

Stomach secretes estrogen in response to blood triglyceride levels in males

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Article

Keywords: Estrogen, lipid homeostasis, blood triglyceride, stomach

Posted Date: March 25th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-289734/v1>

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Version of Record: A version of this preprint was published at Communications Biology on December 7th, 2021. See the published version at <https://doi.org/10.1038/s42003-021-02901-9>.

Abstract

The central nervous system receives body energy information and controls feeding behavior and lipogenesis¹. Ghrelin, insulin, leptin and vagal afferents transmit the status of fasting, blood glucose, body fat, and food intake, respectively²⁻⁵. Estrogen, which is secreted from adipocytes and gastric parietal cells and from the ovaries in females, also acts upon the central nervous system and liver to inhibit feeding behavior and lipogenesis⁶⁻⁹. How blood triglyceride levels are monitored and how estrogen levels are regulated from the perspective of the lipid homeostasis is not well understood. Using male rats, we show that gastric parietal cells secrete estrogen in response to blood triglyceride levels. Parietal cells predominantly use fatty acid as an energy source. When male rats are administered olive oil or glucose, blood estrogen levels increase as the blood triglyceride, but not glucose, levels rise. Estrogen levels in stomach tissues increase as the blood triglyceride levels rise, and blood triglyceride level-dependent increases of blood estrogen levels are cancelled in gastrectomized rats. We therefore propose that in males, parietal cells in the stomach act as a sensor for the blood triglyceride levels and can secrete estrogen to inhibit the hepatic lipogenesis and feeding behavior when blood triglyceride levels are high.

Main Text

Estrogen is a multi-target and multi-functional hormone beyond just a sex hormone; it controls glucose/lipid homeostasis, bone metabolism, brain function and skeletal growth as well as follicular growth and ovulation⁷. Aside from the ovaries in females, estrogen is also secreted from adipose tissues, which are greatly increased in males^{10,11}. Our previous studies showed that parietal cells in rat stomachs also express aromatase, together with 17 α -hydroxylase and 17 β -hydroxysteroid dehydrogenase type III (17 β -HSD type III), and convert testosterone (male) or progesterone (female) to estrogen (17 β -estradiol [E2])^{6,12} (Fig. 1a). Aromatase was prominently expressed in the stomach among the tissues upstream of the portal vein (stomach, duodenum, jejunum, ileum, colon and pancreas)⁶, and the small amounts of aromatase in the rest of the tissues were mainly from the attached adipose tissues (Fig. 1b, c, Extended Data Fig. 1). Parietal cells secrete estrogen (gastric estrogen) into the portal vein, so estrogen levels are higher in the portal vein (ca. x2) than in the artery in male⁶ and female¹³ rats, which is lost in gastrectomized (GX) rats⁶. The role of gastric estrogen and how its secretion is regulated are not widely understood. Here, using male rats, we show that parietal cells act as a sensor for the blood triglyceride levels and gastric estrogen is secreted in response to the blood triglyceride levels. Estrogen suppresses the lipid supply by inhibiting the feeding behavior and the *de novo* lipogenesis in the liver^{8,9}, so we propose that when blood triglyceride levels rise, parietal cells increase the secretion of estrogen, which lowers the blood triglyceride levels to maintain proper blood triglyceride levels in males (Fig. 3d).

Gastric estrogen directly enters the liver via the portal vein, where estrogen controls glucose/lipid homeostasis⁹. This secretion is similar to that of insulin, which is secreted from pancreatic β -cells, enters the portal vein, and directly acts on the liver to keep appropriate blood glucose levels^{14,15}. β -cells, which sense the blood glucose levels, use glucose, not fatty acids, as an energy source¹⁶ (Extended Data Fig.

