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Antidepressant-Like Effect of Amaranth Oil Pre-Treatment In Experimental Myocardial Infarction.

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ABSTRACT

Major depressive disorder (MDD) is a common mood disorder and is highly comorbid with myocardial infarction, heart failure and other cardiovascular diseases. The particular pathophysiological mechanisms are known to link major depressive disorders and coronary artery disease (CAD). CAD and MDD share a common involvement of oxidative stress in their pathophysiological mechanisms; the potential therapeutic role of antioxidants could be very promising. Myocardial infarction (MI) in rats reproduces a behavioral syndrome similar to human depression/cardiovascular comorbidity. In the present study, we aimed at investigation and comparison of amaranth oil and squalene effects on depression in post-infarct period in rats.There were no significant differences between squalene and amaranth oil in two weeks regimen of pre-treatment in behavior tests - time of swimming and immobility in forced swimming test and sucrose preference. The natural composition of cold press amaranth oil with 6% squalene concentration, polyunsaturated fatty acids and tocotrienol tocopherols significantly improved behavioral deficit in both 2 and 4 weeks pretreatment, decreased immobility time and presence of anhedonia in isoproterenol-induced experimental myocardium infarction after 28 days of pre-treatment.

Keywords: squalene, amaranth oil, anhedonia, depression, myocardial infarction, experiment.

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INTRODUCTION

Major depressive disorder (MDD) is a common mood disorder and is highly comorbid with myocardial infarction, heart failure and other cardiovascular diseases. It is considered to be the leading cause of disability and independent risk factor in patients with coronary artery disease all over the world[24, 40]. There is an increased incidence of major depressive disorder and moderate depression in patients with myocardial infarction [13, 26]. Major depression is a strong, well evidenced predictor of mortality after myocardial infarction [9, 10]. The particular pathophysiological mechanisms are known to link major depressive disorders and coronary artery disease. There is much evidence of the stress pathways activation in co-morbid CAD and MDD patients [6, 28, 37]. Since CAD and MDD share a common involvement of oxidative stress in their pathophysiological mechanisms, the potential therapeutic role of antioxidants could be very promising. Amaranth oil, prepared with the cold press method, contains up to 9% of squalene. Squalene, an isoprenoid molecule, can be found in products derived from deep-sea shark (Squalus spp.) liver oil, vegetable oils like amaranth, olive and brown rice oil and is widely used in folk medicine [11]. Antioxidant [18], singlet oxygen quencher [19], membrane stabilizing [5,17] and lipid-lowering properties of squalene contribute to most of beneficial effects of amaranth oil, like hypolipidemic, antiatherosclerotic, anticancer and other activities [35]. Toco-trienol tocopherols, unsaturated fatty acids and polyphenols form unique combination of important nutritive factors of amaranth can also contribute to some effects [27,12,22,29,42].

Myocardial infarction (MI) in rats reproduces a behavioral syndrome similar to human depression/cardiovascular comorbidity. Isoprenaline induces myocardial necrosis primary by an enhance in lipid accumulation in the myocardium and stimulation of lipid peroxidation. Isoprenaline induced myocardial infarction is a a well standardized model for evaluation different effects of many drugs [4, 31].

In the present study, we aimed at investigation and comparison of amaranth oil and squalene effects on depression in post-infarct period in rats.

MATERIALS AND METHODS

Drugs

Isoprenalinel was obtained from Teva Pharmaceutical Ind. LTD, squalene from Sigma-Aldrich Co, St. Louis, MO, USA (Specific gravity: 0.858). Amaranth oil with 6% of squalene was obtained from “RusOliva”, Voronezh, Russia.

Animals

Male albino rats, weighing 180–200 g, were randomly housed in groups of five in a temperature-controlled environment (22 ± 2°C) under a 12-h light/dark cycle, with *ad libitum* access to food and water except during experimental procedures. The experimental protocol was approved by the Voronezh State University Ethics Committee.

