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INTERACTION OF A β-3 AGONIST, CGP 12 177, AND DIETARY LIPIDS IN ACCUMULATION OF FATS IN RAT BODY

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Keywords: Dietary lipids, β-adrenoceptors, β-3 agonists, CGP12, 177

Background:

It has been shown that obesity, excess accumulation of fats in the body, is associated with a number of metabolic, endocrine diseases, such as diabetes, and cardiovascular, e.g. ischemic heart diseases. Therefore, many researchers have tried to manipulate fat metabolism with the hope of reducing excess fat accumulation in the body. Lipolysis, break down of fat storage (mainly triglycerides) to fatty acids and glycerol for energy production, can be considered as one of the potential ways. Lipolysis is controlled by several mechanisms in animal body. Adrenergic system, especially β-adrenoceptors, is one of them. β-adrenergic system basically contains β-1, β-2 and recently β-3 (and very recently a putative β-4) receptors. It has been believed that β-1 is involved in body thermogenesis and energy economy. Currently, it is believed that another β-receptor β-3, is also involved in fat metabolism through the induction of lipolysis. The CGP 12 177, basically a β-1 and β-2 antagonist, in high doses can induce thermogenesis and also lipolysis, both in vivo in rats body and in vitro in adipocyte cell culture through the agnostic stimulation of β-3 adrenoceptors (Van Liefde, 1993).

On the other hand, the effects of different types of dietary lipids, specially animal fats, on health is considered recently. There are a lot of researches and some of them with controversial results regarding the effects of different dietary lipids on health. It has been observed that different dietary lipids show different patterns in fat accumulation in animal body. Some studies indicate that such difference is possibly due to interactions of intaked lipids with β-adrenergic lipolytic activities. Additionally, it has been suggested that dietary lipids change the chemical composition of cell membrane, resulting in the alteration of the cell membrane fluidity and then such alteration can affect adrenoceptor activity (For details refer to Fotovati A. & T. Ito, 1998).

Objective:

Previous studies of the authors have shown distribution and metabolism of intaked dietary fats rich in saturated fatty acid (SFA), polyunsaturated fatty acid (PUFA) and monounsaturated fatty acid (MUFA) in the rats body. In this study, possible interactions between β-adrenergic activity and various dietary fats were studied by examining the accumulation and composition of fat in the rat body after raising the rats with or without oral dose of a specific β-3 agonist, CGP 12 177.

Materials and Methods:

Forty 7-weeks old male SD rats(purchased from Seac Co. Ltd., Japan) were raised on commercial diet (purchased from the same company) for one week for adaptation. Then, they were divided into 2 groups, i.e. one group was fed agonist-free diets as control and the other, fed diets containing β-3 agonists; CGP 12 177{(-)-4-(3-*t*-butylamino-2-hydroxypropoxy)[5,7-3H]benzimidazol-2-one}; developed and kindly donated by Novaritis Pharma AG}. The agonist was dosed at the level of 0.5 mg/kg/day. Each group was further divided into 4 sub-groups fed different diets containing 12% of either beef tallow, canola oil, olive oil or safflower oil. Composition of the diets was the same for 4 dietary groups except lipids, i.e., 20% beef powder, 1% AIN-76 vitamin mixture, 3.5% AIN-76 mineral mixture, 0.3% DL-methionine, 0.2% choline bitartrate, 5% cellulose, 27.9% corn starch, 30% sucrose, 0.1% cholesterol. In beef tallow diet, 0.03% alpha-tocopherol (wt/wt) was added to beef tallow itself before mixing with other ingredients, as an antioxidant. All rats have been raised on these diets ad lib and under a controlled condition (12 hr light/day, 20C temperature and 60% relative humidity) for 8 weeks in separated cages in animal raising facilities of Biotron Institute of Kyushu University. Weight gain and feed intake were measured every other day. Feces out-put was also measured weekly throughout the study. After eight weeks, the rats were killed after anesthetization with diethyl ether (carried out under the control of guideline for Animal Experiment in Faculty of Agriculture and the Graduate Course, Kyushu University and the Law [No.105] and Notification [No.6] of the Government) and their abdominal fat mass, liver and thigh muscle were dissected out and weighted. Fat content of abdominal fat mass, liver and thigh muscle and also feces, collected throughout the study, was extracted by Folch's method and their fatty acid composition was analyzed by gas chromatography (GC-14B, GAS CHROMATOGRAPH, SHIMADZU Co. Ltd., Japan)

Results:

There was no significant difference in daily feed intake among dietary sub-groups. Daily weight gain was significantly higher in CGP12 177-intaked group (5.18g/d) of beef tallow sub-group compared to the control group (3.63 g/d) of the given sub-group ($P<0.05$). Daily fecal out-put was lower in the agonist intaked groups than control, but the difference was not statistically significant. In olive oil sup-group, liver weight was significantly higher in the agonist intaked (23.68 g/d) group than control (18.98 g/d) ($P<0.05$). Compared to control groups, amounts of abdominal fat were lower in all agonist-intaked sub-group except beef tallow group. However, the difference was not statistically significant. Fatty acids composition of collected samples also showed no significant differences between agonist-intaked and control dietary groups.

Discussion:

It has been indicated that fatty acid composition of diet can affect adipocyte cell membrane composition. Comparative studies by feeding beef tallow and safflower oil, have shown that beef tallow diet promotes body fat accumulation possibly through the reduction in lipolytic activities This reduction is probably due to lower β-receptor binding and sympathetic activity in adipose tissues . It has been shown that binding affinities of β-receptors in adipose tissues were significantly lower in the beef tallow diet group . It is also believed that reduced β-adrenoceptor binding affinity was correlated with reduced membrane fluidity in beef tallow-fed group (Matsuo 1995). It has been shown that adipocyte cell membrane in rats fed beef tallow contained larger proportion of SFAs. As well known, increasing the amount of SFAs in the cell membrane of adipocytes, results in the reduction of the fluidity of cell membrane. Decrease of membrane fluidity was associated with lower adrenoceptor activity without a completely understood mechanism. Therefore, there was a significant accumulation of fat in the rats fed beef tallow possibly due to the reduction in adrenergic-induced lipolytic activities (Matsuo et al. 1995).However, our recent studies regarding the effect of dietary lipids on the weight gain of rats have shown that the weight of the rats fed with beef tallow lower than that of the rats with vegetable oils (Tajima et al., 1995 ; Kawahara et al, 1997; Notake et al, 1999). Therefore, it is necessary to elucidate the reason of the difference between the author's and above mentioned study. In the present study, the inclusion of CGP 12,177 to the diet, didn't reduce fat accumulation in the body through the mechanism of the adrenergic-induced lipolysis. However, when compared to canola, olive and safflower groups where the amounts of abdominal fat were lower in agonist-intaked group than control, beef tallow group showed almost the same level of abdominal fat in control. Such insignificant difference was possibly because of low level of agonist after oral dose. As is indicated above, CGP 12 177 was originally considered as β-1 and β-2 antagonist. Later, β-3 agonist activity of it at high doses was shown. Therefore, low level of CGP 12 177 can act reversibly due to the antagonistic blockade of β-1 adrenoceptor. Increasing the dosage could be helpful in increasing the lipolytic effect of the agonist. Since there was no significant differences in fatty acid composition of collected samples between agonist-intaked and control groups, it can be concluded that induction of lipolysis by CGP 12177, if any, is non-selective.

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The authors would like to thank Novaritis Pharma Company for providing the agonist.

* *This study was in part supported by a grant from Ministry of Education and Welfare and Uehara Memorial Foundation*