

ELEVATION OF SERUM HEPATIC GROWTH FACTOR AND NERVE GROWTH FACTOR IN PATIENTS WITH OVERACTIVE BLADDER IMPLIES NERVE FIBERS INCREASING IN URINARY BLADDER

Hypothesis / aims of study

Recent investigations have linked overactive bladder syndrome (OAB) with neurogenic inflammation. Neurotrophic factors have been implicated in the pathophysiological mechanisms underlying the sensitization of bladder afferent nerves. Nerve growth factor (NGF), initially described as a prototypical trophic factor in the development of sensory and sympathetic innervation, has emerged as a complex regulator of neural plasticity along the micturition pathways. Hepatocyte growth factor (HGF), a novel neurotrophic factor also can promote neuronal survival and growth. In our previous studies, serum and urinary NGF have been demonstrated to increase in patients with OAB. To evaluate the possible role of neurotrophic factors HGF, NGF in the pathophysiology of OAB, serum HGF, NGF expressions and suburothelial neuron marker PGP9.5 expression were investigated in OAB patients.

Study design, materials and methods

Serum samples were collected from 30 OAB patients and 28 control subjects. Bladder mucosa biopsies were performed in 10 patients with OAB and 5 control patients.

Concentrations of the serum NGF were quantified using a bead-based human serum adipokine panel B kit (Millipore, Billerica, MA, USA). Western blot were used to measure neuron marker protein PGP9.5 levels in bladder mucosa from OAB patients and controls. Differences in serum HGF, NGF and mucosal PGP9.5 levels between OAB and controls were compared by the non-parametric Mann-Whitney U test. Furthermore, Pearson's correlation coefficients were calculated between the serum HGF and NGF levels.

Results

The results of serum adipokine assay shown both serum HGF and serum NGF levels were significantly higher in patients with OAB than in controls, P values were 0.00 and 0.04 respectively (Table1, Fig.1). There was a significant correlation between serum HGF and serum NGF levels in the patients with OAB. (Fig. 2) Although the age of OAB patients were older than control subjects, however, neither serum HGF nor NGF were correlation with age in all of the subjects. Comparing the mucosal neuron marker PGP9.5 levels between OAB and control subjects, the results indicated OAB patients have higher mucosal PGP9.5 expressions than control (Table1, Fig. 3).

Interpretation of results

HGF is a strong neurotrophic factor that promotes cell survival and proliferation. Some studies have reported that HGF cooperates with NGF to enhance the growth of neurons *in vitro*. In our study, both serum HGF and NGF levels were high and were significantly correlated with each other in patients with OAB. Study of Brady in 2004 have found PGP9.5- and TRPV-1 expressing nerve fibers were increased in bladder mucosa of neurogenic detrusor overactivity (NDO) patients, and increased numbers of nerve fibers in patients with NDO are mainly of sensory origin. In our study, the PGP9.5 suburothelial neuron marker expression in all of the patients with OAB was significantly higher than in the controls, suggesting nerve fibers were increased in the bladder mucosa of OAB patients. Several studies demonstrated that sensory dysfunction could be involved in pathogenesis in OAB as a result of endocrine disorders. Moreover, several reports and our recent studies have also demonstrated that OAB patients have higher serum and urinary NGF expressions than controls, indicating that HGF has neurotrophic properties. In our current study, significantly higher serum HGF and serum NGF levels and increased mucosal nerve protein PGP9.5 expression were found in OAB patients, which suggest systemic neurotrophic factors elevation induced increase of nerve fibers in the suburothelium of the bladder might play a role in urgency and frequency sensory disorder in OAB patients.

Concluding message

Elevation of serum HGF and NGF in patients with OAB is associated with an increase in PGP9.5 expression, which implies that nerve fibers are increased in the urinary bladder tissue of OAB patients. Our findings suggest that OAB is a disease of systemic neuroendocrinal disorder.

