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Original Article

Promotive Excretion of Causative Agents of Yusho by One Year Intake of FBRA in Japanese People

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Abstract Thirty-six years have passed since the outbreak of Kanemi rice oil poisoning, namely, Yusho in the western Japan. However, even now the patients with Yusho have been still suffering from several objective and subjective symptoms. In order to improve or, if possible, to cure the such symptoms, the most important therapeutic treatment is considered to actively excrete the causative agents, that is, polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzo-*p*-dioxins (PCDDs) from the bodies of the patients and to reduce their body burdens.

In rats, dietary fiber and chlorophyll have been shown to promote the fecal excretion of dioxins and to reduce their levels in rat liver. In this study, we examined whether such kinds of effect were also observed by FBRA, which was the health food and relatively rich with dietary fiber and chlorophyll, in nine married Japanese couples.

As a result, concentrations of PCDFs and PCDDs on the lipid weight basis in the blood of the FBRA-intake group in which they took 7.0 to 10.5g of FBRA after each meal and three times a day for one year were more lowered than those in the blood of the non-intake group; Blood levels of PCDFs and PCDDs in the FBRA-intake group were decreased by 41.0 and 37.2 %, respectively, and those decreases were 33.7 and 29.4 % in the non-intake group.

Their total body burdens just before and one year after the study were calculated on the assumptions that the body fat was also contaminated with these dioxins at their blood levels on the lipid weight basis and the content of body fat was 20 % of the body weight. Then, we computed the average amounts in excretion of PCDFs and PCDDs from the body in both the FBRA-intake and non-intake groups. Consequently, the amounts of excretion of PCDFs and PCDDs in the FBRA-intake group were 1.81 and 1.74 times, respectively, greater than those in the non-intake group. Therefore, FBRA seemed to promote the fecal excretion of causative agents of Yusho, from the human body.

We also expect FBRA to reduce their body burdens of patients with Yusho and to improve some objective and subjective symptoms of Yusho patients.

Introduction

Our environments including foods have been polluted with extremely toxic dioxins such as polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzo-*p*-dioxins (PCDDs) not only in Japan[1)2)] but also other countries[3)~7)]. Consequently, human beings also have already been contaminated with these dioxins[8)~10)]. We already have investigated the effects of this kind of compounds on the foetus and suck-

lings which are considered the most sensitive stages of human beings as well as animals, and observed their unfavorable effects on thyroid hormone and immune response systems in Japanese infants perinatally and lactationally exposed to them[11)~14)]. Their adverse effects on developmental condition have also been found in 10-month-old breast-fed Japanese infants[15)16)].

PCDFs and PCDDs have been the most important etiological agents of Yusho[17)], a mass food poisoning that occurred in western Japan in 1968 and even now[18)]. At present, namely, more than 35 years after the outbreak, many patients with Yusho are still suffering from several objective and subjective symptoms.

In order to prevent or avoid their adverse health consequences on fetuses and sucklings, active reduction of their contamination levels in mother's body seems quite important. And also, in order to improve or to cure various symptoms of patients with Yusho, their promotive excretion from the body of Yusho patients is considered very useful. In rats, dietary fiber and chlorophyll have been shown to promote the fecal excretion of dioxins, probably due to the restriction or some inhibition of their absorption and re-absorption in the digestive tract and therefore to reduce their levels in rat liver[19)20)]. In this study, we examined whether such kinds of effect were observed by FBRA, which was the brown rice fermented with *Aspergillus-oryze* and rich with dietary fiber, or not in Japanese adults.

Materials and Methods

FBRA has been manufactured for over 30 years with Genmaikouso Corp., Sapporo, Japan, and taken by more than 100,000 people as one of the health foods. Ingredients of FBRA have already been reported in our previous study[21)].

Nine married couples of 37 to 48 years old were voluntarily participated in this study, and divided into two groups which were tried to match for sex and age, namely, FBRA-intake and non-intake groups. FBRA-intake group consisted of 5 males and 4 females with the mean age of 44.3 years old and non-intake group 4 males and 5 females with that of 43.8 years old. In FBRA-intake group, they took 7.0 to 10.5g of FBRA after each meal and three times a day for one year and in non-intake group they didn't.

Before starting this study, 60 to 80 ml of the peripheral blood was individually taken by venipuncture in both the FBRA-intake and non-intake groups twice at one week intervals. These blood samples were analyzed for PCDFs and PCDDs by HRGC-HRMS technique using a Micromass Autospec-Ultima mass spectrometer directly interfaced with Hewlett Packard 6890 Series gas chromatograph[22)].

