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SCHIZOPHRENIC PATIENTS TREATED WITH HIGH DOSE PHENOTHIAZINE OR THIOXANTHENE BECOME DEFICIENT IN POLYUNSATURATED FATTY ACIDS IN THEIR THROMBOCYTES

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Abstract—Total fatty acids were analysed in thrombocytes of schizophrenic patients treated with a "high dose" or "low dose" monotherapy of neuroleptic drugs phenothiazine or thioxanthene. The ratio of the very long chain fatty acid hexacosanoic acid to the long chain fatty acid docosanoic acid (C26:0/C22:0) increased in the "high dose" and "low dose" groups as compared to healthy untreated controls ($P < 0.05$). The polyunsaturated fatty acid arachidonic acid decreased in the "high" and "low dose" groups ($P < 0.01$ and $P < 0.05$). The polyunsaturated fatty acids α-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid were not detectable in most of the "high dose" schizophrenic patients, however, they were found in the "low dose" group and in the controls. There was a negative correlation between the daily dosage of phenothiazine and the percentages of the polyunsaturated fatty acids arachidonic acid and α-linolenic acid + eicosapentaenoic acid + docosahexaenoic acid in thrombocytes ($r = -0.87$, $P < 0.01$ and $r = -0.81$, $P < 0.01$). Two patients of the "high dose" group with an especially high and long lasting monotherapy of neuroleptics were nearly devoid of polyunsaturated fatty acids in their thrombocytes. Untreated schizophrenic patients exhibited a fatty acid pattern in their thrombocytes not markedly different from that of the healthy untreated control group. We conclude that neuroleptic drugs phenothiazine or thioxanthene can alter the fatty acid pattern of thrombocytes.

Fatty acids undergo β-oxidation to acetyl-CoA in mitochondria and peroxisomes. However, very long chain fatty acids like hexacosanoic acid are solely oxidized in peroxisomes. Therefore, accumulation of hexacosanoic acid takes place in the congenital syndrome of Zellweger caused by deficiency of peroxisomes [1]. Recently, it has been shown that peroxisomal β-oxidation of fatty acids is selectively inhibited in the experimental animal by phenothiazine [2]. Therefore, we investigated whether a similar phenomenon is caused in humans by therapeutic doses of phenothiazine or thioxanthene.

METHODS AND MATERIALS

Patients

Individuals taking part in the study were divided into four groups. Group A consisted of nine patients (two females, seven males; age 24–42 years) who were treated for acute exacerbation of schizophrenia with a "high dose" monotherapy of phenothiazine (perazine, 275–400 mg daily) or thioxanthene (flupentixol, 20–30 mg daily). One patient of the "high dose" group received 360 mg levomepromazine daily in addition to 30 mg flupentixol. Group B consisted of seven patients (five females, two males; age 35–53 years) who were treated for schizophrenia with a "low dose" monotherapy of phenothiazine (perazine, 100–200 mg daily) or thioxanthene (flupentixol, 10–15 mg daily). Generally, patients of the "high dose" group A were in-patients of the psychiatric ward of the hospital whereas patients on the lower maintenance dose (group B) were out-patients. Two schizophrenic patients without any neuroleptic medication also participated and were assigned to group C. Furthermore, a control group of six healthy individuals (six males; age 21–41 years) not taking any medication was included in the study (group D). Groups and characteristics of patients, their medication, dosage and duration of medication are shown in Table 1.

Study protocol

Blood was drawn from an antecubital vein into lithium heparinate to gain platelet rich plasma and washed thrombocytes. Also liver parameters ALT, AST and γ-GT were determined and a blood cell count was performed (leukocytes, erythrocytes, thrombocytes). Differential blood cell count included neutrophils, lymphocytes, monocytes, eosinophils and basophils.

Analytical methods

Platelet isolation. Platelet-rich plasma was gained by low speed centrifugation for 15 min of the heparinized blood (800 rpm). Platelets were separated from plasma by higher speed centrifugation (3000 rpm), washed twice with saline and finally suspended in 0.5 mL saline. Heptadecanoic acid (5 μg) (C17:0) was added as the internal standard.

