Nutritional omega-3 deficiency starting at adolescence impairs synaptic plasticity and emotional behavior at adulthood: implication of the mGluR5-endocannabinoid signaling complex

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In the last century, the rapid expansion of Western Countries has been associated with drastic changes in the diet reflected by low levels of essential omega-3 polyunsaturated fatty acids (n-3 PUFAs). Our previous studies demonstrated that lifelong n-3 PUFAs dietary deficiency ablates endocannabinoid synaptic plasticity in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc)(Lafourcade et al., 2011). These synaptic alterations were correlated with impairments in emotional-related behaviors (Larrieu et al., 2012; Zamberletti et al., 2016). However, the onset of these deficits has never been studied. To address this issue, C57BL6/J mice were fed with an n-3 deficient diet (rich in linolenic acid, LA, 18:2n-6) starting at postnatal day (PND) 28 until adulthood (PND 90) when they were tested for synaptic plasticity and emotional and cognitive outcomes.

Our results showed that starting nutritional deficits in dietary n-3 PUFAs during adolescence decreased n-3 PUFAs levels in both mPFC and NAc, increased anxiety-like behavior and decreased cognitive function in adult mice. Importantly, we discovered that endocannabinoid/mGlu5-mediated long-term depression in the mPFC and NAc was abolished in adult n-3-deficient mice. Additionally, mPFC NMDAR-dependent long-term potentiation was also lacking in the n-3-deficient group. Pharmacological enhancement of the mGlu5/eCB signaling complex, by positive allosteric modulation of mGlu5 or inhibition of endocannabinoid 2-arachidonylglycerol (2-AG) degradation, fully restored synaptic plasticity and normalized emotional and cognitive behaviors in malnourished adult mice.

Our data support a model where nutrition is a key environmental factor influencing the working synaptic range into adulthood, long after the end of the perinatal period. These findings have important implications for the identification of nutritional risk factors for disease and design of new treatments for the behavioral deficits associated with nutritional n-3 PUFAs' deficiency.

Lafourcade et al. (2011). Nat Neurosci. 14(3):345-350.

Larrieu et al. (2012). J Physiol Biochem. 68(4):671-81.

Zamberletti et al. (2016). J Lipid Res. 58(2):301-316.