Chemogenic activation of oxytocin neurons improves pain in a reserpine-induced fibromyalgia rat model

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INTRODUCTION: Fibromyalgia (FM) is a syndrome characterized by chronic pain with depression as a frequent comorbidity. However, efficient management of the pain and depressive symptoms of FM is lacking. Given that endogenous oxytocin (OXT) contributes to the regulation of pain and depressive disorders, herein, we investigated the role of OXT in an experimental reserpine-induced FM model.

METHODS: Adult male OXT-monomeric red fluorescent protein 1 (OXT-mRFP1) transgenic (Tg) rats and OXT-human muscular acetylcholine receptor (hM3Dq)-mCherry designer receptors exclusively activated by designer drugs (DREADDs) Tg rats were used. Vehicle (0.5% acetic acid, 1 mL/kg) (Control group) or reserpine (1 mg/kg) (FM group) was administered subcutaneously (once/day) on the back for 3 days. The von Frey test, forced swim test (FST), open field test (OFT), and sucrose preference test (SPT) were performed before and after subcutaneous administration in OXT-mRFP1 Tg rats and OXT-hM3Dq-mCherry Tg rats. Hypothalamic OXT-mRFP1 fluorescence intensity and the number of tryptophan hydroxylase (TH)-immunoreactive (ir) neurons in the dorsal raphe nucleus (DR) and tyrosine hydroxylase (TH)-ir neurons in the locus ceruleus nucleus (LC) were measured after injection. OXT mRNA was measured using in situ hybridization. OXT DREADDs Tg rats were divided into saline and clozapine-N-oxide (CNO) groups 6 days after reserpine administration, and subjected to the von Frey test, FST, OFT, and SPT. After administration of OXT receptor antagonist (OXTR-A), the rats were further treated with CNO and then performed the von Frey test and FST. The number of TH-ir neurons in the DR and the number of TH-ir neurons in the LC were determined after CNO administration. Statistical analysis was performed using the Student’s t-test for comparisons of two groups and one-way analysis of variance (ANOVA) for comparisons of three or more groups.

RESULTS SECTION: In reserpine-induced FM model, OXT-mRFP1 Tg rats exhibited increased depressive behavior and sensitivity in a mechanical nociceptive test, suggesting reduced pain tolerance (P < 0.01, Fig. 1A, B). No significant differences in OXT-mRFP1 fluorescence intensity were observed, but the development of the FM-like phenotype in OXT-mRFP1 FM model rats was accompanied by a significant reduction in OXT mRNA expression in the magnocellular neurons of the paraventricular nucleus (P < 0.01, Fig. 2A, B). OXT-mRFP1 FM model rats also had significantly fewer TPH- and TH-ir neurons as well as reduced 5-HT and NE levels in the DR and LC (P < 0.01). To investigate the effects of stimulating the endogenous OXT pathway, rats expressing OXT-hM3Dq-mCherry Tg rats were also assessed in the FM model. Treatment of these rats with CNO, an hM3Dq-activating drug, significantly improved characteristic FM model-induced pathophysiological pain, but did not alter depressive-like behavior. The chemogenetically induced effects were reversed by pre-treatment with an OXTR-A, confirming the specificity of action via the OXT pathway (P < 0.01, Fig. 3).

DISCUSSION: Unlike previous reports of OXT-mRFP1 Tg rats using our pain model, the reason why no change in fluorescence intensity was observed in the reserpine-induced FM model could be due to the depletion of monoamines and reduced signaling to the OXT neurons. Previously we demonstrated that endogenous OXT might exert anti-nociceptive and anti-inflammatory effects in neuropathic and inflammatory pain models. Hence, endogenous OXT might reduce nociception not only by activating monoamine neurons but also by exerting anti-inflammatory effects in reserpine-induced FM model rats. Activation of endogenous OXT neurons in the FM model also showed analgesic effects via the OXT receptor-mediated pathway. In conclusion, we demonstrated that OXT might exert analgesic effects in a reserpine-induced FM rat model via a mechanism mediated by OXTRs, whereas the anti-depressive effects of OXT should be further clarified.

SIGNIFICANCE/CLINICAL RELEVANCE: The dynamics of OXT in FM are still unclear. However, our results indicate that activation of endogenous OXT may have analgesic effects in FM, and could be a potential target for effective pain management strategies for this disorder.