Drug treatment

Five days after acclimatization, the animals were randomly distributed into six groups (n = 14). All groups received daily gavage of 1 ml/kg of amaranth oil (AO groups 1 and 2), or squalene composition (6% of squalene in refined corn oil as a vehicle, SQ groups 3 and 4) 2 or 4 weeks before modelling of myocardial infarction and 14 days after isoproterenol injection. Group 5 and 6 received vehicle only (V, refined corn oil). In 15 or 29 days of experiment odd and even-numbered groups correspondingly were intraperitoneally (i.p.) injected with 110 mg/kg isoprenaline (i.p.) for 2 days to produce myocardial infarction [8]. After 2 weeks of last injections of isoprenalinel groups of animals were randomly divided into subgroups for two behavioral tests - sucrose preference test (SPT) and forced swim test (FST). Forced swimming test needs pre-test period with special conditions for a correct assessment of antidepressant effect. Therefore, it was necessary to divide animals into subgroups to avoid cross timing of the tests.

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Sucrose preference test (SPT) was used to evaluate anhedonia. Every cage was offered two bottles containing 250 ml of water and 1% sucrose water for 6 h/day for 5 consecutive days (14-18 days of the experiment). Bottles positions (left vs right) were switched daily to avoid side preference. The preference for the sucrose solution was calculated as a percentage of total liquid consumed. The criterion for anhedonia was based on the ≥ 65% sucrose preference of control animals [16]. Forced Swim Test (FST) [33] was used to assess the immobility of the rats as a measure of their helplessness or depressive-like behavior. Rats were placed individually in a round glass cylinder 18 cm in diameter and 80 cm in height for 5 minto record immobility time. The cylinder was filled with 50 cm water (24±2 °C) to avoid touch the bottom of the pool with animal hind paws or tails. Water was changed every time before the next animal. The rats were exposed to 15 min pretest 24 hr before the test for a correct assessment of antidepressant effect [34]. Immobility, swimming and trying to escape were considered as behavioral states. Swimming behavior was defined as movement throughout the cylinder. The animal was considered immobile when no additional movements were observed other than that required to keep the rat's head above the water.

Statistical analysis

All results were expressed as the mean ± S.D. for seven animals in each group. All the grouped data was statistically evaluated with SPSS 10.0 software. Hypothesis testing methods included one way analysis of variance (ANOVA) followed by Least Significant Difference (LSD) test; significance level at $p < 0.05$ was considered to indicate statistical significance.

RESULTS AND DISCUSSION

In the present investigation, there were similar levels of sucrose water consumption between groups before the experiment. After the myocardial infarction (MI), the sucrose intake was significantly lower in post-MI depression groups ($p< 0.05$, Table 1). The total liquid did not differ significantly between groups in every point of observation. Further comparison showed that amaranth oil 14-days pre-treated rats did not differ significantly from the squalene-treated 14 days group with respect to sucrose intake. After 28 days of treatment, the sucrose intake in amaranth oil group was not sufficiently higher than in squalene group (Table 1).

Table1: Percentage of sucrose intake during 5 days on the sucrose preference test in experimental groups of rats (n = 7 per group, *P < 0.05).

Group №	Pre-treatment	Days	Sucrose intake, % (n = 7 per group).
group 1	Amaranth oil	14	82*
group 2	Amaranth oil	28	89#■
group 3	Squalene+ vehicle	14	83*
group 4	Squalene+ vehicle	28	83#
group 5	Vehicle	14	61
group 6	Vehicle	28	60

Values that have ■ differ significantly ($p < 0.05$) with group 4
Values that have * differ significantly ($p < 0.05$) with vehicle group 5
Values that have # differ significantly ($p < 0.05$) with vehicle group 6

Table 2: Performance of rat groups in the forced swim test (n = 7 per group, *P < 0.05).