Platelet total fatty acids. Platelet total fatty acids

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Table 1. Groups and characteristics of patients, medication, dosage and duration of medication

	Age (years)	Sex	Medication	Dosage (mg; daily)	Duration of medication (days)
Group A (high dosage patients)					
1. DJ	42	F	Perazine	400	18
2. SG	24	M	Perazine	400	29
3. AK	32	F	Perazine	300	16
4. VT	30	M	Perazine	300	140
5. ST	38	M	Perazine	275	56
6. BA	32	M	Levomepromazin + Flupentixol	360 + 30	56
7. MH	31	M	Flupentixol	20	10
8. DH	28	M	Flupentixol	20	20
9. KK	33	M	Flupentixol-D	40*	14
Group B (low dosage patients)					
1. MJ	53	F	Perazine	150	84
2. SG	35	F	Perazine	150	98
3. BM	35	F	Perazine	100–200	6
4. FS	49	M	Perazine	100	>700
5. FH	56	F	Perazine	100	>700
6. SG	39	F	Flupentixol	10–15	>28
7. WF	53	M	Flupentixol	10–15	28
Group C (untreated patients)					
1. TM	33	F	—	—	—
2. SG	24	M	—	—	—
Group D (healthy controls without any medication)					
1. BU	31	M	—	—	—
2. BF	41	M	—	—	—
3. SB	21	M	—	—	—
4. SG	37	M	—	—	—
5. BE	35	M	—	—	—
6. CW	32	M	—	—	—

* i.m./14 daily.

were determined as described in detail for plasma total fatty acids by Moser *et al* [1, 3]. In short, the platelet suspension was extracted for total lipids with 5 mL of chloroform/methanol (1:1), centrifuged after 1 hr, chloroform (2.5 mL) and water (1.5 mL) added to the supernatant and the upper phase discarded. The lower phase was washed twice with chloroform/methanol/water (15:240:235) according to Folch *et al.* [4], evaporated under N_2 and fatty acids were converted to methylesters by 1 N methanolic HCl in capped tubes (75°, 16 hr). The fatty acid methylesters were purified by TLC using silica plates with toluene/ether (97:3) as the solvent system. Fatty acid methylesters were visualized with iodine vapor and eluted with hexane/benzene (6:4). The eluate was dried under N_2 and dissolved in 250 μL hexane for gas–liquid chromatography.

Capillary gas–liquid chromatography. Gas–liquid chromatography was performed with a CP Sil 88 fused silica capillary column of 25 m length and 0.32 mm i.d. (Chrompack, The Netherlands). The temperature program ranged from 80° to 200° with an increase of 12°/min and hydrogen was used as carrier gas.

Materials

Authentic standards of palmitic acid (C16:0), heptadecanoic acid (C17:0), stearic acid (C18:0), oleic acid (C18:1 n–9), linoleic acid (C18:2 n–6), α-linolenic acid (C18:3 n–3), arachidonic acid (C20:4 n–6), eicosapentaenoic acid (C20:5 n–3), docosanoic acid (C22:0), docosahexaenoic acid (C22:6 n–3), tetracosanoic acid (C24:0) and hexacosanoic acid (C26:0) were purchased from Sigma (Munich, F.R.G.). All solvents were of analytical grade.

RESULTS

Increased ratio of hexacosanoic to docosanoic acid (C26:0/C22:0) in platelet total fatty acids

The ratio of the very long chain fatty acid C26:0 to the long chain fatty acid C22:0 was significantly higher in the "high dose" group A as compared to the "low dose" group B or the control group D ($P < 0.05$). In two untreated patients the ratio was comparable to that of healthy controls. Ratios C26:0/C22:0 are shown in Table 2.

Decreased levels of polyunsaturated fatty acids (PUFAs) in platelet total fatty acids*

The pattern of total fatty acids in the platelets of the different groups of patients is shown in Table 3. Whereas C16:0 remained at the same percentage in the various groups, C18:0 was higher in group A as compared to groups B ($P < 0.05$) and D ($P < 0.01$). C18:0 was also higher in group B as compared to group D ($P < 0.01$). C18:1 only tends to be lower in

* Abbreviations: PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

Table 2. Ratios of the very long chain fatty acid hexacosanoic acid (C26:0) to the long chain fatty acid docosanoic acid (C22:0) in thrombocytes of the individuals of groups A–D

