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Research Paper

Effects of *Schisandra chinensis* extract on the relaxation of isolated human prostate tissue and smooth muscle cell

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ABSTRACT

Ethnopharmacological relevance: Schisandra chinensis has been commonly used as a traditional herbal medicine to treat various diseases including body weakness, dysentery, impotence, enuresis and frequent urination in many countries including Korea, China and Russia. Benign prostate hyperplasia is a common disease for the elderly men and it induces lower urinary tract symptoms which hinder general activity and quality of life. We evaluated the therapeutic potential of *Schisandra chinensis* extract (SCE) in benign prostate hyperplasia using human prostate tissue.

Materials and methods: Schisandra chinensis fruit was collected and extracted with ethanol. Human prostate tissues were obtained from 14 prostate cancer patients. Macroscopically normal tissue was excised from the transition zone and the periurethral regions. Isolated prostate tissue strips were mounted in an organ-bath system, and the relaxation effect of SCE was evaluated by cumulative addition to prostate strips pre-contracted with 10^{-5} M norepinephrine. The effect of tamsulosin was compared, and the additive effect was evaluated. Electrophysiological studies using cultured human prostate smooth muscle cells (HPrSMC) were conducted.

Results: Cumulative dosing of SCE induced concentration-dependent relaxation in contracted prostate tissue ($n=18$, $P<0.05$). Simultaneous dosing of SCE and tamsulosin showed an additive relaxation effect. The relaxation effect of SCE was abolished by inhibition of K+ channels by pre-treatment with tetraethylammonium. In HPrSMC, extracellular application of 100 μg/mL SCE significantly increased outward currents, and this effect was significantly attenuated by treatment with 100 nM Iberiotoxin.

Conclusions: SCE showed a dose dependent relaxation effect on human prostate tissue as well as an additive effect with tamsulosin. The relaxation effects of SCE on HPrSMC were, in part, due to the activation of K+ channels.

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1. Introduction

Benign prostatic hyperplasia (BPH) is a major cause of lower urinary tract symptoms that include urinary intermittency, frequency, straining, urgency, weak stream, incomplete emptying and nocturia in men aged 50 or older (Madersbacher et al., 2004; Choi et al., 2012; Huh et al., 2012). The symptoms of BPH are not normally life threatening, but often drastically affect quality of life. α1-adrenoceptor antagonists and 5α-reductase inhibitors are the primary medical treatment agents for BPH (Ventura et al., 2011). Despite the effectiveness of conventional treatments, efforts to develop other therapeutic agents that would relieve symptoms or prevent disease progression are ongoing (Ventura et al., 2011; Ko et al., 2013; Ma et al., 2013). Phosphodiesterase type 5 inhibitors (PDE5i) used for treating erectile dysfunction also have shown clinical benefits in BPH patients (McVary et al., 2007; Roehrborn et al., 2010). The relaxation effect of PDE5i seems to contribute this effect.

Schisandra chinensis (Fig. 1), a member of the Magnoliaceae family, has been commonly used as a herbal medicine to treat various

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Fig. 1. *Schisandra chinensis.*

diseases including erectile dysfunction and premature ejaculation, enuresis, frequent urination, protracted diarrhea, dysentery, impairment of body fluids, spontaneous sweating, night sweating in Korea, China and Russia (Huang et al., 2005; Panossian and Wikman, 2008). Some experimental studies found that *Schisandra chinensis* extracts have various pharmacological effects on cancer cells, blood vessels and the gastrointestinal system (Park et al., 2009; Gnabre et al., 2010; Smejkal et al., 2010; Song et al., 2011). Recent studies showed that *Schisandra chinensis* and its active components have relaxation effects on the pre-contracted penile corpus cavernosal tissues (Kim et al., 2011; Han et al., 2012).

Large-conductance Ca^{2+}-activated K+ (BK_{Ca}) channels play a crucial role in the control of contractile tone in numerous smooth muscle cells including prostate (Lang et al., 2004; Niwa et al., 2012). Activation of BK_{Ca} channels causes smooth muscle relaxation via hyperpolarization of the membrane potential (Niwa et al., 2012). Our previous study regarding the effects of SCE on corpus cavernosal smooth muscle showed that the relaxation effects of SCE were, in part, due to the activation of K+channels (Han et al., 2012).

