PREVENTING IMMEDIATE AND LONG-TERM ADOLESCENT STRESS-INDUCED COGNITIVE DEFICITS AND GUT MICROBIOTA ALTERATIONS BY OMEGA 3 POLYUNSATURATED FATTY ACIDS/ VITAMIN A DIET ENRICHMENT

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Introduction: Early-life stress in humans and rodents has been shown to represent a neurodevelopmental risk with implications to subsequent cognitive abilities during adulthood. Likewise, poor nutritional habits are closely intertwined with mood regulation, stress perception and stress responses. Evidence suggests that a healthy diet, rich in polyphenols, vitamins, omega-3 polyunsaturated fatty acids (w-3 PUFAs) and vitamins, exerts positive effects on cognitive performance, stress reactivity and neuroinflammation. However, little is known about the influence of these micronutrients on the cognitive and neurochemical consequences of chronic stress during adolescence. Therefore in this study we evaluated the impact of diet enrichement with w-3 PUFA (0.79g/100g), and vitamin A (45 IU/g) in the acute and long-term behavioural, neurochemical and gut microbiota alterations induced by the social instability stress.

Materials and methods: Male Wistar rats fed with normal or enriched diet were submitted to a stress protocol that included a combination of repeated 1h daily isolation in a small container (akin to restraint) followed by pairing with a new partner in a new cage. As rodents use social bonds to moderate stress, the social instability blunts habituation to repeated isolation. The stressful procedure was repeated for 15 days starting on post-natal day (PND) 30. The behavioural repertoire of the animals was assessed at the end of the stress protocol, i.e. during adolescence (PND 45-50) as well as in adulthood (PND 70-75) using a battery of tests comprehensive of several domains affected by stress: mood (sucrose preference), anxiety (open field, elevated plus maze) and cognition (novel object recognition, fear conditioning). One day after the end of behavioural tests, rats were sacrificed and brains and caecal content were collected for neurochemical (BDNF and Synaptophysin) and gut microbiota composition analysis. Results from stressed animals were compared with a control group fed with normal chow, that were not submitted to stressful manipulations.

Results: Adolescent stressed rats gained less weight than non-stressed rats, an effect that persisted until adulthood. Such impairment was counteracted by the enriched diet. When tested for emotional and reference memory, both adolescent and adult stressed animals performed poorly with respect to the non-stressed control animals, indicating a persistent cognitive deficit due to the stressful manipulation. Diet enrichement had a beneficial effect since rats fed with w-3 PUFAs/Vitamin A enriched diet exhibited performance undistinguishable from non-stressed rats in both memory tests. No anhedonia-like nor anxiety-like behaviour were observed in stressed animals. We found a good fit between rats' memory performance and of brain derived neurotrophic factor (BDNF) expression in the hippocampus, as both were significantly decreased in stressed adolescent and adult rats, and the enriched diet prevented both effects. Chronic stress during adolescence altered gut microbiota composition (b diversity) and short- and branched-chain fatty acid content; the dietetic intervention prevented also these changes.

Discussion and conclusions: Our study highlighted the beneficial effect of the enriched diet on cognitive memory impairment induced by social instability stress. Furthermore, the decline BDNF expression in the hippocampus and microbiota shifts in composition observed in stressed rats were normalized by the enriched diet. The detrimental behavioural and neurochemical effects of adolescent stress as well as the protective effect of the enriched diet were maintained through adulthood, long after the exposure to the stressful environment was terminated. Taken together, our results strongly suggest a beneficial role of nutritional components to ameliorate stress-related behaviours and associated neurochemical and microbiota changes, opening new venues in the field of nutraceutics.