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MECHANISMS OF THE INFLUENCE OF ADIPONECTIN ON APOLIPOPROTEINS A-1 AND B PRODUCTION BY HUMAN HEPATOCYTES

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The aim of the study was to find out the mechanisms of the adiponectin effect on apolipoproteins (apo) A-1 and B production by human hepatocytes.

Materials and methods. The study was performed on the human hepatoma cell line HepG2. The expression of the *apoA-1* gene was evaluated at the mRNA level by quantitative PCR with reverse transcription, and the production of apoB – by ELISA method. The activity of lipogenesis was assessed by the inclusion of labeled ^{14}C-acetate in triglycerides, as well as by mRNA expression of lipogenesis genes, and by the estimation of total triglycerides content in cells. To determine the involvement of signaling pathways, the RNA interference method was used.

Results. Knockdown of genes, coding the specific receptors, AMP-activated protein kinase, and its regulated transcription factors inhibited adiponectin-dependent stimulation of *apoA-1* gene expression in hepatocytes. Adiponectin had no effect on lipogenesis and apoB production under basal conditions, but suppressed these processes induced by the addition of oleate.

Conclusion. Adiponectin stimulates the production of apoA-1 in hepatocytes by inducing the transcription of the *apoA-1* gene and suppresses the secretion of apoB by affecting lipogenesis. These effects may underlie the effect of adiponectin on lipoproteins metabolism.

Keywords: adiponectin; apolipoproteins; hepatocytes; nuclear receptors; lipogenesis; metabolic syndrome.

МЕХАНИЗМЫ ВЛИЯНИЯ АДИПОНЕКТИНА НА ПРОДУКЦИЮ АПОЛИПОПРОТЕИНОВ А-1 И В ГЕПАТОЦИТАМИ ЧЕЛОВЕКА

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Цель исследования — выяснить механизмы влияния адипонектина на продукцию аполипопротеинов (апо) А-1 и В гепатоцитами человека.

Материалы и методы. Исследование проводили на клетках линии гепатомы человека HepG2. Экспрессию гена *apoA-1* оценивали на уровне мРНК методом количественной полимеразной цепной реакции с обратной транскрипцией, продукцию апоВ — методом иммуноферментного анализа. Активность липогенеза определяли по включению меченого ^{14}C-ацетата в триглицериды, по экспрессии генов липогенеза на уровне мРНК и по общему содержанию триглицеридов в клетках. Для выяснения участия сигнальных путей использовали метод РНК-интерференции.

Результаты. Нокдаун генов специфических рецепторов, АМФ-активируемой протеинкиназы и регулируемых ею факторов транскрипции приводил к отмене адипонектин-зависимой стимуляции экспрессии гена *apoA-1* в гепатоцитах. Адипонектин не влиял на липогенез и продукцию апоВ в базальных условиях, но при этом подавлял данные процессы, индуцированные добавлением олеата.

Заключение. Адипонектин стимулирует продукцию апоА-1 в гепатоцитах путем индукции транскрипции гена *apoA-1* и подавляет секрецию данными клетками апоВ посредством влияния на липогенез. Указанные воздействия могут лежать в основе влияния адипонектина на обмен липопротеинов.

Ключевые слова: адипонектин; аполипопротеины; гепатоциты; ядерные рецепторы; липогенез; метаболический синдром.

Abbreviations

apo – apolipoprotein; RT-PCR – reverse transcription polymerase chain reaction; TG – triglycerides; AdipoRs – adiponectin receptors; AMPK – AMP-activated protein kinase; BSA – bovine serum albumin; FCS – fetal calf serum; LXRα – liver X receptor alpha; PPARα – peroxisome proliferator-activated receptor alpha.