Regarding the relaxation effects on smooth muscles, we considered that *Schisandra chinensis* could be a potential therapeutic candidate for the treatment of BPH. Here, we investigated the relaxation effects of *Schisandra chinensis* extract (SCE) on human prostate tissue.

2. Materials and methods

This study was approved by the Institutional Review Board of Samsung Medical Center (IRB No. SMC 2012-03-061).

2.1. Plant materials

The fruit of *Schisandra chinensis* was collected in September 2009 from Jangsu, Korea, and identified. Shade-dried *Schisandra chinensis* fruits (50 g) were pulverized and extracted three times with 200 mL of ethanol (95% ethanol/water, v/v) for 3 h using an ultrasonic bath (model 8510 DHT; Branson, Danbury, CT, USA). After filtration, the extracts were evaporated in vacuo and lyophilized to yield the total extract. The ethanol extract yield of dried fruit was 15%. HPLC analysis was performed to determine the components of the extract in the previous study. The content of lignans in the extract were schisandrol A (9.11 mg/g), schisandrol B (3.04 mg/g), schisandrin A (1.74 mg/g), schisandrin B (1.04 mg/g), gomisin N (3.88 mg/g) and schisandrin C (0.39 mg/g) (Lee and Kim, 2010; Kim et al., 2011). The voucher specimen (accession number SC-1) was deposited at the Natural Products Research Center of the KIST Gangneung Institute (Gangneung, Korea) (Han et al., 2012).

2.2. Tissue source

Human prostate tissues were obtained from 14 male patients who had undergone radical prostatectomy for localized prostate cancer. Written informed consent was obtained from every patient. The mean age of the patients was 63.5 ± 1.9 years old (range: 51–73). Mean number of positive cores were 2.6 ± 0.5. Nine patients had Gleason score 6 and five had Gleason score 7. All patients had positive cores only in unilateral side. On the opposite side, macroscopically normal tissue was excised from the transition zone and periurethral region. The mean volume of the harvested prostate was 36.5 ± 3.1 mL, and the mean prostate specific antigen level of patients was 7.3 ± 1.5 ng/mL. Tissues were immediately placed in chilled Krebs solution and transported to the laboratory for tissue strip preparation.

2.3. Prostate tissue strip preparation

Three to four rectangular-shaped prostate tissue strips of approximately equal size ($2 \times 2 \times 10\ mm^3$) were obtained from each patient and prepared separately for organ bath studies. Each prostate strip was tied with silk in an organ chamber, with one end fixed to a tissue holder and the other end secured to a force transducer. The force transducer was connected to an appropriately calibrated four-channel polygraph (PowerLab; ADInstruments, Sydney, Australia) in which the transducer output was recorded. Prostate strips were maintained in Krebs solution at 37 °C in the organ bath for the duration of the study using a thermoregulated water circuit and with continuous bubbling with a mixture of 95% O_2 and 5% CO_2. Each prostate strip was stretched to an optimal isometric tension of 1.0 g and equilibrated for 60 min. During the equilibration period, tissues were washed with fresh Krebs solution every 20 min and the tension was adjusted, if necessary.

2.4. Organ bath studies in vitro

The prostate strip was equilibrated for 60 min with several adjustments of length until a baseline force stabilized at 1 g. After stabilization, Norepinephrine (NE, 10^{-5} M) was added. After stable contraction plateaus were reached, the relaxation effect of SCE was studied by cumulative addition at concentrations ranging from 0.1 to 2.0 mg/mL. Concentrations of SCE were selected based on previous studies (Kim et al., 2011; Han et al., 2012). For comparison with the relaxation effects of α-adrenergic blockers, tamsulosin was added in a cumulative manner at concentrations ranging from 10^{-10} M to 10^{-7} M. The effects of combining tamsulosin and SCE were investigated by the simultaneous addition of SCE 1.0 mg/mL and tamsulosin 10^{-8} M.

To investigate the relaxation pathway of SCE mediated relaxation, we examined the effect of SCE on NE-induced tone after pre-incubation of strips in non-specific potassium channel inhibitor tetraethylammonium (TEA, 1 mM) and nitric oxide synthase (NOS) blocker N-nitro-L-arginine methyl ester (L-NAME, 10^{-4} M) for 30 min. We compared the magnitude of relaxation before and after incubation in TEA and L-NAME.

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