Original Paper

Anxiety and Adipose Essential Fatty Acid Precursors for Prostaglandin E1 and E2

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Key words: humans, stress, anxiety, adipose tissue, essential fatty acids, prostaglandins, Δ6 and Δ5 desaturase

Objective: The purpose of the present study was to investigate the relation between state and trait anxiety and adipose tissue essential fatty acid precursors for prostaglandins E1 and E2.

Methods: The sample consisted of 144 male and female Cretan adults, 23 to 69 years of age. Anthropometric and arterial blood pressure measurements were taken, and adipose tissue samples as well as data concerning general health habits were collected. Dietary data were collected using the weekly food frequency questionnaire and the 24-hour dietary recall method, while state and trait anxiety was assessed through the use of the Spielberger State-Trait Anxiety Inventory (STAI) and the Zung anxiety scale.

Results: State anxiety (STAI) related positively with sex ($p < 0.0003$) and negatively with adipose fat myristic acid (C14:0) ($p < 0.004$). Similarly, Zung trait anxiety related positively with sex ($p < 0.0001$) and negatively with adipose tissue myristic acid (C14:0) ($p < 0.04$). Spielberger trait anxiety related positively with adipose (LA + ALA)/(AA + EPA) ratio ($p < 0.0002$) and negatively with (C14:0) ($p < 0.02$) and dietary monounsaturated fat ($p < 0.03$).

Conclusion: It appears that the positive relation between trait anxiety and adipose (LA + ALA)/(AA + EPA) ratio may stem from the inhibiting role of catecholamines on Δ6 and Δ5 desaturases.

INTRODUCTION

There is a growing interest on the effects of essential fatty acids (EFA) on nervous system development [1,2] and psychopathological states [3–6]. The prostaglandins (PGs) are products of EFA metabolism, often referred to as eicosanoids [7]. Dihomo-gamma-linolenic acid (DGLA) (C20:3*n6*) is the precursor for prostaglandin E1 (PGE1), arachidonic acid (AA) (C20:4*n6*) is the precursor of prostaglandin E2 (PGE2), while Eicosapentaenoic acid (EPA) (C20:5*n3*), is the precursor of prostaglandin E3 (PGE3) [8] (Fig. 1). PGs are released from sympathetically innervated tissues, they are present in the brain and cerebrospinal fluid and mediate pre- and postsynaptic events [9–11]. It is believed that PGs are neuromodulators, i.e., they mediate neurotransmission either by signal transduction or amplification of the signals initially generated by neurotransmitters [9–11]. PGE2 and to a lesser degree PGE1 are reported to inhibit the release of stress-related hormones (epinephrine, norepinephrine, dopamine, histamine, serotonin, and gastrin) [12,13].

A previous study [6] showed that adipose linoleic acid (LA) (C18:2*n6*), an essential fatty acid, related negatively to Type A behavior. Type A behavior is characterized by ambitiousness, perfectionism, competitiveness, hostility, impatience, time urgency and accelerated pace of activities or phenomenological (subjective/self-imposed) stress. LA is a precursor for DGLA and AA, which as already stated, are immediate precursors for PGE1 and PGE2. It was suggested that the inverse relation between LA and Type A behavior reflected the antagonistic role of PGE1 and PGE2 to the hormones released under stress.

Much like stress, anxiety is also associated with sympathetic activation and elevated catecholamine levels [14,15]. The purpose of the present study was to explore the extent to which adipose LA and the derivative eicosanoic precursor pool

Abbreviations: C18:2n6 = LA = linoleic acid, EFA = essential fatty acid, PUFA = polyunsaturated fatty acids, C20:4n6 = AA = arachidonic acid, C14:0 = myristic acid, C16:0 = palmitic fatty acid, C20:3n6 = DGLA = dihomo-gamma-linolenic acid, C18:3n6 = GLA = gamma-linolenic acid, C18:3n3 = ALA = a-linolenic acid, C20:5n3 = EPA = eicosapentaenoic acid, C22:6n3 = EPA = docosahexaenoic acid.