1b), and parietal cells require energy (NADPH) in the production of estrogen (3 x NADPH from testosterone in male, 6 x NADPH from progesterone in female, Fig. 1a). We therefore focused on the energy sources of parietal cells to obtain clues on how the production of gastric estrogen is regulated. Blood estrogen levels change in the menstrual cycle in females, so in this study we used male rats to exclude the effect of estrogen from the ovaries. Triglyceride (fatty acids) and glucose are major sources of energy for mammals. We examined the expression of the enzymes used in the generation of energy from fatty acids (acyl-CoA dehydrogenase medium chain [ACADM], an enzyme involved in β -oxidation) and glucose (glucokinase [GCK], a glycolytic enzyme) in the gastric mucosa (Figs. 1c, d). We identified the estrogen-producing cells and parietal cells using the antibodies against aromatase and H⁺/K⁺ ATPase (ATP4B), respectively⁶. Aromatase-positive cells expressed high levels of ACADM, but little if any GCK. Conversely, aromatase-negative cells showed strong GCK but weak ACADM expressions (Fig. 1c). ATP4B-positive parietal cells showed the same result as the aromatase-positive cells (Fig. 1d). We therefore conclude that parietal cells exclusively produce estrogen in the stomach and predominantly use fatty acids as an energy source.

Parietal cells secrete estrogen in an energy-dependent manner^{6,12} (Fig. 1a), and they predominantly use fatty acids as an energy source (Fig 1c and d). Moreover, estrogen from parietal cells directly enters the liver via the portal vein where lipogenesis occurs when blood triglyceride levels are low¹⁷, and it suppresses the increase of blood triglyceride levels by inhibiting the hepatic *de novo* lipogenesis⁹ and the feeding behavior⁸. We therefore hypothesized that parietal cells increase the secretion of estrogen as blood triglyceride levels rise, which suppresses the supply of lipid to maintain appropriate blood triglyceride levels.

To test this hypothesis, we designed a series of experiments. First, we investigated the relationship between the blood triglyceride and estrogen levels (Fig. 2). Triglyceride (olive oil, 2.5 ml/kg body weight) or control water was orally administered to rats and we measured their triglyceride and estrogen (E2) levels in the tail venous blood before (0 h) and at 1, 2, 3, 4, 5 h after the administration (Fig. 2a). Blood triglyceride levels (basal levels: ~130 mg/dL) increased, peaked at 2 h post-administration (~300 mg/dL), and then declined to the basal levels (5 h) as reported previously¹⁸. Blood E2 levels (basal levels: ~50 pg/ml) also increased, peaked at 2 h after the administration (~80 pg/ml), and then returned to the basal levels (5 h). Control rats did not show apparent changes in their blood triglyceride or in E2 levels. We then analyzed the relationship between the blood triglyceride and E2 levels at 2 h after the administration; there was a positive correlation between them (Fig. 2b). We further examined the effect of blood glucose on the blood estrogen levels. Glucose administration is known to decrease blood triglyceride levels via insulin-mediated inhibition of lipolysis in adipose tissues^{19,20}, so we also monitored the blood triglyceride levels. Rats were orally administered glucose (2 g/kg body weight) or control water, and we measured their tail venous blood glucose, E2, and triglyceride levels before (0 h) and at 0.5, 1, 1.5, 2, 3, 4, 5 h after administration (Fig. 2c). Blood glucose levels (basal levels: ~60 mg/dL) increased, peaked at 1 h after the administration (~170 mg/dL), and then declined toward the basal levels²¹. Blood E2 and triglyceride

levels did not increase, however, they actually decreased when blood glucose levels were high. Blood estrogen levels are indicated to increase as blood triglyceride levels, but not glucose levels, rise.

Next, we investigated the effect of blood triglyceride levels on the production of estrogen in parietal cells. Parietal cells exclusively produce estrogen in the stomach and the elevated estrogen level in the portal vein compared with the artery is cancelled in GX rats⁶. We therefore measured the E2 levels in the stomach tissues with the triglyceride levels in the tail venous blood at 2 h after the administration of olive oil or control water (Fig 3a). Rats administered olive oil showed elevated blood triglyceride (~280 mg/dL) and stomach E2 (~3,500 pg/g tissue) levels compared with the controls (blood triglyceride: ~110 mg/dL, stomach E2: ~1,900 pg/g tissue), and there was correlation between the blood triglyceride and stomach E2 levels. Parietal cells in the stomach were shown to produce estrogen in response to the blood triglyceride levels.

