Some notes on insulin-regulated aminopeptidase in depression

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We read with great interest the recently published article by Loyens et al. (2012) about the putative role of insulin-regulated aminopeptidase (IRAP) in mediating the antidepressant-like effects of oxytocin (OT) and wish to comment from a ‘human’ perspective on selected aspects of this topic. Loyens and colleagues have demonstrated that the antidepressant-like effect of subcutaneously administered OT in the forced swim test is absent in IRAP knockout mice and abolished by angiotensin IV in IRAP wild-type mice (Loyens et al., 2012). Since OT is increasingly discussed as a promising therapeutic target for depression (reviewed in Slattery and Neumann 2010), we would like to add some thoughts concerning the emerging role of IRAP in human mood disorders. As part of our ongoing search for implications of IRAP for neuropsychiatric disorders (Bernstein et al., 2011), we have performed immunohistochemical studies on the expression of IRAP in human post mortem brains of individuals with affective disorders. In particular, we were interested in elucidating possible alterations of IRAP expression in hypothalamic nuclei of depressive patients. We investigated 16 patients with affective disorder (seven cases with major depression and nine cases with bipolar disorder who all died during a depressive episode, nine females/seven males, mean age 49.3 yr) and 11 subjects with no medical history of neurological or psychiatric diseases (five females/six males, mean age 51.5 yr). All psychiatric patients had a long-term medication (for details, see Bernstein et al., 2012). All brains were obtained from the Magdeburg brain collection. Case selection procedures, the acquisition of personal data, autopsies and the handling of autopic material were all conducted in strict accordance with the Declaration of Helsinki and were approved by the responsible Magdeburg Ethics Committee.

Overall, IRAP was widely distributed in the hypothalamus, being most abundantly expressed in paraventricular (PVN) and supraoptic (SON) neurons, the infundibular stalk and the neurohypophysis. Qualitatively, the regional and cellular distribution of IRAP showed no obvious difference between subjects with mood disorders and the unaffected controls. In a quantitative analysis, we estimated the numerical cell density of IRAP-immunoreactive neurons in the hypothalamic PVN and the SON. Compared with controls a statistically significant increase of IRAP immunopositive neurons by about 30% was found in the left PVN in subjects with unipolar depression disorders (p=0.40; Fig. 1) and bipolar disorder (p=0.029; Fig. 1). No differences were found between patients with major depression and patients with bipolar disorder. Interestingly, no correlation was seen between the densities of IRAP-immunoreactive neurons in the PVN and the dose of antidepressive medication administered over the last 90 d before death. Hence, increased IRAP expression can hardly be attributed to long-term treatment with antidepressants. Taking into account the findings of Loyens et al. (2012), we tend to suggest that the increased IRAP expression in the PVN represents a compensatory effect to the cerebral pathology in affective disorders. A higher cleavage rate of OT by IRAP could imply increased levels of OT metabolites in the brain, which are suggested to exert the antidepressant-like effect of OT (Loyens et al., 2012). It is not fully clear, however, how the endogenous OT levels are altered in brains of depressive patients. Purba et al. (1996) demonstrated elevated numbers of both OT and vasopressin (VP) containing neurons in the PVN of subjects with depression. Since IRAP does not only degrade OT but also VP, which most probably plays its own important role in depression (as recently reviewed by Neumann and Landgraf, 2012), the significant increase of IRAP in this hypothalamic nucleus could represent an adaption to the higher amount of both key substrates, OT and VP. However, Wallis et al. (2007) demonstrated that endogenous plasma VP levels are increased twofold in IRAP−/− mice as a result of the absence of IRAP cleavage. As a compensatory effect, the VP synthesis in the brain, as measured by peptide and mRNA levels, was decreased in IRAP minus mice (Wallis et al., 2007). Unfortunately, a similar mechanism could not be revealed for OT. However, in major
depression plasma OT levels are reduced (Frasch et al., 1995), which might be caused, in part, by an increased cleavage by IRAP. Thus, the increased OT and VP expression in the PVN of depressive patients (Purba et al., 1996) could be a consequence of the higher hypothalamic IRAP level and its increased catalytic activity.

In sum, data published by Loyens et al. (2012), together with our own human post mortem findings and a recently established genetic association between the chromosome region coding for IRAP and major depression (Bulaev et al., 2011), clearly show that IRAP is an important, yet largely underestimated, player in the pathophysiology of affective disorders.

**Statement of Interest**

None.

**References**


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