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URODYNAMIC EFFECTS OF LEUPROLIDE ACETATE IN OVARIECTOMIZED RATS WITH URINARY BLADDER OVERACTIVITY

Hypothesis / aims of study

This original study was aimed at testing the hypothesis that drugs with neuroregenerative properties may play a role in the treatment of OAB after hypogonadism. The pathophysiology of the overactive bladder syndrome (OAB) is multifactorial and includes neurogenic, myogenic, urothelial and idiopathic components. In fact, menopause is a risk factor of OAB. While the relationship between OAB and hypogonadism is not entirely clear in humans, experimental models of menopause whit castrated animals suggest that hypogonadism plays an important role in the genesis of OAB because low levels in steroidal hormones produce changes in the density of muscle fibers and innervation of the bladder. Gonadotropin-releasing hormone (GnRH) and his agonist Leuprolide Acetate (LA) have shown neuroregenerative properties in cellular cultures and animal models of multiple sclerosis and spinal cord injury. The objectives of this study were to investigate the effect of LA treatment on bladder overactivity using a castrated rat model, and the plausible role of the gonadotropin-releasing hormone receptor (GnRH-R) in this pathology.

Study design, materials and methods

A total of 26 female Wistar rats (250-300 g) were used. Animals were randomly divided into three groups: 1) Sham group (SHAM, n=9); 2) Ovariectomized group (OVX, n=8); and 3) Ovariectomized treated with leuprolide acetate (OVX+LA, n=9). In the OVX and OVX+LA groups, both ovaries were surgically removed. In the sham group the ovaries were exposed but not dissected. In the OVX+LA group, twenty days after ovariectomy, animals received LA (10 µg/kg i.m.) for 3 consecutive days as priming dose, and then every 48 hours until 10 doses were completed. Rats in the SHAM and OVX group received the same treatment scheme with physiological saline. Cystometry was performed under urethane anesthesia throughout a suprapubic tube (PE-50) and saline infused to measure intercontraction interval (ICI), pressure threshold (PTh), baseline bladder pressure (BP), urinary volume (Uv), average urinary flow rate (AFr), compliance (C) and frequency of non-voiding contractions (NVC). After cystometric evaluations the bladders were collected, formaldehyde fixed, and used for immunostaining with a specific anti-GnRH-R antibody. Immunoreactivity in the urothelium was quantified by image analysis.

Results

When compared with SHAM, the OVX animals shown a significant decreases in ICI ($p=0.0045$), UV ($p=0.0015$) and C ($p=0.012$). However, BP increased significantly ($p<0.0001$) while no significant changes were found for PTh, AFr nor NVCs. When comparing against the OVX group, the application of LA improved the voiding pattern in OVX+LA rats by decreasing BP ($p<0.0001$), but increasing ICI ($p=0.0002$), UV ($p=0.0007$), PTh ($p=0.0034$) and NVCs ($p=0.01$) without affecting C nor AFr. The presence of GnRH-R was confirmed in the urothelium of SHAM rats. In agreement with the cystometric evaluation, bladder from OVX rats had reduced expression of the receptor. Surprisingly, in the OVX+LA group the expression level of the GnRH-R was similar to that determined in the SHAM group.

Interpretation of results

Using an OVX rat model we found that hormonal changes can cause bladder overactivity by decreasing ICI, Uv and C, while simultaneously increasing BP. Degenerative changes in smooth muscle density and bladder innervation may explain these results. For instance, when compared with the OVX group the increased ICI and C, and decreased BP in the OVX+LA rats could have been generated by a higher number of nerve fibers, as it has been shown for the influence of GnRH and its agonists on neural regeneration in the spinal cord. Our results suggest that nerve degeneration caused by hypoestrogenism may be reversed by the neurotrophic effect of LA administration, thus explaining the improvements on voiding patterns. Although we found a significant increase in the number of NVCs in the OVX+LA rats, this effect correlates with previous reports showing that activation of GnRH-R increases the number of NVCs. The presence of these contractions can be explained by the fact that treatment with LA increased the extent of GnRH-R in the urothelium, and the non-voiding activation generated by the agonist on its own. We predict that this pharmacological effect could disappear when ceasing the treatment, but the trophic effects on neurons could be semi-permanent.

Concluding message

The GnRH-R analogue LA generates significant improvements on cystometric parameters in rats with overactive bladder conditions induced by castration. Our results suggest the possibility of using agonists or antagonists of GnRH receptors as an alternative treatment for post-menopausal bladder dysfunctions.

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Disclosures
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