LIPOSOMES TREATMENT ANTAGONIZED DENDRITIC SPINE LOSS AND REDUCTION OF NEUROGENESIS IN HIPPOCAMPUS OF CHRONICALLY STRESSED RATS

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Introduction: Major depression is a disorder that impairs mood, emotional behavior and various physical functions, such as sleep and appetite. The etiology of depression is multifactorial and still largely unknown; however, there is evidence that a relationship between genetic, environmental/behavioral, epigenetic factors associated to chronic stress play a central role in the etiology of this mental disorder. Elevated glucocorticoid and glutamate levels, as a result of a chronic stress, cause a reduction of neurogenesis, dendritic arborization, spines and synaptic connectivity in the rat hippocampus and prefrontal cortex; a process that involves proinflammatory cytokines. Current treatments with antidepressant drugs have some limitations. Often, to enhance treatment efficacy and tolerability, clinicians have become increasingly interested in pharmaceutical compounds chemically different from the "classical antidepressants". In this respect, particularly interesting seems the use of phospholipid liposomes (PL-Liposome Forte®), made by phosphatidylserine and phosphatidilcholine. Phosphatidylserine and phosphatidilcholine are two of the naturally occuring phospholipids found in the cell membranes of a wide variety of organism from bacteria to man. The presence of phosphatidylserine and phosphatidilcholine in the neuronal membranes is not limited to a static structural function but it also important to the regulation of many metabolic processes, indicating that these phospholiopids may play a role in regulating cerebral functions such as neuronal excitability, message tranduction, neurotransmitter activity and neuronal plasticity. Given that treatment with phospholipids improves brain neuronal activity while pathological processes and/or natural aging reduce the renewal of the phospholipids membrane components, we used phospholipids liposomes, containing phosphotidilserine and phosphatidilcoline to prevent or ameliorate the negative effects of chronic stress on neuronal plasticity.

Methods: Adult male rats were treated with vehicle or Liposom Forte (50 mg/kg, i.p., once a day), and a group of these rats were exposed to chronic unpredictable mild stress for 5weeks, a procedure that contained 9different stressors randomly arranged day and night. Corticosterone level, proliferation, neurogenesis and dendritic spines density were evaluated in all experimental group.

Results: As expected, while plasma corticosterone level was increased in the rats exposed to chronic stress, the proliferation, neurogenesis and dendritic spine density were significantly decreased in same rats. Liposomes treatment markedly reduced the increase of corticosterone level and the reduction of neuronal plasticity elicited by chronic stress. Moreover, treatment with liposomes increased the density of dendritic spines in control not stressed rats.

Discussion: These results demonstrate that chronic treatment with liposomes antagonizes the neurochemical and molecular consequences elicited by chronic exposure to stress in the brain. The mechanisms underlying the beneficial effects of liposomes might be mediated through actions exerted by phospholipids on neuronal membranes, neurotransmitters and/or interaction with trophic factors (NGF, BDNF). These mechanisms in turn might ameliorate the efficacy of antidepressants in depressed patients with impairment of cognitive function.