Cellular and mitochondrial stress in depression and suicidality

Abstract

Aim: To better understand the role of mitochondrial and cellular stress in depression and suicidality

Background: Major depressive disorder (MDD) is one of the leading causes of morbidity globally, and also related to increased mortality via somatic co-morbidity and suicide. A steadily increasing number of studies in recent years suggest that alterations in stress and inflammatory systems are linked to psychiatric disorders. Biological processes of particular interest are, among others, the regulation of cortisol through the hypothalamic-pituitary-adrenal (HPA)-axis, various inflammatory cascades involving certain cytokines, mechanisms regulating cell aging through telomere shortening, and more recently a growing interest for the “powerhouse” of the cell, the mitochondrion. Disturbances of the normal functioning of mitochondria seem to be linked to a dysregulation of stress and inflammatory systems as well as the depressive phenotype. One possible way to quantify mitochondrial dysfunction is to measure the number of mitochondrial DNA copies outside of the cell, where it is circulating in cell-free plasma (ccf-mtDNA).

Methods and Results: In the studies presented in this halftime thesis, mitochondrial DNA have been measured in two different psychiatric populations. The first study cohort consists of 37 unmedicated suicide attempters from a Swedish inpatient clinic, matched to an equal number of healthy controls. In this study we found that i) levels of ccf-mtDNA is substantially increased in suicide attempters compared to controls and ii) that increased ccf-mtDNA levels were associated with HPA-axis hyperactivity. The second cohort consists of 50 unmedicated MDD subjects recruited from an outpatient clinic and 55 controls. A subgroup of these patients underwent open-label treatment with an SSRI for 8 weeks. Blood samples were collected pre- and post-treatment. The main findings were that i) ccf-mtDNA levels were significantly elevated in MDD patients compared to controls and ii) in patients who responded to SSRI treatment, no further elevation of ccf-mtDNA was observed after 8 weeks. In non-responders, however, ccf-mtDNA levels was significantly increased at 8 weeks, compared to baseline measurements.

Conclusion: These two studies suggest that levels ccf-mtDNA are elevated in suicidal and depressed subjects. The exact mechanisms by which mtDNA is translocated from inside the mitochondrion to the extracellular space are still unknown. In future studies we aim to gain a better understanding of these mechanisms, and also investigate CNS-correlates of peripheral mtDNA alterations.