中の乳酸、ピルビン酸値もモニターした。
結果は、一か月間治療を行い、ピルビン酸投与により、NPMDS のセクション IV の QOL で 17 から 13 へ改善した。患者は、前腕、下肢を上げることができるようになり、把握出来るようになった。指示に従って行う動作も回数も増して力強くなった。臨床的改善は診られたが、血中乳酸、ピルビン酸、L/P 比の変化はなかった。ピルビン酸ナトリウムの 0.5g/Kg/ Day 投与で、ミトコンドリア DNA 欠乏症による Liegh 脳症の患者で NPMDS のスコア―を改善させた。

① ピルビン酸脱水素酵素 PDHE1α欠損症による Leigh 脳症に対する治療効果 [2)]

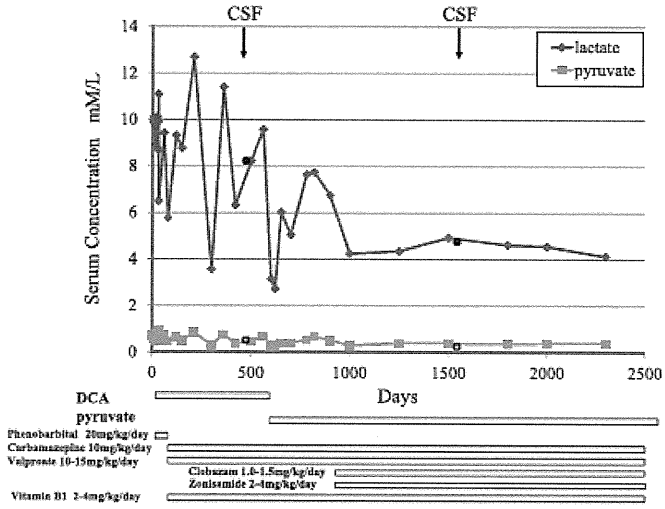


Fig. 2. Entire clinical course.

ピルビン酸脱水素酵素PDHE1α欠損症(N200T)によるLeigh脳症で新生児期から入院し、その間、ジクロロ酢酸(Dichroloacetate:DCA)25mg/kg/day、その後、DCAを中止し、ピルビン酸ナトリウム0.5g/Kg/Day TIDを投与し、その効果について検討した。全経過につき、臨床的(けいれんの頻度、入院期間、緊急受診回数)および生化学的(血中乳酸、ピルビン酸、L/P比、アラニン濃度、髄液中の乳酸、ピルビン酸、L/P比)に評価した。その結果、DCA投与中は、血中乳酸、ピルビン酸の濃度は、軽度低下したものの、臨床的にはけいれんが頻発し臨床的には症状は進行性に悪化していった。脳波では、Lennox Gastaut syndromeであり、一日のけいれん回数も10回以上であった。ピルビン酸ナトリウム0.5g/Kg/Day TID投与により、けいれんは数か月に一回となり、脳波でも著明に改善した。お座りが出来、呼びかけに対して表情も豊かになり、歌が歌え、自分で食事ができるようになった(それまではチューブ栄養が主体であった)。臨床症状の改善とともに、血中乳酸、ピルビン酸、アラニン濃度も有意に低下した。また、髄液中の乳酸、ピルビン酸もDCAでは低下しなかったが、ピルビン酸投与で有意に改善した。ピルビン酸ナトリウムは、臨床的改善のみでなく、血中の乳酸、ピルビン酸も低下し、かつ髄液の乳酸代謝を改善することが分かった。

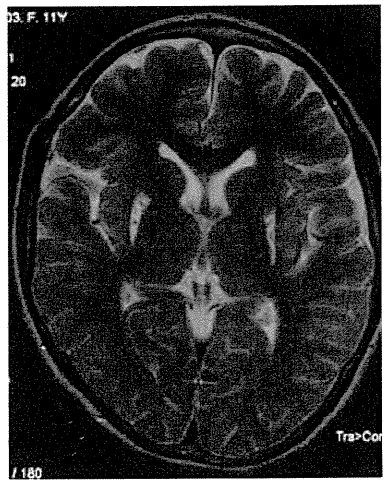


Fig. 1. T2-weighed magnetic resonance imaging (MRI) of the brain of the patient at 11 years of age.

② チトクロームC酸化酵素欠損症によるLeigh脳症に対する治療効果[3)]

11歳のチトクロームC酸化酵素欠損症によるLeigh脳症を来した患者で、ピルビン酸ナトリウムの効果を検討した。患者は、11歳女児で、歩行時の転倒と徒競走で遅い事を主訴に受診した。周産期の異常なく3590gにて出生。6歳時に複視を認め、眼振と両側外転神経障害を認めた。MRIで、両側大脳基底核被核、淡蒼球のT2、Flairで高信号異常所見を認め、Leigh脳症と診断された。髄液の乳酸値31mg/dlと異常高値であった。筋生検では、チトクロームC酸化酵素染色で全般的な染色性の低下を認め、赤ボロ線維やSSVは認めなかった。筋生検でのチトクロームC酸化酵素活性は、正常の17%と低下していた。8歳より経口的なコエンザイムQ10の内服を開始したが、運動発達の退行が進行していた。10歳時には、心エコーにて心機能の低下を認め、EFが52%となった。血中乳酸・ピルビン酸は、20.5 mg/dl 、1.13 mg/dlで、L/P比は18.1となった。11歳からピルビン酸ナトリウムを0.5g/Kg/Day TID投与開始したところ、血中乳酸・ピルビン酸は、10.3 mg/dl 、0.88 mg/dlと低下し、L/P比は11.7と改善した。ピルビン酸ナトリウム内服後は、学校の体育の授業に参加できるようになり、一年後には神経学的兆候の改善はないものの、心機能は正常化した。消化管感染症に罹患時、ピルビン酸ナトリウムを中断すると、血中乳酸・ピルビン酸は、11.3 mg/dl から14.3 mg/dl、0.96 mg/dl から0.94 mg/dlへと変化し、ピルビン酸ナトリウム内服がL/P比改善に有効であることを示唆した。

2. シトリン血症Ⅱ型での臨床研究

③ 早期発症Ⅱ型シトリン血症のシトリン欠損の治療でアルギニンとピルビン酸ナトリウムの効果[4)]

シトリン欠損では、高アンモニア血症に由来する神経学的障害をなくすには肝移植が重要であるが、アルギニンは高アンモニア血症を軽減するのに有効であり、また、高タンパク低炭水化物食は小児における成長障害を予防するのに有効と考えられる。今回の研究では、13 歳のシトリン血症Ⅱ型(CTLN2)で、経口的なアルギニンとピルビン酸ナトリウムの効果を調べた。患者は、食思不振と疲労性、成長障害を著明に認め、生化学的には血症シトルリンの上昇、スレオリン/セリン比の増加、膵分泌性トリプシン抑制因子の増加と典型的な所見を示した。3 年間の経口的なアルギニンとピルビン酸ナトリウム投与で、臨床症状も改善し、生化学的異常も正常化した。このことから、経口的なアルギニンとピルビン酸ナトリウム投与と低炭水化物食は、有効な治療法であり、肝移植療法と遜色ない効果を示す。副作用はなかった。

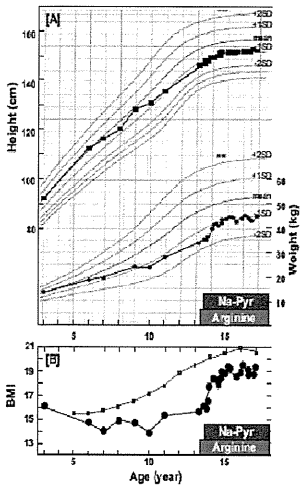


Fig. 1 Changes in body height and weight (A) and body mass index (BMI; B) of patient M.I. over time and showing the effect of arginine and sodium pyruvate (Na-Pyr) administration. Growth curves (mean, ± 1SD and 2SD values; A) and median BMI values (squares in B) for the Japanese population (Tin and Murata 2002) are also shown

