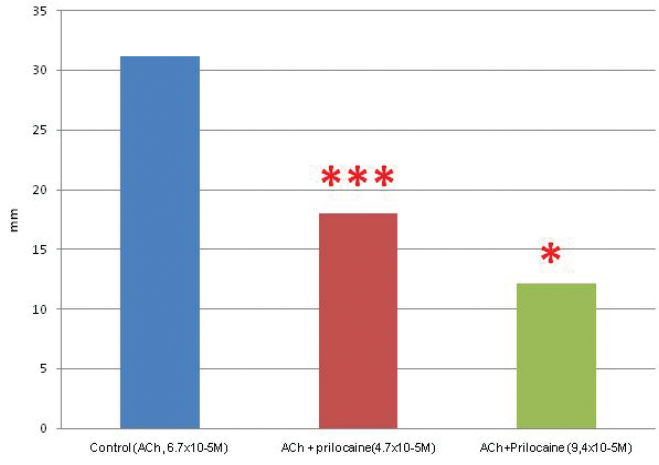

FIGURE 2. The ACh-induced contraction of different doses of prilocaine with 3.6×10^{-6}M nifedipine

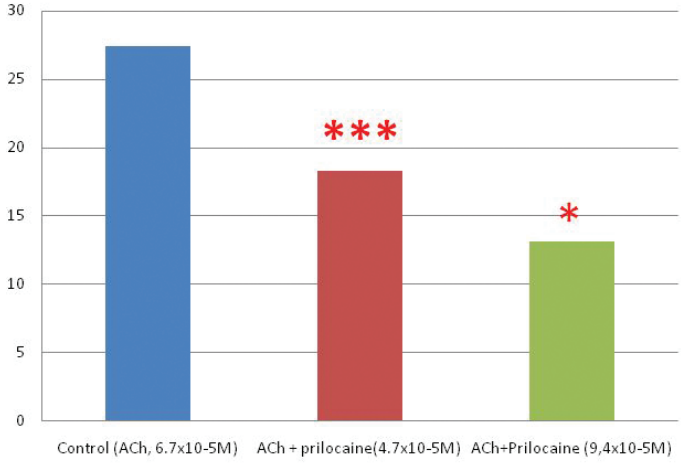

FIGURE 3. The ACh-induced contraction of different doses of prilocaine with 7.2×10^{-6}M nifedipine

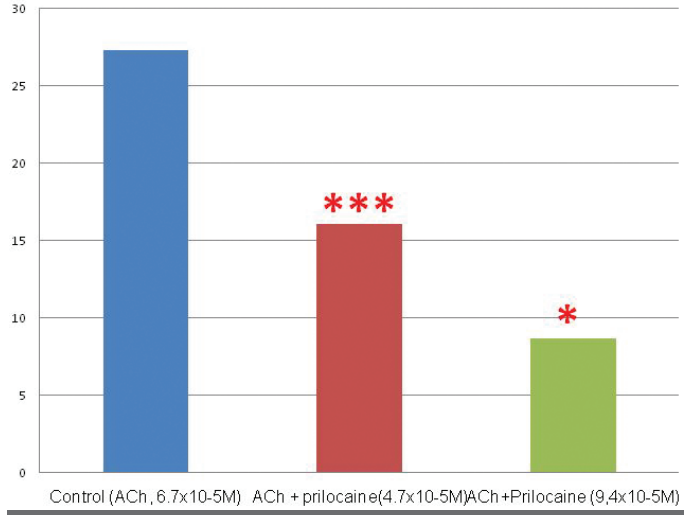

FIGURE 4. The ACh-induced contraction of different doses of prilocaine with 1.4×10^{-5}M nifedipine

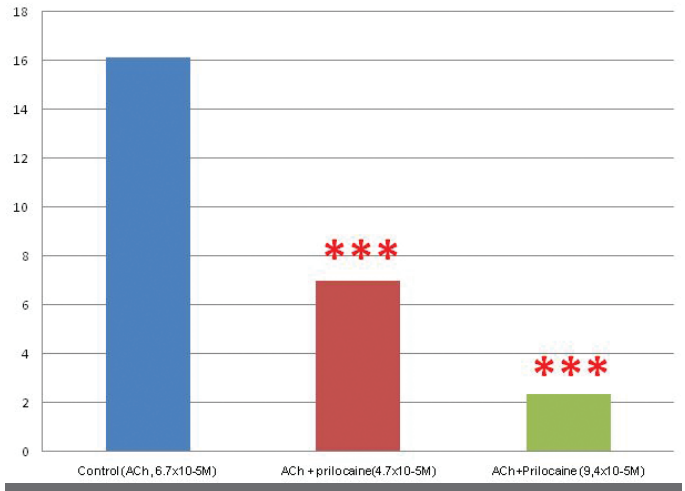

FIGURE 5. The ACh-induced contraction of different doses of prilocaine with 7.2xI0^{-5}M nifedipine

