Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
Accessible at: www.pvj.com.pk

RESEARCH ARTICLE

Antidepressant and Anxiolytic Effects of Cod Liver Oil in Rats

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ARTICLE HISTORY

Received: January 11, 2012
Revised: June 24, 2012
Accepted: July 16, 2012

Key words:
5-HT
Antidepressant
Anxiolytic
Cod-liver oil
Rats

ABSTRACT

Cod-liver oil is a rich source of omega 3 fatty acids and has been widely used as omega 3 fatty acids supplementation. Regarding omega-3 fatty acid beneficial effects in humans, this study was designed to investigate the effect of repeated administration of cod-liver oil on the locomotion and behaviors of rats, including depression, anxiety and the 5-Hydroxy tryptamine (5-HT) metabolism. After four weeks oral administration of cod-liver oil, open field test was used to measure the locomotor and exploratory activity. Elevated plus maze test was used to measure anxiety. Cod-liver oil significantly increased locomotion and produced anxiolytic effects in rats. Antidepressant effect of cod-liver oil was monitored by forced swim test (FST) in which struggling time of test animals was increased significantly. 5-HT turnover also increased significantly following the oral repeated administration of cod liver oil in test animals. The results suggest that cod-liver oil has antidepressant and anti-anxiety effects.

To Cite This Article: Perveen T, F Razi, S Haider, H Qayyum and DJ Haleem, 2013. Antidepressant and anxiolytic effects of cod liver oil in rats. Pak Vet J, 33(1): 57-59.

INTRODUCTION

Cod liver oil has a very long history of usage as a medicinal oil, before the advent of synthetic vitamins, cod-liver oil was consumed regularly by the general population for its vitamin A and D supplementation (Johansson *et al*., 1998) later on, it has been found that various health benefits of cod liver oil is associated with omega 3 fatty acids (Connor, 2000). Omega 3 fatty acids found in cod-liver oil are long chain essential fatty acids (eicosapentaenoic acids) EPA and (docosahexaenoic acid) DHA which are concentrated in synaptic neuronal membrane and regulate vascular and immune function that affects the central nervous system (Salem *et al*., 2001). Dietary deficiency of these fatty acids in humans has been associated with bipolar mood disorder and schizophrenia (Ranjekar *et al*., 2003).

Intake of omega 3 fatty acids found in the cod liver oil can lower symptoms of depression (Raeder *et al*., 2007), and could be beneficial in the treatment of some patients with anxiety disorders (Buydens-Branchey and Branchey, 2008). Furthermore, animal models of mental illness have suggested that omega-3 fatty acids can affect brain processes such as those that control mood and anxiety (Yehuda *et al*., 2005), and also produce antidepressant activity (Lakhwani *et al*., 2007; Smith *et al*., 2011). Omega 3 fatty acids (DHA) can modulate monoamines neurotransmitter (Carlezon *et al*., 2005) and abnormalities in these fatty acids have been particularly linked to dysfunction of 5-HT system (Garland and Hallahan, 2006). Previously pure omega-3 fatty acids have been used, the present study highlight the use of cod liver oil to monitor the neurochemical and behavioral changes in rats.

MATERIALS AND METHODS

Animals and Treatment: Locally bred white Albino Wistar rats (n=12) weighing about 150-250g (purchased from HEJ Research Institute of Chemistry, University of Karachi) were caged individually in pacifically designed cages in a quite room with free access to water and cubes of standard rat food for at least 1 week before starting the experiment. Rats were divided into control and test groups. Test group was given cod liver oil orally at a dose of 0.5ml/day for 4 weeks at the set time between 10:00 am -11:00am while the control group received the equal amount of tap water daily for 4 weeks. After 4 weeks of repeated administration of cod liver oil, different behavioral activities were monitored.

Behavioral Analysis: Following the four weeks administration of cod liver oil different behavioral tests were performed to monitor the exploratory activity,

anxiolytic and antidepressant effects. The activity of control and drug treated rats were monitored in an open field apparatus, which consisted of square area of 76x76 cm with opaque walls of 42 cm high .The floor was divided by lines into 25 equal squares. The test was performed in a quiet room under white light to avoid any noise effect as described earlier. Animals were placed in the center square of the open field (one at a time). Activity in open field was determined by monitoring latency period and counting number of squares crossed for five minutes as described earlier (Naqvi *et al*., 2012). Activities of control rats and drug treated rats were monitored alternatively to avoid order effect.

Assessment of depressive symptoms was monitored by Forced swim test (FST) following 4 weeks of oral administration of drug. FST was performed as described earlier (Khaliq *et al.*, 2012) to monitor the antidepressant activity. Rats were placed individually in a tank (53, 19, 28 cm). The water was filled up to 18cm. The height of the water was such that escape was not possible. Rats were placed in the container for 5 minutes and behavioral scoring was performed by observing struggling time. After each test, rats were dried with towel and placed in their home cage.

The anxiolytic activity of drug in elevated plus maze model was measured according to method as previously reported (Haider *et al*., 2006). Plus maze apparatus consist of 4 equal size arms. The two opposite arms are open while 2 are closed. The length of each arm was 50cm and width was 10cm. Arms were joined by the central area of 5cm. The length of the wall of the closed arm was 40cm. The maze was elevated from floor at 60cm. To determine activity a rat was placed in the center of the plus maze and the time spent in the open arm was monitored for 5minutes.

Neurochemical Estimation: At the end of experiment animals were decapitated using guillotine. Brains were removed immediately and dipped in chilled saline and stored at –70°C for the determination of 5-HT and 5HIAA by HPLC-EC (Moin *et al.*, 2012). Data were analyzed by Student's *t*-test using SPSS version 13.0. P<0.05 was considered as significant.