Group A	Group B	Group C	Group D
1. DJ 0.029	1. MJ 0.012	1. TM 0.009	1. BU 0.024
2. SG 0.032	2. SG 0.017	2. SG 0.010	2. BF 0.016
3. AK 0.030	3. BM 0.013		3. SB 0.013
4. VT 0.055	4. FS 0.003		4. SG 0.009
5. ST 0.007	5. FH 0.047		5. BE 0.011
6. BA 0.046	6. SG 0.010		6. CW 0.012
7. MH —	7. WF 0.013		
8. DH 0.010			
9. KK 0.042			
mean ± SD 0.031 ± 0.016*,*	mean ± SD 0.016 ± 0.014		mean ± SD 0.014 ± 0.005

The unpaired t-test was used to calculate significancies.
* $P < 0.05$. In group A the first significancy is relative to group B, the second significancy is relative to group D.

group A as compared to groups B and D. C18:2 was lower in group A as compared to groups B ($P < 0.05$) and D ($P < 0.005$). It was also lower in group B as compared to group D ($P < 0.05$). C18:3 was not detectable in any of the participants of the "high dose" group A. Arachidonic acid C20:4 was lower in the "high dose" group A as compared to group B ($P < 0.01$) and as compared to the control group D ($P < 0.0005$). This PUFA was also lower in group B as compared to group D ($P < 0.05$). C20:5 and C22:6 were not detectable in many participants of group A. C22:6 in group A was lower as compared to groups B ($P < 0.005$) or D ($P < 0.0005$). Whereas C20:5 in group B was not different to group D, C22:6 was lower in group B as compared to group D ($P < 0.05$). The saturated fatty acid (SFA) C22:0 was higher in group A as compared to groups B and D ($P < 0.05$). SFAs C24:0 and C26:0 only tended to be higher in the "high dose" group A as compared to groups B and D due to high variability. The two untreated schizophrenic patients of group C did not show marked differences in the fatty acid pattern of their platelets as compared to group D of healthy controls without any medication.

Increased ratios of saturated fatty acids to polyunsaturated fatty acids in platelets

The ratios of fatty acids in the platelets of the different groups of patients are shown in Table 4. The ratio SFAs/PUFAs in group A was higher as compared to groups B and D ($P < 0.05$) as was the ratio in group B compared to group D ($P < 0.05$). The ratios SFAs/C18:2, C20:4, C20:5 and C22:6 in group A were not different when compared to group B, however, the ratios SFAs/C18:2 and SFAs/C22:6 were higher when compared to group D ($P < 0.005$ and $P < 0.05$). The ratio C22:0/C20:4 in group A was not different when compared to group B and D. When ratios of platelet fatty acids in group B were compared to those of group D they were significantly higher ($P < 0.05$) except the ratio SFAs/C20:5. Ratios of platelet fatty acids of the two untreated patients (group C) showed no marked difference to ratios of platelet fatty acids of healthy controls (group D).

Very high ratios of SFAs/PUFAs in two patients

In the platelets of the two patients VT and BA, ratios of SFAs/PUFAs and of SFAs/C20:4 were especially high: 32 and 32 (VT) and 36 and 178 (BA), respectively (Table 4).

Negative correlation between daily dose of phenothiazine and platelet PUFA content

The correlation between the daily intake of phenothiazine and the percentage of the PUFAs C20:4 and C18:3 + C20:5 + C22:6 in platelets was negative (Fig. 1). Also the correlation between phenothiazine intake and content of C18:2 was negative ($= -0.56$, $P < 0.05$). The ratio SFAs/PUFAs correlated positively to the daily intake of phenothiazine ($r = 0.58$, $P < 0.02$). There was also a positive correlation between the daily intake of phenothiazine and the percentage of the SFAs C18:0 and C22:0 in platelets ($r = 0.63$, $P < 0.01$ and $r = 0.56$, $P < 0.02$).

Unaltered liver parameters and blood cell counts

Liver parameters ALT, AST and γ-GT were in the normal range in the patients. Also the blood cell counts and the differential blood cell counts in the patients were in the normal range.

DISCUSSION

One finding of this study was that in humans the widely used neuroleptic drugs phenothiazine and thioxanthene inhibit the β-oxidation of very long chain fatty acids thus confirming previous reports from animal experiments [2, 5–7]. However, the new and surprising result of our study was the strong and dose-dependent decline of PUFAs in the thrombocytes of schizophrenic patients treated with a monotherapy of these drugs.

We chose thrombocytes as a model system as these blood cells are easily accessible and have a life span of 1–2 weeks. Likewise, the duration of medication for many patients was in the range of 6–30 days. Three groups of schizophrenic patients and a healthy, untreated control group were studied.