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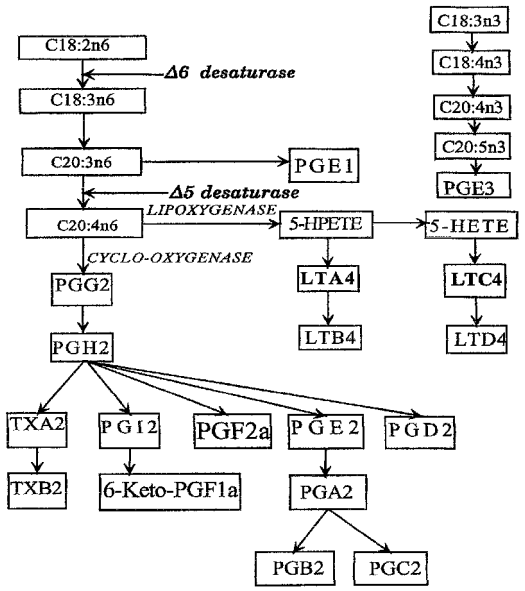

Fig. 1. Pathways in the formation of prostaglandins E1, E2 and E3 in humans.

(DGLA + AA) for PGE1 and PGE2 relate to both state and trait anxiety.

SUBJECTS AND METHODS

In an attempt to evaluate the health and nutrition status of the lawyers of Iraklion County, Crete, Greece, it was agreed that all members of the lawyers association of the particular county would participate in a preventive medicine and nutrition program. Among the 400 members of the association, 286 agreed to participate in this study, while 144 lawyers consented to both an adipose tissue aspiration and psychological testing. All subjects were informed about the nature and the purpose of this study and signed a consent form. The ethical committee at the University of Crete had previously approved the protocol of this research. The mean age of the group was 38 years. The minimum age was 23 while the maximum age was 69 years. The group consisted of 59 female and 85 male subjects. Subjects were interviewed by appointment at the Preventive Medicine and Nutrition Clinic of the University of Crete where they underwent a thorough physical examination and clinical testing. Anthropometric measurements taken included height, weight, Quetelet or body mass index (BMI) (kg/m^2), skinfold thickness and mid-arm circumference. Arterial blood pressure (BP) measurements were taken with a mercury sphygmomanometer. Data concerning dietary habits were collected using the weekly food frequency questionnaire and the 24-hour dietary recall method.

Anxiety was assessed through the use of the Spielberger State-Trait Anxiety Inventory (Form X) [16] and the Zung anxiety scale [17]. The Spielberger State-Trait Anxiety Inventory consists of two questionnaires of 20 items each. The first questionnaire measures state anxiety (how one feels at the moment), while the second questionnaire measures trait anxiety (how one generally feels). Subcutaneous adipose tissue samples were collected by aspiration using methods of Beynen and Katan [18]. Adipose tissue samples were stored in −80°C. Methyl esters of the component fatty acids were then synthesized according to Metcalfe et al [19]. These had been prepared from a human microbiopsy sample and injected into a Perkin-Elmer GC-split ratio 60:1, carrier gas: nitrogen, 70 kPa, column: 50 m × 0.25 μ, Wcot Fused Silica with a programmed oven temperature 1: 140°C and programmed oven temperature 2: 170°C and programmed oven temperature 3: 205°C and programmed oven temperature 4: 225°C. The fatty acid profile of adipose tissue at one site reflects composition at other sites [20]. Nevertheless, samples were taken from same site in all subjects, namely, the left upper outer quadrant of the gluteal area.

Results reported here are those associated with two-tailed probabilities of error of <0.05. Data were analyzed with the aid of the Statistical Package for the Social Sciences (SPSS) software package.

