Changes in glucocorticoid receptor expression and regulation in human hippocampus, amygdala during depression and dementia

PJ Lucassen, SILS-Center for Neuroscience, Science Park 904, University of Amsterdam.

Research question and background
An activated stress system is common in depression and dementia. Chronic stress is considered a risk factor for depression affecting plasticity (1,4) and cognition. Stress is mediated by the glucocorticoid receptor (GR) abundant in limbic regions. So far, little was known about GR levels in the human hypothalamus, hippocampus, prefrontal cortex and amygdala; key regions in feedback regulation, cognition and emotional regulation. In this project, we studied GR in various human brain regions in relation to aging, depression and dementia. We further study molecular regulation of GR by focusing on microRNAs.

Methods and tissues used
We used a well validated GRα-specific antibody in hippocampi of an aging control cohort (1-98 years of age). Abundant GR-immunoreactivity was present in hypothalamic parvocellular but not magnocellular CRH neurons and in hippocampal neurons. GR was also expressed in 50% of the astrocytes and remained stable with age. This indicates this region forms an important target for corticosteroids(9).

We next studied the hippocampus in depression. While GR-ir in the DG correlated positively with age in the depressed group and no differences were found between depressed and control groups, a significant increase was present in depressed females versus depressed males which is of interest given the increased incidence of depression in females(5).

We used QPCR to determine mRNA levels of 17 stress-related genes in the prefrontal cortex (PFC) of depressed patients. MR levels were decreased and ratios of GRα to MR mRNA levels were increased. A selective disturbance of MR and of the GRα/MR ratio may be present in the PFC and contribute to HPA-axis hyperactivity(8).

We also studied GR in the amygdala, involved in fear and anxiety. In major but not bipolar depressed patients, GR protein level and GR-containing astrocytes were increased, indicating this region can form an important target for stress and may be involved in major, not bipolar depression(10).

In the hippocampus of Alzheimer patients (2,3,4,6) GR protein expression was not different from groups, suggesting GR changes are likely not implicated in AD (Wang in prep). For molecular regulation of GR in depression and dementia, we currently study microRNAs using deep-sequencing.

Publications:


