SHORT COMMUNICATION

Promethazine Hydrochloride Inhibits Ectopic Fat Cell Formation in Skeletal Muscle

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Skeletal muscle is responsible for exercise and physical activity, and therefore is a vital organ for healthy life. But in some pathologic conditions such as Duchenne muscle dystrophy, 1 aging, 2 and trauma, 3 ectopic fat cells emerge in skeletal muscle. Fatty degeneration of skeletal muscle leads to muscle weakness 4 and reduction in quality of life. 3 Thus, preventing ectopic fat cell formation in skeletal muscle is an important task in the clinical setting.

Although the origin of ectopic adipocytes in skeletal muscle was unclear for a long time, we and others identified platelet-derived growth factor receptor α (PDGFRα)-positive mesenchymal progenitors in murine muscle interstitium and showed that these cells are the origin of ectopic fat cells. 5,6 Subsequently, we further showed that the same is true in humans. 7 Therefore, mesenchymal progenitors can be an ideal target to prevent fatty degeneration of skeletal muscle. Recently, we optimized isolation and culture conditions, which enabled us to obtain a large number of mesenchymal progenitors derived from human skeletal muscle. 8,9 Thus, it now is possible to perform drug screening by using human mesenchymal progenitors as target cells.

Discovering and developing new drugs requires enormous amounts of time and money. Despite that, recent successful case rates are only 4%. 10 Therefore, more economical and efficient strategies are required. Drug repositioning, which is a method to discover new applications of drugs that had been used for certain

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Fatty degeneration of skeletal muscle leads to muscle weakness and loss of function. Preventing fatty degeneration in skeletal muscle is important, but no drug has been used clinically. In this study, we performed drug repositioning using human platelet-derived growth factor receptor α (PDGFRα)-positive mesenchymal progenitors that have been proved to be an origin of ectopic adipocytes in skeletal muscle. We found that promethazine hydrochloride (PH) inhibits adipogenesis in a dose-dependent manner without cell toxicity. PH inhibited expression of adipogenic markers and also suppressed phosphorylation of cAMP response-element binding protein, which was reported to be a primary regulator of adipogenesis. We established a mouse model of tendon rupture with intramuscular fat deposition and confirmed that emerged ectopic adipocytes are derived from PDGFRα þ cells using lineage tracing mice. When these injured mice were treated with PH, formation of ectopic adipocytes was suppressed significantly. Our results show that PH inhibits PDGFRα þ mesenchymal progenitor-dependent ectopic adipogenesis in skeletal muscle and suggest that treatment with PH can be a promising approach to prevent fatty degeneration of skeletal muscle. (Am J Pathol 2017, 187: 2627–2634; https://doi.org/10.1016/j.ajpath.2017.08.008)
diseases, has been receiving attention in recent years. Because
drug repurposing uses existing drugs, it can reduce the time and
cost for drug development and shorten the transition time to
clinical use.\(^1\)

In this study, we performed drug repurposing using human
PDGFR\(\alpha^+\) mesenchymal progenitors to find drugs that inhibit
fatty degeneration of skeletal muscle. This screening identified
promethazine hydrochloride (PH) as a candidate compound. PH
inhibited adipogenic differentiation of human PDGFR\(\alpha^+\)
mesenchymal progenitors almost completely and suppressed
ectopic fat cell formation in a mouse model of tendon rupture
with intramuscular fat deposition. Our results suggest that PH
can be a promising drug for the treatment of fatty degeneration
of skeletal muscle.