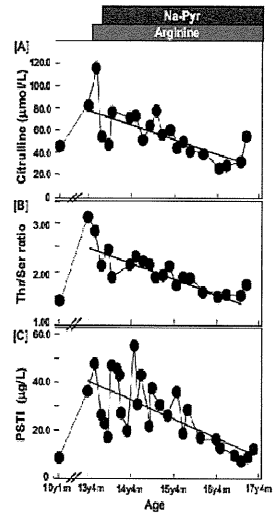
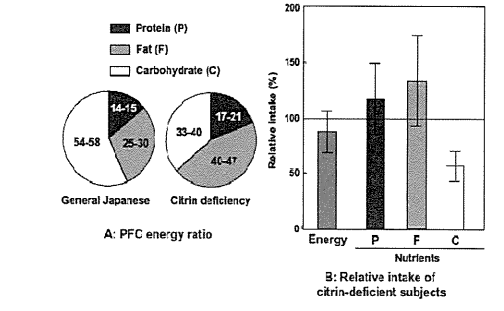
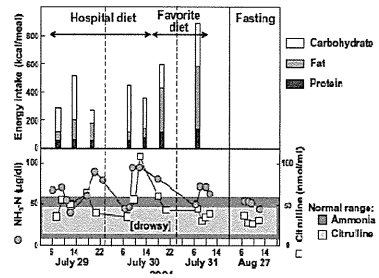


Fig. 2 Changes in plasma citrulline levels (A), threonine/serine (Thr/Ser) ratio (B), and serum pancreatic secretory trypsin inhibitor (PSTI) levels (C) of patient M.I. during arginine and sodium pyruvate (Na-Pyr) administration. x-Axis shows age in years (y) and months (m)



itional assessment of 18 citrin deficiency subjects revealed their characteristic dietary intakes. (A) Energy ratio of protein, fat and carbohydrate nese (left) and of citrin deficiency subjects (right), and (B) intake of energy and nutrients relative to age- and sex-matched controls [32].



④ シトリン欠損症と現在の治療方法 [5)]

シトリン血症（CTLN2）では、10%グリセオールや5%フルクトースの栄養を入れることで、高血糖、高アンモニア血症を来し死亡する。このように高炭水化物による毒性は、致命的となる。入院中に高炭水化物の入院食を食べると、血中のアンモニアとシトリンが上昇し、意識障害を来した。

Table 1 Changes in laboratory data of patient M.I.

Parameter	Age (years [y] months [m])						
	13y 4m	13y 6m	13y 8m	13y 9m	14y 9m	15y 9m	16y 9m
Total bilirubin (2–12 mg/L)	4.4	3.8	3.2	5.4	2.9	3.1	4.1
AST (2–37 IU/L)	31	27	27	24	23	17	15
ALT (2–40 IU/L)	19	16	16	15	16	13	13
Amylase (40–160 IU/L)	116	109	141	126	140	133	137
Total cholesterol (4.14–5.66 mmol/L)	6.16	5.28	5.43	5.64	5.53	5.63	5.17
HDL-cholesterol (1.03–2.28 mmol/L)	3.83	3.29	2.53	2.95	2.95	2.79	2.56
Triglyceride (0.56–1.68 mmol/L)	1.22	1.00	5.25	1.85	1.27	1.54	0.85
Urea-N (2.1–8.2 mmol/L)	7.6	6.7	7.2	6.0	8.2	7.6	5.3
Uric acid (0.17–0.36 mmol/L)	0.31	0.27	0.29	0.29	0.30	0.30	0.27
Ammonia (7–43 μmol/L)	nt	25	39	29	32	36	28
Total protein (67–82 g/L)	72	70	73	70	71	73	78
Lactate (0.47–1.89 mmol/L)	nt	nt	1.04	1.82	1.11	1.71	0.9
Pyruvate (0.03–0.10 mmol/L)	nt	nt	0.11	0.11	0.09	0.06	0.05
Sodium ion (135–147 mEq/L)	137	140	139	142	143	141	138
PSTI (5.9–22.7 μg/L)	36.4	47.4	25.9	23.5	37.6	16.6	9.1
Plasma amino acids[a]							
Citrulline (17.9–43.0 μmol/L)	81.6	114.4	54.2	40.4	75.7	39.0	54.1
Arginine (35–150 μmol/L)	102	231	133	191	225	147	191
Glutamine (418–740 μmol/L)	555	671	659	671	655	735	930
Alanine (259–615 μmol/L)	348	450	394	436	411	420	299
BCAA/AAA ratio (2.20–4.30)	3.10	2.60	2.90	3.56	3.30	3.80	3.90
Thr/Ser ratio (0.88–1.19)	3.09	2.79	2.14	1.68	1.88	1.58	1.72

Values in parentheses indicate normal ranges.
nt, not tested.
[a] Only relevant acids related are listed.

そこで、彼女の好きな高脂肪高タンパク低炭水化物食を摂取すると、症状は速やかに改善した。シトリン血症では、経口的なアルギニンとピルビン酸ナトリウム投与および低炭水化物食が有効と考えられた。

3. 心筋症に対するピルビン酸投与の効果

⑤ 鬱血性心不全患者の冠動脈にピルビン酸を投与することで収縮期および拡張期心機能が改善した。[6)]

ピルビン酸が分離した心筋細胞での心機能を改善し、鬱血性心不全患者での血流動態を改善する事が示されてきた。本研究は、心不全患者での収縮期、拡張期の左心室パラメーターについてピルビン酸の効果を検証する。拡張型心筋症患者でピルビン酸を異なる濃度で心臓カテーテル先端から投与した。LV容積はシネ心室グラフィーで測定した。ピルビン酸は、LV同容量圧を802±106 から 1125±103 mmHgys (P＜0.05)へ増加させ、LV拡張末期圧を17±2から12±2 mmHg (P＜0.05) へ減少させ、心拍数は79±4 から72±5/min (*P*＜0.05)へ減少させた。ストロークボリュームインデックスは34±4 から 43±6 ml/m^2 (P＜0.05)、拡張末期LV量は変化なかった。このことから、LVEFはピルビン酸投与により、30±4 から 39±4% (P＜0.05)へ有意に増加した。ピルビン投与を中止するとこのような効果は速やかにもとに戻った。結果:ピルビン酸を鬱血性心不全患者の冠動脈から投与することで、心拍を増加させることなく、収縮期および拡張期心機能を改善することが出来た。ピルビン酸は、慢性心不全患者の心機能を改善する効果が考えられるが、急性心不全に使用できるかが今後の課題である。

Table 1
Influence of intracoronary pyruvate on left ventricular volumes before and during pyruvate application. LVEDV=left ventricular end-diastolic volume (ml), LVESV=left ventricular end-systolic volume (ml)

Condition	Left ventricular volumes	
	LVEDV (ml)	LVESV (ml)
Baseline (saline)	237±48	175±41
Pyruvate 360 ml/h	232±53	151±43

⑥ 鬱血性心不全患者に冠動脈からピルビン酸を投与することでの血流動態:オープンスタディー[7)]

8名の拡張型心筋症でピルビン酸もしくは食塩水を左主幹冠動脈から注入し、血流動態の変化を調べた。その結果、2つのピルビン酸濃度では、変化はなかったが、ピルビン酸投与で、心機能が23%増加し、ストローク容量が38%増加、肺動脈圧が36%減少した。心拍は11%減少した。平均大動脈圧や体血管の抵抗に変化はなかった。最も効果が大きな時間帯は、注入後15分であった。ピルビン酸は、心不全患者での有効な治療と考えられた。

⑦ 心原性ショック患者にピルビン酸を投与することでの血流動態の改善に寄与[8)]

心筋梗塞で心原性ショックを来した患者にカテ先からピルビン酸ナトリウム(300mmol/L)を360ml/H投与し、血流動態を検討した。ピルビン酸は、cardiac index (CI 2.23 ± 0.53 vs. 1.95 ± 0.45 L /min/m^2; p<0.05), stroke volume

Table 2 Hemodynamic effects of intracoronary pyruvate in addition to catecholamines and IABP

Intervention (point in time)	Pyruvate (40 min)	NaCl 0.9% (50 min)
HR (min^{-1})	76 ± 9	76 ± 7
CI (L min^{-1} m^{-2})	2.23 ± 0.53	1.95 ± 0.45*
SVI (mL m^{-2})	29 ± 6	26 ± 5*
Mean SAP (mmHg)	95 ± 9	87 ± 9
Mean PAP (mmHg)	33 ± 6	31 ± 4
Mean PCWP (mmHg)	23 ± 7	22 ± 4
Mean RAP (mmHg)	16 ± 3	16 ± 3
SVR (dyn s cm^{-5})	1,608 ± 354	1,635 ± 325
PVR (dyn s cm^{-5})	216 ± 136	236 ± 159

* Means $p < 0.05$

index (SVI, 29 ± 6 vs. 26 ± 5 mL/m^2; P<0.05), mean systemic arterial pressure (mean SAP, 95 ± 9 vs. 87 ± 9 mmHg; p<0.05)と改善した。一方、心拍を増加させることはなかった。

