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Neonatal treatment with clomipramine induces morphological and cellular changes in the adult rat brain

Valeria Colavito[1], Cristina Tognoli[1], Laura Tiberio[2], Marina Bentivoglio[1], Gigliola Grassi-Zucconi[1], Giuseppe Bertini[1]

[1] Section of Anatomy and Histology, D.N.N.M.M.S., University of Verona
[2] Dept. Biomedical Sciences & Biotechnology, School of Medicine, University of Brescia

Clomipramine (CLI) is a tricyclic serotonin reuptake blocker, widely used to treat depression, obsessive compulsive disorder (OCD), and other psychiatric conditions in human patients. Chronic CLI administration in the neonate rodent alters serotonergic circuits and serotonine levels in the brain, and has been reported to cause a complex pattern of behavioral changes in the adult life, including abnormalities of rapid eye movement sleep, decreased aggression and sexual behavior, anhaedonia and helplessness. Such symptoms suggest a parallel with humans endogenous depression and have been proposed as a novel animal model of OCD. The present study was aimed at identifying morphological and cellular changes after chronic neonatal treatment with clomipramine (daily i.p. injections, 20 mg/kg, from P5 to P21) in the brain of 5 month-old male Sprague-Dawley rats, compared to saline-treated littermates, using three distinct experimental approaches.

1) In vivo volumetric analyses based on structural MRI scans performed at 4.7T on 6 CLI-treated and 6 control rats revealed a significant reduction in total brain and hippocampal volume, as well as enlarged ventricles in CLI-treated rats, compared to saline-treated cohorts.

2) In order to investigate treatment-related developmental disorders, we studied the dendritic arborization of newly generated cells in the hippocampus of 7 CLI and 7 control rats. Two-dimensional dendritic tracing diagrams were reconstructed with Neurolucida, and quantitative analyses of total dendritic length and arborization indices in the two groups are still ongoing.

3) Brain-derived neurotrophic factor (BDNF) levels were assessed in the hippocampus and neocortex of 5 CLI and 5 control rats by ELISA assay. Interestingly, we found significant region-specific, between-group differences. In particular, BDNF levels, important for neurogenesis, differentiation and neuronal survival, and highly expressed in brain areas involved in cognitive and emotional behavior, were significantly decreased in the hippocampus of CLI rats compared to controls, whereas no differences were found in the cortex.

Taken together, the data suggest that interfering with serotonergic regulation during early postnatal development can produce permanent brain changes. These resemble brain abnormalities repeatedly observed not only in human depression but also in schizophrenia. Further morphological analyses as well as experiments aimed at characterizing the behavioral correlates of early CLI administration are in progress.

Keywords: Depression, hippocampus, MRI, BDNF, morphology