**Materials and Methods**

**Cell Preparation from Human Skeletal Muscle**

Human skeletal muscle tissue was obtained from gluteus medius
muscles of patients who underwent total hip arthroplasty. Written
informed consent was obtained from all patients. Experiments
using human samples were approved by the Ethical Review
Board for Clinical Studies at Fujita Health University. Human
skeletal muscles were transferred to phosphate-buffered saline.
Muscles were minced with scissors and digested with 0.2%
collagenase type II (Worthington, Lakewood, NJ) at 37°C for 30
minutes. Digested muscles were passed through an 18G needle
several times and digested again at 37°C for 15 minutes. The
digested slurry was filtered through a 100-μm cell strainer, and
then through a 40-μm cell strainer (BD Biosciences, Franklin
Lakes, NJ). Erythrocytes were eliminated by treating the cells with
Tris-buffered 0.83% NH_4Cl. Cells were cultured on 60-mm
collagen I–coated dishes (Iwaki, Tokyo, Japan) in growth me-
dium (GM) consisting of Dulbecco’s modified Eagle’s medium
with 20% fetal bovine serum (FBS), 1% penicillin–streptomycin,
and 2.5 ng/mL basic fibroblast growth factor (Katayama Chem-
ical, Osaka, Japan) at 37°C in 3% O_2 and 5% CO_2. Cells were
trypsinized and suspended in washing buffer consisting of
phosphate-buffered saline with 2.5% FBS. Then, cells were
washed using the LIVE/DEAD viability/cytotoxicity assay
kit (Thermo Fisher Scientific, Waltham, MA). The percentage of live cells was
measured using ArrayScan VTI-HCS (Thermo Fisher Scientific, Waltham, MA). The degree of adipogenic differen-
tiation was determined by dividing the Bodipy-stained area
by the number of nuclei.

**Cell Viability Assay**

PDGFR\(\alpha^+\) cells were cultured on Matrigel-coated 6-well or
96-well plates in GM as described earlier. Then cells were
cultured in Dulbecco’s modified Eagle’s medium containing
10% FBS and 1.25, 2.5, 5, or 10 μmol/L PH for 3 days at
37°C in 21% O_2 and 5% CO_2. For the LIVE/DEAD assay,
cells were trypsinized and detached from 6-well plates, and
then stained using the LIVE/DEAD viability/cytotoxicity assay
kit (Thermo Fisher Scientific). The percentage of live cells was
analyzed using FACS Verse (BD Biosciences). For the water-
soluble tetrazolium salt-8 assay, 10 μL of water-soluble
tetrazolium salt-8 reagent (Cell Counting Kit-8; Dojindo Mo-
olecular Technologies, Kumamoto, Japan) was added to each
well of 96-well plates and incubated for an additional 2 hours.
Absorbance at 450 nm was measured by Multiskan JX
(Thermo Fisher Scientific). These experiments were repeated
three times using PDGFR\(\alpha^+\) cells obtained from three inde-
pendent preparations.

**RNA Extraction and Real-Time RT-PCR**

Ten thousand PDGFR\(\alpha^+\) cells were cultured on Matrigel-coated
48-well plates and subjected to adipogenic differentiation as
described earlier with or without 10 μmol/L PH. Total RNA was
extracted on days 0, 4, 8, and 12 of adipogenic differentiation

**Screening of Food and Drug Administration—Approved
Compounds**

A Food and Drug Administration–approved chemical
compound library (Prestwick Chemical, Illkirch, France)
consisting of 1186 compounds was used. Five hundred and
seventy-nine compounds were excluded because they were
not appropriate for chronic treatment and 287 additional
compounds were also excluded because they were unavail-
able in Japan. The remaining 320 compounds were
screened. PDGFR\(\alpha^+\) cells were seeded in wells of 96-well
plates coated with Matrigel (BD Biosciences) at a density of
5 × 10^3 cells/well in GM and incubated at 37°C in 3% O_2
and 5% CO_2. When cells reached 90% confluency, the GM
was changed to adipogenic induction medium consisting of
Dulbecco’s modified Eagle’s medium with 10% FBS, 0.5
mmol/L insulin (Sigma-Aldrich, St. Louis, MO), 0.25 μmol/L
dexamethasone (Sigma-Aldrich), and 10 μg/mL insulin
(Sigma-Aldrich) for 3 days, and then cultured in adipogenic
maintenance medium consisting of Dulbecco’s modified
Eagle’s medium with 10% FBS and 10 μg/mL insulin for 1
day at 37°C in 21% O_2 and 5% CO_2. These treatments were
repeated three times. Compounds were added at a concen-
tration of 10 μmol/L in triplicate through the differentiation
process. To assess the degree of adipogenic differentiation,
cells were fixed with 10% neutral buffered formalin solution
(Wako, Osaka, Japan), and then stained with Hoechst 33258
for nuclei and Bodipy for lipid droplets using an Adipocyte
Fluorescent Staining Kit (Cosmo Bio, Tokyo, Japan). The
number of nuclei and boron–dipyromethene-stained areas
were measured using ArrayScan VTI-HCS (Thermo Fisher
Scientific, Waltham, MA). The degree of adipogenic differen-
tiation was determined by dividing the Bodipy-stained
area by the number of nuclei.
using an RNeasy Micro Kit (Qiagen, Hilden, Germany), and equal amounts of RNA were reverse-transcribed into cDNA using a QuantiTect Reverse Transcription Kit (Qiagen). Quantitative real-time PCR was performed using a Thermal Cycler Dice Real Time System (Takara, Shiga, Japan) and SYBR Premix Ex Taq II (Takara).