⑨ピルビン酸は心肺循環を使用する外科領域で心保護作用に寄与[9)]

目的:冠動脈再建術でピルビン酸を用いた心肺循環と乳酸を用いた心肺循環で、術後の左心機能の回復と虚血性バイオマーカーを指標にピルビン酸がより有効かどうかをか検証する。

方法:前方視的、ランダム化、半盲検臨床試験

エントリー:血液と心停止保護液を4対1にまぜ、一群にはピルビン酸溶液を、他の群には乳酸をベースとした保護液を用いた。血行動態と生化学検査は心停止前、心拍再開後、およびバイパス手術の4、6、8、12時間後に検査した。

結果:乳酸をベースとした保護液に比較し、ピルビン酸溶液を用いた場合がバイパス後4時間から12時間までのleft ventricular stroke workが良かった(***p < 0.001***)。coronary sinus troponin I とcreatine phosphokinase-MB 活性も 67% (p < 0.001) と53% (p < 0.01)と低く、coronary sinus hemoglobin 飽和度も 18% (p < 0.001)と高かった。乳酸を用いた心肺循環患者の10人がB-刺激剤を必要としたが、ピルビン酸群では4人のみであった。ピルビン酸溶液を用いた場合、入院期間が有意に短縮した(6.3 ±0.3 から 5.2 ±0.1 days、 (p < 0.002)。

Table 1. Characteristics of Control and Study Patients

	Lactate Group	Pyruvate Group
Men, women (N)	12, 3	11, 4
Age (years)	72 (46–76)	71 (52–78)
Cardiopulmonary bypass time (min)	81 (60–120)	88 (58–110)
Crossclamp time (min)	58 (46–96)	62 (48–90)
Cardioplegia infusion volume (mL)	310 (200–400)	350 (300–450)
Preoperative LV ejection fraction (%)	56 (45–68)	54 (38–68)

NOTE. Patients in the lactate group received lactate-based cardioplegia during the period of cardiac arrest; patients in the pyruvate group received pyruvate-fortified cardioplegia. Values are means; ranges are within the parentheses. No statistically significant differences were detected between the groups.
Abbreviation: LV, left ventricular.

結論:ピルビン酸溶液を用いた場合、冠動脈手術時のバイパスを行う場合の心筋障害を緩和する可能性があり、心機能の回復に良好な効果がえられた。したがって、冠動脈再建術では、乳酸ベースよりピルビン酸ベースでの心肺循環が好ましい。

⑩ピルビン酸の代謝的な心筋保護作用:最近の進歩[10)]

ピルビン酸は、自然界に存在する代謝燃料であり心筋や他の組織の抗酸化剤でもあり、生理的濃度以上に上げた場合、種々の程度の心筋保護を発揮する。ピルビン酸は、心筋収縮力を増し、心筋細胞のエネルギー状態を増加させ、内因性の抗酸化システムを活性化し、虚血再灌流やオキシダントストレスからの心筋保護に働く。このレビューでは、最近数年間に明らかになったピルビン酸の心筋収縮と心筋保護についての基礎および臨床研究の成果を紹介する。特にピルビン酸の筋小胞体でのCa転送、抗酸化作用、心筋障害における可逆性および不可逆性の作用について解説する。これらの研究は、基本的にはピルビン酸治療の臨床的適応に基づく研究努力であり、心肺バイパス手術、心肺蘇生術、心筋障害と心不全などが含まれる。

4. 肥満症におけるピルビン酸投与の効果

⑪低コレステロールおよび低脂肪食におけるピルビン酸の投与、高脂血症患者における血清脂質濃度と体組成[11)]

TABLE 3
Dietary intake as determined by 3-d food records*

	Placebo		Pyruvate	
	Week 0	Week 6	Week 0	Week 6
Energy (MJ/kg body wt)	0.091 ± 0.008	0.096 ± 0.006	0.096 ± 0.009	0.099 ± 0.009
P:S†	2.5 ± 0.1	2.4 ± 0.1	2.3 ± 0.1	2.2 ± 0.1
Total fat				
(%)	24 ± 2	23 ± 2	23 ± 1	22 ± 2
(g)	46.1 ± 1.7	46.9 ± 1.6	47.4 ± 2.2	49.7 ± 3.3
Saturated fatty acid				
(%)	18 ± 1	18 ± 1	19 ± 1	20 ± 1
(g)	8.3 ± 0.4	8.5 ± 0.5	9.2 ± 0.7	9.8 ± 0.9
Monounsaturated fatty acid				
(%)	31 ± 1	31 ± 1	30 ± 1	29 ± 1
(g)	14.3 ± 0.8	14.5 ± 0.8	14.1 ± 0.8	14.6 ± 1.2
Polyunsaturated fatty acid				
(%)	45 ± 1	44 ± 1	44 ± 1	44 ± 1
(g)	20.6 ± 0.5	20.8 ± 0.5	20.8 ± 0.6	21.9 ± 1.0
Cholesterol (mg)	165 ± 8.4	163 ± 8.0	176 ± 7.9	180 ± 9.6
Total carbohydrate				
(%)	60 ± 2	60 ± 2	61 ± 2	61 ± 2
(g)	257.4 ± 14.6	272.9 ± 16.6	287.3 ± 13.3	308.0 ± 14.3
Total protein				
(%)	16 ± 1	16 ± 1	16 ± 1	17 ± 1
(g)	71.3 ± 3.8	75.0 ± 5.4	77.4 ± 3.5	86.1 ± 5.0
Total dietary fiber (g)	14.3 ± 1.8	17.6 ± 2.3	13.1 ± 1.1	14.6 ± 1.7

* $\bar{x}$ ± SE; n = 17 per group. There were no significant differences between groups.
† Ratio of polyunsaturated to saturated fatty acids.

3炭素組成であるピルビン酸の血漿中濃度と体組成を低コレステロール食(165-180 mg)、および低脂肪食(総エネルギーの22-24%:エネルギーの18-20%を飽和脂肪酸で取っていた)を行っている高脂血症患者で検討した。この食事療法を4週間続けた後で、血清脂質の値は低下したが、その後、34名はランダムにピルビン酸群(22-44g/日)とポリグルコース群(18-35g/日)に分けられた。ピルビン酸を用いた群で体重と体脂肪の有意な減少を示した以外($P<0.05$)、血漿中のコレステロール、LDL、HDLとトリグリセリドは両群間で差はなかった。食事療法で引き起こされる血症脂質濃度低下に加えて、ピルビン酸を低コレステロールおよび低脂肪食に追加することで、脂質の濃度を変えることなく体重減少と脂肪減少を達成できる。

⑫体組成、エネルギー利用、窒素代謝に与えるピルビン酸の影響[12)]

TABLE 1
Patient profile

Diet and subject	Waist/hip circumference	Initial weight	Initial body fat	Initial BMI*	Initial REE†	Weight loss	Fat loss	Energy deficit
		kg	*kg*		*MJ/d*	*kg*	*kg*	*MJ*
Placebo								
1	0.83	140.7	71.4	47.5	9.4	5.2	3.0	146.2
2	0.78	114.7	61.7	47.8	6.4	3.7	1.9	83.0
3	0.98	103.2	48.8	36.1	8.6	5.1	3.1	125.4
4	0.86	98.0	42.2	33.1	8.0	4.3	2.7	122.5
5	0.78	97.4	46.8	35.3	6.4	3.3	2.3	71.4
6	0.83	97.2	44.3	34.0	8.1	5.1	3.4	124.0
7	0.78	78.1	32.9	28.0	6.7	3.2	2.4	86.2
$\bar{x}$	0.83	104.2	49.7	37.4	7.7	4.3	2.7	108.4
SE	0.03	7.3	4.9	2.8	0.4	0.3	0.2	10.5
Pyruvate								
1	0.80	149.0	79.8	51.6	8.6	9.2	6.1	145.5
2	0.83	138.2	72.0	52.7	8.8	6.6	4.7	145.8
3	0.78	114.6	61.6	47.7	6.5	4.0	2.1	83.8
4	0.76	101.7	45.2	35.6	8.5	6.4	4.7	118.5
5	0.96	101.7	48.8	38.2	7.4	5.0	3.5	106.7
6	0.77	97.2	47.6	43.2	7.9	5.9	3.8	117.9
7	0.93	74.9	28.6	27.8	6.2	3.9	3.1	75.4
$\bar{x}$	0.83	111.0	54.8	42.4	7.7	5.9‡	4.0‡	113.4
SE	0.03	9.6	6.6	3.4	0.4	0.7	0.5	10.3

* In kg/m^2.
† Resting energy expenditure.
‡ Significantly different from placebo, $P < 0.05$.