Finally, using GX rats, we investigated the involvement of the stomach in the regulation of blood estrogen levels by blood triglyceride levels (Fig. 3b, c). GX rats showed weaker increase of the blood triglyceride levels than normal rats when administered olive oil (data not shown), so we used 5 ml/kg body weight of olive oil in the studies using GX rats. Five days after total gastrectomy, GX rats were administered olive oil or control water. We measured triglyceride and E2 levels in the tail venous blood before (0 h) and at 1, 2, 3, 4, 5 h after the administration (Fig. 3b). Blood triglyceride levels of GX rats (basal levels: ~90 mg/dL) increased, peaked at 2 h post-administration (~210 mg/dL), and then declined to the basal levels (5 h); but, blood E2 levels did not show apparent changes (~60 pg/ml). We also analyzed the relationship between the blood triglyceride and E2 levels at 2 h after the administration, but we found no correlation between them (Fig. 3c). The stomach is indicated to be the organ responsible for controlling the blood estrogen levels in response to the blood triglyceride levels.

In conclusion, we showed that parietal cells in the stomach predominantly produce estrogen among the tissues upstream of the portal vein. Production of estrogen requires energy, and parietal cells predominantly use triglyceride as the energy source. Blood estrogen levels increase as blood triglyceride levels rise, but not as glucose levels rise. Levels of estrogen in the stomach tissues increase as blood triglyceride levels rise, and in GX rats, increases of blood estrogen levels dependent on blood triglyceride are cancelled.

To maintain proper lipid conditions, hypothalamic NPY neurons collect the body lipid status to control hepatic lipogenesis and feeding behavior¹. Ghrelin from the stomach, leptin from adipose tissues and vagus afferent nerves from the intestines and the liver report the levels of fasting, body fat and ingested lipids, respectively, and play a part in activation (ghrelin) or inhibition (leptin and vagus afferent nerves) of the NPY neurons^{2,4,5}. Little is known, however, about the hormones or nerve fibers that inform the blood lipid levels. On the other hand, estrogen inhibits the hepatic *de novo* lipogenesis and the subsequent secretion of VLDL directly^{9,22,23} or by suppressing the NPY neurons^{8,24,25}. Little is known, however, about what information blood estrogen levels represent in terms of the lipid homeostasis. Among the organs upstream of the portal vein, the stomach and the pancreas do not take up nutrients

and are suitable for sensing and directly informing the liver of the levels of “circulating” nutrients. Indeed, the pancreas secretes insulin or glucagon depending on the circulating blood glucose levels to control the blood glucose levels primarily by acting on the liver. We therefore collectively conclude that the stomach, a digestive organ, also acts as a blood triglyceride sensor organ, and parietal cells in the stomach secrete estrogen according to the blood triglyceride levels (Fig. 3d). When blood triglyceride levels rise, parietal cells increase the secretion of estrogen into the portal vein, which in turn lowers the blood triglyceride levels by inhibiting the hepatic *de novo* lipogenesis and feeding behavior. Conversely, when blood triglyceride levels lower, parietal cells decrease the secretion of estrogen to supply more lipid to the circulation.

This is the first demonstration of a mechanism by which gastric parietal cells sense the blood lipid levels and secrete estrogen to keep proper blood triglyceride levels by controlling the hepatic *de novo* lipogenesis and feeding behavior. Our model is consistent with previous reports on the daily rhythms of hepatic lipogenesis, blood triglyceride levels, and blood and gastric estrogen levels. Hepatic lipogenesis is regulated by daily feeding rhythm and rises when blood triglyceride levels are low¹⁷. Blood estrogen levels increase at night when rats eat actively, which is regulated by the secretion of gastric estrogen²⁶.

Adipocytes dominantly use fatty acids as the energy source like parietal cells, and express high levels of ACADM (Extended Data Fig. 1c) and low levels of GCK (data not shown). Blood triglyceride-dependent changes of blood estrogen levels are regulated by the stomach, but not by other tissues, such as adipose tissues. Adipocytes are filled with triglyceride, but parietal cells are not. Intracellular triglyceride levels are thus more susceptible to the extracellular (blood) triglyceride levels in parietal cells than in adipocytes. We therefore think parietal cells, not adipocytes, are suitable for the real-time monitoring of blood triglyceride levels.