To express the toxic potency of the mixture of dioxin congeners in the blood samples, the 1998 WHO toxic equivalency factor (TEF) approach was used for PCDFs and PCDDs[23)]. By multiplying the concentration (pg / g lipid) and TEF value, the toxic equivalent (TEQ) of each congener was calculated and expressed as pg TEQ / g lipid. The TEQ-sum of all 2, 3, 7, 8-substituted PCDFs / DDs congeners was summarized as the total TEQ concentrations. The average TEQ concentration of PCDFs or PCDDs in the two blood samples of the same person was expressed as the individual original level in both groups. In order to evaluate the effect of FBRA on their excretion from the human body, their blood TEQ concentra-

tions were determined again exactly with the same manner one year later in both the FBRA-intake and non-intake groups. Then, their mean levels were individually compared each other.

Results

Respective initial levels of PCDFs (mean±S.D.) in the blood were 9.6±4.6 and 6.4±2.0 pg TEQ / g lipid in FBRA-intake and non-intake groups. In the same manner, those of PCDDs were 13.5±6.7 and 9.9±4.7 pg TEQ / g lipid. Accordingly, the average initial concentrations of PCDFs and PCDDs in the FBRA-intake group were somewhat higher than those in the non-intake group. One year later, blood levels of PCDFs or PCDDs showed a decreasing tendency in both FBRA-intake and non-intake groups. In order to see the changes in their blood levels more clearly, their relative concentrations were computed based upon their respective initial ones as the standard (1.0). In case of PCDFs, relative blood levels in the FBRA-intake group decreased in all the nine subjects with the average relative level of 0.62 and three people were less than 0.5. Meanwhile, in the non-intake group seven of nine subjects showed less than 1.0 in relative blood levels with the average of 0.66 and three people were less than 0.5. In case of PCDDs, the relative blood levels in the FBRA-intake group showed decreasing tendency in all the nine subjects with the average of 0.65. However, in the non-intake group six of nine people were less than 1.0 with the average of 0.75.

Average concentrations of PCDFs and PCDDs in the blood of FBRA-intake and non-intake groups are indicated in Figs. 1 and 2, respectively. The concentrations (mean±S.D.) at one year after the FBRA intake were 5.7±3.2 pg TEQ / g lipid in PCDFs and 8.5±4.9 pg TEQ / g lipid in PCDDs. In the non-intake group, respective those were 4.2±2.1 and 7.0±3.2 pg

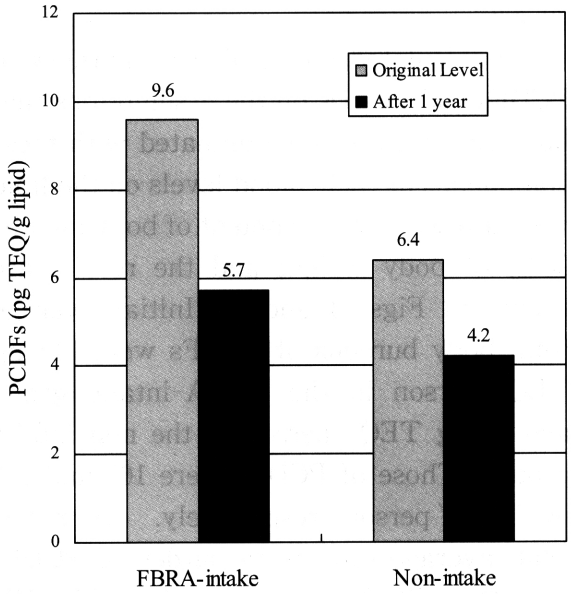

Fig. 1 Changes in average concentrations of PCDFs in the blood of FBRA-intake (left) and non-intake (right) groups for one year.
FBRA-intake Group ; −40.6%, Non-intake Group ; −34.4%

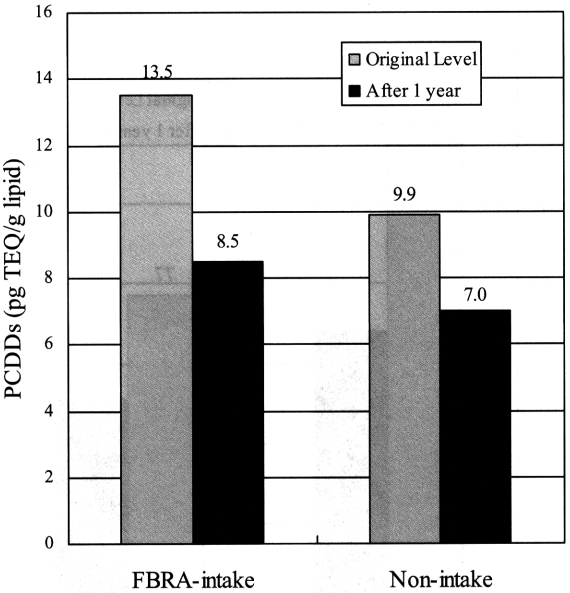

Fig. 2 Changes in average concentrations of PCDDs in the blood of FBRA-intake (left) and non-intake (right) groups for one year.
FBRA-intake Group ; −37.0%, Non-intake Group ; −29.3%

TEQ / g lipid. Therefore, blood levels of PCDFs and PCDDs in the FBRA-intake group were decreased by 40.6 and 37.0 %, respectively. In the meantime, in the non-intake group respective those were 34.4 and 29.3 %.