Table 3. Pattern of total fatty acids (rel%) in the platelets of the different groups of patients

	C16:0	C18:0	C18:1	C18:2	C18:3	C20:4	C20:5	C22:0	C22:6	C24:0	C26:0
Group A (high dose patients)											
1. DJ	19.0	42.1	10.2	4.0	ND	1.9	ND	14.6	ND	8.2	0.4
2. SG	22.6	30.3	25.6	3.0	ND	7.1	0.1	7.8	0.3	3.2	0.2
3. AK	32.9	29.0	17.9	4.6	ND	4.9	ND	6.7	ND	4.1	0.2
4. VT	9.9	61.0	0.8	—	ND	3.0	ND	16.4	ND	8.1	0.9
5. ST	21.2	31.7	25.9	3.4	ND	6.8	0.3	7.0	0.7	2.9	0.05
6. BA	7.9	42.4	8.4	2.0	ND	0.5	ND	22.2	ND	16.7	1.02
7. MH	23.4	29.6	24.8	2.9	ND	7.7	ND	8.3	ND	3.3	ND
8. DH	20.2	31.9	26.9	2.9	ND	6.3	ND	8.4	0.2	3.2	0.08
9. KK	25.3	35.4	18.7	3.9	ND	5.1	ND	8.3	ND	3.3	0.3
mean ± SD	20.3 ± 7.6	37.0 ± 10.3*†	17.7 ± 9.3	3.0 ± 1.3*‡	ND	4.8 ± 2.5†§	0.04 ± 0.1	11.1 ± 5.4**	0.1 ± 0.2‡§	5.9 ± 4.6	0.35 ± 0.37
Group B (low dose patients)											
1. MJ	23.9	26.5	22.4	6.4	ND	11.5	0.6	6.1	0.6	2.1	0.07
2. SG	17.5	34.1	23.4	2.9	ND	6.0	0.1	10.0	0.3	5.6	0.2
3. BM	24.0	31.8	20.0	3.1	0.2	7.6	0.2	8.6	0.2	4.1	0.1
4. FS	21.8	25.7	22.6	4.2	0.1	16.3	0.4	5.6	1.1	2.4	0.02
5. FH	16.9	29.8	21.3	4.5	0.1	12.6	0.7	7.6	1.2	5.0	0.4
6. SG	19.8	25.1	20.3	4.8	ND	18.0	0.6	7.1	1.1	3.2	0.07
7. WF	27.6	28.3	22.1	3.5	ND	7.5	0.4	6.8	0.3	3.5	0.09
mean ± SD	21.6 ± 3.9	28.8 ± 3.3†	21.7 ± 1.2	4.2 ± 1.2*	0.06 ± 0.08	11.4 ± 4.6*	0.4 ± 0.2	7.4 ± 1.5	0.7 ± 0.4*	3.7 ± 1.3	0.14 ± 0.13
Group C (untreated patients)											
1. TM	23.3	27.1	22.4	4.7	ND	13.2	0.3	6.0	0.5	2.5	0.05
2. SG	22.6	31.7	23.1	5.0	0.09	8.1	0.2	5.9	0.3	2.8	0.06
Group D (healthy controls without any medication)											
1. BU	11.6	26.5	17.7	5.5	ND	20.5	0.5	10.0	1.7	5.9	0.24
2. BF	23.0	23.5	23.5	4.9	0.04	13.1	1.2	5.8	1.4	3.6	0.09
3. SB	23.0	24.0	21.3	5.0	ND	15.3	0.5	5.8	0.9	3.4	0.08
4. SG	22.5	23.8	22.3	6.3	0.08	14.3	0.1	6.3	1.0	3.3	0.06
5. BE	23.7	24.4	19.7	4.4	0.03	16.5	0.5	6.2	1.1	3.5	0.07
6. CW	23.2	23.8	22.5	5.0	0.06	16.5	0.5	4.8	1.2	2.5	0.06
mean ± SD	21.3 ± 4.8	24.3 ± 1.1	21.2 ± 2.1	5.2 ± 0.6	0.04 ± 0.03	16.0 ± 2.6	0.6 ± 0.4	6.5 ± 1.8	1.2 ± 0.3	3.7 ± 1.1	0.10 ± 0.07

Fatty acids are designated by number of carbon atoms and number of double bonds. C16:0 = palmitic acid, C18:0 = stearic acid, C18:1 = oleic acid, C18:2 = linoleic acid, C18:3 = α-linolenic acid, C20:4 = arachidonic acid, C20:5 = eicosapentaenoic acid, C22:0 = docosanoic acid; C22:6 = docosahexaenoic acid, C24:0 = tetracosanoic acid, C26:0 = hexacosanoic acid.

