

The effect of docosahexaenoic acid (DHA) supplementation on experimental depression in mice

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Received: 21 November 2017

Accepted: 28 December 2017

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ABSTRACT

Background: Depressive disorder is a prevalent psychiatric disorder, which affects 21% of the world population. Many drugs which are available as effective antidepressants produce various side effects like sedation weight gain postural hypotension etc., so there is need to develop novel compounds with minimized side effects. Hence this study was aimed to investigate the antidepressant activity of DHA, an omega-3 polyunsaturated fatty acid in albino mice.

Methods: Animals were divided into four groups, consisting six mice in each group. Out of these, group I served as control (2% gum acacia), group II and III received test drug in two different doses 200mg/kg and 300mg/kg respectively and group IV received fluoxetine (20mg/kg) as standard drug. To determine the antidepressant-like activity, we used forced swim test and tail suspension test in mice. These methods are based on the observation that a mouse show alternating agitation and immobility; the immobility is indicative of a state of depression.

Results: DHA produced significant antidepressant effect at all the doses, as indicated by reduction in immobility times as compared to control in both FST and TST. ($P < 0.05$) The efficacy of DHA at dose of 300 mg/kg was comparable with that of fluoxetine. DHA at 200mg/kg dose showed significantly less antidepressant activity compared to fluoxetine. ($P < 0.05$).

Conclusions: The result specifies that compared to two doses of DHA (200mg/kg and 300mg/kg), higher dose of DHA found as an effective dose for treating depression produced due to stress.

Keywords: Docosahexaenoic acid, Forced swim test, Fluoxetine, Tail suspension test

INTRODUCTION

Depression is one of the leading causes of global disease burden and disability affecting 10-15% of the population at some time in their lives.¹ The high prevalence of suicide in depressed patients (up to 15%), coupled with complications arising from stress and its effects on the cardiovascular system, have suggested that it will be the second leading cause of death by the year 2020 and studies show depression as a contributory factor to fatal coronary disease.²

It is a heterogeneous disorder that affects a person's mood, physical health, and behaviour. Patients with major depression have symptoms that reflect changes in brain monoamine transmitters, specifically norepinephrine,

serotonin, and dopamine.² The current modalities of treatment for depression include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs). These antidepressant medications have many adverse effects like sedation, weight gain, sexual disturbances and delayed onset of therapeutic effect.³ This latency is problematic as it prolongs the impairments associated with depression, leaves patients vulnerable to an increased risk of suicide, increases the likelihood that a patient will prematurely discontinue therapy and increases medical costs associated with severe depression.⁴ Thus, there is continuous search for newer novel compounds that have better efficacy or can augment the effect of conventional antidepressants in these patients.

Docosahexaenoic acid (DHA) is an omega-3 derivative of alpha-linolenic acid (ALA), containing 22 carbons and six double bonds in their structure. It is high quality easily digestible nutrient mostly found in marine algae, fatty fish like salmon, fish oil, mother's milk and at low amount in meat and egg.^{5,6} DHA is a primary structural component of the human brain, cerebral cortex, skin, sperm, testicles and retina.⁷ DHA is the major PUFA in the neuronal membrane. DHA affects serotonergic and dopaminergic neurotransmission and is thus expected to positively influence the various neuropsychiatric disorders.^{8,9}

At present there are a number of formula feeds for infants and school going children containing DHA are available in market. Therefore present study was planned to study the effect of pure DHA supplementation in depression and, these effects are compared with the standard antidepressants drugs, respectively.

METHODS

All animals were available in animal house of Department of Pharmacology GR medical college Gwalior. Mice were housed in clean polypropylene cages; mice were accommodated in each cage in a controlled environment (26°-28°C) with a 12 hour light and dark cycle and provided with food and water.

The experimental protocol was approved by institutional Animal Ethics Committee (IAEC) of G. R. M. C. Gwalior registration no: 846/GO/Ere/S/04/CPCSEA.

