CHRONIC ANTIDEPRESSANT TREATMENTS INDUCES SPECIFIC CHANGES IN BDNF EXPRESSION AND SUBCELLULAR LOCALIZATION

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Depression is a complex disorder characterized by heterogeneous symptoms. Although associated with reduced synaptic concentration of monoamines, mood disorders may be characterized by a general reduction of brain plasticity. Infact, while antidepressant drugs rapidly enhance monoamine levels, their clinical effects are delayed by several weeks suggesting that adaptive changes are required for their therapeutic activity. It is believed that these events might normalize brain function through the modulation of an array of proteins important for cellular plasticity. To this regard, one the most extensively investigated target is brain-derived neurotrophic factor (BDNF), a neurotrophin important in cellular plasticity and neuronal remodeling, whose involvement in the therapeutic action of antidepressant has been postulated. In the present study we have investigated the modulation of BDNF following chronic administration of the new antidepressant drug duloxetine, a potent and balanced serotonin and norepinephrine reuptake inhibitor, in comparison to a selective serotonin reuptake inhibitor fluoxetine. Our results demonstrate that duloxetine, but not fluoxetine, produces significant changes in BDNF levels at cortical levels, but not in hippocampus. Indeed we found, by RNase protection assay, that chronic duloxetine, and not fluoxetine, produces a robust increase of BDNF mRNA level in frontal cortex of animals sacrificed 1 or 24 hours (+179% and +104% $p<0.001$) after the last injection. Moreover we found that these changes are primarily related to a significantly increased transcription of BDNF exon I, IIc and III. In order to understand if the regulation of BDNF mRNA after prolonged duloxetine administration was paralleled by changes at protein level, we performed western blot analysis of the neurotrophin. We found that, in frontal cortex, the mature form of BDNF was markedly increased (+261%, $p<0.001$) in the crude synaptosomal fraction of rats chronically treated with duloxetine, whereas the levels of its precursor form were not altered. Conversely the levels of mature as well as of proBDNF were reduced (-44% and -28%, $p<0.05$) in the cytosolic compartment. Our results suggest that chronic antidepressant treatment not only increases BDNF transcription, but may also alter its subcellular distribution with a relevant increase in the synaptosomal compartment where the neurotrophin may modulate synaptic function and play a beneficial role in cellular resilience.