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Potential for daily supplementation of n-3 fatty acids to reverse symptoms of dry eye in mice

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ABSTRACT

The purpose of this study was to determine the change in tear volume, as a predominant symptom of dry eye syndrome, in dietary n-3 fatty acid deficient mice compared with n-3 fatty acid adequate mice. The tear volume in n-3 fatty acid deficient mice was significantly lower than that in n-3 fatty acid adequate mice. In addition, the concentration of n-3 fatty acid in the lacrimal and meibomian glands, which affects the production of tears, was markedly decreased compared with n-3 fatty acid adequate mice. However, the tear volume recovered almost completely after one week of continuous administration of fish oil containing EPA and DHA in n-3 fatty acid deficient mice. Also, the concentration of DHA in the meibomian gland of n-3 fatty acid deficient group recovered to approximately 80% more than that of n-3 fatty acid adequate group. These results suggested that dietary n-3 fatty acids deficiency showed reversible dry eye syndrome, and that n-3 fatty acids have an important role in the production of tears.

1. Introduction

The n-3 fatty acids that are present in fish oil, particularly docosahexaenoic acid (DHA, 22: 6n-3), are accumulated and distributed at high concentration in the nervous systems such as brain and retina [1–3]. In animal studies and human clinical trials, it has been revealed that n-3 fatty acids have an important role in learning and memory, emotional behavior and visual function [4,5]. Retina is the main organ responsible for the visual function, and contains approximately 50 mol% DHA in the rod outer segment membranes. The n-3 fatty acid deficient (n-3 Def) animals significantly decreased retinal sensitivity compared with the animals fed with n-3 fatty acid adequate (n-3 Adq) diet [6,7]. These results suggest that the retinal function has correlation with the concentration of retina DHA.

The dry eye syndrome is a common ocular surface disease with chronic symptoms such as eye irritation and blurred vision, although it is not a severe disorder. The main cause of this disease has been thought to be a decrease in tear secretion and/or inflammation around eye. It has been known that the n-3 fatty acids and its metabolic products suppress the inflammation around the eye. The dietary α-linolenic acid (ALA, 18:3n-3)

Table 1
Composition of experimental diets.

	Amount (g/100 g diet)	
	n-3 Adq.	n-3 Def.
Casein, vitamin free	20	20
Carbohydrate:	63	63
Cornstarch	15	15
Sucrose	13	13
Glucose	20	20
Dextrose	7.5	7.5
Maltose-dextrin	7.5	7.5
Cellulose	5	5
Mineral–salt mix	3.5	3.5
Vitamin mix	1	1
L-Cystine	0.3	0.3
Choline bitartrate	0.25	0.25
TBHQ	0.002	0.002
Fat:	7	7
Hydrogenated coconut oil	5.43	5.67
Safflower oil	1.24	1.33
Flaxseed oil	0.34	None
Fatty acid composition (% of total fatty acids)		
Saturates	77.6	80.8
Monounsaturates	4.5	3.7
18:2n-6	14.2	14.3
18:3n-3	2.7	0.1
n-6/n-3	5.3	109.5

The two experimental diets, an n-3 fatty acid adequate diet (n-3 Adq) and an n-3 fatty acid deficient diet (n-3 Def), were based on the AIN-93 formulation with several modifications to obtain the extremely low basal level of n-3 fatty acid required in this study.

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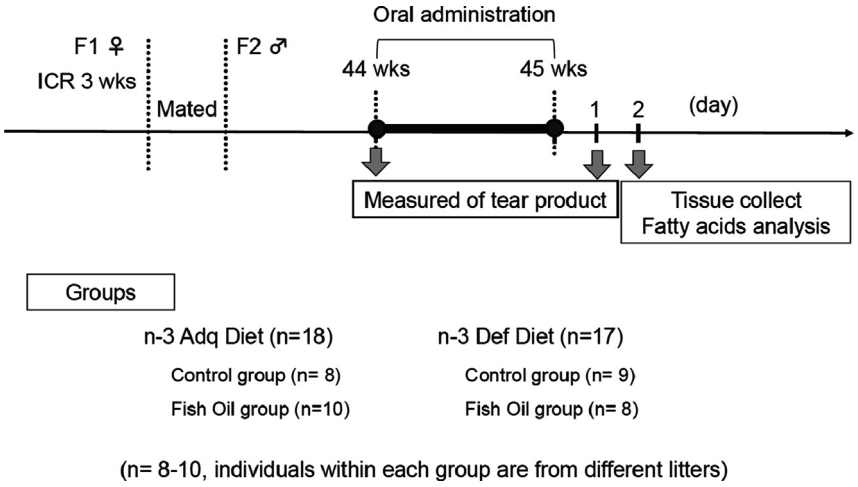

Fig. 1. A schematic diagram of the study design. Following the first measurement of the tear production, a half of the mice in each diet group were administrated either fish oil or palm oil for a week. After the administration of fish oil, the tear production of each mouse was measured again, and plasma and the eye circumference organs were collected in order to analyze fatty acid composition.