As for gastric estrogen in females, parietal cells of female rats also secrete estrogen and increase the estrogen levels in the portal vein¹³; but estrogen and progesterone, a precursor for gastric estrogen in females, are mainly secreted from the ovaries. Moreover, the blood levels of estrogen and progesterone change dramatically with the menstrual cycle. The roles and regulation of gastric estrogen in females require further careful investigation.

Materials And Methods

Animals

Male Wistar rats were purchased from Kiwa Laboratory Animals Co., Ltd. (Wakayama, Japan). Animals were housed in an air-conditioned environment with 12 h light/dark cycle and allowed access to food (MF diet, Oriental Yeast Co. Ltd., Tokyo, Japan) and water *ad libitum* unless otherwise stated. All experiments were conducted according to the protocol approved by the Wakayama Medical University Animal Care and Use Committee.

Immunoblotting

Crude extracts of the stomach, duodenum, jejunum, ileum, colon and pancreas were obtained from adult male rats. Proteins (10 µg for aromatase, 1 µg for b-actin) were separated by SDS-PAGE, transferred to a polyvinylidene fluoride membrane (Immobilon-P, Millipore) and detected with antibodies against aromatase (MCA2077S, BioRad) and b-actin (A5060, Sigma-Aldrich). Band intensities were quantified with LuminoGraph \boxtimes (ATTO) using a standard enhanced chemiluminescence protocol. Processing of the images was performed with ImageJ 1.52 (National Institutes of Health).

Fluorescence staining

We performed immunostaining of rat tissue sections using a standard protocol²⁷. Rats were anesthetized using isoflurane and fixed by perfusion with 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.2). Tissues were then embedded in paraffin, sectioned at 5 µm thickness using a microtome (model RX-860; Yamato Kohki Industrial), and subjected to heat-induced epitope retrieval treatment (pH 6.0) according to the standard method. After blocking with Block One Histo (Nacalai Tesque), sections were incubated with the following primary antibodies: anti-aromatase, anti-ATP4B (MA3-923, Invitrogen), anti-ACADM (GTX100488, GeneTex), anti-GCK (HPA007093, Sigma-Aldrich), and anti-insulin (66198-1-Ig, Proteintech). Sections were then incubated with Alexa Fluor-conjugated secondary antibodies from Thermo Fisher. After quenching the autofluorescence using TrueView from Vector Laboratory, samples were observed under an LSM-700 confocal laser-scanning microscope equipped with C-Apochromat 40/1.2W or Pan-Apochromat 20/0.8 lens (Carl Zeiss). Images processing and analyses were performed with ImageJ 1.52 (National Institutes of Health).

Gastrectomy

Total gastrectomy (GX) was performed on 7-week-old male rats by anastomosing the duodenum and esophagus from end to end, as described elsewhere²⁸. GX rats were used for the subsequent studies 5 days after the surgery.

Oral administration of olive oil and glucose

At 8 weeks of age, rats were deprived of food for 4 h before the experiment. Olive oil ("Yoshida", Yoshida Pharmaceutical Company, Tokyo, Japan) or control distilled water was orally administered, and blood samples from the tail vein were collected at 0 (before), and 1, 2, 3, 4 and 5 h after the administration¹⁸. GX rats showed weaker increase of blood triglyceride levels than normal rats when administered olive oil, so a smaller amount of olive oil was applied in the normal rats (2.5 mg/kg body weight) compared with the GX rats (5 mg/kg body weight). In some studies, we sacrificed rats 2 h after the administration to obtain stomach tissues. Regarding oral administration of glucose, 8-week-old rats, deprived of food for 18 h, were orally administered glucose (2 g/kg body weight, FUJIFILM Wako Pure Chemical Corp.) or control distilled water²¹. Blood samples from tail veins were collected at 0 (before) and 0.5, 1, 1.5, 2, 3, 4 and 5 h after the administration. We excluded the rats whose tail venous triglyceride levels prior to the administration were higher than 200 mg/dL.