Group №	Pre-treatment	Days	Swimming, sec	Escape, sec	Immobility, sec
group 1	Amaranth oil	14	203,57±2,51*	73,71±2,81	22,71±4,64*
group 2	Amaranth oil	28	215,85±2,91#●■	68,57±2,44	15,57±3,6#●■
group 3	Squalene+ vehicle	14	202,86±3,34*	78,29±2,92	18,86±4,10*
group 4	Squalene+ vehicle	28	202,43±3,15#	75,43±2,23#	22,14±4,60#
group 5	Vehicle	14	172,43±4,43	88,71±2,06	38,86±4,3
group 6	Vehicle	28	182,14±3,13	87,57±2,23	30,29±3,73

Results are mean ± SD for 7 animals; one way ANOVA.

Values that have ● differ significantly ($p < 0.05$) with group
Values that have ■ differ significantly ($p < 0.05$) with group 4
Values that have * differ significantly ($p < 0.05$) with vehicle group 5
Values that have # differ significantly ($p < 0.05$) with vehicle group 6

In the forced swim test, we observed that MI calls an increase in immobility and a decrease in swimming time in vehicle groups 5-6 compared to pre-treated groups. Escape time was similar between groups whereas vehicle groups demonstrated lengthening of immobility time and less swimming time than all pre-treated groups (groups 1-4). Both amaranth oil and squalene shortened immobility time. The significant difference ($P < 0.05$) was evaluated between groups that received amaranth oil and squalene pre-treatment during 28 days (Table 2).

Both behavioral tests are specific to antidepressant like activity. The reduced sucrose preference is an indicator of anhedonia in rodents. The results suggest that MI induces anhedonia can be reversed by a long term pre-treatment with squalene and amaranth oil. The current data reports decrease anhedonia in experimental groups received amaranth oil or squalene during 14 and 28 days before the experiment. In the forced swim test, we observed that pre-treated animals improved behavioral deficit. The duration of pre-treatment was a significant factor in the group that received amaranth oil. 28 days treatment improved results of swimming test, in comparison with 14 days treatment.

Earlier reported studies proved effectiveness of antioxidants in depression. Major depression is characterized by low concentration of antioxidants (zinc, coenzyme Q10, etc). [23].Depression is correlated with lipid peroxidation [39].It was estimated that rats under chronic unpredictable stress (CUMS) or in post-MI depression treated with some antioxidants, showed reduced neuronal apoptosis and inhibited inflammatory cytokines [36], enchances of memory function in depression[14], improve the depression-like emotional status and associated cognitive deficits in CUMS rats [20, 3]. The higher antidepressive activity of cold-pressed amaranth oil in comparison with the same concentration squalene composition is possibly not only based on squalene antioxidant properties. The important nutrients like poly- and monounsaturated fatty acids, tocopherols, phytorosterols and polyphenols are present in cold press amaranth oil. The mechanisms involved in the antidepressant activity of essential fatty acidsin experimental myocardial infarction or cardiomyopathy, are associated with their anti-oxidant, anti-inflammatory, and anti-apoptotic properties [41]. Polyunsaturated fatty acids may be more likely to improve depressive symptoms in CAD patients with pre-treatment evidence of oxidative stress [25]. Another potent antioxidant, Vitamin E (Vit E), is presented in amaranth oil in its most active tocotrienol form. It is considered to prolong survival in patients and animals after myocardial infarction. Vit E may exert beneficial effects both on heart and brain by reducing oxidative stress in acute myocardial infarction [38].Polyphenols and flavonoids were also reported as potent antioxidants effective as a cell protector against oxidative injury in myocardial infarction and depression [1,7].

CONCLUSIONS

The long-term squalene and amaranth oil pre-treatment demonstrated protective activity against post-myocardial infarction depression in rats. There were no significant differences between squalene and amaranth oil in two weeks regimen of pre-treatment in behavior tests - time of swimming and immobility in forced swimming test and sucrose preference. The natural composition of cold press amaranth oil with 6% squalene concentration, polyunsaturated fatty acids and tocotrienol tocopherols significantly improved behavioral deficit, decreased immobility time and presence of anhedonia in isoproterenol-induced experimental myocardium infarction after 28 days of pre-treatment.

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