代謝病棟に入院中の14名の肥満女性で一日4.25-MJ/d 液体食(68% carbohydrate, 22% protein) 21日間行いピルビン酸の有るなしでの体組成、エネルギー損失、窒素代謝について検討した。体組成とロイシン酸化、およびターンオーバーは体重の変動する前後で解析した。エネリギー欠損は、定常状態の代謝率で計算した。ピルビン酸を与えた群が、体重減少が有意に診

られた。窒素バランスとロイシン代謝、ターンオーバーは両群で変化はなかった。3炭素組成であるピルビン酸は、6炭素組成であるグルコースの代わりに同じエネルギー源として働くことで脂肪と体重を減少させると考えられた。

⑬高脂血症患者における脂質組成に与えるピルビン酸の影響[13)]

TABLE 2
Dietary intake*

	Placebo (n = 21)		Pyruvate (n = 19)	
	Week 0	Week 6	Week 0	Week 6
Energy (MJ/kg body wt)	0.114 ± 0.014	0.116 ± 0.012	0.107 ± 0.006	0.117 ± 0.008
P:S†	0.34 ± 0.04	0.30 ± 0.03	0.35 ± 0.03	0.30 ± 0.03
Total fat				
(%)	46.6 ± 1.4	46.7 ± 1.6	45.2 ± 1.4	45.6 ± 1.5
(g)	106 ± 10	110 ± 9	101 ± 6	110 ± 7
Saturated fatty acid				
(%)	42 ± 1	42 ± 1	40 ± 1	42 ± 1
(g)	44 ± 5	46 ± 4	40 ± 2	46 ± 3
Monounsaturated fatty acid				
(%)	35 ± 1	35 ± 1	37 ± 1	35 ± 1
(g)	37 ± 4	38 ± 3	38 ± 3	38 ± 3
Polyunsaturated fatty acid				
(%)	14 ± 1	13 ± 1	14 ± 1	13 ± 1
(g)	15 ± 2	14 ± 1	14 ± 1	14 ± 1
Cholesterol (mg)	594 ± 30	575 ± 31	566 ± 40	620 ± 39
Total carbohydrate				
(%)	37.1 ± 1.6	37.8 ± 1.6	38.0 ± 1.3	37.7 ± 1.3
(g)	200 ± 19	211 ± 18	202 ± 11	215 ± 15
Total protein				
(%)	16.3 ± 0.7	15.7 ± 0.6	16.9 ± 0.5	16.6 ± 0.7
(g)	86 ± 6	85 ± 5	87 ± 4	92 ± 5
Total dietary fiber (g)	14.0 ± 1.2	13.8 ± 1.5	13.1 ± 1.1	13.9 ± 1.3

* $\bar{x}$ ± SE. Data are based on 3-d food records.
† Ratio of polyunsaturated to saturated fatty acids.

高脂血症患者で high-cholesterol (560-620 mg), high-fat (45-47% ofenergy; 18-20% of energy as saturated fatty acid), anabolic diet (0. 1 1-0. 12 MJ/kg body wt) を 6 wk与えている方で、3炭素組成であるピルビン酸の血漿脂質組成に与える影響を解析した。40名は、36-53 g のピルビン酸 (n = 19)、2 1-37 g のポリグルコース(placebo, Polycose, n = 2 1) as a portion of carbohydrate energyの2群に分けられた。TCとLDLはプラセボ群で変化しなかったが、ピルビン酸群では、4%、5%とそれぞれ低下した(P < 0.05 vs placebo)。HDL、HDL3とTGはどちらも同じ程度で差が無かった。心拍数、拡張期血圧は6週間の治療でプラセボでは変化しなかったが、ピルビン酸投与群では、9%、6%、12%と減少した(P < 0.05 vs placebo)。

5. ピルビン酸ナトリウムのstable isotopeを用いたin vivo代謝

⑭高脂血症患者における脂質組成に与えるピルビン酸の影響[14)]

ミトコンドリアは、代謝疾患、神経変性疾患、老化などの病態で重要な役割を示す。それゆえ、ミトコンドリアの代謝機能を非侵襲的に検証する必要がある。C13の呼気テストは、ミトコンドリアの代謝機能を検証するのに有用である。動的なミトコンドリア代謝を非侵襲的にかつ60分以内で解析できる。患者の臨床的評価のみでなく、今後の種々の評価に利用できる。

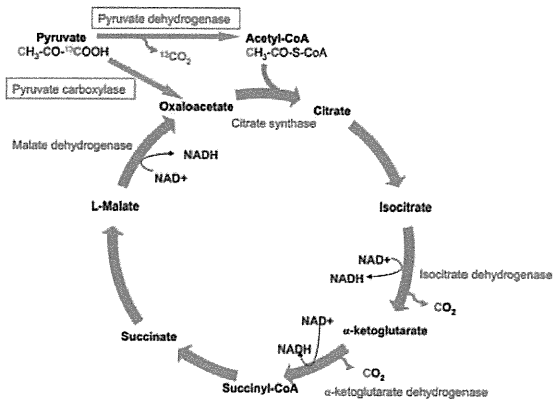
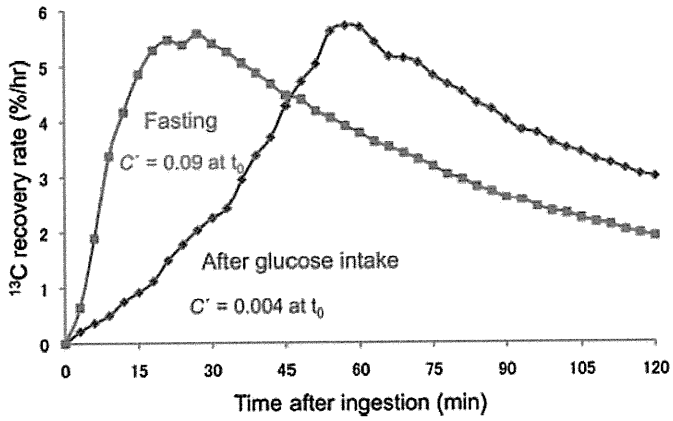
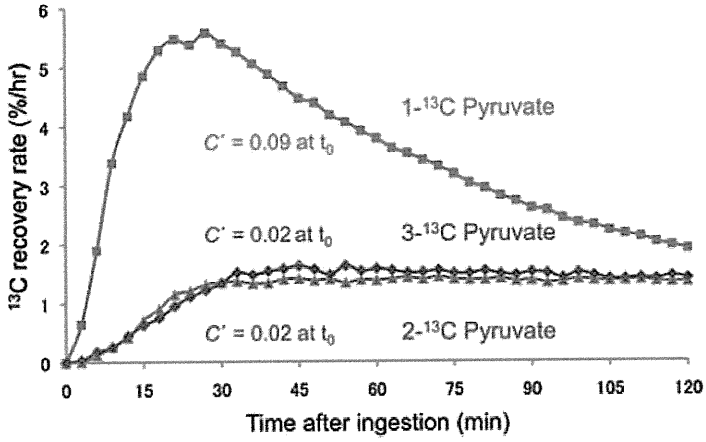


Figure 1. Metabolic pathway of ^{13}C-labeled pyruvate. Administered pyruvate is converted to acetyl-CoA via the action of pyruvate dehydrogenase, and subsequently fed into the citric acid cycle. The fate of the labeled carbon depends on its position in the pyruvate molecule. Labeled carbon in [1-^{13}C] pyruvate is released in the form of $^{13}CO_2$ during pyruvate oxidation by pyruvate dehydrogenase. On the other hand, labeled carbons in [2-^{13}C] pyruvate and [3-^{13}C] pyruvate are released as $^{13}CO_2$ after completing the second turn of the citric acid cycle.

