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CHRONIC ADMINISTRATION OF CORTICOSTERONE MAY INDUCE DETRUSOR OVERACTIVITY SYMPTOMS

Hypothesis / aims of study

Epidemiological studies demonstrated that patients suffering from overactive bladder often presents different mental problems, amongst which depression is the most frequently observed. Despite a close and clinically confirmed association between depression and OAB, it is still not resolved if this affective disorder is an OAB-inducing factor or whether OAB is a specific manifestation of psychosomatic disorders. Co-existence of some neurochemical dysfunctions that underlie etiopathogenesis of both diseases cannot be ruled out. It was proved that dysregulation of serotonergic or adrenergic neurotransmission as well as abnormalities in function of corticotropin releasing factor (CRF) may play a significant role in pathophysiology of both depression and OAB.

The aim of our study was to check if the chronic administration of corticosterone (CORT), that induced depressive-like behaviour in the pre-clinical studies, is also able to evoke detrusor overactivity (DO) symptoms. At the same time, we wanted to investigate whether the administration of antidepressants (imipramine, 30 mk/kg and fluoxetine, 15 mg/kg) and antymuscarinic (oxybutynin chloride, 0.5 mg/kg) or CRF_1 antagonists (SN 003, 1 mg/kg) has an impact on the cystometric parameters, locomotor activity of animals as well as their behaviour in the forced swim test (FST).

Study design, materials and methods

Animals were given CORT for 14 days. On the 14th day, the surgical procedures were performed. After 3 days, the following studies were carried out: cystometry, Porsolt test and locomotor activity measurement. Immediately after the behavioral test, animals' blood was collected by cardiac puncture. CRF level was assessed using a commercially available enzyme immunoassay.

Results

Three main findings should be particularly underlined: (1) chronic administration of CORT may induce DO symptoms in rats without producing any histopathologic changes in the urinary bladder, (2) CORT-induced DO responds to OXY, (3) inhibition of CRF_1 receptors may reverse symptoms of both depression and DO in animals exposed to CORT treatment. All detailed results are presented in Table 1.

Table 1. The influence of the repeated administration of corticosterone (CORT) on the cystometric parametrs in conscious rats.

Parameter	BP cm H_2O	VV ml	PVR ml	ICI sec	BC ml/ cm H_2O	DOI cm H_2O/ml	ANVC cm H_2O	FNVC times/ filling phase	VTNVC %
CON	2.947 ±0.160	0.842 ±0.039	0.076 ±0.004	902.3 ±18.71	0.189 ±0.007	114.7 ±4.732	2.407 ±0.081	0.861 ±0.122	47.93 ±1.909
CORT	5.033 ±0.359***	0.610 ±0.052**	0.065 ±0.004	716.0 ±38.60**	0.136 ±0.009***	312.9 ±29.59***	5.940 ±0.334***	7.107 ±0.837***	35.07 ±1.926***
CORT + IMI	4.480 ±0.240	0.554 ±0.033	0.066 ±0.005	652.3 ±37.23	0.130 ±0.008	319.5 ±25.39	5.207 ±0.389	5.793 ±0.564	36.87 ±1.393
CORT + FLX	4.560 ±0.244	0.545 ±0.036	0.053 ±0.003	695.1 ±41.04	0.114 ±0.008	274.6 ±25.25	5.647 ±0.500	5.740 ±0.513	40.67 ±2.643
CORT + SN 003	3.353 ±0.222^^^	0.822 ±0.045^^	0.071 ±0.006	869.9 ±34.61^	0.177 ±0.008^	188.3 ±15.95^^^	4.253 ±0.349^^	3.667 ±0.341^^^	44.13 ±2.671^
CORT + OXY	3.240 ±0.197^^^	0.814 ±0.044^	0.087 ±0.004^	911.9 ±27.27^^	0.176 ±0.008^	141.6 ±5.198^^^	3.653 ±0.223^^^	3.253 ±0.219^^^	46.20 ±1.993^^

All results are presented as the means ± SEM (n=15 rats per group). The obtained data were assessed by the one-way analysis of variance (ANOVA) followed by Tukey's *post hoc* test. **p < 0.01, ***p < 0.001 versus vehicle (CON), ^p < 0.05, ^^p < 0.01, ^^^p < 0.001 versus CORT.

Abbreviations: basal pressure (BP, cm H2O), voided volume (VV, ml), post-void residual (PVR, ml), intercontraction interval (ICI, sec), bladder compliance (BC, ml/cm H_2O), detrusor overactivity index (DOI, cm H_2O/ml), nonvoiding contractions (NVC): frequency (FNVC, times/filling phase) and amplitude (ANVC, cm H2O), volume threshold to elicit NVC (VTNVC, %).

Interpretation of results

Chronic administration of CORT may induce both depressive and DO symptoms in rats, which are reversed by inhibition of CRF_1 receptors. In the histologic specimens of the bladders from the tested animals subjected to CORT treatment, neither signs of bladder inflammation nor destructive changes in umbrella cells, urothelium, or detrusor muscle were observed.

Concluding message

It seems that the CRF_1 receptor could be an interesting target for overactive bladder pharmacotherapy, particularly in patients with co-existing depression.

Disclosures

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