Colocalization of corticotropin-releasing hormone and estrogen receptor-α in the human paraventricular nucleus in depression

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Objective: To determine whether the activity of the hypothalamic-pituitary-adrenal (HPA) axis in depression might be directly modulated by estrogens via estrogen receptors (ERs) in the corticotropin-releasing hormone (CRH) neurons of the human hypothalamic paraventricular nucleus (PVN).
Methods: Brains of 13 subjects ranging in age between 45 and 79 years suffering from major depression/major depressive disorder (8 cases) or bipolar disorder (5 cases), and of 13 controls, matched for sex, age, brain weight, postmortem delay, fixation time, and season and clock time at death, were studied. The total number of CRH-immunoreactive (IR) neurons, CRH neurons that colocalized ERα in the neuronal nucleus, and the number of only nuclear ERα containing neurons in the PVN were measured using an image analysis system. In addition, the volume of the PVN delineated on the basis of CRH neurons was determined.
Results: The total number of CRH-IR neurons in depressed patients was nearly 1.7 times higher than in controls ($p = 0.034$). A novel finding was that the total number of CRH-IR neurons and the number of CRH-nuclear ERα double-staining neurons in the PVN were strongly correlated both in controls and in depressed subjects ($rho = 0.852$; $p < 0.001$ and $rho = 0.626$; $p = 0.022$, respectively). The ratio of the CRH-nuclear-ERα double-staining neurons to the total CRH-IR neurons in depressed patients was similar to that in the controls (48% vs. 37%, respectively, $p = 0.448$). The volume of the subpopulation of the PVN that was delineated on the basis of CRH neurons was significantly larger in depressed patients than in controls (20.88 vs. 13.74 mm^3, $p = 0.022$). Another novel finding was the large population of extra-hypothalamic CRH neurons that was found in the thalamus.
Conclusions: Estrogens can directly influence CRH neurons in the human PVN. The increased number of neurons expressing CRH in depression is accompanied by increased ERα colocalization in the nucleus of these neurons, and by an increased volume of the CRH subpopulation in the PVN.

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