Orexin-A (hypocretin-1) changes in depression and suicide: gender differences

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Research question and background

Neurophysiological and behavioral processes regulated by orexin (hypocretin) are severely affected in depression. Alterations in orexin have so far not been studied in the human brain.

Methods and tissues used

We explored its putative involvement in depression (with or without suicide) by quantifying i) the changes in orexin-A expression in the lateral hypothalamus (LH); ii) orexin-A levels in postmortem ventricular cerebrospinal fluid (CSF); and iii) the alterations in orexin receptors (OXR)-mRNA expression in the prefrontal cortex. In addition, iv) we compared the observed alterations in the human orexin system with those in an animal depression model, the chronic unpredictable stress (CUS) rat.

Results

We found that the amount of LH orexin-A-immuoreactivity (ir) was significantly increased in depression, but only in female patients ($P = 0.022$). There was a trend ($P = 0.065$) for a positive correlation between LH orexin-A-ir and corticotropin-releasing hormone (CRH)-ir in the hypothalamic paraventricular nucleus in depressive patients, whose CRH-ir had been measured in an earlier study. This correlation was significant ($P = 0.04$) in the small number of female-, but not male, depressive patients. In addition, in the control subjects LH orexin-ir showed a clear diurnal fluctuation, with higher levels during the nighttime (1900h-0700h, $P = 0.031$), which was absent in depression. Moreover, male depressive patients who had committed suicide showed significantly ($P = 0.015$) increased OXR2-mRNA expression in the anterior cingulate cortex compared with male controls. Furthermore, in female CUS rats there was a significant positive correlation ($P = 0.007$) between the mRNA levels of CRH and prepro-orexin in the hypothalamus and a significantly increased OXR1-mRNA expression ($P = 0.019$) in the frontal cortex, which was not found in male rats.

Conclusion

Our data show the presence of clear sex-, brain area-, and suicide-dependent changes in the orexin system in depression, which are closely related to CRH activity but only partly reflected in the animal model for depression.