DHA (IUPAC name: all cis- docosa-4,7,10,13,16,19-hexaenoic acid, trivial name- Cervonic acid, chemical formula: C₂₂H₃₂O₂, and molecular weight: 328.488) was obtained from Green Heaven India (An Herbal Manufacturing Unit). Fluoxetine (Cadila Pharma) was purchased from the medical stores.

Experimental procedures

The study was carried out in 24 male Albino mice weighing 30-40g. The animals were randomly divided into 4 groups of 6 mice each. The animals in group 1 (GA10) were given 0.5 ml of the vehicle orally 2% GA suspension. Animals in group 2 (DHA200) and group 3 (DHA300) were administered DHA 200mg/kg and 300mg/kg p. o. suspended in 0.5ml of 2% gum acacia suspension respectively. Animals in group 4 (FXT20) were administered fluoxetine 20mg/kg p. o. which is a known antidepressant. All the groups received the respective treatments for a period of 30 days. On the 30th day, 1 h after administration of the drug the effect of the drugs on depression recorded by FST and TST.

Forced swim test (FST)

This paradigm was performed as described previously Porsolt et al and Siuciak et al with some modifications and presently considered a standard method.¹⁰⁻¹³ Depression

was produced in albino mice by forcing them to swim individually in a glass jar (diameter 20cm, height 30cm) containing fresh water of 20 cm height and maintained at 25°C±1°C. Rats were placed in an acrylic cylinder for 15 min (pretest session) after 30 day treatment. After 24 hours of the pretest session, the animals were once again exposed to same condition for 5 min (test session). Between the pretest session and main session drug solutions were administered two times as follows: just after the pretest session and 1 hour before the main test. A rat was judged immobile if it remained floating in the water, except for small movements to keep its head above the water. A decrease in the duration of immobility is indicative of an antidepressant like effect. Following every session, the animal were removed from the cylinder, dried with towels and placed in heated cage for 15 min before returning to their home cage.

Tail suspension test (TST)

Tail suspension test (TST) was performed according to Steru et al.¹⁴ Mice were suspended on the edge of a table, 50cm above the floor, with the help of an adhesive tape placed approximately 1 cm from the tip of the tail on the 30th day 1 hour after drug administration. Immobility time was recorded during 6 min period. The standard immobility period for tail suspension method was 3 min. The animals are considered to be immobile when it did not show any movement of the body and hanged passively.

Statistical analysis

Values obtained for FST and TST were given as mean±SEM. All the groups were analysed by one-way ANOVA followed Tukey's multiple comparison test. P <0.05 was considered statistically significant.

RESULTS

Forced swimming test

DHA200 and DHA300 significantly lowered the mean immobility time as compared to GA10 (p<0.05). Effect of DHA300 was more than DHA200 but it was statistically not significant. Standard drug FXT20 significantly decreased the mean immobility time as compare to control and DHA200 (p<0.05). Anti-depressant effect of DHA300 was comparable (p>0.05) with FXT20.

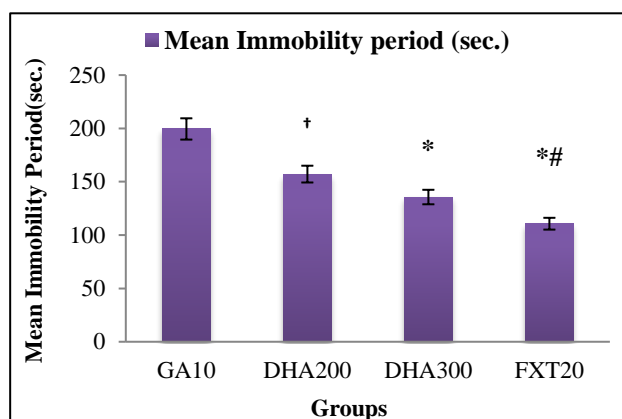
Tail suspension test

Figure 1 shows that DHA200 and DHA300 significantly lowered the mean immobility time as compared to GA10 (p<0.05). The effect of DHA300 was more than DHA200 but was statistically not significant. Standard drug FXT10 also showed significantly decreased mean immobility time as compare to control and DHA200 (p<0.01). Anti-depressant effect of DHA300 was comparable (p>0.05) with FXT20.