We calculated the total body burdens of PCDFs and PCDDs on the assumptions that body fat was also contaminated with these compounds at their blood levels on the lipid weight basis and the content of body fat was 20 % of body weight and the results are shown in Figs. 3 and 4. Initial average total body burdens of PCDFs were 115 ng TEQ / person in the FBRA-intake group and 77 ng TEQ / person in the non-intake group. Those of PCDDs were 163 and 118 ng TEQ / person, respectively. After one year, average total body burden of PCDFs were 68 ng TEQ / person and that of PCDDs 102 ng TEQ / person in the FBRA-intake group, and respective those of the non-intake group 51 and 83 ng TEQ / person. Accordingly, as indicated in Fig. 5, average

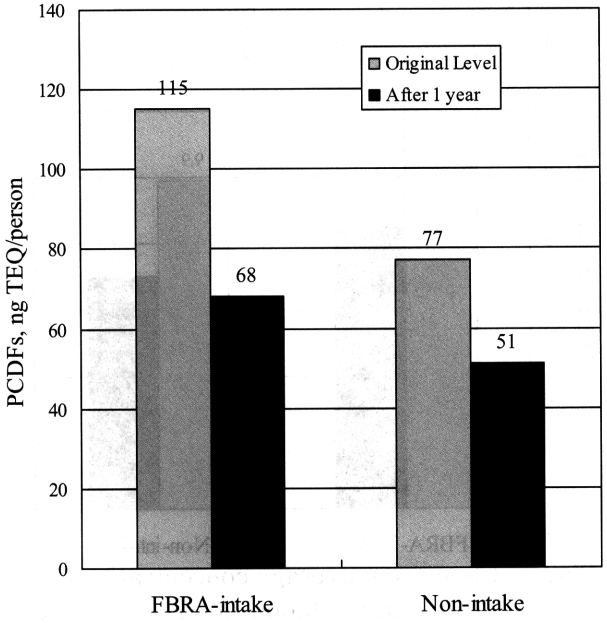

Fig. 3 Changes in mean total body burdens of PCDFs in the FBRA-intake (left) and non-intake (right) groups for one year.

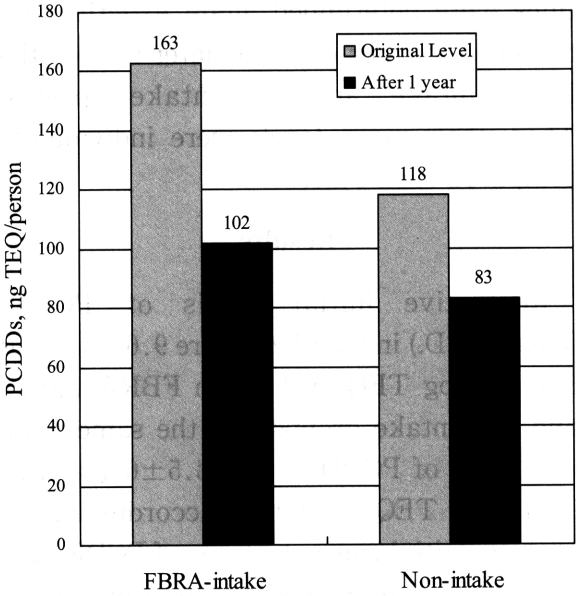

Fig. 4 Changes in mean total body burdens of PCDDs in the FBRA-intake (left) and non-intake (right) groups for one year.

amounts in excretion of PCDFs from the body for one year were 47 ng TEQ / person in the FBRA-intake group and 26 ng TEQ / person in the non-intake group. Respective those of PCDDs were 61 and 35 ng TEQ / person. Therefore, amounts of excretion of PCDFs and PCDDs in the FBRA-intake group were 1.81 and 1.74 times, respectively, greater than those in the non-intake group.

