

## Opposite effects of chronic stress and antidepressant treatment on the efflux pump P-glycoprotein at the blood-brain barrier : an experimental PET study in rats.

de Klerk OL<sup>1,2</sup>, Bosker FJ<sup>1</sup>, Willemsen ATM<sup>2</sup>, Van Waarde A<sup>2</sup>, Visser AKD<sup>3</sup>, de Jager T<sup>3</sup>, Dagey G<sup>3</sup>, den Boer JA<sup>1</sup>, Meerlo P<sup>3</sup>.

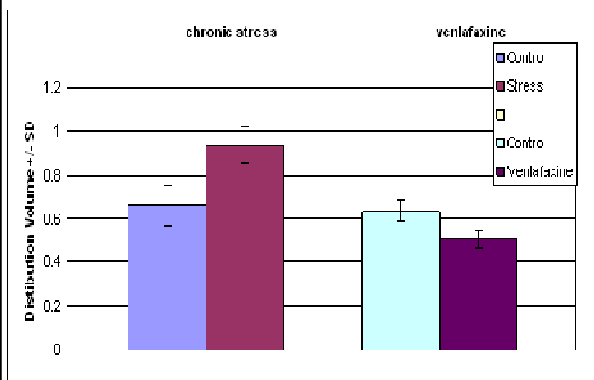
University Medical Center Groningen (UMCG), Department of Psychiatry<sup>1</sup>, Dept. of Nuclear Medicine and Molecular Imaging<sup>2</sup>, and University of Groningen, Dept. of Molecular Neurobiology<sup>3</sup>, the Netherlands. E-mail: [o.l.klerk@ngmb.umcg.nl](mailto:o.l.klerk@ngmb.umcg.nl)

**Introduction** In normal circumstances the blood-brain barrier (BBB) protects the brain from potentially harmful substances. A major efflux pump at the BBB is P-glycoprotein (P-gp), which acts as a gate keeper for toxic substances. P-gp is a key determinant of drug entry to the brain. Modulation of P-gp function can be accomplished by a wide variety of stimuli, such as proinflammatory cytokines. Depressive disorders have been linked to neuroinflammatory events. In a recent PET study, an increased function of P-gp at the BBB was found in medicated patients with major depressive disorder (MDD).<sup>1</sup> The interpretation of this finding was complicated by the use of antidepressants. In the present study we aimed to disentangle the possible influence of the disorder itself and the use of an antidepressant on the function of P-gp. We hypothesised that chronic stress would lead to inhibition of P-gp function and that chronic antidepressant treatment at a therapeutic level would lead to increased P-gp function. [<sup>11</sup>C]-verapamil positron emission tomography (PET) has been found to be a suitable methodology for the in vivo assessment of P-gp function

**Methods** In a first experiment, 16 male Wistar rats underwent a 3-week footshock procedure as a model of human depression. In a second experiment, 8 rats were chronically treated with the antidepressant venlafaxine (25 mg/kg/d via an implanted osmotic minipump). In both experiments, control animals were left undisturbed in their home cages. At the end of the 3-week treatment PET brain imaging with [<sup>11</sup>C]-Verapamil as radiotracer was performed in two study

groups, i.e. a chronic stress model and a continuously administered antidepressant model, and two control groups of male Wistar rats. The distribution volume (VT) of [<sup>11</sup>C]-verapamil was used as a measure of total P-gp function

**Results** In the chronically stressed rats, the distribution volume (VT) of [<sup>11</sup>C]-verapamil was significantly increased, whereas treatment with venlafaxine had the opposite effect and caused a significant reduction in VT. The changes in VT could not be attributed to a difference in the influx rate (see figure 1)



**Conclusion** Our data indicate that P-gp function at the BBB is inhibited by chronic stress and increased by chronic administration of venlafaxine. our results suggest that chronic stress in rats leads to a loss of integrity of the blood-brain barrier due to a decreased function of P-glycoprotein. The implication of this might be an increased brain vulnerability and increased sensitivity to central nervous system malfunction and disease. This finding supports the hypothesis that reduced BBB-function might contribute to the pathophysiology of stress related disorders such as depression. Furthermore, our results suggest that antidepressants may in part exert their therapeutic effect by normalization of P-gp activity and BBB-function. Further studies using other antidepressants from different pharmacological classes are warranted to confirm our findings.

Reference:

1. de Klerk OL, Willemsen AT, Roosink M, Bartels AL, Harry HN, Bosker FJ, *et al* (2009). Locally increased P-glycoprotein function in major depression: a PET study with [<sup>11</sup>C]verapamil as a probe for P-glycoprotein function in the blood-brain barrier. *Int.J.Neuropsychopharmacol.* 1-10.