Introduction

One of the primary risk factors for atherosclerosis is metabolic syndrome, a complex of pathogenetically interrelated disorders, such as obesity, insulin resistance, dyslipoproteinemia, and hypertension [1]. The adipose tissue proteins (adipokines) are involved in the formation of these disorders [2]. Adiponectin increases the sensitivity of tissues to insulin and stimulates the oxidation of fatty acids. Thus, it favorably affects plasma lipoproteins spectrum and is of greatest interest among all adipokines [3, 4]. The metabolic effects of adiponectin are realized by activating type 1 and type 2 adiponectin receptors (AdipoR1/2). They transmit a signal to AMP-activated protein kinase (AMPK) and nuclear peroxisome proliferator-activated receptors alpha (PPARα) [3].

Another way that adiponectin affects lipoprotein metabolism is through hepatic apolipoprotein (apo) production. Adiponectin increases apoA-1 (the main protein of high-density lipoproteins) production and decreases apoB (the main protein of low-density lipoproteins) production by hepatocytes [4–6]. At the same time, the mechanisms of these adiponectin effects remain poorly understood.

In this regard, the aim of the study was to identify the mechanisms of adiponectin's effects on apoA-1 and apoB production by human hepatocytes.

Materials and methods

This study was performed on cells of the human hepatoma cell line HepG2 (Russian collection of cell cultures, Institute of Cytology, Russian Academy of Sciences). The cells were cultured in Dulbecco's modified Eagle medium (DMEM) supplemented with 4 mM glutamine, 0.1 mg/ml gentamicin (all-Biolot, Russia), 10% fetal calf serum (FCS) (Hyclone, USA) in an atmosphere of 5% CO_2 at 37°C. The cells were seeded on 96-well culture plates (Sarstedt, Germany) with a density of 1×10^4 cells/cm^2 and grown in complete medium for 2–3 days until subconfluence (~70%–80%). Further, the culture medium was replaced with FCS-free medium supplemented with adiponectin (catalog number RD172023100-C, Biovendor, Czech Republic) at concentrations of 10 or 30 μg/ml or 1 mM AICAR (5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside) (Calbiochem, USA) or phosphate-buffered saline for 24 hours. In several experiments, a complex of bovine serum albumin (BSA) with 290 μM oleate (all-"Sigma," USA) or fatty acids free BSA at a final concentration of 5 g/l was added. By the end of the incubation, cells were harvested for RNA isolation (Evrogen, Russia) or intracellular protein determination (BCA Protein Assay, ThermoScientific, USA) and triglycerides (TG) (Randox enzymatic kits, UK) content. The culture media of HepG2 cells were collected to determine apoB concentration using an enzyme-linked immunosorbent assay.

Transfection of HepG2 cells with siRNA was performed using the Lipofectamine RNAiMAX reagent (Invitrogen, USA), according to the manufacturer's instructions. The cells were transfected for 72 h and kept in DMEM with 10% FCS. On the last day of transfection, cells were incubated with 10 μg/ml adiponectin or 1 mM AICAR or phosphate-buffered saline under serum-free conditions. The cells were then lysed for gene expression determination by reverse transcription polymerase chain reaction (RT-PCR). Transfection efficiency was assessed by using RT-PCR. For transfection, siRNAs were used against AdipoR1, AdipoR2 [7], α1/2-subunits of AMPK [8] (all-Syntol, Russia), PPARα (sc-36307), LXRα (hepatic receptors-X) (sc-38828), and nonspecific siRNA (sc-37007) (all Santa Cruz, USA).

RNA isolation, reverse transcription, and real-time PCR were performed, as described previously [9, 10]. The relative mRNA content of the desired genes was normalized to the levels of the housekeeping (constitutive) genes (of β-actin, ribosomal protein RPLP0, and cyclophilin A) expression.

The synthesis of TG in cells was assessed by inclusion of ^{14}C-acetate into TG. For this, 1 μCi of ^{14}C sodium acetate (specific radioactivity = 20,000 cpm/nmol) in the presence of 10 or 30 μg/ml adiponectin or 10 μg/ml BSA (negative control) was added to HepG2 cells for 5 h under serum-free conditions. Then, lipids were extracted from the cells with a mixture of hexane–isopropanol (3:2 by volume) and separated by thin-layer chromatography in the system heptane–isopropyl ether–acetic acid (15:10:1 by volume) on Kieselgel 60 aluminum

plates (Merck, Germany). After developing with iodine (J_2), spots corresponding to the TG fraction were excised, placed in vials, and filled with scintillation liquid for radioactivity counting (RakBeta, LKB, Sweden). Delipidated cell pellets were solubilized with 0.2 M NaOH to determine the protein concentration.

