AB085. Improvement of erectile function through combination of anti-fibrotic effect by LIM-kinase 2 inhibitor with suppression of apoptosis and potentiation of endothelial function by type 5 phosphodiesterase inhibitor in a rat model of cavernous nerve injury

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Background: The cavernosal apoptosis and fibrosis are considered to be important pathophysiologies of post-radical prostatectomy (RP) erectile dysfunction (ED). Recently, we demonstrated that inhibition of LIMK2 alleviate ED through suppression of cavernosal fibrosis in a rat model of cavernous nerve (CN) injury. Also, some previous studies showed that administration of PDE5 inhibitors improved both cavernosal apoptosis and endothelial dysfunction in a rat model of CN injury, leading to improvement of ED. Thus, the aim of this study was to determine whether combined administration of LIMK2 inhibitors and PDE5 inhibitors could restore erectile function by combination of anti-fibrotic effect with suppression of apoptosis or potentiation of endothelial function in a rat model of CN injury.

Methods: Seventy 12-week-old Sprague-Dawley (SD) rats were distributed equally into five groups: sham surgery (S), CN crush injury (I), CN crush injury treated with daily intraperitoneal administration of 10.0 mg/kg LIMK2 inhibitors (I+L), daily oral administration of 20.0 mg/kg udenafil (I+U), and combined administration of 10.0 mg/kg LIMK2 inhibitors and 20.0 mg/kg udenafil (I+L+U). The I+L, I+U and I+L+U groups was treated for 2 weeks from the following day after surgery. At 2 weeks after surgery, erectile response was assessed using electrostimulation. Penile tissue was processed for Masson's-trichrome staining, immunohistochemical staining to alpha-SMA (smooth muscle actin), TUNEL, Western blot, and double immunofluorescence with antibody to vimentin (a fibroblast marker) and phosphorylated LIMK2.

Results: The I group showed significantly lower intracavernous pressure (ICP)/mean arterial pressure (MAP), lower area under the curve (AUC)/MAP, decreased immunohistochemical staining of alpha-SMA (SM content), higher apoptotic index, lower smooth muscle/collagen ratio, increased amount of fibroblasts positive for phosphorylated LIMK2, decreased Akt or endothelial NO synthase (eNOS) phosphorylation, decreased protein expression of total neuronal nitric oxide synthase (nNOS), increased NOS phosphorylation, increased LIMK2 phosphorylation, compared to the S group. In all of the I+L, I+U and I+L+U groups, the ICP/MAP and AUC/MAP significantly improved, but did not recover to values observed in the S group. The SM content in the I+U and I+L+U groups significantly improved compared to the I group, but did not recover to the control value observed in the S group. The I+L group did not show a significant improvement in the SM content compared to the I group. For the SM/collagen ratio, all of the three treatment groups showed its significant improvement compared to the I group, but it did not recover to the value observed in the S group. According to the TUNEL analysis, apoptotic index in the I+U and I+L+U groups significantly improved compared to the I group, but the I+L group did not show its improvement. The amount of fibroblasts positive for phosphorylated LIMK2 in the I+L and I+L+U groups was normalized, but that in the I+U group was not. According to the densitometry, the Akt and eNOS phosphorylation in the I+U and I+L+U groups significantly improved compared to the I group, but the I+L group did not show its improvement. The LIMK2 phosphorylation in the I+L and I+L+U groups significantly improved compared to the I group, but that in the I+U group did not. The protein expression of total nNOS and dysregulated NOS phosphorylation did not improve in any of the three treatment groups (I+L, I+U and I+L+U).

Conclusions: Our data indicate that combined treatment with a LIMK2 inhibitor and udenafil can improve

erectile function by suppression of cavernosal apoptosis or potentiating endothelial function via alleviating AKT/eNOS pathway and by suppression of cavernosal fibrosis via normalizing LIMK2 phosphorylation, although it does not recover to normal level. Thus, an early combined treatment with LIMK inhibition and PDE5 inhibitors may be helpful to effectively suppress structural alterations of cavernosum after CN injury, leading to alleviation of ED.

Keywords: Erectile dysfunction (ED); cavernous nerve; fibrosis; apoptosis; endothelium

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