Measurement of triglyceride, estrogen and glucose concentrations

The plasma triglyceride concentrations were measured using a LabAssay Triglyceride (FUJIFILM) according to the manufacturer's instructions. The total estrogen (E2) concentrations in the plasma fractions of blood samples and the stomach tissues²⁹ were determined using an Estradiol ELISA kit (Cayman Chemical Company, Ann Arbor, MI, USA) according to the manufacturer's instruction. Blood glucose levels were measured using FreeStyle Libre (Abbott Japan) according to the manufacturer's instructions.

Statistical analysis

Statistical analyses were performed using JMP Pro ver. 14 (SAS Institute Japan). *P* values < 0.05 were considered to be significant.

Method References

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Declarations

Data availability There is no accession code, unique identifier, or special data set used in this study.

Acknowledgements We thank Yuki Yamazaki, Shota Nasu, Yamato Tsunoda and Keigo Matsui from the Kanai Laboratory for technical assistance. We acknowledge proofreading and editing by Benjamin Phillis at Wakayama Medical University. This study was supported by Medical Research Support from Wakayama Medical University (to Y.K.). This paper is dedicated to the late professor Takashi Ueyama (Wakayama Medical University, Wakayama, Japan).

Author contributions Y.K. conceived the project, invented the hypothesis, designed the experiments, wrote the manuscript, and made the figures including the drawing of the model diagram. Y.Y. and N.Y. performed immunoblot studies. Y.K. and T.I. performed immunofluorescence studies. T.I. generated GX rats. T.I. and Y.Y. performed olive oil and glucose administration experiments. T.I. measured blood TG and blood and stomach E2 levels. T.I. and Y.Y. measured blood glucose levels. Y.Y. performed statistical analysis. T.I, Y.Y. and N.Y. contributed equally.

Competing interests The authors declare no competing interests.

