

Pathophysiology of depression and mechanisms of antidepressant treatment

Focus on neurogenesis and gene expression in the chronic mild stress animal model of depression

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This PhD dissertation was accepted by the Faculty of Health Sciences, Aarhus University, and defended on September 21, 2007.

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Dan Med Bull 2007;54:377

ABSTRACT

The PhD project has been carried out at the Centre for Psychiatric Research, Aarhus University Hospital. The objective of the project was to extend the knowledge of pathology of depression and mechanisms of antidepressant actions.

Background: Depression is a serious mental disorder, which is characterized by a significant change in mood that is protracted and severely debilitating. According to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV TR 2000), a diagnosis of major depression requires a presence of at least one of two core symptoms: depressed mood and inability to experience pleasure (anhedonia). The therapeutic management of major depression has evolved rapidly over the past two decades. Nevertheless, Treatment of Resistant Depression (TRD) continues to represent a frequent problem. It has been recognized that at least 30% of depressives fail to respond fully to antidepressants, despite adequate treatment. Even though a large number of studies in this area have been conducted, the pathophysiology of the depression and the mechanism of antidepressant actions are still not completely understood.

One of the current approaches in studying pathology and treatment of major depressive disorder is investigation of changes in the hippocampal formation (HF). The novel neurogenic and structural plasticity theory of depression is based on observation that depressed untreated patients have some hippocampal symptoms (e.g. reduced cognitive functions and motivation) and often show hippocampal atrophy. Moreover, the hippocampal formation has been shown to be a target of stress and antidepressant induced structural changes.

Result: In the PhD project the author has demonstrated that, in the valid pre-clinical model of depression (the chronic mild stress model), there is a number of pathological changes correlating with anhedonia-like state in rats. These include a reduction in a number of proliferating cells, neurons in specific phases of development, and in the total number of hippocampal granule neurons. The author has also demonstrated that the reduction in hippocampal cell number was normalized by chronic treatment with a selective serotonin re-uptake inhibitor (SSRI) escitalopram, but only in animals that responded to the treatment.

Conclusions: The results of this project lead to the hypothesis that the loss of hippocampal neurons may be a consequence of stress induced neuronal degeneration. A reversal from this state caused by

escitalopram may be the result of a neuroprotective effect of antidepressants. Consequently, if the neuroprotective action of antidepressant fails in certain subgroups, this can result in a lack of recovery from depressive symptoms (treatment resistance).