Primers were repeated three times using PDGFR antibody. Western Blot Analysis

Cells were rinsed with phosphate-buffered saline, and primary antibodies at 4°C overnight, followed by secondary staining. Primary and secondary antibodies used were anti--peroxisome proliferator-activated receptor gamma (PPARY) antibody (2435, 1:100; Cell Signaling, Danvers, MA), anti-perilipin (P1873, 1:250; Sigma-Aldrich), anti--green fluorescent protein (GFP) antibody (EYFP) mice were purchased from the Jackson Laboratory (Bar Harbor, ME) and MyoD-iCre mice were a gift from Dr. David Goldhamer (University of Connecticut).12

Drugs Inhibiting Adipogenesis in Muscle

Experiments using mice were approved by the Institutional Animal Care and Use Committee at Fujita Health University. C57BL/6 female mice were purchased from Japan SLC (Hamamatsu, Japan) at 8 weeks old. One Achilles tendon was resected and the skin was sutured, while a sham surgery was performed by only skin incision. Four weeks after surgery, the mice were sacrificed, and gastrocnemius muscles were excised and frozen rapidly. Sections (7-μm thick) were cut at a position 2.5 mm from the proximal side and subjected to hematoxylin and eosin staining. To assess the effects of oral administration of PH, mice received PH in drinking water (0.05 or 0.1 mg/mL) after surgery. Oral administration doses were calculated by measurement of the amount of water intake and the concentration of PH in the drinking water. The water was changed twice a week. Four weeks after surgery the mice were sacrificed and gastrocnemius muscle sections were cut as described earlier and subjected to immunofluorescent staining.

PDGFRz-CreER mice and R26R-enhanced yellow fluorescent protein (EYFP) mice were purchased from the Jackson Laboratory (Bar Harbor, ME) and MyoD-iCre mice were a gift from Dr. David Goldhamer (University of Connecticut).12

PDGFRz-CreER mice or MyoD-iCre mice were crossed with R26R-EYFP mice. Four milligrams of tamoxifen were injected intraperitoneally for 5 consecutive days into 10-week-old PDGFRz-CreER/R26R-EYFP mice to induce EYFP expression. Achilles tendons of generated mice were excised. Four weeks after surgery these mice were sacrificed, and gastrocnemius muscles were excised and fixed with 4% paraformaldehyde and embedded in paraffin. Sections (5 μm thick) were cut and stained with hematoxylin and eosin staining as described previously.5

Immunofluorescent Staining

Cells were rinsed with phosphate-buffered saline, and fixed with 4% paraformaldehyde. Specimens were blocked with protein block serum-free reagent (Dako, Glostrup, Denmark) for 5 minutes and incubated with primary antibodies at 4°C overnight, followed by secondary staining. Primary and secondary antibodies used were anti-α-laminin (sc-59854, 1:400; Santa Cruz, Dallas, TX), Alexa Fluor-488 anti-rabbit IgG antibody (A21206, 1:1000; Molecular Probes, Eugene, OR), Alexa Fluor-488 anti-goat IgG (A11055, 1:1000; Molecular Probes), Alexa Fluor-594 anti-rabbit IgG (111-585-144, 1:1000; Jackson Immunoresearch, West Grove, PA), and Alexa Fluor-647 anti-rat IgG (A21472, 1:1000; Molecular Probes). Stained samples were counterstained with DAPI (Invitrogen, Waltham, MA) and mounted with SlowFade Gold anti-fade reagent (Invitrogen). Stained images were obtained using Opera Phenix (Perkin Elmer, Waltham, MA), a confocal laser scanning microscope system LSM700 (Carl Zeiss, Oberkochen, Germany), and an inverted fluorescence microscope BZ-9000 (Keyence, Osaka, Japan). The percentage of PPARγ-positive cells in cultured cells was analyzed by Opera Phenix (Perkin Elmer), and the fat-occupied area in muscle sections was analyzed by BZ-II analyzer software version 2.2 (Keyence). In some cases, stained sections subsequently were subjected to hematoxylin and eosin staining as described previously.7