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Figures

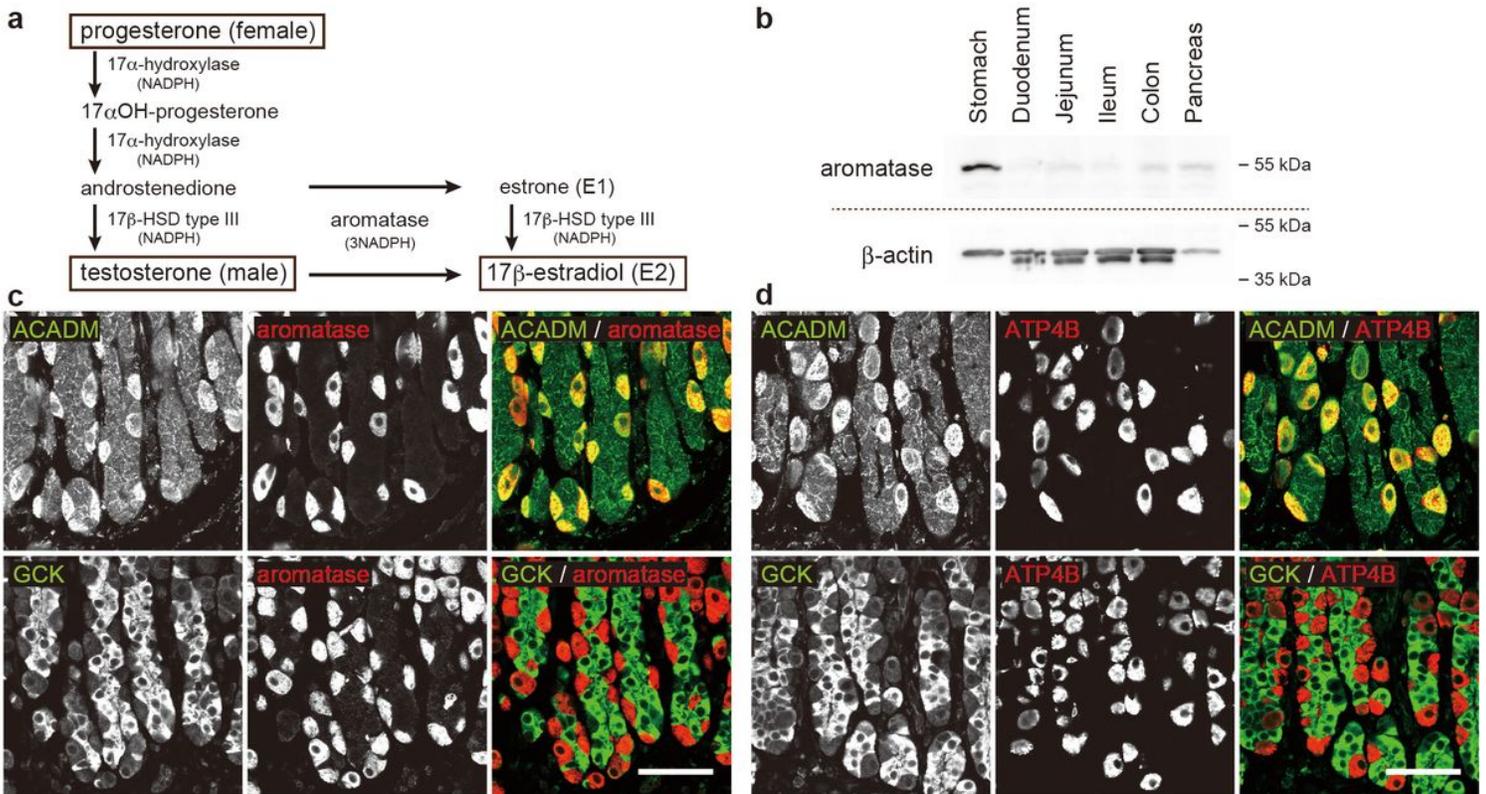


Figure 1

Estrogen producing gastric parietal cells use fatty acid as energy source a, Scheme of testosterone (progesterone)-17 β -estradiol (E2) conversion pathway in rat gastric parietal cells. b, Immunoblotting of crude extracts from the stomach, duodenum, jejunum, ileum, colon and pancreas of adult male rats using antibodies against aromatase and control β -actin. c, Rat gastric mucosa was double stained for ACADM (acyl-CoA dehydrogenase medium chain, an enzyme involved in β -oxidation) or GCK (glucokinase, a glycolytic enzyme) (green) with aromatase (red). d, Rat gastric mucosa was double stained for ACADM or GCK (green) with ATP4B (H⁺/K⁺ ATPase, a gastric parietal cell marker; red). Bars: 50 μ m.