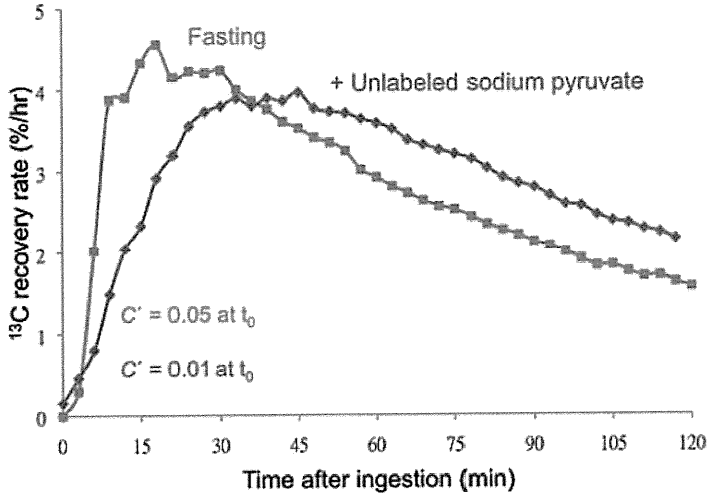
左図は、stable isotopeを用いたピルビン酸の代謝図である。



{1-^{13}C}を用いたピルビン酸代謝は、ピルビン酸ナトリウム100mgを50mlの水で溶解した場合、その回収率は、絶食状態では18分でピークを示す。一方、50gのブドウ糖を服薬後60分で投与した場合、回収率のピークは60分となる。



同様に、{1-^{13}C}、{2-^{13}C}、{3-^{13}C}をそれぞれピルビン酸ナトリウム100mgを50mlの水で溶解して用いた場合、{1-^{13}C}では回収率のピークは18分、{2-^{13}C}および{3-^{13}C}では、30分後にプラトーとなり、以後は継続して呼気に出現してくる。



{1-^{13}C}ピルビン酸を2gの非標識ピルビン酸と同時に摂取すると、回収率のピークは30分となり、その後、徐々に代謝されることがわかった。

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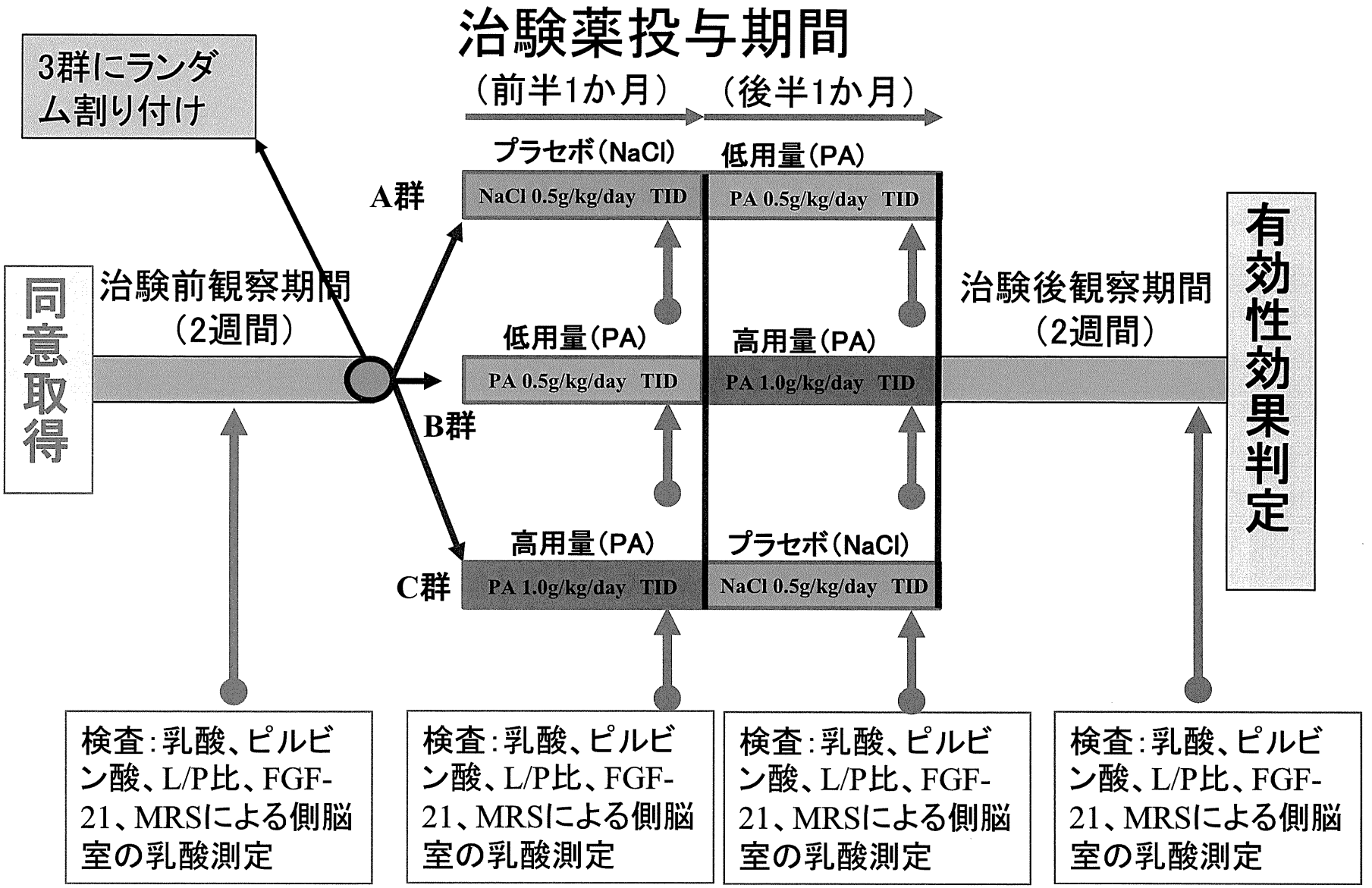
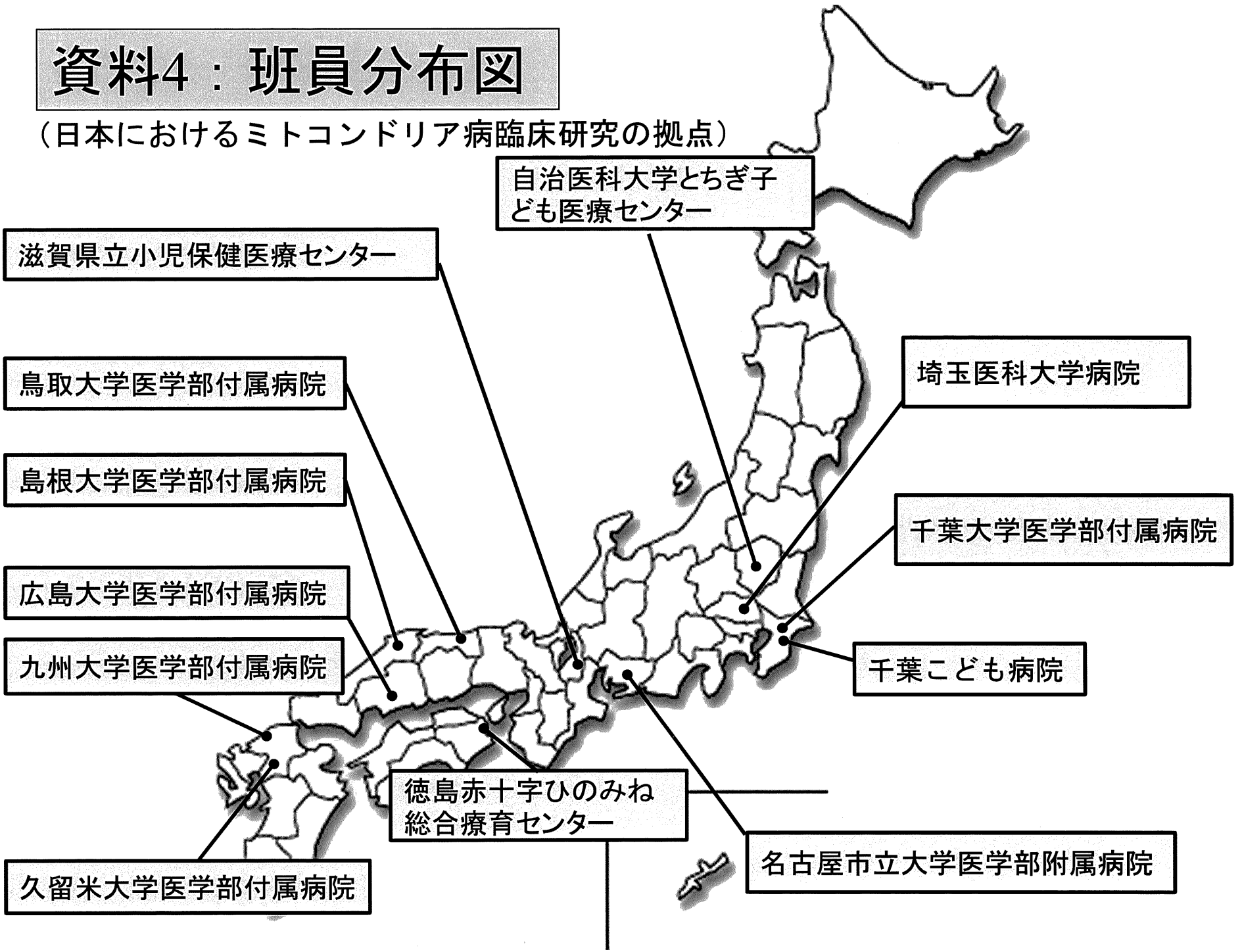
資料3:ピルビン酸ナトリウムの第2相試験のダイアグラム



