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SN003, A CORTICOTROPIN-RELEASING FACTOR RECEPTOR TYPE-1 (CRF1) ANTAGONIST, ATTENUATES DEPRESSIVE-LIKE BEHAVIOR AND DETRUSOR OVERACTIVITY SYMPTOMS INDUCED BY 13-CIS-RETINOIC ACID ADMINISTRATION IN RATS

Hypothesis / aims of study
A large body of evidence has pointed to the co-occurrence of overactive bladder (OAB) and depression [1]. Antimuscarinic drugs are currently the first-line therapy for OAB. However, there is no gold standard for the treatment of OAB co-existing with depression. The corticotropin-releasing factor system participates in the pathophysiology of both disorders. Inhibition of CRF_1 was found to produce antidepressant-like effect and to improve cystometric parameters in a model of detrusor overactivity (DO). We compared the effects of an antimuscarinic drug, solifenacin; a ß-3 adrenoreceptor agonist, mirabegron, which is the second-line treatment for OAB; a tricyclic antidepressant, imipramine, which is approved for enuresis treatment and SN003, a reversible CRF_1 receptor antagonist, in a model induced by 13-cis-retinoic acid (13-cis-RA) administration in rats, which causes detrusor overactivity (DO) symptoms and depressive-like behavior [2].

Study design, materials and methods
We tested the effects of acute treatment with a reversible CRF receptor type-1 (CRF_1) antagonist, SN003 (1 mg/kg, i.v.), representatives of first (solifenacin, SOL, 0.03 mg/kg, i.v.) and second (mirabegron, MIR, 1 mg/kg, i.v.) line treatments for OAB as well as an antidepressant imipramine (IMI, 30 mg/kg, i.p.) on changes in behavior and detrusor overactivity (DO) symptoms induced by a 6-week administration of 13-cis-retinoic acid (13-cis-RA, 1 mg/kg/day, i.p.), using in vivo cystometric investigations, forced swim test (FST) and spontaneous locomotor activity test in female Wistar rats.
60 min after drug injection cystometric investigations were performed in conscious unrestrained rats. The following cystometric parameters were recorded: basal pressure (BP, cm H_2O), threshold pressure (TP, cm H_2O), micturition voiding pressure (MVP, cm H_2O), voided volume (VV, ml), post-void residual (PVR, ml), volume threshold (VT, ml), voiding efficiency (VE, %), intercontraction interval (ICI, s), bladder contraction duration (BCD, s), relaxation time (RT, s), bladder compliance (BC, ml/cm H_2O), detrusor overactivity index (DOI, cm H_2O/ml), nonvoiding contractions amplitude (ANVC, cm H_2O), nonvoiding contractions frequency (FNVC, times/filling phase), and volume threshold to elicit NVC (VTNVC, %).
The locomotor activity of rats was measured 24 h after cystometric studies. The locomotor activity was assessed with the aid of a Digiscan apparatus: an Optical Animal 2` ``SActivity Monitoring System. Horizontal activity was assessed. This was defined as the total number of beam interruptions that occurred in the horizontal sensors during 1 hour of measurement. The forced swim test (FST) was also performed.
Following cystometric and behavioral studies, tissue was harvested and CRF level was assessed in the hypothalamus, amygdala and plasma of rats. CRF concentration was assessed using Mouse/Rat CRF-HS ELISA Kit (Alpco, Salem, NH, U.S.A.) in plasma, hypothalamus and amygdala, according to the manufacturer's protocol. Each sample was measured in duplicate.

Results
13-cis-RA-induced depressive-like behavior and DO symptoms were associated with increased CRF level in the hypothalamus, amygdala and plasma. SOL and MIR attenuated DO symptoms induced by 13-cis-RA, did not display antidepressant-like activity and did not influence CRF levels in brain tissues or plasma. IMI and SN003 displayed antidepressant-like activity and lowered increased levels of CRF in brain tissue and plasma. IMI attenuated changes in some of the cystometric parameters, which are associated with OAB dry (without urge incontinence), whereas SN003 attenuated changes in almost all cystometric parameters that were induced by 13-cis-RA.

Interpretation of results
The present study shows that 13-cis-RA-induced depressive and DO symptoms were associated with increased CRF levels in the hypothalamus, amygdala and plasma. A large body of preclinical and clinical evidence has linked disturbances of the CRF system to depression. A decrease in the CRF concentration in either brain regions or plasma was observed after administration of drugs which exerted antidepressant-like activity, namely SN003 and imipramine, but not after treatment with drugs that did not exhibit this action, namely mirabegron and solifenacin. These observation supports inhibitory effect of antidepressants on hyperactivity of the CRF system. In parallel to antidepressant-like action, SN003 and imipramine (partially) attenuated DO symptoms in 13-cis-RA-administered rats. The current study demonstrates that co-occurrence of depressive and DO symptoms is associated with higher concentration of CRF in brain regions (hypothalamus, amygdala) and plasma.
Although the data on the role of CRF receptors in the urinary bladder are scarce, it is plausible that conditions which are present with DO symptoms are associated with alterations in CRF receptors expression in the urinary bladder, which may have a consequence for voiding function. It is also possible that CRF receptor antagonists exert positive effects on cystometric parameters via modifying CRF receptors expression and/or function in the urinary bladder. Moreover, the transcript levels of CRF_1 were significantly increased in the hypothalamus of rats after chronic all-trans retinoic acid administration, which produces depressive-like behavior in the FST. Therefore, both OAB and depression may cause peripheral and central alterations of CRF and its receptors while treatment with CRF antagonists may be beneficial in depression co-existing with OAB via normalization of these changes.

Concluding message
Based on the observation that first (solifenacin) and second (mirabergon) line treatments for OAB did not improve depressive-like symptoms, whereas imipramine and a reversible CRF1 receptor antagonist, SN003 improved both DO and depressive-symptoms

induced by 13-cis-RA, the two latter compounds could be beneficial in case of co-occurrence of depression and OAB. Importantly, while imipramine attenuated only changes in the following cystometric parameters: DOI, ANVC, FNVC and VTNVC, SN003 attenuated changes in almost all cystometric parameters that were induced by 13-cis-RA. These findings suggest that imipramine could be useful in case of OAB dry, while SN003 in case of both, OAB dry and wet. Our data point to CRF1 inhibition as a potential therapeutic strategy for co-existing depression and OAB. The possible mechanism may be related to the effects on central/peripheral level of CRF and/or its receptors.

References

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2. Wrobel A, Rechberger T (2016) An animal model of detrusor overactivity induced by depression. J Pharmacol Toxicol Methods 80:19-25.

Disclosures

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