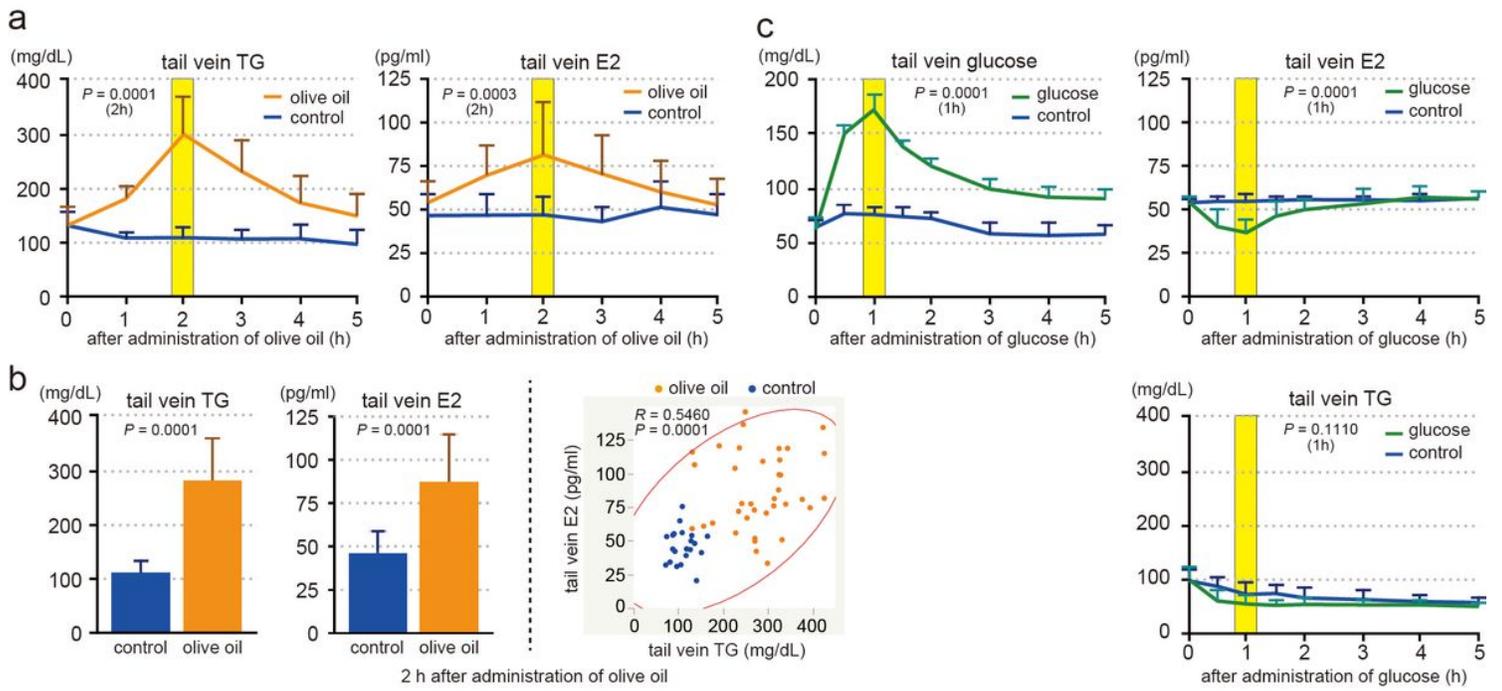


Figure 2

Blood estrogen levels increase as blood triglyceride levels, but not glucose levels, rise a, Rats were orally administered olive oil ($n = 13$) or control water (control, $n = 8$). TG and E2 levels in the tail venous blood measured before (0) and at 1, 2, 3, 4, 5 h after the administration. b, TG and E2 levels in the tail venous blood measured at 2 h after the administration of olive oil ($n = 37$) or control water ($n = 21$) (left), and the correlation diagram between the blood TG and E2 levels ($n = 58$, right). c, Rats were orally administered glucose ($n = 10$) or control water ($n = 9$). Glucose, E2 and TG in the tail venous blood measured before (0) and at 0.5, 1, 1.5, 2, 3, 4, 5 h after the administration. n, number of rats. Data are mean \pm s.d. P values determined by two-sided Student's t-test at 2 h (a, b, left) or 1 h (c) after the administration. b, right, R and P values determined by Pearson's product moment correlation with 95% density ellipse.