Table 1. Comparison of serum HGF, serum NGF and mucosal PGP9.5 between OAB and controls

	Control (n=26)	OAB (n=30)	P Value
Gender	F:16 M:10	F: 17 M: 13	
Age	32.36±1.556 (22~55)	61.03±1.59 (37~93)	P=0.000**

HGF (pg/ml)	104.45 ± 11.39 (4.24~267.39)	193.59 ± 17.72 (50.11~430.57)	P=0.000**
NGF (pg/ml)	2.78 ± 0.22 (1.00~5.85)	3.88 ± 0.60 (1.70~17.54)	P=0.04*
PGP9.5	0.37 ± 0.059 (n=5)	0.54 ± 0.06 (n=10)	P=0.03*

Mean ± standard error (range)

Fig. 1. Scatter plots of serum HGF and serum NGF in control and OAB patients.

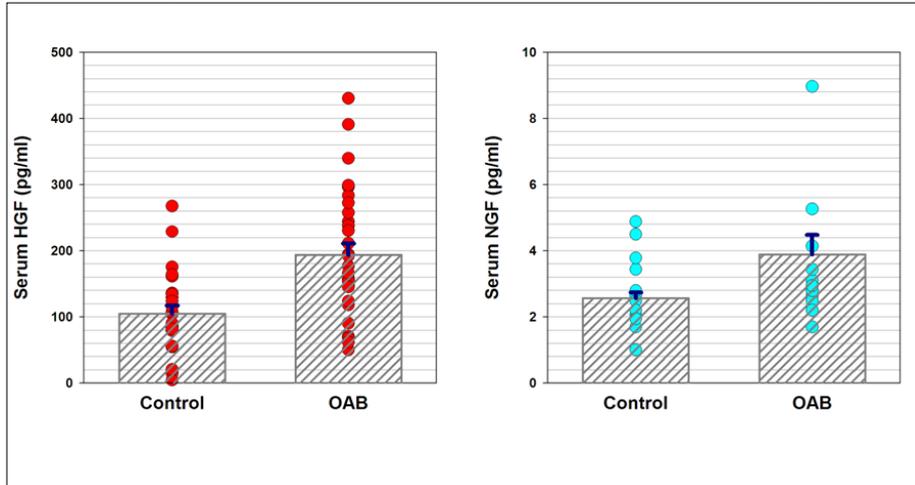


Fig. 2. Correlation between serum HGF and serum NGF in OAB patients.

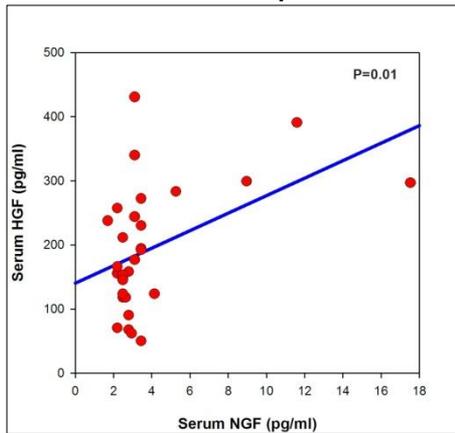
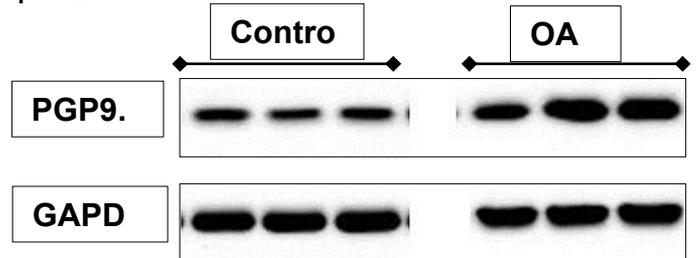


Fig. 3. Mucosal PGP9.5 expression in controls and OAB patients



Disclosures

Funding: None **Clinical Trial:** No **Subjects:** HUMAN **Ethics Committee:** Buddhist Tzu Chi General Hospital Research Ethics Committee **Helsinki:** Yes **Informed Consent:** Yes