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学位論文題目	High animal-fat intake changes the bile-acid composition of bile juice and enhances the development of Barrett's esophagus and esophageal adenocarcinoma in a rat duodenal-contents reflux model. (ラット十二指腸液逆流モデルにおいて、動物性の高脂肪食摂取は胆汁酸分画を変化させ、バレット食道及び食道腺癌の発生を促進する。)
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別紙様式３

論　文　内　容　要　旨

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学位論文題目	ラット十二指腸液逆流モデルにおいて、動物性の高脂肪食摂取は胆汁酸分画を変化させ、バレット食道及び食道腺癌の発生を促進する。 **High animal-fat intake changes the bile-acid composition of bile juice and enhances the development of Barrett's esophagus and esophageal adenocarcinoma in a rat duodenal-contents reflux model.**		

(Introduction)

More than 90% of esophageal cancers are either squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). It is widely accepted that the development of ESCC is associated with smoking and alcohol consumption, whereas EAC is considered to develop from Barrett's esophagus (BE). BE is now known as a precancerous condition of EAC, and recent reports showed that BE and EAC are caused by duodenal reflux containing bile. The incidence of EAC and BE is now increasing in Western countries but low in Japan and Asia, and obesity and high fat-intake are a risk factor for the development of BE and EAC. In the present study, we studied whether or not high fat-intake may change the total level and the composition of bile acids, and studied if high fat-intake may promote the development of BE and EAC, using the rat duodenal reflux model.

(Materials and Methods 1)

We compared the total level and the composition of bile acids between control rats and the rats with duodenal reflux operation. Eight-week-old male Wistar rats were divided into 4 groups based on their diet: low soybean-oil diet (CE-2, containing 4.80% soybean oil) and high soybean-oil diet (containing 13.9% soybean oil), low cow-fat diet (containing 4.80% cow fat), and high cow-fat diet (Quick fat, containing 13.9% cow fat). They were fed for 1 month and bile juice was directly collected from the common bile duct. Aspirated bile juice was then assayed enzymatically using commercially available reagent kits at MEDIC laboratory (Yasu, Shiga-Pref.). All samples of bile acids were evaluated using high-performance liquid chromatography.

(Results 1)

There was no significant difference in the total bile-acid level among 4 groups, and there was no significant difference in free bile acids and glycine conjugates among 4 groups. However, a significant increase in the concentration of taurocholic acid (TCA) was detected in the animals fed with the high cow-fat diet (median concentration, 13.0 ± 2.52 mmol/L), compared with other 3 groups (the 2nd high was in the animals fed with low cow-fat diet (9.01 ± 1.66 mmol/L) and the lowest was in the animals fed with high soybean-oil diet) (Student's t-test, $p < 0.05$). And the concentration of taurodeoxy cholic acid (TDCA) tended to be higher in the high cow-fat group (2.34 ± 0.97 mmol/L), compared with other 3 groups (1.50 ± 0.53 mmol/L in low soybean-oil group ($p = 0.066$)). We then set the animal fed with low soybean-oil diet (CE2) and with high cow-fat diet (Quick fat) in order to carry out the next experiment to find out the difference in the incidence of BE and EAC after duodenal reflux operation.

（備考）１．論文内容要旨は、研究の目的・方法・結果・考察・結論の順に記載し、２千字程度でタイプ等で印字すること。

２．※印の欄には記入しないこと。

(Materials and Methods 2)
Rats were divided into 2 groups with and without duodenal reflux operation. In the 2nd group, the rats were fasted for 24 hours and undergone esophago-jejunostomy. The animals were sacrificed at postoperative weeks 10, 20, and 30. Resected esophagus was fixed in 10% formalin and embedded in paraffin, and we compared sequential morphological changes between 2 groups up to 30 weeks, and we examined the occurrence of BE, dysplasia and EAC.

(Results 2)
At 10 weeks after surgery, BE (37.5%) was detected in the high-fat group but not in the low soybean-oil group (Fisher's exact test, $p < 0.05$). At 30 weeks, the rats with duodenal reflux in the high cow-fat group showed a significantly higher incidence of BE and Barrett's dysplasia (100.0% and 78.6%, respectively) than those in the low soybean-oil group (50.0% and 12.5%, respectively) ($p < 0.05$). The incidence of EAC in the high-fat group (42.9%) also tended to be higher than that in the low soybean-oil group (12.5%) ($p = 0.10$). We detected EAC (2 out of 16) in the low soybean-oil group, but these EACs were in relatively earlier stage reaching not to the adventitia. However, 2 out of 6 EACs in the high fat group were more advanced reaching beyond the adventitia than those in the low soybean-oil group.

(Discussion)
In the rats with duodenal reflux operation, a significant increase in the concentration of taurine-conjugated bile acids, especially TCA and TDCA, was detected in the high cow-fat group, compared with the other groups fed with the soybean-oil diets and the low cow-fat diet. In human cases, Nehra et al. reported that only TCA among the primary bile acids significantly increased in BE patients with stenotic syndrome, compared to asymptomatic patients, implying that high TCA may be related to the development of BE. The present finding thus conforms to this description, whereas how the increase in TCA and TCDA is related to the development of BE remains to be answered. And the present study showed that the high cow-fat intake caused the much more development of EAC in rats with duodenal reflux operation. This may explain in part the rising rates of BE and EAC in Western countries, and the low rates of these diseases in Asian countries including Japan.

別紙様式８（課程・論文博士共用）

学位論文審査の結果の要旨

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（学位論文審査の結果の要旨）

本研究は、ラット十二指腸液逆流モデルを用いて、高脂肪食摂取が Barrett 食道から食道腺癌の発生に関与するか否かを検討したものである。まず、脂肪源として大豆油もしくは牛脂を用いた計４種類の低及び高脂肪食を設定し、手術をしないラットに１ヶ月間摂取させた。その後、胆汁中の総胆汁酸濃度と胆汁酸分画を高速液体クロマトグラフィーにて測定した。その結果、牛脂を用いた高脂肪食群では、他の群に比べて、タウリン抱合型胆汁酸濃度の有意な上昇を認めた。次に、逆流モデル作成後、牛脂を用いた高脂肪食群と大豆油を用いた低脂肪食群の２群に分け、手術後 30 週において、食道の組織学的検討を行った結果、高脂肪食群では、Barrett 食道や食道腺癌の発生率の上昇を認めた。以上より、高脂肪食摂取によるタウリン抱合型胆汁酸の上昇が Barrett 腺癌の発生に大きく関与していると結論した。本研究は、Barrett 腺癌の発生の原因を、高脂肪食摂取による胆汁中の胆汁酸分画の変化という観点から解明しており、学位論文に値するものと評価される。

（平成 20 年 8 月 28 日）