資料4：班員分布図

（日本におけるミトコンドリア病臨床研究の拠点）



別紙５

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yasutoshi Koga, Nataliya Povalko, Koujyu Katayama, Noriko Kakimoto, Toyojiro Matsuishi, Etsuo Naito, Masashi Tanaka.	Beneficial effect ofpyruvate therapy on Leigh syndrome due to a novel mutation in PDH E1・gene.	Brain & Dev	34	87-91	2012
Yasutoshi Koga, Nataliya Povalko, Junko Nishioka, Koujyu Katayama, Noriko Kakimoto, and Toyojiro Matsuishi.	Molecular Pathology of MELAS and L-Arginine Effects.	Biochem Biophys Acta General	1820	608-614	2012
Shuichi Yatsuga, Nataliya Povalko, Kojyu Katayama, Junko Nishioka, Noriko Kakimoto,Toyojiro Matsuishi, Yasutoshi Koga.	MELAS: A nationwide prospective cohort study of 96 patients in Japan.	Biochem Biophys Acta General	1820	619-624	2012
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Original article

Beneficial effect of pyruvate therapy on Leigh syndrome due to a novel mutation in PDH E1α gene

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Abstract

Leigh syndrome (LS) is a progressive untreatable degenerating mitochondrial disorder caused by either mitochondrial or nuclear DNA mutations. A patient was a second child of unconsanguineous parents. On the third day of birth, he was transferred to neonatal intensive care units because of severe lactic acidosis. Since he was showing continuous lactic acidosis, the oral supplementation of dichloroacetate (DCA) was introduced on 31st day of birth at initial dose of 50 mg/kg, followed by maintenance dose of 25 mg/kg/every 12 h. The patient was diagnosed with LS due to a point mutation of an A–C at nucleotide 599 in exon 6 in the pyruvate dehydrogenase E1α gene, resulting in the substitution of aspartate for threonine at position 200 (N200T). Although the concentrations of lactate and pyruvate in blood were slightly decreased, his clinical conditions were deteriorating progressively. In order to overcome the mitochondrial or cytosolic energy crisis indicated by lactic acidosis as well as clinical symptoms, we terminated the DCA and administered 0.5 g/kg/day TID of sodium pyruvate orally. We analyzed the therapeutic effects of DCA or sodium pyruvate in the patient, and found that pyruvate therapy significantly decreased lactate, pyruvate and alanine levels, showed no adverse effects such as severe neuropathy seen in DCA, and had better clinical response on development and epilepsy. Though the efficacy of pyruvate on LS will be evaluated by randomized double-blind placebo-controlled study design in future, pyruvate therapy is a possible candidate for therapeutic choice for currently incurable mitochondrial disorders such as LS.

Keywords: Leigh syndrome; PDH E1α mutation; Pyruvate; Lactic acidosis; Therapy

1. Introduction

LS, originally reported as subacute necrotizing encephalomyelopathy by Dr. Denis Leigh in 1951 [1], is an early-onset progressive neurodegenerative disorder characterized by developmental delay or regression, lactic acidosis, and bilateral symmetrical lesion in the basal ganglia, thalamus, and brainstem [2]. The clinical presentations of the disease are heterogeneous, due to the severity of biochemical defects caused by mutations in both nuclear and mitochondrial genes involved in energy metabolism. Though many molecular defects are reported to be associated with LS [3], the underlying gene defects remain unidentified in nearly half of the patients [4,5]. Since LS is associated mainly with the respiratory chain deficiency, there is no established treatment except for a limited number of patients such as those with thiamine-responsive pyruvate dehydrogenase deficiency [6], or those with defects in the biosynthetic pathway of coenzyme Q [7]. We have proposed that pyruvate has a therapeutic potential for mitochondrial diseases, because: (a) pyruvate can stimulate the

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glycolytic pathway by reducing the NADH/NAD ratio in the cytoplasm, (b) pyruvate can activate PDHC by inhibiting pyruvate dehydrogenase kinase, and (c) pyruvate can scavenge hydrogen peroxide by non-enzymatic reaction [8]. Recently, we reported that pyruvate produced a slightly favorable change in the plasma lactate and pyruvate levels in LS with cytochrome c oxidase deficiency [9]. In the present report, we describe a clinical experience of pyruvate therapy in a child with LS having PDH deficiency caused by a novel mutation in PDH E1α gene.

2. Patient and methods

2.1. Patient

The 5-years-old boy, presented as severe psychomotor retardation with severe lactic acidosis, was born weighing 1797 g at full term gestational age as the second child of unconsanguineous parents. He was transferred to neonatal intensive care units because of fatal distress with the severe lactic acidosis. The concentrations of lactate and pyruvate in blood were 6–10 times higher than normal range, with normal lactate/pyruvate ratio (Table 1). He was under respiratory care with medication of severe metabolic acidosis. Aminogram of his plasma showed an elevated alanine concentration of 1.82 mM (normal range, 0.21–0.52). Since he was showing continuous lactic acidosis, the oral supplementation of DCA was introduced on 31st day of birth at initial dose of 50 mg/kg, followed by maintenance dose of 25 mg/kg/every 12 h. Though he showed severe floppy infant, his mechanical ventilation has been terminated at the 45th day of birth, and starting oral administration of ingredient nutrient. Although the concentrations of lactate and pyruvate in blood were

Table 1
Biochemical parameters during therapy with none, DCA, or pyruvate.

	None ($n = 8$)	DCA therapy ($n = 12$)	Pyruvate therapy ($n = 10$)
Lactate (mM) (normal: 0.03–0.17)	9.6 ± 0.54	8.6 ± 2.63	5.28 ± 1.73[a,b]
(Range: minimum–maximum)	(8.70–10.10)	(3.56–12.70)	(2.73–7.75)
Pyruvate (mM) (normal: 0.003–0.10)	0.69 ± 0.13	0.61 ± 0.19	0.42 ± 0.13[a,b]
(Range: minimum–maximum)	(0.49–0.82)	(0.31–0.93)	(0.26–0.68)
L/P ratio (normal: 10–15)	14.5 ± 3.10	14.2 ± 2.12	12.6 ± 1.52
(Range: minimum–maximum)	(10.6–18.7)	(11.5–17.9)	(10.5–15.1)
Alanine (mM) (normal: 0.21–0.52)	1.7 ± 0.28	1.13 ± 0.27[a]	0.77 ± 0.38[a]
(Range: minimum–maximum)	(1.11–1.82)	(0.76–1.51)	(0.39–1.42)

All date are presented as mean ± SD during each treatments.
Lactate, pyruvate L/P ratio, and alanine were analyzed the significance between periods of none, DCA and pyruvate therapy using the two-tailed Mann–Whitney *U*-test. *P* value less than 0.05 showed significant.
[a] It showed significance between none and DCA or pyruvate therapy.
[b] It showed significance between DCA and pyruvate therapy. *n*: number of measurements.

Table 2
Entire clinical course and symptoms.

