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URINARY LEVELS OF NEUROTROPHINS DO NOT DECREASE IN OVERACTIVE BLADDER PATIENTS AFTER TREATMENT WITH MIRABEGRON

Hypothesis / aims of study

Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) play a key role in the pathophysiology of overactive bladder (OAB), most probably by changing the threshold for response of bladder sensory neurons.

Several groups reported high urinary levels of NGF and BDNF in OAB patients, which subsided after successful antimuscarinic treatment (1,2). Mirabegron is an agonist of beta3-adrenoceptor with a distinct mechanism of action. It causes detrusor relaxation during the storage phase of the micturition cycle by activation of adenylyl cyclase, with the subsequent formation of cyclic adenosine monophosphate. The effect of mirabegron on urinary neurotrophins' levels is currently unknown.

In this study we investigated, for the first time, urinary levels of NGF and BDNF in OAB patients treated with mirabegron.

Study design, materials and methods

The local ethics committee approved the study. Informed consent was obtained from all participants.

Twenty-two female OAB patients were enrolled. Those medicated with antimuscarinics, but not satisfied with the treatment completed a washout period of 4 weeks. An age-matched group of 15 women without LUTS, including hospital and faculty employees and their relatives, were used as controls.

At baseline urine samples were collected from all participants. Concurrently, King's Health Questionnaire (KHQ) and Patient Perception of Bladder Condition (PPBC) questionnaire were completed.

OAB patients were treated with mirabegron 50 mg once daily and reevaluated at 4 and 12 weeks. At these time points, urine sampling and completion of the same questionnaires were carried out.

During follow-up, two patients were excluded due to urinary tract infection (UTI), one at 4 weeks and the other at 12 weeks.

Urine samples were processed for enzyme-linked immunosorbent assay (ELISA) analysis of NGF and BDNF and the values were normalized against creatinine (Cr) concentration. Neurotrophin concentration values were logarithmized to improve distribution characteristics.

Data was expressed as the mean ± standard deviation. The Mann-Whitney U test and Wilcoxon signed-rank test were used for statistical analysis between groups when considering nonparametric data, while paired samples t-test was used for analysis of parametric data.

Results

At baseline, urinary NGF/Cr and BDNF/Cr were significantly higher in OAB patients compared to healthy controls (NGF/Cr: 3.3±0.6 vs. 2.4±0.5, p<0.01; BDNF/Cr: 2.9±0.5 vs. 2.6±0.4, p=0.028).

After treatment with mirabegron there was a decrease in urinary NGF/Cr and BDNF/Cr, which however did not reach statistical significance. Eighteen out of 22 patients reported marked symptomatic improvement, reflected in the variations of KHQ and PPBC scores.

Data are summarized in the table.

			Baseline (n=22)	4 weeks (n=21)	12 weeks (n=20)
NGF/Cr		pg/mg	3.3 ± 0.6	3.2 ± 0.5	3.0 ± 0.8
BDNF/Cr		pg/mg	2.9 ± 0.5	2.7 ± 0.6	2.7 ± 0.5
KHQ					
Part 1	General Health Perception	0 – 100%	58 ± 18	56 ± 13	55 ± 19
	Incontinence Impact		75 ± 21	48 ± 27 *	49 ± 31 *
Part 2	Role Limitations	0 – 100%	71 ± 17	38 ± 32 *	32 ± 30 *
	Physical Limitations		66 ± 24	40 ± 30 *	27 ± 27 *
	Social Limitations		24 ± 23	7 ± 15 *	7 ± 21 *
	Personal Relationships		13 ± 26	8 ± 20	12 ± 24
	Emotions		43 ± 21	15 ± 20 *	9 ± 18 *
	Sleep/Energy		49 ± 27	17 ± 21*	18 ± 18 *
	Severity Measures		42 ± 23	22 ± 21 *	24 ± 21 *
Part 3	Frequency	Severity Scale: 0 – Omitted 1 – A little 2 – Moderately 3 – A lot	2.3 ± 0.6	1.9 ± 0.8 *	1.5 ± 0.7 *
	Nocturia		1.4 ± 0.9	0.3 ± 0.6 *	0.5 ± 0.7 *
	Urgency		2.5 ± 0.5	1.5 ± 0.6 *	1.5 ± 0.7 *
	Urgency Incontinence		2.1 ± 0.8	0.8 ± 1.0 *	1.0 ± 1.2 *
PPBC		Severity Scale: 1 – 6	3.6 ± 0.9	2.4 ± 1.0 *	2.4 ± 1.4 *

Data is expressed as the mean ± standard deviation
Higher KHQ subscale score indicates lower health-related quality of life
Higher PPBC score indicates more severe bladder problems
** a p<0.05 is statistically significant when compared to baseline*

Interpretation of results

Urinary neurotrophins do not change in overactive bladder patients after treatment with mirabegron. This finding is in contrast with previously published observations carried out with antimuscarinics and onabotulinumtoxinA.The difference between mirabegron and the two other drugs can be explained by the fact that mirabegron primarily acts directly on bladder smooth muscle, with a reduced effect in the urothelium, which is believed to release most of neutrophins detected in urine (1). Actually, up to now, little is known about the expression and functional role of beta3-adrenoceptors in human urothelium (2). Moreover, it was demonstrated that, in contrast to antimuscarinics, mirabegron predominantly affects the A-delta population of bladder primary afferents, which are known to be less sensitive to neurotrophins (3).

Concluding message

In contrast to antimuscarinic drugs, mirabegron does not decrease urinary neurotrophins' levels in overactive bladder patients, despite causing symptomatic improvement. These data might reflect the different capacity of both classes of drugs to influence the release neurotrophins by urothelial cells.

References

1. Cruz CD: Neurotrophins in bladder function: what do we know and where do we go from here? Neurourol Urodyn. 2014 Jan; 33(1):39-45
2. Michel MC and Vrydag W: Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. Br J Pharmacol. 2006 Feb: 147 Suppl 2:S88-119
3. Aizawa N, Homma Y and Igawa Y: Effects of mirabegron, a novel beta3-adrenoceptor agonist, on primary bladder afferent activity and bladder microcontractions in rats compared with effects of oxybutynin. Eur Urol. 2012 Dec; 62(6):1165-73

Disclosures

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