Table 2
Fatty acid composition of fish and palm oil.

Fatty acid	Fish oil	Palm oil
Total sat.	**10.4**	**50.1**
Total monounsat.	**24.1**	**39.0**
18:2n-6	1.1	9.9
20:4n-6	1.0	nd
Total n-6 PUFAs	**2.6**	**9.9**
18:3n-3	0.7	0.2
20:5n-3	29.9	nd
22:5n-3	2.6	nd
22:6n-3	13.0	nd
Total n-3 PUFAs	**51.1**	**0.2**
Total fatty acids (mg/g)	**961.3**	**900.1**

Fatty acid methyl esters from 10:0 to 24:1n-9 were analyzed; nd was not detected (*i.e.* < 0.01%).

prevented the increase of the murine dry eye signs, through suppression of the inflammation [8]. Also, neuroprotectin D1 derived from DHA protects the retinal pigment epithelial cells from oxidative stress-induced apoptosis and inhibits IL-1β-stimulated expression of a promoter transfected into those cells [9], and ocular instillation of resolvin E1 derived from eicosapentaenoic acid (EPA, 20:5n-3) decreases inflammation in the corneal epithelial cells and promotes the tear production in a dry eye mouse model [10]. These studies, using the dry eye model with treatment of chemicals, had been focused on the effects of n-3 fatty acids and its metabolites on the inflammation. However, there is little research on relationship between tear secretion and dietary n-3 fatty acids.

In the present experiment, therefore, we examined the relationship of tear secretion and dietary n-3 fatty acids, and investigated the reversibility by supplementation of dietary n-3 fatty acids in the dry eye syndrome without inflammation.

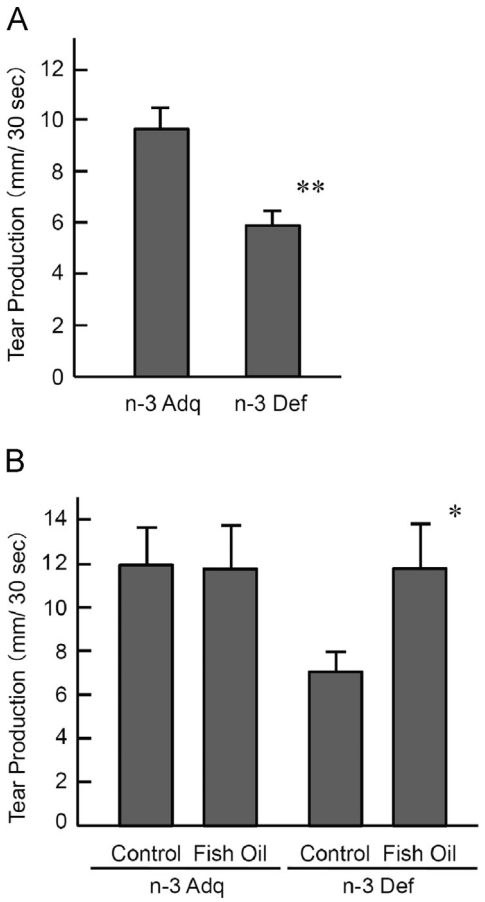

Fig. 2. The difference of the tear production between n-3 Adq and n-3 Def groups (A). The data are presented as mean ± SEM (n = 17–18). *$P < 0.05$; n − 3 Adq *vs.* n − 3 Def (t-test). The effect of fish oil on the tear production in each diet group (B). The data are presented mean ± SEM (n = 8–10). **$P < 0.001$; control *vs.* fish oil in n − 3 Def (t-test).

2. Materials and methods

2.1. Experimental diets

The two experimental diets (n-3 Def and n-3 Adq) were based on the AIN-93G dietary recommendations for rodents [11] (Table 1). The fat content in both diets was 7% (w/w) and mainly consisted of hydrogenated coconut and safflower oils. The major difference between two experimental diets was the concentration of n-3 fatty acids by addition of flaxseed oil containing ALA in n-3 Adq diet. The concentrations of n-3 fatty acids in n-3 Def and n-3 Adq diets were 0.1% and 2.7%, respectively. There was no difference in the total n-6 fatty acids, consisting of only linoleic acid (LNA, 18:2n-6), in the two diets (n-3 Def, 14.4%; n-3 Adq, 14.3%).