	Clinical course		
	None	DCA	Pyruvate
Study periods	1 month (1 m)	17 months (2–18 m)	58 months (1 year 6 months–6 years 4 months)
Hospitalization (day)	31	124	3
Emergency visit (time)	0	14	4
Diagnosis by EEG	Infantile epilepsy	West syndrome or Lennox–Gastaut syndrome	Lennox–Gastaut syndrome
Convulsion			
Frequency	15 or more/days	18 or more/days	2–3/months
Duration	5–15 s/Epilepsy	5–20 s/Epilepsy	5–10 s/Epilepsy
Series formation	None	Series formation	No series formation
Anticonvulsants	Phenobarbital 20 mg/kg/day	Carbamazepine 10 mg/kg/day Valproate 10–15 mg/kg/day Clobazam 1.0 mg/kg/day Zonisamide 2–4 mg/kg/day	Carbamazepine 10 mg/kg/day Valproate 15 mg/kg/day Clobazam 1.5 mg/kg/day Zonisamide 2–4 mg/kg/day
JMDRS	58	58	57
Developments	Severe floppy infant Respiratory care	Cannot head control Cannot sit alone Cannot rolling over Floppy infant Eating mainly by S-tube	Floppy infant Head control (21 months) Rolling over (42 months) Sit alone (56 months) Eating mainly by mouth

slightly decreased by DCA, his clinical conditions were deteriorating progressively. He could not fix the head control, and roll over at 6 months of age. He was diagnosed with West syndrome at 6 months-old because of his intractable generalized convulsions. Though he received two types of anti-convulsants as shown in Table 2, his convulsion did not stop and showed several seizures a day with series formation. Brain MRI on 7-months-old showed a premature myelination and atrophy in frontal lobe with callosal hypoplasia, and brainstem abnormality. He showed severe floppiness, loose head control, inability to sit alone and roll over, feeding difficulty, and no significant words at the age of 18 months-old. His EEG pattern changed to Lennox–Gastaut syndrome at that time (Fig. 1A). Nerve conduction velocity in both motor and sensory nerve showed low amplitude with delayed velocity indicating severe neuropathy. At this point, we thought that severe neuropathy seen in the patient may caused by the severe adverse effects of DCA, since he received the DCA supplementation for more than 17 months period. Because of the severe neuropathy, we decided to terminate the DCA at his age of 18 months-old, and after received written informed consent, we started the oral supplementation of sodium pyruvate at 0.5 g/kg/day TID. Three months later, he started to roll over and showed the facial expression of happiness and sadness. He could start to chatter and swallow the liquid food. Six months after starting pyruvate supplementation, he had almost no epileptic seizure and was demonstrated the significant improvement by EEG (Fig. 1B). The entire clinical course is summarized in Fig. 2 and Table 2.

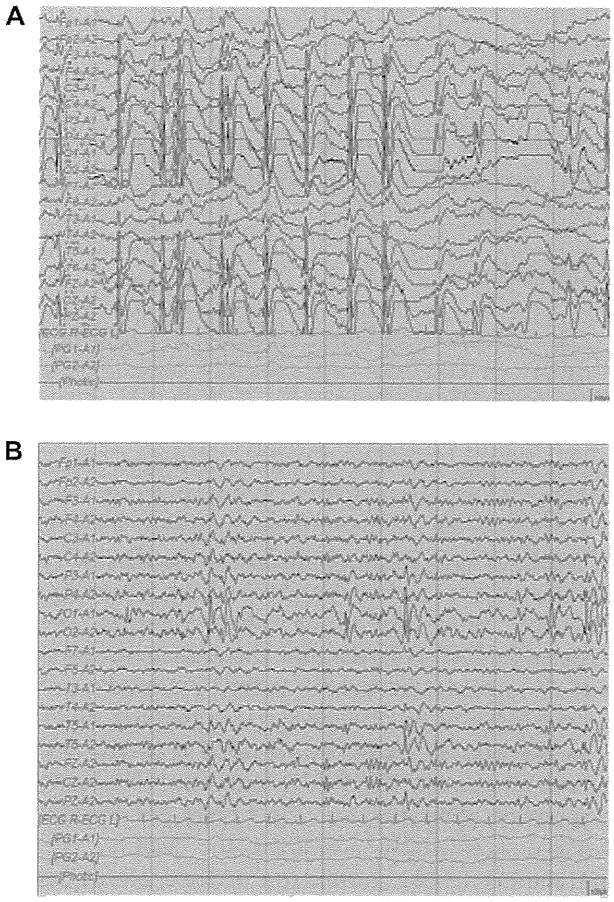

Fig. 1. (A) EEG taken at 18 months old. A grossly abnormal inter-ictal EEG showed continuous, high-amplitude, sharp-slow-waves or spike-slow-waves indicating a multifocal and generalizing sharp-slow-wave-discharges at 1.5–2.5 Hz. Patient showed intractable epilepsy with 15–20 times a day of grandmal, and/or myoclonic type seizure. (B) EEG taken at 36 months old. An abnormal inter-ictal EEG pattern showed with continuous, sharp-slow-waves or spike-slow-waves. However it showed low-amplitude and less multi-focality. Patient showed no grandmal or myoclonic type seizure by daily base frequency.

The lactate and pyruvate concentrations in cerebral spinal fluid were 8.23 mM, and 1.26 mM under the period of DCA therapy, and 4.61 mM and 0.68 mM under the period of pyruvate therapy (Fig. 2).

2.2. Lactate, pyruvate, L/P ratio and alanine determination

In order to investigate the energy state of patient in each time period of therapy, we measured the plasma level of lactate, pyruvate and aminogram including alanine, 8 times in the periods of 31 days with free of DCA and pyruvate, 12 times in 17 months during DCA therapy, and 10 times in 58 months during pyruvate therapy. Analysis of amino acids was performed on protein-free extracts of fresh plasma using described methods.

2.3. Enzyme assays

The PDHC activity in cultured skin fibroblasts was assayed using two different concentrations of TPP (0.4 and 1104 mM) after the activation of PDHC using DCA as previously described [10].

2.4. Genetic analysis

Mutation analysis of the E1α gene, a major cause of PDHC deficiency, was performed using genomic DNA from cultured skin fibroblasts. For the genetic analysis of the 11 exons of the E1α gene, the individual exons were amplified using primer pairs and conditions as described previously [11].

2.5. Statistical analysis

Statistical analysis of the biochemical data including lactate, pyruvate, L/P ratio, and alanine was performed using two-tailed Mann–Whitney *U*-test or Student's *t*-test. A value of $P < 0.05$ was considered as statistically significant.

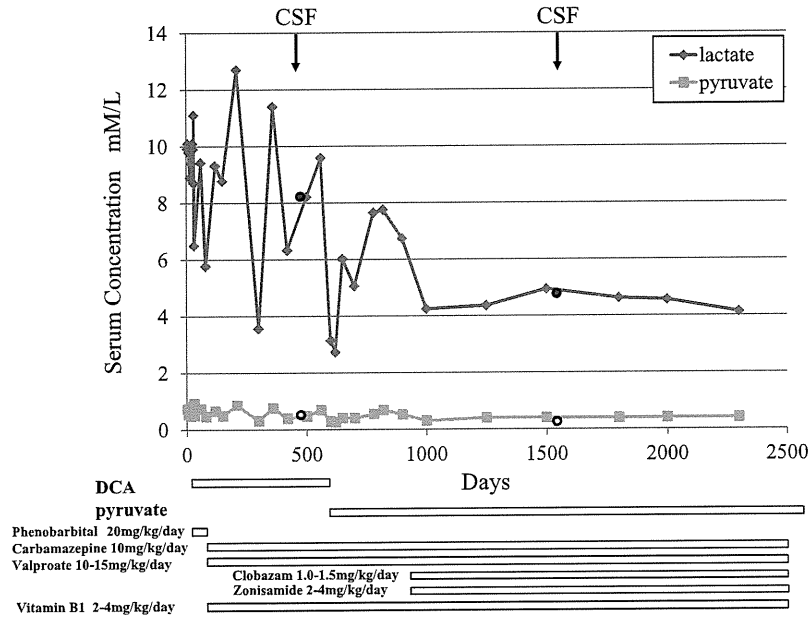

Fig. 2. Entire clinical course.

3. Results

Since patient showed lactic acidosis with normal lactate/pyruvate ratio, we measure the PDHC activity in cultured skin fibroblasts cells. The PDHC activity was 0.94 in the presence of DCA and 0.4 mM TPP (normal: 4.07 ± 0.68 nmol/min/mg protein). Mutation analysis of PDH E1α subunits revealed a point mutation of an A–C at nucleotide 599 in exon 6, resulting in the substitution of aspartate for threonine at position 200 (N200T). Though this mutation has not been reported before, we considered it as the responsible gene defect in this patient because; (1) no other mutations were found in entire PDH E1α gene, (2) conserved amino acid in different species, (3) mother has the mutation in hemizygous condition, and (4) no same mutation found in 50 normal females.

The laboratory data before, and after the treatment by DCA, and after pyruvate treatment are shown in Table 1 and Fig. 2. The concentration of lactate and pyruvate in blood before the treatment was 51–58 times higher than normal range, with normal lactate/pyruvate ratio (Table 1). The concentration of alanine was also increased 2.1–3.5 times higher than normal range. After the treatment by DCA, though the concentration of lactate and pyruvate showed no significance, the concentration of alanine was significantly decreased. The patient showed intractable seizures, and decreased the activity of daily living. After the treatment by pyruvate, the concentration of lactate and pyruvate were significantly decreased in comparison with those without therapy, and with DCA treatment, with significantly decreased level of alanine (Table 1 and Fig. 2). The concentrations of lactate and pyruvate in the CSF were also significantly decreased with significantly decreased plasma level of alanine (Fig. 2).

