

Estradiol Valerate and Remifemin ameliorate ovariectomy-induced decrease in a serotonin dorsal raphe-preoptic hypothalamus pathway in rats.

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Abstract

Perimenopausal syndromes begin as ovarian function ceases and the most common symptoms are hot flushes. Data indicate that the projections of serotonin to hypothalamus may be involved in the mechanism of hot flushes. Therefore, the aim of this study is to investigate the potential role of the serotonin dorsal raphe-preoptic hypothalamus pathway for hot flushes in an animal model of menopause. We determined the changes in serotonin expression in the dorsal raphe (DR) and preoptic anterior hypothalamus (POAH) in ovariectomized rats. We also explored the therapeutical effects of estradiol valerate and **Remifemin** in this model. Eighty female Sprague-Dawley rats were randomly assigned to sham-operated (SHAM) group, ovariectomy (OVX) group with vehicle, ovariectomy with estradiol valerate treatment (OVX+E) group and ovariectomy with **Remifemin** (OVX+ICR) group. Serotonin expression was evaluated in the DR and POAH using immunofluorescence and quantified in the DR using an enzyme-linked immunosorbent assay (ELISA). Apoptosis was analyzed in the DR by TUNEL assay. The number of serotonin immunoreactive neurons and the level of serotonin expression in the DR decreased significantly following OVX compared to the SHAM group. No TUNEL-positive cells were detected in the DR in any group. In addition, following OVX, the number of serotonin-positive fibers decreased significantly in the ventromedial preoptic nucleus (VMPO), especially in the ventrolateral preoptic nucleus (VLPO). Treatment with either estradiol or **Remifemin** for 4 weeks countered the OVX-induced decreases in serotonin levels in both the DR and the hypothalamus, with levels in the treated rats similar to those in the SHAM group. A fluorescently labeled retrograde tracer was injected into the VLPO at the 4-week time point. A significantly lower percentage of serotonin with CTB double-labeled neurons in CTB-labeled neurons was demonstrated after ovariectomy, and both estradiol and **Remifemin** countered this OVX-induced decrease. We conclude that serotonin pathway is changed after ovariectomy, including the serotonin synthesis in DR and serotonin fibers in PO/AH, both E and **Remifemin** have an equivalent therapeutic effect on it.

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KEYWORDS: Dorsal raphe (DR); Estradiol valerate; Ovariectomy; Preoptic anterior hypothalamus (POAH); **Remifemin**; Serotonin pathway

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