RESULTS

Spielberger state anxiety had a mean of 36.97, a standard deviation of ±11.22, a standard error of the mean of +0.96, a minimum value of 20 and a maximum value of 66. The mode was 29, while the median was 35. Spielberger trait anxiety had a mean of 39.31, a standard deviation of ±9.12, a standard error of the mean of +0.75, a minimum value of 20 and a maximum value of 62. The mode was 37, while the median was 38. Zung trait anxiety had a mean of 31.62, a standard deviation of ±6.10, a standard error of the mean of +0.54, a minimum value of 21 and a maximum value of 49. The mode was 26, while the median was 30. Table 1 depicts means and standard deviations of the adipose fat data by sex. Table 2 shows means and standard deviations of the anthropometric data by sex. Table 3 depicts means and standard deviations of the 24-hour recall dietary data by sex, while Table 4 depicts Pearson's correlations between anxiety and adipose fat variables. Significant Pearson's correlations manifested between the Spielberger state anxiety and adipose palmitic acid C16:0 ($r = -0.16$, $p < 0.05$), adipose C20:5*n3* (EPA) ($r = -0.16$, $p < 0.05$), dietary saturated fatty acid intake ($r = -0.15$, $p < 0.04$) and dietary polyunsaturated to saturated fat ratio ($r = +0.14$, $p < 0.05$). Spielberger trait anxiety correlated with adipose eicosanoic acid (C20:1) ($r = +0.21$, $p < 0.01$) adipose palmitoleic acid (C16:1) ($r = -0.19$, $p < 0.02$), adipose C20:3*n6* (DGLA) ($r = -0.18$, $p < 0.05$), adipose C20:4*n6* (AA) ($r = -0.16$, $p < 0.05$), adipose C22:6*n3* (DHA) ($r = -0.18$, $p < 0.05$), adipose (LA + ALA)/(AA + EPA) ratio ($r = +0.25$,

Table 1. Means and Standard Deviations of the Adipose Fat Data by Sex

	Males n = 85		Females n = 59	
	Mean %	SD	Mean %	SD
C14:0	1.67***	0.49	2.07***	0.44
C16:0	18.02	1.71	17.85	1.79
C16:1	4.1	1.28	4.17	0.83
C18:0	2.97*	0.58	3.23*	0.67
C18:1	53.29*	3.98	51.52*	4.65
LA	11.06***	1.94	12***	2.09
C20:1	0.65	0.15	0.68	0.13
DGLA	0.28	0.15	0.24	0.14
AA	0.39***	0.2	0.29***	0.1
(LA + ALA)/(AA + EPA)	26.98***	9.38	38.39***	11.87
ALA	0.47	0.1	0.47	0.11
EPA	0.08*	0.17	0.05*	0.06
C22:5*n3*	0.26	0.16	0.23	0.15
DHA	0.3**	0.2	0.2**	0.14
n3	1.10**	0.42	0.95**	0.31
n6	11.9**	1.93	12.8**	2.15
n3/n6	0.9***	0.04	0.07***	0.03
Monounsaturated fat	58.2*	3.9	56.6*	4.52
Polyunsaturated fat	13.1*	1.99	13.8*	2.19
Saturated fat	23.6	2.44	24.4	2.71

Independent samples t-test: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.0005$, n = 144.

Table 2. Means and Standard Deviations of the Anthropometric Data by Sex

	Males n = 85		Females n = 59	
	Mean	SD	Mean	SD
Bicep skinfold (mm)	7.8	4	9.4	3.5
Tricep skinfold (mm)	16**	5.3	22.4**	5
Supraliac skinfold (mm)	23.8*	7.8	18.4*	7.2
Subscapular skinfold (mm)	21.8	8.4	19.1	7.8
Sum of skinfolds (mm)	69.3	21	69.3	21
BMI (kg/m^2)	27.2**	3.2	23.4**	3.1
Body fat (%)	27**	3.2	23.4**	3.1

Independent samples t-test: * $p < 0.005$, ** $p < 0.0005$, n = 144.

Table 3. Dietary Data by Sex

	Males n = 85		Females n = 59	
	Mean	SD	Mean	SD
Calories (kcal)	2081.4*	917.7	1761.5*	700.5
Total fat (g)	95.9	53.7	84.9	41.1
Carbohydrate (g)	226.1*	92.2	187.7*	79.5
Cholesterol (mg)	203.5	185.8	263.2	165.6
Fiber (g)	6.4**	4.4	4.2**	2.8
Protein (g)	74.4*	41.1	60.3*	27.5
Monounsaturated fat (g)	48*	27.1	39.3*	20.8
Polyunsaturated fat (g)	9.8	9.2	9.3	9.1
Saturated fat (g)	27.7	20	26.5	13.5

Independent samples t-test: * $p < 0.05$, ** $p < 0.005$, n = 144.

