**Author’s response to reviews**

**Title:** Increased expression of neuregulin 1 in the urothelium of rat bladder with partial bladder outlet obstruction

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**Author’s response to reviews:**

Dear reviewers,

Thank you for reviewing our manuscripts.

Our study group have investigated roles and clinical application of neuregulin 1 by bladder outlet obstruction. So we have two parts with neuregulin 1 study, one of them have investigated role of neuregulin 1 and the other have researched neuregulin 1 as clinical application by Dr. Yuk who was corresponding author, BMC Urol. 2013 Oct 23;13:54 (Jang H, Han DS, Yuk SM. Changes of neuregulin-1 (NRG-1) expression in a rat model of overactive bladder induced by partial urethral obstruction: is NRG-1 a new biomarker of overactive bladder?). Dr. Yuk had been received a degree of Ph.D. at Chungnam national university. The number of IRB (institutional review board) of Dr. Yuk’s report (BMC Urol. 2013 Oct 23;13:54) was CNU-00289 and IRB number of our study was CNU-00261. Dr. Yuk’s paper and our manuscript were made in the same urology laboratory of CNU (Chungnam national university).

Dr. Yuk is currently studying about the clinical biomarker of NRG1 by OAB. We are investigating mechanisms of NRG-1 in BOO (including regeneration, cell proliferation and ischemic injury).

First report was reference 31 (Kim HG, Lee CK, Cho SM, Whang K, Cha BH, Shin JH, Song KH, Jeong SW ; Neuregulin 1 up-regulates the expression of nicotinic acetylcholine receptors through the ErbB2/ErbB3-PI3K- MAPK signaling cascade in adult autonomic ganglion neurons. J Neurochem. 2013;124(4):502-13) that investigated effects of neuregulin 1 (NRG1) on the expression of nicotinic acetylcholine receptor in pelvic ganglion from adult rat.
Second paper was reported by Dr. Yuk who was corresponding author, BMC Urol. 2013 Oct 23;13:54 (Jang H, Han DS, Yuk SM. Changes of neuregulin-1 (NRG-1) expression in a rat model of overactive bladder induced by partial urethral obstruction: is NRG-1 a new biomarker of overactive bladder?).

Third paper was reported by Dr. Song (Int Neurourol J. 2015;19(3):158-63 Song KH, Youn CS, Lee CL, Yang SW, Chang YS, Jeong SW, et al. Increased Expression of Neuregulin 1 and erbB2 Tyrosine Kinase in the Bladder of Rats With Cyclophosphamide-Induced Interstitial Cystitis).

Sincerely yours

2017. 10. 07

To Giorgio Ivan Russo (Reviewer 1)

Thank you for taking the time for the review.

We reported NRG1 on adult rat autonomic ganglion neurons (Kim HG et al., J Neurochem 2013 reference 31) at first time.

Dr. Yuk reported a correlation between NRG1 and others expression and detrusor thickness measure in BMC Urol. 2013 Oct 23;13:54 (Jang H, Han DS, Yuk SM. Changes of neuregulin-1 (NRG-1) expression in a rat model of overactive bladder induced by partial urethral obstruction: is NRG-1 a new biomarker of overactive bladder?). We reported a correlation between NRG 1 and others expression and inflammatory status in Int Neurourol J. 2015;19(3):158-63 (Song KH, Youn CS, Lee CL, Yang SW, Chang YS, Jeong SW, et al. Increased Expression of Neuregulin 1 and erbB2 Tyrosine Kinase in the Bladder of Rats with Cyclophosphamide-Induced Interstitial Cystitis).

In our future study, neuregulin knockout mouse will be needed, however it is difficult to make a transgenic mouse because neuregulin acts on neural development. Now we are preparing primary urothelial cell culture in BOO animal model using microRNA or not and working on additional mechanisms of NRG1 as mentioned in the conclusion part.

Manuscripts has been carried out at the correction site recommended by BMC urology, and the proof is attached.

Sincerely yours

2017. 10. 07
To R. Lombardo (Reviewer 2)

Thank you for taking the time for the review.

PBOO were created by using previously reported methods. (Methods section, line 12, page 4).

In Jang H, Han DS, Yuk SM. BMC Urol. 2013, there is a correlation between NRG1 and a clinical marker in OAB. We wanted to explain a mechanism of NRG1, and evaluation in BOO, not OAB in our paper.

As mentioned above, we have studied with two parts of neuregulin 1 in our urology laboratory at Chungnam national university. Dr. Yuk reported a correlation between NRG1 and others expression and detrusor thickness measure, cistometrogram (Jang H, Han DS, Yuk SM. BMC Urol. 2013 Oct 23;13:54).

We have investigated the mechanisms of NRG 1 in BOO (including regeneration, cell proliferation and ischemic injury) rather than a clinical application to OAB. Dr. Yuk is currently studying about the clinical application of NRG1.

Sincerely yours

2017. 10. 07