RESULTS

Table 1 show the behavioral and neurochemical changes following the repeated administration of cod liver oil in rats. Data analyzed by Student's *t*-test showed a significant decrease (P<0.01) in latency period and a significant increase (P<0.01) in number of square crossings in test rats than control rats in open field. The anxiolytic effect of cod liver oil in Elevated plus maze showed a significant increase (P<0.01) in time spent in open arm and also a significant increase (P<0.05) in number of entries in open arm in cod liver oil treated rats. The antidepressant effect of cod liver oil was measured using the forced swim test. Data analyzed by Student's *t*-test showed that struggling time in cod liver oil treated rats was significantly (P<0.01) increased in swim tank as compared to control rats. Neurochemical analysis showed that cod liver oil significantly decreased (P<0.01) the 5-HT levels of test animals, while 5-HIAA levels were comparable in cod liver oil treated rats. However 5-HT turnover was significantly (P<0.01) increased in cod liver oil treated rats.

Table 1: Effect of repeated administration of Cod liver oil on Neurochemical and Behavioral changes in rats

Parameter	Unit	Control	Test
Open Field Activity			
Latency to move	Sec	3.29±1.15	1.57±0.38**
No of Square Crossed		76±28.7	136±22.5**
Plus Maze Activity			
Time spent in open arm	Sec	25.7±10.7	37.7±10.3**
No of entries in open arm		3.8±1.9	6.3±1.3*
Force Swim Test			
Struggling time	Sec	130±15.3	188.8±45**
Neurochemical Estimations			
Brain 5-HT	ng/g	45.8±4.301	32.64±5.3**
Brain 5-HIAA	ng/g	103.8±15.38	100.38±24.16
5-HIAA/5-HT ratio		2.25±0.64	3.36±0.31**

Values are mean±SD (n=6). Significant differences by Student's *t*-test * P<0.5, **P<0.01

DISCUSSION

Strong evidence is now showing the importance of omega 3-fatty acids in certain brain functions such as neurotransmission processes and behaviors (Gertsik *et al.*, 2012). Several animal behavioral models such as open-field and elevated plus maze have been used to investigate possible anxiolytic activity; forced swim test was used for screening antidepressant activity. These tests are classical models for screening central nervous system actions providing information about psychomotor performance, anxiety and depression (Silva *et al*., 2007). Omega-3 fatty acids from fish has been reported to produce anti-depressant effects and are potentially beneficial in enhancing mood and reducing symptoms of mood disorders (Smith *et al*., 2011).

Open field is used to measure the exploratory activity, anxiety effects and locomotor activity of rats (Frye and Rhods, 2008). The animals treated with cod liver oil showed increased motor activity in open field. The numbers of squares crossed by the drug treated animals was significantly greater than their respective controls. The test animal also had significantly lower latency period. This all leads to suggest the anxiolytic behavior of cod liver oil. Behavior in the elevated plus maze is also utilized to assess exploration, anxiety, and motor behavior (Haider *et al*., 2006). Anxiolytic compounds reduce the animal's aversion to the open arms and promote the exploration thereof (Silva *et al*., 2007). The results in present study support the evidence of anti-anxiety effect of ω-3 fatty acids supplementation in the diet of patients with anxiety disorder and aggressive behavior (Buydens-Branchey and Branchey, 2008). Forced swim test is suitable for detecting anti-depressant activity in rats (Borsini and Meli, 1998). It is a non-escapable stressful situation in which rats are forced to swim and become immobile after vigorous activity. Reduced immobility or increased struggling time in the FST by standard antidepressant is accepted as antidepressant-like effect and increased struggling in FST following cod liver oil administration indicates its antidepressant activity (Slattery and Cryan, 2012) and this antidepressant effect of cod liver oil observed is due to omega-3-fatty acid as describe previously (Lakhwani *et al*., 2007).

Serotonin appears to play a key role in the modulation of various behaviors such as mood, motor behavior, memory and appetite (Khaliq *et al*., 2006, Naqvi *et al*., 2012) through different 5-HT receptors. However 5-HT (1A) subtype is main mediator of 5-HT activity among all subtypes which regulate the synthesis and release of 5-HT through feedback mechanism via the stimulation of 5-HT-1A auto receptor and regulates the function of several neurotransmitter system via postsynaptic receptors. Research on omega 3 fatty acids indicates that it has positive impact on serotonin neurotransmission and important in regulating the reuptake of brain serotonin (Mantzioris *et al*., 1994). An increase in brain serotonin turnover following the administration of cod liver oil was observed in the present study which means rate of transmitter synthesis, catabolism and release is increased. This may determine the activation of 5HT-1A receptors and may result in inhibition in 5HT neuronal activity and decrease their firing activity. This effect of cod liver oil may suggest its anxiolytic property. It is however difficult to explain cod liver oil induced hyperactivity in open-field test in terms of increased 5-HT turnover because an increase in 5-HT function decreases motor activity (Villegier *et al*., 2006). Antidepressant-like effects of cod liver oil following increased 5-HT turnover in the present findings may represent its mechanism of action other than classical antidepressants.

Conclusion: A variety of nutritional factors can affect mood and risk of depression. Omega-3 fatty acids from fish produce antidepressant effect and are potentially beneficial in enhancing mood and reducing symptoms of mood disturbance. In the present study long term administration of cod liver oil increased 5-HT turnover and produced antidepressant and anxiolytic effect. It is therefore suggested that eating fish and supplementing fish oil may be used for the treatment of depression and anxiety.

Acknowledgment: The authors wish to acknowledge the University of Karachi, Karachi, Pakistan for providing the funds for this study.

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