Western Blot Analysis

PDGFRz+ cells were cultured on Matrigel-coated 6-well plates at a density of 1 × 10⁵ cells/well and subjected to adipogenic differentiation as described earlier with or without 10 μmol/L PH. Cells were extracted on days 0, 4, 8, or 12 of adipogenic differentiation. Cells were lysed in lysis buffer consisting of 50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, 1 mmol/L NaF, 1% NP-40, and a protease inhibitor cocktail (Roche, Basel, Switzerland). For detection of the phosphorylated proteins, a phosphatase inhibitor cocktail (Roche) was added. Ten micrograms of protein were separated on SDS-PAGE and transferred to a polyvinylidene difluoride membrane, followed by immunoblotting with anti-cAMP response element binding protein (CREB) (9197, 1:1000; Cell Signaling), anti-phospho-CREB (9198, 1:1000; Cell Signaling), and anti--glyceraldehyde-3-phosphate dehydrogenase (2118, 1:1000; Cell Signaling) antibodies. After incubation with a horseradish-peroxidase--conjugated secondary antibody (70745, 1:10,000; Cell Signaling) and chemiluminescence reactions, images of the immunoblots were obtained using a Light-Capture imaging system (ATTO, Tokyo, Japan). Intensity of the immunoblots was quantified using Win ROOF software version 5.6.0 (Mitani, Fukui, Japan). Phosphorylated CREB was normalized for CREB. These experiments were repeated three times using PDGFRz+ cells obtained from three independent preparations.

Mouse Experiments

Experiments using mice were approved by the Institutional Animal Care and Use Committee at Fujita Health University. C57BL/6 female mice were purchased from Japan SLC (Hamamatsu, Japan) at 8 weeks old. One Achilles tendon was resected and the skin was sutured, while a sham surgery was performed by only skin incision. Four weeks after surgery, the mice were sacrificed, and gastrocnemius muscles were excised and frozen rapidly. Sections (7-μm thick) were cut at a position 2.5 mm from the proximal side and subjected to hematoxylin and eosin staining. To assess the effects of oral administration of PH, mice received PH in drinking water (0.05 or 0.1 mg/mL) after surgery. Oral administration doses were calculated by measurement of the amount of water intake and the concentration of PH in the drinking water. The water was changed twice a week. Four weeks after surgery the mice were sacrificed and gastrocnemius muscle sections were cut as described earlier and subjected to immunofluorescent staining.

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Digestion of human skeletal muscle and culturing of isolated cells

In vitro expansion

Adipogenic differentiation with FDA-approved compounds

Sorting of PDGFrα+ cells

High-throughput imaging

**A**

B

Control

PH 10 μmol/L

Hu68

Hu74

C

Control

PH 1.25 μmol/L

PH 2.5 μmol/L

PH 5 μmol/L

PH 10 μmol/L

D

Control

PH 1.25 μmol/L

PH 2.5 μmol/L

PH 5 μmol/L

PH 10 μmol/L

E

Absorbance at 450 nm

Live cell (%)
7-μm–thick sections were cut at a position 2.5 mm from the proximal side and subjected to immunofluorescent staining.

**Statistical Analysis**

Data were presented as the means ± SEM. The Jonckheere-Terpstra trend test was used to assess dose-dependency. One-way analysis of variance followed by the Dunnett or Tukey post hoc test was used to assess cell toxicity and fat area proportion and muscle weight. Two-way analysis of variance was used to assess the effects of the compound in quantitative real-time PCR, immunofluorescent staining, and immunoblotting. *P* values less than 0.05 were considered significant. The statistical analyses were performed with SPSS statistics 21 (IBM, Armonk, NY).

**Results**

To identify drugs that suppress ectopic adipocyte formation in skeletal muscle, we searched for compounds that inhibit adipogenic differentiation of human PDGFRα<sup>+</sup> mesenchymal progenitors using the Food and Drug Administration–approved compound library. PDGFRα<sup>+</sup> cells were isolated from human skeletal muscle and expanded them according to the previously established procedure,<sup>3,9</sup> and cultured them in adipogenic medium, which contains adipogenic inducers, with or without compounds, followed by high-throughput fluorescent imaging of lipid droplets (Figure 1A). Among the compounds examined, PH was selected and used for further experiments because PH inhibited adipocyte formation strongly and consistently compared with compound-free control (Figure 1B). We next examined dose-dependency of PH and confirmed dose-dependent inhibition of adipocyte formation (Figure 1C). To exclude the possibility that the inhibitory effect of PH on adipogenesis is caused simply by the toxic effect on PDGFRα<sup>+</sup> cells, we examined the number of cells shown by nuclear staining. PH did not affect cell number even at the highest concentration used (Figure 1C). Cell viability was examined by LIVE/DEAD and water-soluble tetrazolium salt-8 assays and it was confirmed that PH does not have any toxicity on PDGFRα<sup>+</sup> cells (Figure 1, D and E).