ND, not detectable.

The unpaired *t*-test was used to calculate significancies. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.005$; § $P < 0.0005$. In group A the first significancy is relative to group B, the second significancy is relative to group D. In group B the significancy is relative to group C.

Table 4. Ratios of fatty acids in the different patient groups

	Ratios of fatty acids						
	SFAs PUFAs	SFAs C18:2	SFAs C18:3	SFAs C20:4	SFAs C20:5	SFAs C22:6	C22:0 C20:4
Group A (high dose patients)							
1. DJ	14	21	—	44	—	—	7.7
2. SG	6.1	21	—	9.0	641	214	1.1
3. AK	7.7	16	—	15	—	—	1.4
4. VT	32	—	—	32	—	—	5.5
5. ST	5.6	19	—	9.3	210	90	1.0
6. BA	36	45	—	178	—	—	44
7. MH	6.1	22	—	8.4	—	—	1.1
8. DH	6.8	22	—	10	—	319	1.3
9. KK	8.0	19	—	14	—	—	1.6
mean ± SD	14 ± 12**	23 ± 9.0^{NS}†	—	36 ± 55$^{NS.NS}$	426$^{NS.NS}$	208 ± 115^{NS}*	7.2 ± 14.0$^{NS.NS}$
Group B (low dose patients)							
1. MJ	3.1	9.2	—	5.1	98	98	0.5
2. SG	7.2	23	—	11	674	225	1.7
3. BM	6.1	22	343	9.0	343	343	1.1
4. FS	2.5	13	555	3.4	139	50	0.3
5. FH	3.1	13	596	4.7	85	50	0.6
6. SG	2.3	12	—	3.1	92	50	0.4
7. WF	5.7	19	—	8.8	166	221	0.9
mean ± SD	4.3 ± 2.0*	16 ± 5.4*	498 ± 136*	6.4 ± 3.1*	288 ± 216	148 ± 116*	0.8 ± 0.5*
Group C (untreated patients)							
1. TM	3.1	13	—	4.5	196	118	0.5
2. SG	4.6	13	701	7.8	316	210	0.7
Group D (healthy controls without any medication)							
1. BU	1.9	9.8	—	2.6	108	32	0.5
2. BF	2.7	11	1398	4.3	47	40	0.4
3. SB	2.6	11	—	3.7	114	63	0.4
4. SG	2.6	8.9	699	3.9	559	56	0.4
5. BE	2.6	13	1927	3.5	116	53	0.4
6. CW	2.3	11	905	3.3	109	45	0.3
mean ± SD	2.5 ± 0.3	11 ± 1.4	1157 ± 429	3.6 ± 0.6	176 ± 190	48 ± 11	0.4 ± 01

The unpaired *t*-test was used to calculate significancies. NS, not significant; * $P < 0.05$; † $P < 0.005$. In group A the first significancy is relative to group B, the second significancy is relative to group D. In Group B the significancy is relative to group D.

Patients underwent a "high dose" or "low dose" monotherapy or had no medication at all. PUFAs in thrombocytes declined especially in the "high dose" group as compared to the healthy controls. To our knowledge a similar decrease of PUFAs in tissue of patients with peroxisomal disease has not yet been described [8]. Percentage of fatty acids in platelets was variable in the "high dose" group suggesting a disturbance in the fatty acid pattern especially by a "high dose" monotherapy. The two patients VT and BA with a long lasting "high dose" monotherapy were nearly devoid of PUFAs whereas the healthy controls had a portion of 23% PUFAs in their thrombocytes. These two patients had, furthermore, a low percentage of palmitic and oleic acid, but exhibited enhanced levels of stearic, docosanoic, tetracosanoic and hexacosanoic acids suggesting a preferred incorporation of long chain SFAs.

The fatty acid pattern of the two untreated schizophrenic patients was not markedly different from that of healthy untreated controls, indicating disturbance in the fatty acid pattern caused by the neuroleptic drug and not by the disease. During administration of the drug, cell counts in blood and liver parameters in serum were not affected in the patients, suggesting a normal rate of blood cell formation and normal liver function.

