DEPRESSION AND BRAIN FOG "CLEARING UP" BY PALMITOYLETHANOLAMIDE IN DIET-INDUCED OBESE MICE

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Introduction: During critical periods for neurodevelopment and neuronal plasticity, obesity could constitute a risk factor for developing mood and cognitive disorders. Indeed, obesity is characterized by "low grade inflammation", resulting from increased serum levels of pro-inflammatory cytokines, that stimulate microglial proliferation and astrocyte dysfunction with consequent neuroinflammation, mainly in areas that lack an effective blood-brain-barrier (BBB), including hypothalamic arcuate nucleus (ARC). The ARC is strongly connected not only with other regions of the hypothalamus, but also with other brain areas, such as hippocampus, orbitofrontal cortex, nucleus accumbens, striatum and prefrontal cortex, regulating motivation and reward pathways. Up to date, palmitoylethanolamide (PEA) has proven to be a multi-target compound, whose main pharmacological effects are mediated by the activation of peroxisome proliferator activated receptor (PPAR)α, a transcription factor involved in many central effects.

Materials and methods: Male C57Bl/6J mice were randomly divided into 3groups: control group (STD) receiving chow diet and vehicle per os; HFD group receiving vehicle; HFD group treated with PEA (30 mg/kg/die per os). The treatments started after 12weeks of feeding with HFD and lasted 8weeks. At the end of the experimental period, all mice underwent behavioral tests (open field, OF; novel object recognition, NOR; forced swimming, FS; tail suspension, TS; sucrose preference, splash, rotarod) to determine anhedonia-depressive profile and memory deficit. Afterwards, different brain areas were collected for evaluating BBB integrity, neuroinflammation and neurogenesis (BDNF/TrkB/CREB pathway) related to obesity-induced central disorders. To correlate behavioral and biochemical outcomes to neurochemical changes, we quantified monoamines in the same cerebral areas by HPLC coupled to amperometric detection.

Results: In FS and TS tests, HFD caused a significant increase in immobility time, related to depressive-like behaviour of mice. Accordingly, prefrontal serotonin was reduced in HFD mice. After 8weeks of treatment, PEA induced an increase in HFD mice responsiveness and effort to escape than untreated HFD group along with increased serotonin in prefrontal cortex. The beneficial effects of PEA on anhedonia-depressive behaviour were also confirmed by an increased pleasure (sucrose preference) and an improved self-care (splash test). In parallel, dopaminergic impairment in accumbal area was prevented by PEA administration. Furthermore, during the NOR test, HFD impaired the recognition of old object and increased noradrenaline concentration in the hippocampus; conversely, PEA was able to restore such deficits in mice. The OF test highlighted that mice movement, reduced in HFD, was partially stimulated by PEA, and not related to an impairment of motor coordination, as shown by rotarod test. At molecular level, 19week-HFD caused a significant impairment of BDNF/TrkB/CREB pathway in both hippocampus and prefrontal cortex, that was restored by PEA treatment, indicating an improvement of synaptic plasticity. Furthermore, PEA carried out its anti-inflammatory activity reducing the mRNA levels of IL-1b and TNF-a, significantly increased by HFD. Finally, PEA was able to restore mRNA levels of occludin and zonuline-1, two main tight junction involved in BBB integrity.

Discussion and conclusion: The treatment with PEA improved the depressive-like behavior, memory and neurochemical deficit, shown by HFD animals, impacting on BDNF signaling pathway and reducing neuroinflammation, both in hippocampus and prefrontal cortex. In conclusion PEA represents a multifunctional compound for an integrative approach against complex diseases, such as metabolic illness and CNS disorders, due to its pleiotropic mechanism, supporting neuroprotection and anti-inflammatory effects.