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Cotinine normalizes the morphology and abundance of Astrocyte after Chronic Restraint

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Although the effects of acute stress are usually brief and can be overcome quickly, exposure to chronic or extreme forms of un-escapable stress can lead to neurochemical, morphological and functional changes in the brain that have been associated with posttraumatic stress disorder (PTSD) and major depressive disorder (MDD). These stress-induced psychiatric diseases are characterized by symptoms such as intrusive distressing thoughts, anhedonia, and irritability feelings of guilt, sleep disorders, cognitive impairment, anxiety and sometimes treatment-resistant depression. Furthermore, these conditions have been associated with functional and structural changes in several regions of the brain including the amygdala, entorhinal cortex, prefrontal cortex and hippocampus. At cellular level, PTSD and depression are also associated with a decrease of glial fibrillary acidic protein (GFAP) immunoreactive cells (GFAP+) in the brain. GFAP is a family of proteins that includes eight isoforms expressed by different subpopulations of astrocytes as well as immature brain cells. These isoform include GFAP+ 1, GFAP delta and GFAP kappa.

Furthermore, the expression of GFAP has been reported to decrease in response to microgravity. Another pre dominantly-astroglial enzyme, glutamine synthase, has been reduced in the frontal cortex following intraventricular injection of aluminum which paralleled alterations in GFAP expression. These results suggest an impairment of astrocytic responsivity in frontal cortex following toxic insults. Stress-induced depression is associated with a reduction of neurogenesis, Neuroinflammation and a decrease of astrocytes in the brain and reduced GFAP expression has been found associated with schizophrenia, bipolar disorder and depression

Objective: Astrocytes maintain brain homeostasis and support neuronal function. In recent years, it has been shown a decrease in the number of astrocytes that present immunoreactivity (IR) for the fibrillary acidic protein (GFAP) in the brain of rodent models of posttraumatic stress disorder (PTSD). GFAP is a family of proteins used as a marker of astrocytes and in less extent of immature brain cells. Astroglia dysfunction seems to be involved in the development of depression and memory loss induced by stress. Cotinine, a positive modulator of the α7 nicotinic acetylcholine receptor (nAChR), prevented memory impairment, depressivelike behavior, and synaptic loss when co-administered during restraint stress. In here, we studied the effects of post-treatment with intranasal cotinine on depressive behavior, memory as well as number and morphology of GFAP+ cells, in the hippocampus and frontal cortex of chronically restrained mice. After two weeks of treatment with cotinine or vehicle, mice were tested for locomotor activity (Open Field Test), depressive-like behavior (Forced Swim test), and memory (Novel object recognition). After euthanasia, GFAP IR cells and their morphology were assessed using immunohistochemistry. This evidence revealed that in addition to the depression and cognitive impairments, restraint stress induced a significant decrease in the number of GFAP+ cells and their arborization complexity. Cotinine prevented cognitive impairment and depressive behavior and restored GFAP+ cells morphology in both brain regions. This data suggests that cotinine acts by a mechanism involving the restoration of astrocyte function after stress in mice.

Chronic stress underlies and/or exacerbates many psychiatric conditions and sometimes leads to memory impairment also as depressive symptoms. Such afflicted individuals use tobacco quite the overall population and this has been suggested as a sort of self-medication. Cotinine, the predominant metabolite of nicotine, may underlie such behavior because it has been shown to ameliorate anxiety and amnesia in animal models. In this study, we sought to research the consequences of cotinine on memory and depressive-like behavior in mice subjected to prolonged restraint. Cotinine-treated mice displayed better performance than vehicle-treated cohorts on the memory task, the radial arm water maze test. These antidepressant and nootropic effects of cotinine were related to a rise within the synaptophysin expression, a commonly used marker of synaptic density, within the hippocampus also as the prefrontal and entorhinal cortices of restrained mice. Taken together, our results show for the primary time that cotinine reduces the negative effects of stress on mood, memory, and therefore the synapse.

Restraint stress (RS) may be a condition affecting many people worldwide. The investigation of new therapies to alleviate the consequences of prolonged RS is much needed. Cotinine, a nicotine-subordinate, has appeared to stop the lessening in cerebral synaptic thickness, memory shortages, tension, and burdensome like conduct after delayed restriction stress (RS) in mice. Moreover, post-treatment with cotinine diminished the antagonistic impacts of interminable RS on astrocyte endurance and design. On the opposite hand, the nutritional supplement krill oil (KO), has shown to be beneficial in decreasing depressive-like behavior and oxidative stress. In this study, within the look for effective preventative treatments to be utilized in people subjected to reduced mobility, the effect of co-treatment with cotinine plus KO in mice subjected to prolonged RS was investigated. The outcomes show that cotinine in addition to KO forestalled the loss of astrocytes, the vibes of burdensome like conduct and subjective debilitation actuated by RS. The potential use of this mix to alleviate the psychological effects of reduced mobility is discussed.

Conclusion: The evidence obtained in this study permits to conclude that post-treatment with IN cotinine is effective in restoring mood equilibrium and cognitive abilities as well as astrocytes function after chronic restraint stress in mice. The preceding constitutes the first evidence about the action of cotinine on GFAP+ cells. This finding represents a new mechanism of action of cotinine to restore neuronal survival and plasticity after stress. The IN delivery of cotinine proved to be effective as a method of treatment with cotinine for PTSD or restraint stress-associated disorders. It is necessary to supplement the results presented in this work with further clinical research, enabling to establish whether the observed beneficial effects of cotinine in rodents are equally effective in humans