To investigate that PH indeed inhibits adipogenic differentiation, not merely inhibits accumulation of lipid droplets, expression of adipogenic markers was assessed. Quantitative real-time PCR showed that PH down-regulates the expression of PPARG, a master regulator of adipogenic differentiation, and almost completely prevents induction of adiponectin (ADIPOQ) expression, a mature adipocyte marker (Figure 2A). Immunofluorescent staining against PPARγ further showed that treatment with PH leads to a significant reduction of PPARγ<sup>+</sup> cells (Figure 2B). We next investigated more upstream event of adipogenesis. Activation of CREB was shown to be sufficient for the initiation of adipogenesis,<sup>13</sup> and therefore CREB is known as a primary regulator of adipogenesis. Importantly, consistent reduction in the phosphorylation level of CREB during adipogenic differentiation by PH treatment was observed (Figure 2C). These results suggest that PH efficiently inhibits adipogenic differentiation of human PDGFRα<sup>+</sup> mesenchymal progenitors by disturbing the early phase of adipogenesis.

To assess the anti-adipogenic effect of PH in vivo, a mouse model of tendon rupture by exciting Achilles tendons was established with the aim of mimicking a rotator cuff tear, a common disorder accompanied by intramuscular fat deposition in the field of orthopedics. In contrast to muscles on the sham surgery side that showed normal histology, gastrocnemius muscles with tendon excision had increased interstitial cells at 2 weeks after surgery and developed ectopic adipocytes at 4 weeks after surgery (Figure 3A and Supplemental Figure S1). We and others have reported that only PDGFRα<sup>+</sup> mesenchymal progenitors can generate ectopic adipocytes in skeletal muscle by transplanting labeled PDGFRα<sup>+</sup> cells into glycerol-injured muscle.<sup>3,6</sup> To show that endogenous PDGFRα<sup>+</sup> cells contribute to ectopic fat cell formation in more pathologically relevant condition, a tendon rupture model was applied to lineage tracing mice that are generated by crossing PDGFRα-CreER<sub>R26R-EYFP</sub> mice<sup>14</sup> or MyoD-iCre mice<sup>12</sup> with R26R-EYFP mice.<sup>15</sup> Before surgery, tamoxifen was injected into PDGFRα-CreER/R26R-EYFP mice to permanently label PDGFRα<sup>+</sup> cells. We confirmed that only PDGFRα<sup>+</sup> cells became positive for EYFP and labeling efficiency was approximately 70% (data not shown). Four weeks after tenotomy, 79.5% ± 17.5% of emerged ectopic adipocytes expressed EYFP (Figure 3, B and C), indicating that almost all ectopic adipocytes are derived from endogenous PDGFRα<sup>+</sup> cells. On the other hand, no ectopic adipocytes were labeled with EYFP in MyoD-iCre/R26R-EYFP mice, confirming that myogenic cells never contribute to fatty degeneration (Figure 3, B and C). Thus, the established model provides pathologic features relevant to a common orthopedic disorder and is suitable for investigating fatty degeneration of skeletal muscle that is dependent on endogenous PDGFRα<sup>+</sup> mesenchymal...
progenitors. By using this model, we assessed the efficacy of PH in vivo. After tenotomy, mice were given drinking water supplemented with PH for 4 weeks. Immunofluorescent imaging of whole-muscle sections showed that PH significantly suppressed ectopic adipose content (Figure 3D). Although a lower concentration of PH was less effective, a significant reduction in ectopic adipose content was evident even in this group (Figure 3E). Intriguingly, a higher concentration of PH suppressed ectopic adipose content to the level comparable with the sham surgery group (Figure 3E). Although there was clear inhibition of ectopic fat development, PH did not have any effect on muscle weight loss (Figure 3F). These results indicate that PH possesses an inhibitory effect on ectopic fat cell formation in skeletal muscle but not on muscle atrophy evoked by Achilles tendon resection.