The results are presented as mean values ± standard error of mean (mean ± SEM) of three or four independent experiments. The statistical analysis of differences between the control and experimental groups was performed using Dunnett's test. Differences were considered significant at $p < 0.05$. Statistical analysis was performed using the GraphPad Prism v.6 software (USA).

Results and discussion

The production of apoA-1 by hepatocytes is primarily regulated at the transcriptional level with the participation of transcription factors that interact with specific sites located in the 5'-regulatory region of this gene. The transcriptional activators of the *apoA-1* gene are PPARα and HNF4α (hepatocyte nuclear factor 4α), whereas LXR suppress the expression of this gene [9]. In turn, the activity of PPARα and LXRα in hepatocytes is controlled by AMPK [11, 12].

We used the RNA interference method to elucidate the participation of these signaling molecules in adiponectin-dependent activation of the *apoA-1* gene expression in hepatocytes. The knockdown of genes encoding AdipoRs, AMPK kinase, and nuclear receptors, PPARα and LXRα, led to the cancelation of the effect of adiponectin on *apoA-1* gene expression at the mRNA level (Table). Like adiponectin, the AMPK activator AICAR stimulated *apoA-1* gene expression in hepatocytes. This effect was also canceled after the knockdown of genes encoding AMPK and both nuclear receptors (Table). Upon these data we suggest the involvement of both types of adiponectin receptors, AMPK and nuclear receptors PPARα and LXRα in regulation of *apoA-1* gene expression under adiponectin action.

Unlike apoA-1, the production of apoB is regulated mainly at the post-translational level

Table / Таблица

Effect of adiponectin (10 mkg/ml) on the expression of the *apoA-1* gene in human hepatoma HepG2 cells upon the knockdown of the *AdipoRs*, *AMPK*, *PPARα*, and *LXRα* genes

Влияние адипонектина (10 мкг/мл) на экспрессию гена *apoA-1* в клетках гепатомы человека линии HepG2 на фоне нокдауна генов *AdipoRs*, *AMPK*, *PPARα* и *LXRα*

Suppressed gene	Active agent	apoA-1 siRNA, percent (%) of control
–	Control	100.0 ± 1.1
	Adiponectin	150.5 ± 3.5*
	AICAR	140.3 ± 3.3*
AdipoR1	Control	117.5 ± 11.2
	Adiponectin	120.3 ± 12.8
AdipoR2	Control	138.0 ± 15.6
	Adiponectin	131.6 ± 16.8
Subunits α*1-AMPK* and α*2-AMPK*	Control	44.3 ± 1.9*
	Adiponectin	35.7 ± 1.3
	AICAR	30.1 ± 2.1
PPARα	Control	131.8 ± 4.0
	Adiponectin	124.3 ± 2.5
	AICAR	122.0 ± 2.1
LXRα	Control	191.4 ± 7.0*
	Adiponectin	186.9 ± 1.3
	AICAR	148.5 ± 10.2

Note. The results of real-time RT-PCR of the relative content of apoA-1 mRNA, mean ± SEM ($n = 12–16$). *$p < 0.05$ versus control with nonspecific siRNA.