Discussion

In male rats, the fecal excretion of PCDDs was 1.3 to 2.9 times greater in the groups fed with the rice-bran and spinach fibers than in the group fed with a non-fiber diet[19]. Therefore, rice-bran fiber seems to promote the excretion of PCDDs and also hopefully PCDFs from not only rats but also humans. As we previously reported[21], 100g of FBRA contain about 20g of dietary fiber. So, if the subjects take 10g of FBRA after each meal and three times a day, they will have 2g of dietary fiber each time and 6g in

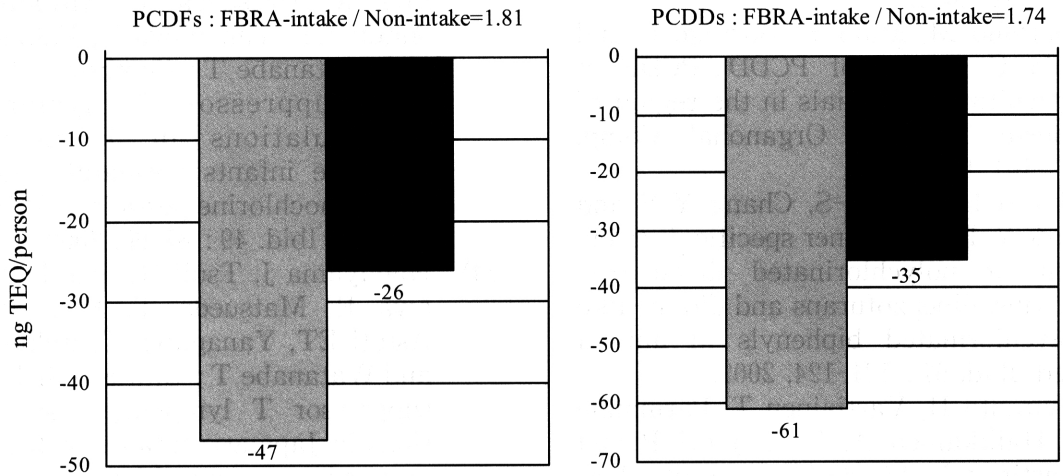

Fig. 5 Changes in average amounts of excretion of PCDFs (left) and PCDDs (right) from the human body in the FBRA-intake and non-intake groups for one year.
▒ : FBRA-intake group
■ : Non-intake group

a day. In addition to dietary fiber, FBRA contains chlorophyll, which also showed the promotional fecal excretion of PCDDs in male rats[20]. Accordingly, we expected FBRA to promote the fecal excretion of PCDFs and PCDDs from the human body and decrease their blood levels. Actually, as shown in Figs. 1 and 2, one year intake of FBRA lowered their blood levels more in the FBRA-intake group than in the non-intake group. Consequently, total body burdens of PCDFs and PCDDs were also markedly decreased more in the former group than in the latter and their elimination rates were about 1.81 and 1.74 times, respectively, higher in the FBRA-intake group than in the non-intake one, as indicated in Figs. 3 to 5.

In conclusion, even though in such small scale clinical trial, FBRA seemed to promote the fecal excretion of PCDFs and PCDDs from the human body probably through the inhibition of their absorption and / or re-absorption in the digestive tract to some extent and to decrease their body burdens.

In addition to the promotive excretion of the causative agents of Yusho, namely, PCDFs and PCDDs, FBRA is a health food and good for health, as shown before[21], so it may also improve various objective and subjective symptoms of patients with Yusho. Hence, the clinical trial of FBRA for Yusho patients is now in progress since March, 2003.

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(和文抄録)

1年間のFBRA摂取による油症原因ダイオキシン類の体外排泄促進

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カネミ油症中毒事件が発生してから36年が経過したが,今でも油症患者は種々様々な自覚および臨床症状で苦しんでいる.このような症状を改善し治療するには,その主要な原因物質であるポリ塩化ダイベンゾフラン(PCDFs)とポリ塩化ダイベンゾ-*p*-ダイオキシン(PCDDs)を積極的に体外へ排泄し,汚染レベルを低下させることが第一である.この研究では動物実験によりダイオキシン類の体外排泄促進作用が認められている食物繊維と葉緑素を比較的多量に含む栄養補助食品FBRA(発酵玄米栄養補助食品ハイ・ゲンキ,㈱玄米酵素,本社:北海道札幌市)によるカネミ油症原因物質の体外排泄促進を9組の夫婦の協力により調べた.

その結果,毎食後7～10.5gのFBRAを1日3回1年間摂取することにより,血液脂質重量当りのPCDFsとPCDDsの濃度が非摂取群よりもそれぞれ6.2%と7.7%低下した.この血液脂質濃度で体脂肪も汚染されており,体脂肪率を体重の20%と仮定し,1人当り1年間の体外排泄量を両化学物質について計算した.そうすると,FBRAを摂取することによりPCDFsとPCDDsの排泄量がそれぞれ1.81倍と1.74倍高まることが示された.以上のような結果より,FBRAは油症原因物質のPCDFsとPCDDsの体外への排泄を促進するので,油症患者の治療にも有効と考えられた.