Table 1: Effect of Docosahexaenoic Acid (DHA) on immobility period in forced swim test in mice.

Groups no.	Group name	Mean immobility period (sec.)
I	GA10	121.83±3.83
II	DHA200	104.83±2.90 [†]
III	DHA300	95.83±2.61 [*]
IV	FXT20	89.50±4.31 ^{*#}

GA10= Gum acacia 10ml/kg; DHA200 and DHA 300 = Docosahexaenoic acid 200 mg/kg and 300 mg/kg respectively; FXT20 = Fluoxetine 20 mg/kg (standard drug). Each group consists of 6 animals (n=6). Values are mean±SEM, df= 3,20 F=16.28 *p<0.01 as compared to GA10 †p<0.05 as compared to GA10 #p<0.05 as compare to DHA200



GA10= Gum acacia 10ml/kg; DHA200 and DHA300=Docosahexaenoic acid 200mg/kg and 300mg/kg respectively; FXT20=Fluoxetine 20mg/kg (standard drug). Each group consists of 6 animals (n=6). Values are mean±SEM, df= 3,20 F=18.96*p<0.01 as compared to GA10 †p<0.05 as compared to GA10 #p<0.05 as compared to DHA200

Figure 1: Effect of DHA on mean immobility period in tail suspension test in mice.

DISCUSSION

The present study was conducted to assess the antidepressant activity of DHA in albino mice by using FST and TST methods. Stress plays an important role in developing depression. FST and TST animal models are quite sensitive and create physical stress and there by leading to depression. These models of depression provide a rapid and reliable behaviour screening test for antidepressants. Both these models are widely used to screen new antidepressant drugs.¹⁵ Fluoxetine was used as a standard drug for both models in this study.

In our study DHA at the dose of 200mg/kg and 300mg/kg and standard drug fluoxetine showed significant reduction in immobility time in both anti-depressant models i.e. FST and TST. (p<0.01) Fluoxetine showed significant (p<0.05) anti-depressant activity as compared with control and DHA 200mg/kg. The effect of DHA 300mg/kg was comparable (p>0.05) with fluoxetine.

Studies have shown that DHA is a primary structural component of the human brain and retina. Its deficiencies are associated unipolar depression.¹⁶

Antidepressant activity of DHA in our study is in accordance with Wietrzych-Schindler, et al who evaluated that after administration on DHA in 3% ethanol by intraperitoneal injections at volume/weight ratio 3mL/kg for 2 days show significant decrease in immobility period in forced swim test.¹⁷ Antidepressant effect of DHA might be due to its effect on monoamine neurotransmitter systems, red blood cell membranes and HPA axis, or may be due to increase release of glial cell line derived neurotrophic factor (GDNF).^{18,19} There are many human studies which show the effect of DHA on depression. Smith et al. conduct an 8-week open-label pilot trial of low-dose DHA, (260mg or 520mg/day) in 28 patients with major depressive disorder.²⁰

All the above studies revealed the possible mechanism of anti-depressant action of DHA. Furthermore in-vivo and in-vitro studies are required to evaluate the actual mechanism of anti-depressant effect of DHA.

The results of this experimental evaluation after the collection of data and its analysis confirm the antidepressant activity of DHA. However, the study has its share of limitations. There is need to conduct further in-vivo study with more number of animals and in-vitro experiments like receptor density assay and ACTH hormone assay for antidepressant activity, so as to know the exact mechanism of anti-depressant activity of DHA.

ACKNOWLEDGEMENTS

Authors would like to thank to Green Heaven India (A Herbal Manufacturing Unit), Hingna, MIDC, Nagpur, Maharashtra, India for supplying the investigational drug.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Animal Ethics committee of G. R. M. C. Gwalior registration no: 846/GO/Ere/S/04/CPCSEA

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Cite this article as: Singhal T, Kothari S. The effect of docosahexaenoic acid (DHA) supplementation on experimental depression in mice. *Int J Basic Clin Pharmacol* 2018;7:288-91.