Table 4. Pearson's Correlations Between Adipose Fat Data and Anxiety

	State anxiety (Spielberger scale)	Trait anxiety (Zung scale)	Trait anxiety (Spielberger scale)
C14:0	−0.12	−0.06	−0.09
C16:0	−0.16*	−0.19*	−0.12
C16:1	−0.15	−0.03	−0.19*
C18:0	0.06	0	0.08
C18:1	0.02	0.09	0.1
C18:2	0.09	0.03	0.05
C20:1	0.1	0.03	0.21**
DGLA	−0.05	−0.11	−0.18*
AA	−0.07	−0.16*	−0.16*
(LA + ALA)/(AA + EPA)	0.14	0.15	0.25**
ALA	0.05	0.03	−0.05
EPA	−0.16*	−0.04	−0.15
C22:5*n3*	0.01	0.03	0
DHA	−0.15	−0.1	−0.18*
n3	−0.1	−0.04	−0.15
n6	0.07	0	0
n3/n6	−0.11	−0.03	−0.12
Monounsaturated fat	−0.02	0.09	0.05
Polyunsaturated fat	0.06	−0.01	−0.02
Saturated fat	−0.05	−0.08	−0.04

* $p < 0.05$, ** $p < 0.01$, n = 144.

$p < 0.01$) and dietary monounsaturated fatty acid intake ($r = -0.16$, $p < 0.05$). Zung trait anxiety correlated significantly with adipose palmitic acid (C16:0) ($r = -0.19$, $p < 0.03$) and adipose C20:4*n6* (AA) ($r = -0.16$, $p < 0.05$).

The application of a stepwise multiple linear regression analysis indicated that 9% of the variability in Spielberger state anxiety was significantly accounted for by sex and adipose C14:0 (Table 5). As indicated by both beta and partial correlation coefficients, sex was a stronger predictor of Spielberger state anxiety than C14:0. The application of forward linear regression led to similar results. The application of a stepwise multiple linear regression analysis indicated that 10% of the variability in Zung trait anxiety was significantly accounted for by sex and adipose C14:0 (Table 6). Again, among the parameters studied in this investigation, sex appeared to be the major predictor of Spielberger state anxiety, followed by C14:0. The application of forward linear regression led to similar results. Stepwise multiple linear regression analysis indicated that 13% of the variability in Spielberger trait anxiety was significantly accounted for by C14:0, dietary monounsaturated fatty acid intake and adipose (LA + ALA)/(AA + EPA) ratio (Table 7). Examination of beta and partial correlation coefficients indicates that the major predictor of Spielberger trait anxiety is adipose (LA + ALA)/(AA + EPA) ratio, followed by adipose C14:0 and dietary monounsaturated fatty acid intake. The particular results persisted after serum total cholesterol, diabetes,

Table 5. Multiple Linear Stepwise Regression with Spielberger State Anxiety as the Dependent Measure*

Variables	B	SE	Beta	Partial r	t	p
Sex	7.55	2.04	0.33	0.3	3.69	0.0003
C14:0	−5.56	1.87	−0.26	−0.25	−2.95	0.004
Constant	51.75	4.41			12.28	0.00005

* $F = 8.17$, $p < 0.0004$, R-square = 0.11, adjusted R-square = 0.09.

Variables used: Age, sex, Quetelet index (kg/m^2), adipose C14:0, C16:0, C16:1, C18:0, C18:1, LA, C20:1, adipose (LA + ALA)/(AA + EPA), sum of adipose *n6* fatty acids, sum of adipose *n3* fatty acids, adipose monounsaturated fatty acids, adipose polyunsaturated fatty acids, adipose saturated fatty acids, dietary monounsaturated fatty acids, dietary polyunsaturated fatty acids, dietary saturated fatty acids, dietary carbohydrate, dietary protein, dietary total fat, dietary calories, systolic blood pressure, diastolic blood pressure, serum total cholesterol. Sex is a dummy variable (female = 1, male = 0).

Table 6. Multiple Linear Stepwise Regression with Zung Trait Anxiety as the Dependent Measure*

Variables	B	SE	Beta	Partial r	t	p
Sex	4.3	1.08	0.36	0.33	3.98	0.0001
C14:0	−2.09	0.98	−0.19	−0.19	−2.13	0.04
Constant	37.96	2.2			17.23	0.00005

* $F = 8.18$, $p < 0.0005$, R-square = 0.11, adjusted R-square = 0.10.