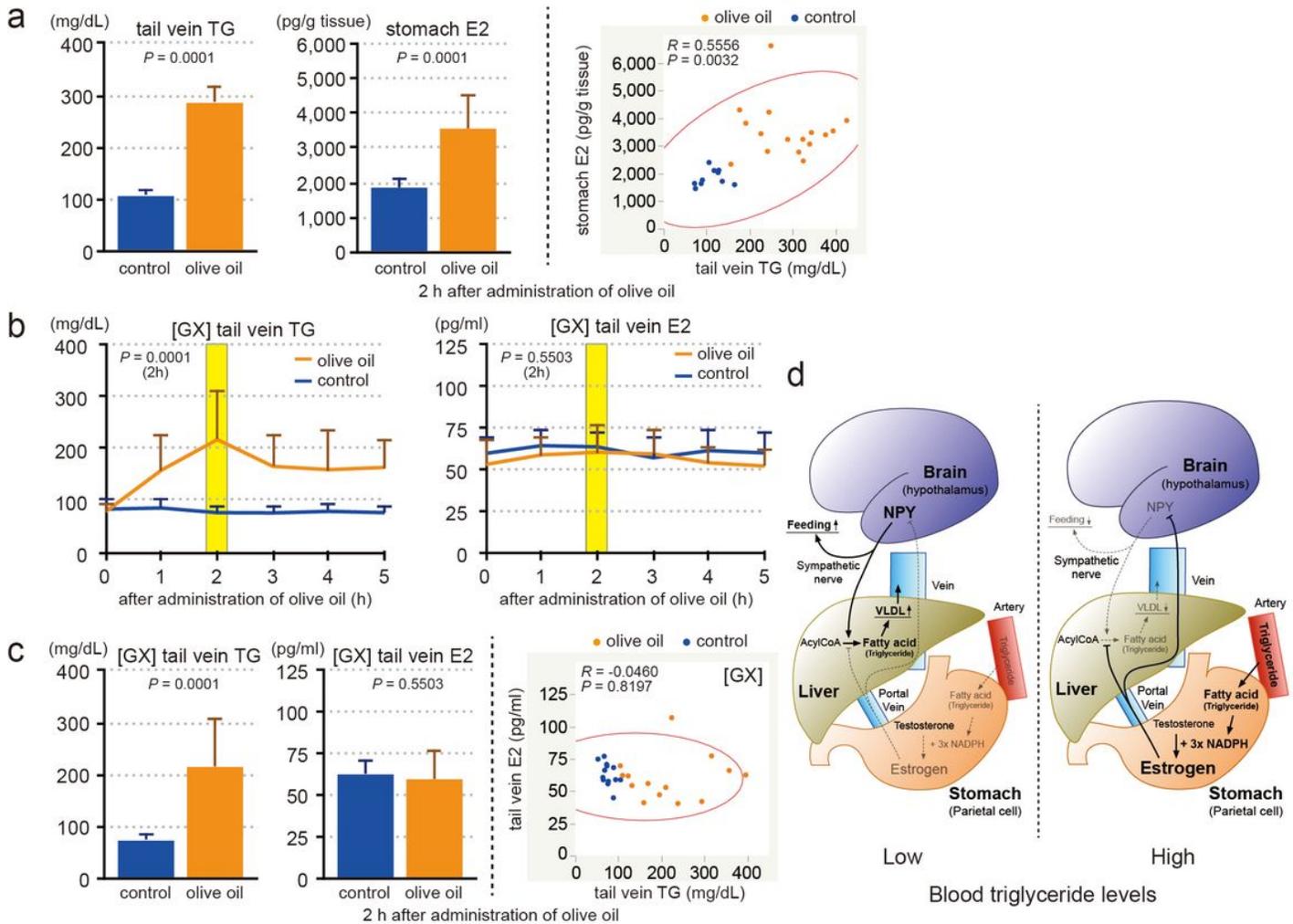


Figure 3

Stomach secretes estrogen in response to the blood triglyceride levels a, Rats were orally administered olive oil ($n = 16$) or control water ($n = 10$). TG levels in the tail venous blood and E2 levels in the stomach tissues measured at 2 h after the administration (left), and the correlation diagram between the blood TG and stomach E2 levels ($n = 26$, right). b, GX rats were orally administered olive oil ($n = 14$) or control water ($n = 13$). TG and E2 levels in the tail venous blood measured before (0) and at 1, 2, 3, 4, 5 h after the administration. c, TG and E2 levels in the tail venous blood of GX rats measured at 2 h after the administration of olive oil ($n = 14$) or control water ($n = 13$) (left), and the correlation diagram between the blood TG and E2 levels ($n = 27$, right). d, Proposed model for the role of gastric estrogen in the control of blood triglyceride levels. When blood triglyceride levels rise, parietal cells in stomach increase the secretion of estrogen (this study), which suppresses the hepatic lipogenesis and the feeding behavior directly or by inhibiting the hypothalamic NPY neurons^{8,9}. n, number of rats. Data are mean \pm s.d. a, left, b, c, left, P values determined by two-sided Student's t-test at 2 h after the administration. a, right, c, right, R and P values determined by Pearson's product moment correlation with 95% density ellipse.

Supplementary Files

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- [ExtendedDatafig1.png](#)