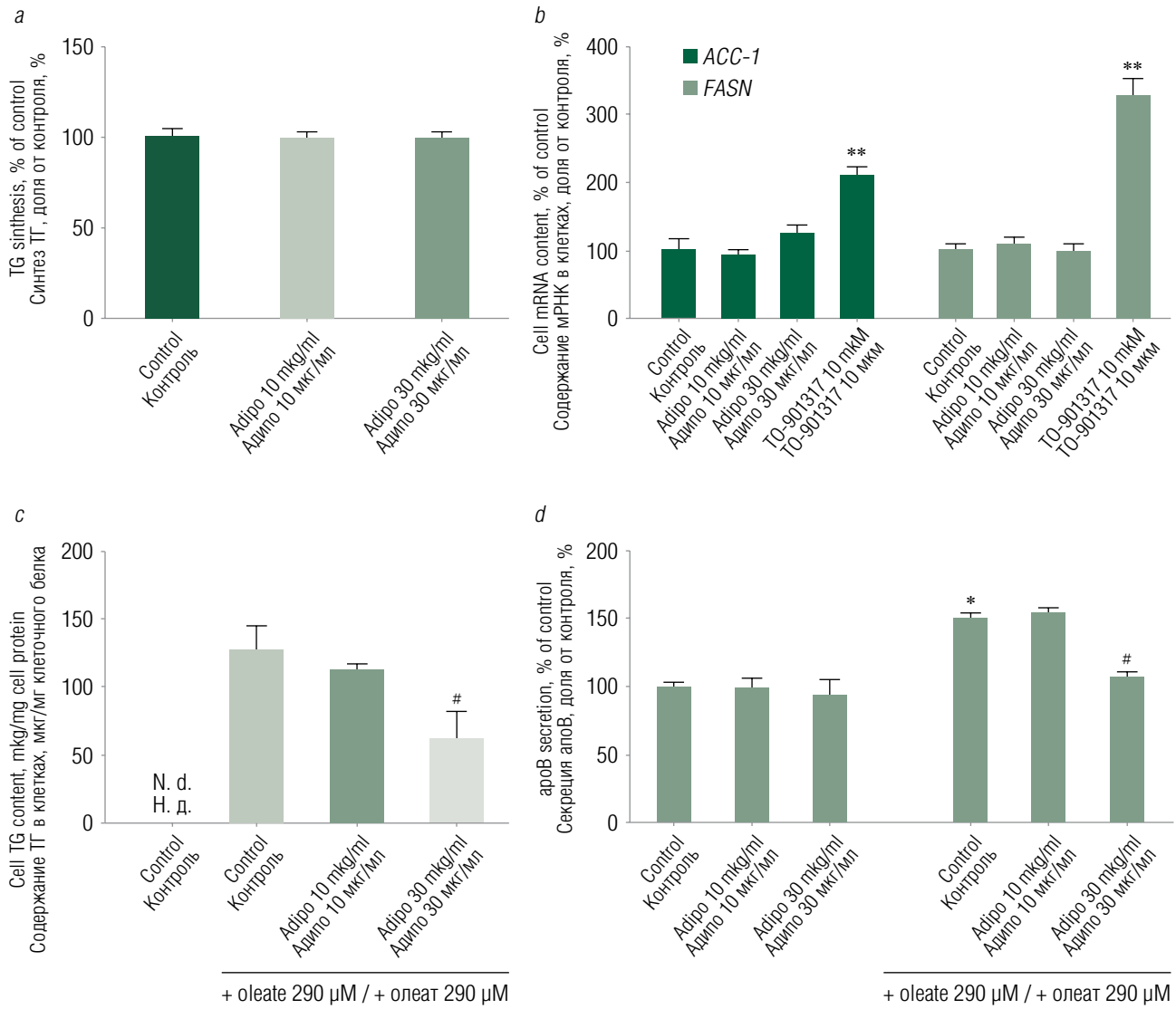

Figure. Effect of adiponectin on TG synthesis and apoB secretion in human hepatoma HepG2 cells. *a* — synthesis of TG was evaluated by the inclusion of ^{14}C-acetate into TG. The results are presented as counts per minutes, normalized for the content of cellular protein, relative to the average value in the control, taken as 100%. *b* — The expression level of lipogenesis genes *ACC-1* (acetyl-CoA-carboxylase) and *FASN* (fatty acid synthase), measured by the reverse transcription PCR assay. TO-901317 — LXR agonist, the activator of lipogenesis [12], positive control. *c* — TG content in cell lysates (enzymatic method), normalized for the level of intracellular protein. N. d. — TG were not detected by this method. *d* — apoB concentrations in hepatocytes' culture media (ELISA assay), normalized for the content of intracellular protein, relative to the control taken as 100% (the absolute values of apoB concentrations were ~5-50 ng/mkg of cellular protein). Mean values ± SEM are given (*a* – n = 8, *b* – *d* – n = 12–16). *$p < 0.05$, **$p < 0.005$ versus the control, #$p < 0.05$ versus control with oleate treatment. Adipo — adiponectin, TG — triglycerides, apoB — apolipoprotein B

Рисунок. Влияние адипонектина на синтез триглицеридов и секрецию аполипопротеина В клетками гепатомы человека линии HepG2: *a* — синтез триглицеридов оценивали по включению ^{14}C-ацетата в триглицеридах; количество импульсов в минуту, нормированное на содержание клеточного белка, относительно среднего значения в контроле, принятого за 100 %; *b* — экспрессия генов липогенеза *ACC-1* (ацетил-КоА-карбоксилазы) и *FASN* (синтетазы жирных кислот), метод — полимеразная цепная реакция с обратной транскрипцией; ТО-901317 — активатор липогенеза, агонист LXR [12], положительный контроль; *c* — содержание триглицеридов в лизатах клеток (энзиматический метод), нормированное на уровень внутриклеточного белка; Н. д. — триглицериды указанным методом не детектировались; *d* — концентрации аполипопротеина В на культуральных средах гепатоцитов (иммуноферментный анализ), нормированные на содержание внутриклеточного белка, относительно контроля, принятого за 100 % (абсолютные значения концентраций аполипопротеина В составляли ~5–50 нг/мкг клеточного белка); средние ± SEM (*a* – n = 8, *b* – *d* – n = 12–16). *$p < 0,05$, **$p < 0,005$ против контроля, #$p < 0,05$ против контроля с добавлением олеата. Адипо — адипонектин, ТГ — триглицериды, апоВ — аполипопротеин В

