Paroxetine ameliorates changes in hippocampal energy metabolism of chronic mild stress exposed rats

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Brain imaging studies have demonstrated an association between stress, depression and a reduction in the volume of the hippocampus. Moreover, several hypotheses have been proposed to delineate the molecular basis of depression and its relationship to the incidence of stress; however, the mechanisms underlying stress-induced depression have not been clearly outlined. The objective of the current study to link the behavioral changes seen in chronic mild stress (CMS), to changes in hippocampal energy metabolism. To this end, 29 male Wistar rats were divided into 3 groups as follows; (i) control; (ii) CMS exposed for 11 weeks; or (iii) CMS receiving paroxetine (10 mg/kg/day i.p.) for the last four weeks of CMS induction. On the behavioral level rats were assessed for sucrose preference as a marker of anhedonia, open-field and forced swimming tests. Biochemically; stress induction was confirmed by assessing serum corticosterone. Cytochrome C and ATP and total adenine nucleotides, as well as nitric oxide metabolites ‘NOX’, were all measured in the hippocampal tissue homogenates. The CMS exposed rats showed a decrease in sucrose preference as well as body weight compared to control. Paroxetine ameliorated the CMS induced behavioral changes. Biochemically, corticosterone serum levels were (124.5±4.44) for CMS vs (90.36±2.41, 91.71±1.8 ng/ml for control and paroxetine respectively. CMS exposed group showed a marked increase in hippocampal ATP (3.85±0.5 nmol/mg protein), total adenine nucleotide (TAN) (7.07±1.09 nmol/mg protein) and a marked decline in ATP/ADP ratio (1.07±0.01). Moreover, CMS induced the expression cytosolic cytochrome c indicative of changes in the mitochondrial membrane. All former events were improved by the administration of the antidepressant paroxetine (ATP 1.8±0.18 nmol/mg; TAN, 2.4±0.25 nmol/mg protein and ATP/ADP ratio 3.8±0.02). Moreover, CMS induced a robust reduction in NOX (0.19±0.02) vs (0.24±0.06) and (1.258±0.035) for control and paroxetine, respectively. From the aforementioned data, we provide evidence that CMS induces depressive behavioral changes, increased serum corticosterone. Moreover, CMS induced changes in mitochondrial function which were alleviated by the antidepressant paroxetine, which further improved depressive behavioral symptoms.