Phenothiazine and thioxanthene are lipophilic drugs and may penetrate the bone marrow where formation of blood cells takes place. The fact that these drugs may cause an agranulocytosis or thrombocytopenia underlines that they can interact with the hematopoetic system. Furthermore, it is very probable that the fatty acid pattern of blood cells is already preformed at an early stage and does no longer change when the cell has become mature [9]. Therefore, it is likely that these neuroleptic drugs influence the fatty acid pattern of thrombocytes at an early stage of their formation. Other kinds of

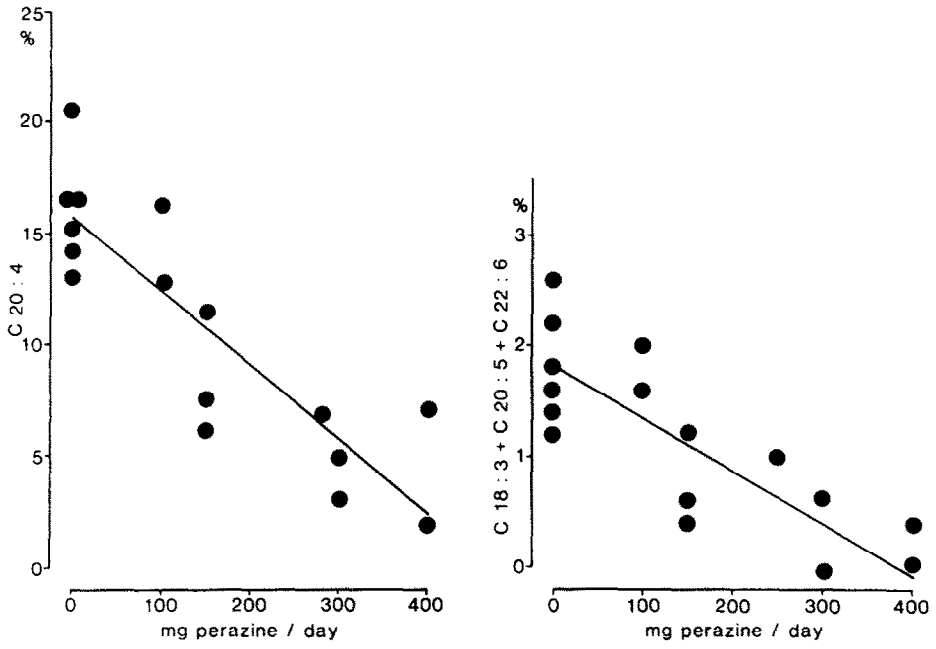

Fig. 1. Correlation between daily intake of perazine and content of PUFAs in thrombocytes (rel%) of "high dose" patients, "low dose" patients and untreated controls. C20:4: $r = -0.87$, $P < 0.01$. C18:3 + C20:5 + C22:6: $r = -0.81$, $P < 0.01$. $N = 16$ pairs of values. Statistics: linear regression analysis.

blood cells may also be affected and one can speculate that the fatty acid pattern in cell membranes of organs like the brain, the kidney or the liver may be changed in the long run when the dosage is high. Thus, membranous lamellae were found in liver cells of rats treated with phenothiazine, and were assumed to contain high levels of very long chain fatty acids [6]. Also, in rat brain an increase of hexacosanoic acid after phenothiazine administration has recently been described [7]. In our study, lack of PUFAs in thrombocytes may alter the properties of membranes, and thereby the ability to form aggregates of thrombocytes. Especially, a diminished content of arachidonic acid may influence the production of proaggregatory thromboxane [10].

Our study was originally aimed at finding out whether phenothiazine drugs inhibit peroxisomal β-oxidation of fatty acids in humans as has been previously described in animals [2, 5]. Indeed, an accumulation of very long chain fatty acids was observed which, however, did not reach the extent seen in peroxisomal diseases [1]. The main finding was the disappearance of PUFAs which may have important effects on various functions of the cell, like membrane fluidity or prostanoid metabolism. Whether the diminished content of PUFAs and accumulation of very long chain fatty acids in thrombocytes induce a distinct state of disease is unknown. A clinical consequence of our study is that a high dose treatment with phenothiazine or thioxanthene for a prolonged time should only be performed when a low dosage does not lead to clinical improvement.

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