by stabilizing this protein in the lipid environment [13]. In this regard, it is most likely that adiponectin affects the production of apoB-containing lipoproteins, influencing the TG synthesis. Although adiponectin reduces lipogenesis activity in rat and bovine hepatocytes [14, 15], these data are not confirmed in studies performed on human hepatocytes [6]. These discrepancies may be due to the different species of hepatocytes and differences in the activity of lipogenesis in the studied cell models. According to our data, adiponectin does not affect basal lipogenesis in HepG2 cells (diagrams in Figures, *a* and *b*). However, upon loading cells with oleate, adiponectin, at a concentration of 30 mkg/ml, decreases TG content in HepG2 cells (Diagram *c*). The described effects of adiponectin on TG synthesis in cells were accompanied by changes in apoB secretion by the cells (Diagram *d*). These data support the hypothesis that adiponectin interferes with hepatic apoB production by the effect of this adipokine on lipogenesis.

Suppression of TG synthesis by adiponectin can be a result of AMPK activation with a further decrease in lipogenesis gene activity at the transcriptional and post-translational levels [3, 16] on the one hand, and by the activation of PPARα and the transcriptional coactivator PGC1α, which increase fatty acids oxidation at the transcriptional level on the other hand [3, 17].

Conclusion

We conclude that adiponectin's effects on apolipoproteins production in hepatocytes occur through the signaling pathways of adiponectin receptors, including AMPK activation and changes in the activity of nuclear receptors, PPARα and LXRα. These effects, along with the activation of fatty acids oxidation and an increase in insulin sensitivity in peripheral tissues by adiponectin, can provide beneficial effects of this adipokine on lipoproteins blood levels and development of dyslipoproteinemia in metabolic syndrome.

Additional information

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Compliance with ethical standards. This study is not related to work on animals and clinical material.

Conflict of interest. The authors declare no conflict of interest.

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