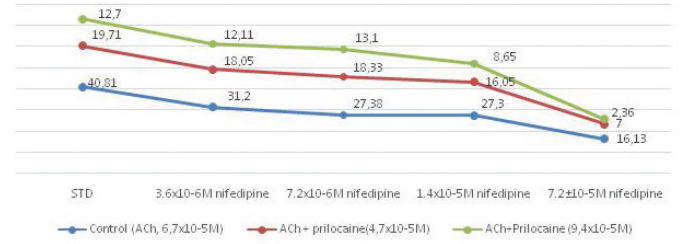

FIGURE 6. TheACh-inducedcontraction in differentdoses of prilocaineandnifedipine

The effect of nifedipine on the isolated ileal contractility was dose-dependent.

In Figures 2, 3, 4, 5 and 6, the effectof prilocaine on ACh-induced contractions in fourdoses of the nifedipine–Tyrode perfusion medium was significantly lowerthanthose of the control (without nifedipine) group.

Statistical Analysis

PASW I8 SPSS were used. Statistical analyses were performed with unpaired t-test. Significant difference from control were accepted as p<0.00I and p>0.05. Values were presented as mean±standard error of mean.

DISCUSSION

This study showed that the application of calcium and sodium channel blockers on perfusion medium has significantly decreased the contractility of isolated ileal segments.In this study, an increase in prilocaine and nifedipineconcentrations hascaused a decrease in the contractility of the ileum, and their effects were dose-dependent.

Several studies have reported the effects of local anesthetics on sodium channels (5, 6). The electrophysiological basis for the action of local anesthetics on nerves was established only within the past several decades. Although several studies have explored the effect of local anesthetics on other ion channels, such as calcium andpotassium channels (7), most of the investigations have focused on the sodium channel (8). However, the exact mechanism of the effect of local anestheticson excitation–contraction coupling and contractile proteins has not been thoroughly examined. Tsuda et al. explored the effects of local anesthetics on actomyosin and reported the actions of local anesthetics on purified proteins at a molecular level (9). They have suggested that the binding and ATPase of actomyosin were governed predominantly by weak and strong ionic binding, which was barely affected by local anesthetics.

In this study, calcium channel blockers significantly decreased the ACh-induced contraction of isolated ileal segments. The inhibition of contraction of rat ileal segments was dependent on nifedipine concentrations, and the effect of nifedipine wasdose-dependent.

Calcium antagonists or calcium channel blockers reduce the contractions of smooth muscles by inhibiting calcium ions (I0). In this study, nifedipine was used asa calcium channel blocker. Patai et al. (II) suggested that nifedipine has inhibited KCI-induced inward Ca^{+2}-induced contraction in a concentration-dependent fashion in the contraction of guinea pig trachea.

Dorkkan (I2) reported that active duodenal calcium transport was completely abolished by L-type nifedipine as well as inhibitors of the major basolateral calcium transporters.

Bladen et al. (I3) showed that a number of I,4-dihidropridine not only blocked L-type calcium channels but also blocked low-voltage-activated T-type calcium channels.

In conclusion, the calcium channel blocker nifedipine and sodium channel blocker prilocainehave significantlydecreased the contractility of isolated rat ileal segments. The effect of prilocaine and nifedipine on ACh-induced contraction was found to be dose-dependent. Prilocaine has decreased calcium and sodium entry to the gastrointestinal smooth musclessimilar to any other smooth muscles in the body. Nifedipine may have inhibited calcium influx through both potential and receptor-operated calcium ion channels. In this study, channel blockers decreased the gastrointestinal contractility. Nevertheless, cellular mechanisms underlying these effects still remain unclear; moreover therefore, further studies are required and results should be confirmed by human investigations.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Near East University (2019/6).

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

Conflict of Interest: Author has no conflicts of interest to declare.

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