OMEGA3PUFA/VITAMIN A ENRICHED DIET CONFERS RESILIENCE TO STRESS-INDUCED COGNITIVE AND NEUROPHYSIOLOGICAL MODIFICATIONS. ROLE OF THE BRAIN HISTAMINERGIC SYSTEM

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Background: Brain histamine is crucial in controlling arousal and cognition and disruption of histaminergic neurotransmission contributes to numerous psychopathologies including anxiety, post-traumatic stress disorder and depression. Common to all these disorders appear to be stress-associated deficits of cognitive processes, such as learning and memory and sociability. Chronic social defeat stress (CSDS) is an ethologically valid model of stress-related disorders leading to severe consequences on cognitive performances. Recently, it was proposed that dietary polyunsaturated omega-3 fatty acid (PUFA) and Vitamin A may help preserve the normal cognitive functions in the face of stress-inducing alterations. Hypothalamic histaminergic neurons serve as a relay station integrating peripheral signals and central functions to influence the emotional value of different experiences and are profoundly affected by stress. However, it is not known whether brain histamine exerts a role in omega-3PUFA and Vitamin A beneficial properties. In our study we addressed this question

Materials and methods: C57/Bl6histidine decarboxylase-null ($HDC^{-/-}$) and wild type ($HDC^{+/+}$) mice were fed with normal or enriched diet starting at weaning and were subjected to the CSDS protocol that consists of a daily exposure of the experimental mice to an aggressive CD1mouse until the first attack occurred, at PND 54for 10 consecutive days. Mice were then separated by a transparent divider that allowed olfactory and visual contact, for 2hours. Non-stressed $HDC^{-/-}$ and $HDC^{+/+}$ mice fed with normal diet served as controls. Social Interaction Test (SIT) was performed at the end of the CSDS to assess social avoidance behaviour, expressed at as the time experimental mice spent in the proximity of a caged aggressive CD1mouse. Cognitive performance was tested by using the Novel Object Recognition test (NOR) and the Novel Object Location Test (NOL). In the NOR test, the time a mouse spends exploring a previously encountered object (familiar) and a novel one is recorded. In the NOL test, one of the objects is displaced in a new location. Mice that have a persistent memory of the familiar object/location show a preference for the novel object/location and interact with it more frequently, spending more time exploring it. To test synaptic plasticity, we recorded field excitatory post-synapatic potentials (fEPSPs) in the CA1stratum radiatum of dorsal hippocampal slices and induced LTP with a theta-burst consisting of 5pulses at 100HZ separated by 200 msec x 5. Furthermore, we evaluated the expression of synaptophysin, an integral membrane protein of small synaptic vesicles in the hippocampus and frontal cortex, by Western blot analysis.

Results: We found that social behaviour was greatly affected by the CSDS protocol: In the SIT invariably, stressed $HDC^{+/+}$ and $HDC^{-/-}$ mice spent less time approaching an aggressive CD1mouse. The CSDS protocol worsened the memory for the familiar object/location of both genotypes. The Omega 3PUFA/Vit A enriched diet prevented these deficits only in $HDC^{+/+}$ as the diet was ineffective in $HDC^{-/-}$ mice Stress increased LTP amplitude in both genotypes, and this modification was prevented by the enriched diet in $HDC^{+/+}$ mice inly. Finally, the enriched diet increased synaptophysin expression only in stressed $HDC^{+/+}$, but not in stressed $HDC^{-/-}$ mice.

Conclusions: We suggest the challenging hypothesis that brain histamine provides the necessary neuromodulation for components of the enriched diet to prevent stress-induced cognitive and neurophysiological impairments.