Title: Fish oil prevents rodent anxious states comorbid with diabetes: a putative involvement of nitric oxide modulation

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<AT>Fish oil prevents rodent anxious states comorbid with diabetes: a putative involvement of nitric oxide modulation.

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<ABS-HEAD>Highlights► Diabetic rats exhibited a pronounced anxiogenic-like behavior. ► Fish oil treatment prevented the anxiogenic-like behavior in diabetic animals. ► Fish oil treatment prevented the high nNOS expression in brain areas related to anxiety. ► <ST>Treatment</ST> with nitric oxide precursor abolished the anxiolytic effect induced by fish oil.

<ABS-HEAD>Abstract

<ABS-P>There is an urgent need to understand the pathophysiological mechanisms related to anxiety associated with diabetes, seeking more effective alternative treatments to treat it. For that, the effect of a preventive and prolonged treatment with fish oil (FO), a source of omega-3 polyunsaturated fatty acid, was tested in streptozotocin-diabetic (DBT) rats submitted to the anxiety tests. Additionally, an immunohistochemistry for neuronal NO synthase (nNOS) was performed in brain areas related to anxiety, such as lateral amygdala (AMY), hippocampus (HIP) and dorsolateral periaqueductal gray (dlPAG). Lastly, the effect of NO precursor L-arginine (L-Arg) or nNOS inhibitor 7-nitroindazole (7-NI) was tested in DBT animals treated with vehicle (VEH) or FO. Our data demonstrated that vehicle-treated DBT animals exhibited a more pronounced anxiogenic-like response and also presented high nNOS levels in the AMY, HIP and rostral dlPAG, what were both significantly prevented by FO treatment. This treatment was able to prevent the impairment in locomotor activity besides improving the high glycemic levels in DBT rats. Interestingly, while injection of 7-NI or L-Arg in VEH-treated DBT animals induced an anxiogenic-like and anxiolytic-like effect, respectively; the previous treatment with both L-Arg and 7-NI in FO-DBT animals abolished the anxiolytic-like effect induced by FO treatment. Altogether, our data support the hypothesis that a dysregulation in the NO production in brain areas as AMY, HIP and dlPAG may contribute to the mechanisms that link anxiety and diabetes, and the prevention of nNOS brain expression changes induced by a prolonged treatment with FO may be an important mechanism related to its anxiolytic-like effect.

<KWD>Keywords: streptozotocin; elevated plus maze; omega-3 polyunsaturated fatty acids; fish oil; neuronal nitric oxide synthase; anxiety.

<H1>1. Introduction

Anxiety comorbid with diabetes are rising problems that demand immediate research attention. Studies point out that the prevalence of anxiety disorders reaches 60% among diabetic individuals, when compared to non-diabetic population [1,2]. Anxiety comorbid with diabetes not only worse the quality of life, but also glycemic control, along with an increase in the morbidity and mortality rates [3,2].

Studying neurobehavioral consequences such as anxiety in the preclinical diabetic model may help to elucidate the pathophysiology of this comorbidity and to identify the