Variables used: Age, sex, Quetelet index (kg/m^2), adipose C14:0, C16:0, C16:1, C18:0, C18:1, LA, C20:1, adipose (LA + ALA)/(AA + EPA), sum of adipose *n6* fatty acids, sum of adipose *n3* fatty acids, adipose monounsaturated fatty acids, adipose polyunsaturated fatty acids, adipose saturated fatty acids, dietary monounsaturated fatty acids, dietary polyunsaturated fatty acids, dietary saturated fatty acids, dietary carbohydrate, dietary protein, dietary total fat, dietary calories, systolic blood pressure, diastolic blood pressure, serum total cholesterol. Sex is a dummy variable (female = 1, male = 0).

Table 7. Multiple Linear Stepwise Regression with Spielberger Trait Anxiety as the Dependent Measure*

Variables	B	SE	Beta	Partial r	t	p
C14:0	−3.6	1.51	−0.21	−0.21	−2.38	0.02
Dietary monounsaturated fat	−0.08	0.03	−0.19	−0.20	−2.3	0.03
Adipose (LA + ALA)/(AA + EPA) ratio	0.25	0.07	0.33	0.32	3.79	0.0002
Constant	41.3	3.55			11.64	0.00005

* $F = 7.37$, $p < 0.0001$, R-square = 0.15, adjusted R-square = 0.13.

Variables used: Age, sex, Quetelet index (kg/m^2), adipose C14:0, C16:0, C16:1, C18:0, C18:1, LA, C20:1, adipose (LA + ALA)/(AA + EPA), sum of adipose *n6* fatty acids, sum of adipose *n3* fatty acids, adipose monounsaturated fatty acids, adipose polyunsaturated fatty acids, adipose saturated fatty acids, dietary monounsaturated fatty acids, dietary polyunsaturated fatty acids, dietary saturated fatty acids, dietary carbohydrate, dietary protein, dietary total fat, dietary calories, systolic blood pressure, diastolic blood pressure, serum total cholesterol. Sex is a dummy variable (female = 1, male = 0).

body fat, milk and cheese consumption were also included in the variable list of the regression analysis. The application of forward linear regression led to similar results.

DISCUSSION

Contrary to our hypothesis, there was no relation between LA or other EFA precursors for PGE and anxiety (Fig. 1). Instead, a positive relation manifested between (LA + ALA)/(AA + EPA) ratio, an index of Δ6 and Δ5 desaturase, and anxiety. It appears that the observed relation has been reflecting the inhibitory role of catecholamines on Δ6 and Δ5 desaturases, the liver enzymes responsible for desaturating and elongating LA and ALA to AA and EPA, respectively (Fig. 1). Animal research has shown that liver microsomal Δ6 and Δ5 desaturase activity is rate limited and inhibited *in vivo* and *in vitro* by epinephrine and norepinephrine [21–24]. In addition to catecholamines, Δ6 and Δ5 desaturations have been demonstrated to be inhibited by the stress of social isolation [21]. To the best of our knowledge, the observed relation between anxiety and (LA + ALA)/(AA + EPA) ratio has been the first indication for a possible inhibitory effect of anxiety via catecholamines on Δ6 and Δ5 desaturases in human subjects. Should anxiety finally prove to inhibit Δ6 and Δ5 desaturase activity in humans, this might have significant implications for a number of longer-chain PUFA insufficiency-related medical conditions and disease states, such as cardiac rate and blood pressure, alcoholic liver disease and atopic eczema, premenstrual breast pain, diabetic neuropathy and possibly depression [25,26]. Consistent with findings of other studies [27], females in the present study had higher anxiety, both state (Spielberger scale) and trait (Zung scale), than males.

Of special note are the negative relations between adipose myristic acid (C14:0) and all anxiety scales implemented. Specifically, there was a negative relation between state (Spielberger scale) and trait (Zung scale and Spielberger scale) anxiety and adipose C14:0 levels. Although reports are inconsistent [28], there is some indication for an inverse relation between dietary saturated fat and catecholamine [29]. Nevertheless,

caution should be exercised concerning elevating C14:0 levels, as is particular fatty acid along with the palmitic one (C16:0) are the saturated fatty acids most effective in raising serum cholesterol concentrations [30]. Finally, there is some indication that C14:0 may interfere with cell-mediated immunity [31].

In summary, the observed positive relation between trait anxiety and adipose (LA + ALA)/(AA + EPA) ratio, may reflect the inhibiting effect of catecholamines on Δ6 and Δ5 desaturase.

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