4. Discussion

LS, the most dominant sub-type of mitochondrial disorders in children, are clinically more severe and patients usually die before the first decade of the life. In another words, LS showed the most severe cytopathy among subtypes of mitochondrial disorders. Therapeutic target of mitochondrial angiopathy is now on-going of L-arginine as an investigator-mediated clinical trial on MELAS [12]. However there are no clinical trial of therapeutic approach for mitochondrial cytopathy especially LS. Since the severe adverse events of DCA reported in 2006 [13], the new therapeutic drugs to prevent or improve the mitochondrial cytopathy or lactic acidosis have to be developed as a substitute for DCA.

In the present study, we reported a patient with LS caused by a novel PDH E1α mutation who responded to pyruvate administration for 3 years period. Pyruvate therapy significantly decreased the lactate, pyruvate and alanine levels, showed no adverse effects such as severe neuropathy seen in this patient under the DCA therapy, and had better clinical response on development and epilepsy. It was reported that pyruvate percolates through the blood brain barrier via monocarboxylate transporters and provides an excellent energy state for neurons and astroglia [14]. As shown in our patient (Fig. 2), pyruvates decreased lactate and alanine levels not only in blood but in CSF, and improved the electroencephalogram in our patient, suggested that pyruvate

may pass through blood-brain barrier and improve the metabolic condition in the brain in our patient. We have proposed that pyruvate has a therapeutic potential for mitochondrial diseases, because: (a) pyruvate can stimulate the glycolytic pathway by reducing the NADH/NAD ratio in the cytoplasm [8], (b) pyruvate can activate the pyruvate dehydrogenase complex (PDHC) by inhibiting the pyruvate dehydrogenase kinase [8,9], and (c) pyruvate can scavenge the hydrogen peroxide by a non-enzymatic reaction [15]. Pyruvate improved the hemodynamic condition by intracoronary infusion in patients with congestive heart failure [16,17], or the neurological recovery following cardiopulmonary arrest and resuscitation [18]. In our patient, we determined the daily supplement of pyruvate by the presence of diarrhea as adverse effects or by the capacity of amount of oral administration. In our patient, daily administration of sodium pyruvate resulted in 0.5d/kg/day TID. The exact pharmacological mechanisms why serum pyruvate is also decreased after the pyruvate therapy, have to be clarified in future study, by using proteome analysis or comprehensive multiple analysis of total cell metabolism.

Considering the progressive nature of LS, pyruvate may prevent the neurodegeneration and lactic acidosis in our patient. Though the efficacy of pyruvate on LS will be evaluated by randomized double-blind placebo-controlled study design in future, pyruvate therapy is a possible candidata for therapeutic choice for currently incurable mitochondrial disorders such as LS.

Acknowledgements

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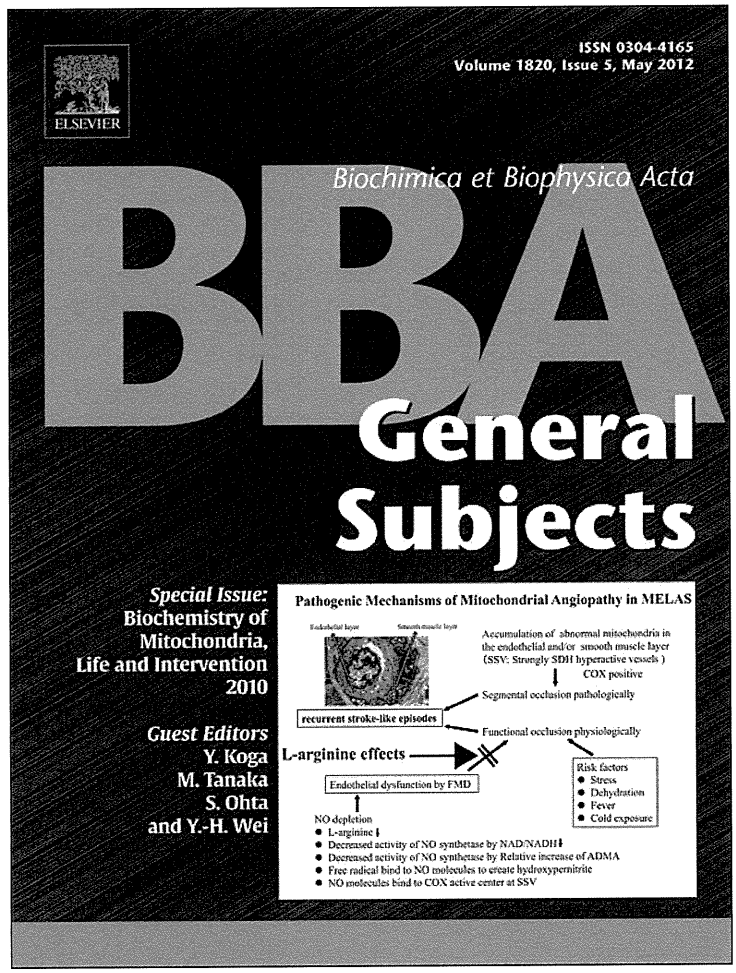

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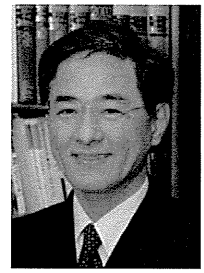
Preface

Biochemistry of mitochondria, life and intervention 2010

Mitochondrial research and medicine have been continuously expanded for the last 40 years. Since mitochondria play a central role in the metabolism of carbohydrates, lipids, and amino acids, alterations of mitochondrial functions have been implicated in various human disorders, such as mitochondrial myopathy, diabetes mellitus, aging-process, Alzheimer's disease, Parkinsonism, cancer, atherosclerosis, obesity, and metabolic syndrome.

Recent developments of clinical research and medicine indicate that the many human disorders have a link to mitochondrial function and possible to indicate the therapeutic application for cure of the disorders. ROS production from the respiratory chain plays pivotal roles not only in the control of proliferation and differentiation of cells but also in the regulation of mitochondrial mass in the cell. ROS is also related with aging and cartinogenesis. Molecular phathophysiology of maintenance of mitohondria is also discovered as fission and fusion mechanism, which are related to the quality control of mitochondria (mitophagy) seen in Parkinsonism. Many animal models are created by KO mice and are investigated the pathophysiology of disorders. Therapeutic clinical approaches are also investigated such as L-arginine on MELAS, sodium pyruvate for lactic acidosis, and hydrogen water for mitochondrial disorders. Assisted reproductive technology for mitochondrial disease patients is well developed in the fields to apply the clinical application. Such fundamental studies of mitochondrial bioenergetics could apply the new therapeutic indication for mitochondrial disorders.

In this special issue of BBA-general on " Biochemistry of Mitochondria, Life and Intervention 2010" which contains selected papers from 7th annual meeting of Asian Society for Mitochondrial Research and Medicine and 10th J-mit (Japanese Society of Mitochondrial Research and Medicine), we discuss the new aspect of mitochondrial functions relating to human disorders, and possible and on-going therapeutic approach of human disorders. This issue is organized in five chapters as follows: (i) Update mitochondrial research field, (ii) Mitophagy (fission and fusion), (iii) Animal model of mitochondrial disorders, (iv) Therapeutic approach of mitochondrial disorders, and (v) Mitochondrial pathophysiology in atherosclerosis, cancer, and aging.



Dr. Yasutoshi Koga is a professor of Pediatrics and Child Health, Kurume University Graduate School of Medicine, Japan. After he completed the MD and PhD, he joined the Mitochondrial Research Group in 1990 as a post doctoral research fellow granted by Muscular Dystrophy Association at the Department of Neurology, College of Physicians and Surgeons of Columbia University (Profs. DiMauro and Schon EA), where he directed his research to mitochondrial genetics especially pathogenic mechanism of MELAS. This led to the development of rho-zero cybrid system in mitochondrial research in 1992. He is the vice-president of Asian Society of Mitochondrial Research and Medicine and is organizing the Joint Symposium of 7th Asian Society of Mitochondrial Research and Medicine, and 10th Japanese Society for Mitochondrial Research and Medicine in 2010 at Fukuoka, Japan. He pioneered the development of a novel therapeutic procedure for MELAS and has completed the investigator-mediated clinical trial of L-arginine on MELAS. He received the Kelsey Wright Award from United Mitochondrial Disease Association (USA) in 2008. He now become a core committee member of International Mitochondrial Research and Medicine especially therapeutic division.

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