Hypothalamic oxytocin mRNA expression and melancholic depression
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One of the main hypotheses about the pathogenesis of depression concerns hyperactivity of the hypothalamo-pituitary-adrenal (HPA) axis. This axis is driven by corticotropin-releasing hormone (CRH) release of neurons located in the paraventricular nucleus (PVN) of the hypothalamus, that causes ACTH release at the level of the pituitary. ACTH release is potentiated by hypothalamic vasopressin (AVP) (Swaab, 2003). AVP differs only two amino-acids from oxytocin (OXT), a neuropeptide with many effects in social interactions (Gimpl et al., 2001). Both neuropeptides are released from the hypothalamic paraventricular and supraoptic (SON) nucleus (Swaab, 2003). While AVP potentiates HPA-axis activity (Scott et al., 1998), animal experiments have shown that OXT attenuates the stress-induced activity of the HPA-axis in various species, including humans (Legros, 2001), and that OXT inhibits basal HPA-axis activity (Neumann et al., 2000). Van Londen et al. found elevated AVP plasma levels in depressed patients and normal OXT levels, but described a larger variability in these levels compared to controls (Van Londen et al., 1997). Plasma OXT does not readily cross the blood-brain barrier, and there is no direct relationship between the release of OXT into the blood by the neurohypophysis and the variations in OXT levels in the cerebrospinal fluid (Swaab, 2003; Gimpl et al., 2001). We therefore previously determined the number of OXT expressing neurons in the PVN of depressed patients and this number turned out to be increased (Purba et al., 1996).

Recently, we found in a post mortem sample of depressed subjects a significant increase of AVP mRNA expression in the SON, and in both the SON and PVN when only the more severe, melancholic subgroup was taken into account (Meynen et al., 2006). In the same group of depressed patients, with one control added, we performed a quantitative OXT mRNA in situ hybridization using the same
technique (Meynen et al., 2006; Guldenaar et al., 1995). Briefly, hypothalami of 9 depressed subjects (6 melancholic-type, 3 non-melancholic-type) and 9 control subjects matched for age and sex were obtained from the Netherlands Brain Bank in accordance with the formal protocols for use of human brain material and clinical information for research purposes (Meynen et al., 2006). Differences among groups were evaluated by the non-parametric Kruskal-Wallis test and Mann-Whitney U test. Correlations were evaluated by Spearman's rho. Statistical significance was set at p<0.05.

A significant increase of OXT mRNA in melancholic-type patients compared to non-melancholic-type patients existed in the PVN (Z=-2.074, p=0.038), while melancholic-type patients compared to controls showed a trend (p=0.099) towards higher OXT mRNA in the PVN (Figure 1). There was no difference in OXT mRNA in either the PVN or SON when comparing the entire group of depressed patients with control subjects. The group of depressed patients did not differ significantly from the control subjects concerning gender, post mortem delay and fixation time.

This is the first report in which OXT mRNA has been quantified in the SON.

**Figure 1.** Oxytocin mRNA in the paraventricular nucleus (PVN). *Statistically significant difference (p<.05). Contr, controls; non-mel, non-melancholic-type depressed patients; mel, melancholic-type depressed patients. Bars show means. Error bars indicate the SEM. a.u. = arbitrary units.
and PVN in depressed patients and control subjects. In the PVN we found an increased OXT mRNA expression in the melancholic patients compared to the non-melancholic subgroup. Recently, in the same group of patients we found an increase in AVP mRNA when comparing melancholic to non-melancholic subtype of depression (p=0.02, data not shown), while also the entire depressed group showed a significant increase in AVP mRNA expression in the SON compared to controls (Meynen et al., 2006). Furthermore, a correlation existed between the amount of AVP mRNA (Meynen et al., 2006) and the amount of OXT mRNA in the PVN (rho=0.870, p=0.002) and SON (rho=0.745, p=0.021) in depressed subjects, while in controls such a correlation was found in the SON (rho=0.786, p=0.021).

When interpreting the results from the present experiment we have to be cautious because of the small groups. The increase in OXT mRNA in melancholically depressed patients could be related to specific symptoms of melancholic type of depression, like weight loss and loss of appetite, since OXT is a satiety peptide (Swaab, 2003). Supportive of this hypothesis we found the highest amount of OXT mRNA in a melancholically depressed subject, whose medical record mentioned 16 kg weight loss during a depressive episode during the last year of her life.

In conclusion, our data, although from a small group, indicate that a distinction should be made between patients with and without the melancholic subtype of depression, when evaluating molecular changes in the brain.

Reference List


Purba JS, Hoogendijk WJ, Hofman MA, Swaab DF. Increased number of vasopressin- and oxytocin-expressing neurons in the paraventricular nucleus of the hypothalamus in depression. Arch Gen Psychiatry 1996; 53: 137-143.