**Discussion**

Fatty degeneration of skeletal muscle leads to muscle weakness and loss of function, which further deteriorates total health. Previous studies, including ours, have shown that fatty degeneration of skeletal muscle occurs through differentiation of PDGFRα+ mesenchymal progenitors into ectopic adipocytes. The importance of PDGFRα+ cells in fatty degeneration also is suggested by a recent study showing that inhibition of PDGFRα signaling attenuated fat infiltration in a mouse model of a rotator cuff tear. This notion is supported further by the present study, in which lineage tracing experiments showed endogenous PDGFRα+ cells as a source of ectopic fat cells in a tendon rupture model. In our previous study, we established a culturing method of human PDGFRα+ mesenchymal progenitors in large scale. This provides a valuable opportunity to search for drugs that would control the pathologic behavior of PDGFRα+ mesenchymal progenitors. By using this culture system, we performed drug repositioning and found that PH has a strong inhibitory effect on PDGFRα+ cell-dependent adipogenesis both in vitro and in vivo. PH is a first-generation antihistamine drug and has been used mainly to treat allergic rhinitis. Histamine H1-receptor signaling was reported to stimulate adipogenic differentiation of the 3T3-L1 preadipocyte cell line and PDGFRα+ mesenchymal progenitors strongly express histamine H1 receptor (Supplemental Figure S2), suggesting that this signaling pathway represents an

**Figure 2** PH down-regulates adipogenic markers. **A**: Relative PPARG and ADIPOQ expression during adipogenic differentiation of platelet-derived growth factor receptor α (PDGFRα+) cells were analyzed by quantitative real-time PCR and presented as means ± SEM of three independent preparations. NDUFA13 was used as an internal control gene. **B**: Promethazine hydrochloride (PH)-treated and control cells were stained with anti-peroxisome proliferator-activated receptor gamma (PPARγ) antibody (green). The PPARγ-positive ratio was quantified. **C**: Phosphorylated cAMP response element binding protein (CREB) and total CREB are assessed by immunoblotting. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is shown as loading control. The ratio of phosphorylated CREB to total CREB was quantified. Data are expressed as means ± SEM of three independent preparations (B and C). *P < 0.05, ***P < 0.001. Scale bar = 100 μm (B).
important regulator of fatty degeneration of skeletal muscle. However, the therapeutic value of antihistamine drugs on fatty degeneration has not been documented. Although it is needed to test the dose of PH in humans carefully, it could be used in a short time in the clinical setting because adverse effects and contraindications already have been established.

To elucidate mechanisms whereby PH exerts anti-adipogenic action on PDGF receptor z+ mesenchymal progenitors, we focused on CREB because it was shown to be activated by histamine H1 receptor in nonadipose cells and is known as a primary regulator of adipogenesis. We found that PH inhibits phosphorylation of CREB during adipogenic differentiation.
of PDGFRα+ cells. Thus, a strong inhibiting effect of PH could be explained by its action on early and critical regulators of adipogenesis. Although PH suppressed PPARγ expression at both the mRNA and protein levels, the inhibitory effect was greater on protein level than on mRNA level. Because PPARγ protein is known to be regulated after translation through ubiquitin-proteasome—dependent degradation and heat shock protein 90—mediated stabilization in adipogenic cells, 19–21 such post-translational regulation of PPARγ protein may account for the different inhibition seen in mRNA and protein. Ectopic fat cell formation usually is accompanied by muscle atrophy, and muscle atrophy also is major cause of loss of strength and function. We showed that PH inhibited ectopic adipocyte formation but did not exert any effect on muscle atrophy in the tendon rupture model. Although PH could not prevent muscle atrophy, inhibiting fatty degeneration still should be beneficial because accumulated ectopic adipocytes can hinder recovery from atrophy and therefore further deteriorate muscle function.

In conclusion, we identified PH as the candidate drug for the treatment of fatty degeneration of skeletal muscle. Because PH is already in clinical use, it could be applied to muscle disorders in a short time. Use of PH will be an effective means for preventing the decrease of muscle function and improving the effect of rehabilitation.

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Supplemental Data

Supplemental material for this article can be found at https://doi.org/10.1016/j.ajpath.2017.08.008.

References

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