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Bifurcation of the insulin signaling pathway in rat liver: mTORC1 is required to stimulate lipogenesis, but not to inhibit gluconeogenesis - Review of the evidence

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1. ABSTRACT

The analyzed study examined how insulin separates two important functions in the liver: the reduction of glucose production and the activation of fat synthesis. In rat hepatocytes, insulin markedly increased the messenger RNA of SREBP-1c, a transcription factor that activates genes involved in fatty acid production, and reduced that of PEPCK, a gluconeogenesis gene. Inhibition of mTORC1 blocked the increase in SREBP-1c without preventing the reduction of PEPCK.This result contributes to the section of "The Choice to Live Healthy or in Disease" by Dr. A. Colonnese and R. Panzironi dedicated to the insulin activation of SREBP-1c and the selective role of mTORC1 in lipogenesis. Independent studies in hepatocytes, mice, and other cellular models confirm that mTORC1 is necessary for a significant part of SREBP-1c activation and lipogenesis. However, genetic evidence indicates that persistent activation of mTORC1, on its own, is not sufficient to reproduce the lipogenic program. The confirmation therefore concerns primarily the mechanistic and preclinical level, not clinical outcomes in humans.

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MISSION

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Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

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2. ANALYZED STUDY

The research question was whether insulin uses the same molecular pathway to control both glucose production and fat production in the liver. The authors evaluated the hypothesis of a bifurcation in insulin signaling: a common initial segment, followed by different branches for gluconeogenesis and lipogenesis.The central point for paragraph 5.3 is as follows: insulin activates SREBP-1c, a protein that enters the nucleus and increases the activity of genes necessary for the synthesis of fatty acids and triglycerides. The study verified whether this response depended on PI3K and AKT, two proteins that transmit the insulin signal, and on mTORC1, a protein complex that coordinates growth and nutrient availability.The publication is relevant to "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it directly documents the insulin PI3K/AKT mTORC1 increased SREBP-1c segment. However, it cannot demonstrate on its own that chronic hyperinsulinemia in humans causes inflammation, hepatic steatosis, or other metabolic diseases: the study uses cells and rodents and primarily evaluates short-term molecular signals.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material is only the abstract. The authors exposed rat hepatocytes, i.e., liver cells cultured in the laboratory, to insulin and measured the messenger RNA of SREBP-1c and PEPCK. Messenger RNA is the molecule that carries the instructions for producing a protein: a variation in it therefore signals a change in gene activation.To separate the different signaling steps, pharmacological inhibitors of PI3K, AKT, and mTORC1 were used. Rapamycin, used at concentrations lower than one nanomolar, was employed as an inhibitor of mTORC1. An inhibitor of S6 kinase, a protein located downstream of mTORC1, was also used.The authors then verified the phenomenon in the livers of rats and mice subjected to a fasting protocol followed by refeeding, a condition that causes an increase in insulin. The number of animals, detailed characteristics of the cell cultures, precise exposure times, inclusion and exclusion criteria, secondary endpoints, and statistical analyses are not reported in the available material.

4. RESULTS

In rat hepatocytes, insulin increased SREBP-1c messenger RNA by 25-fold. In practical terms, the insulin signal strongly activated the genetic program that promotes lipid synthesis. In the same cells, insulin reduced the messenger RNA of PEPCK by 95%, an enzyme important for gluconeogenesis, i.e., hepatic glucose production.PI3K and AKT inhibitors blocked both the increase in SREBP-1c and the reduction of PEPCK. This indicates that PI3K and AKT are necessary for both responses studied. Rapamycin, on the other hand, selectively blocked the induction of SREBP-1c by insulin but did not alter the reduction of PEPCK. The result therefore suggests that, after AKT, the signal splits: mTORC1 is required for the lipogenic branch, but not for the branch that suppresses PEPCK.A similar selective effect of rapamycin was observed in the liver of rats and mice after fasting and refeeding. The S6 kinase inhibitor did not block the insulin-induced increase in SREBP-1c. This suggests that the pathway from mTORC1 to SREBP-1c does not necessarily depend on S6 kinase in this specific transcriptional control. The available material does not report P values, confidence intervals, or complete numerical data from the experiments.

5. INTERPRETATION

The biological significance is that insulin does not act as a single metabolic switch. In liver cells, it can keep the program that promotes fat synthesis active even when another of its effects, the control of glucose production, follows a different regulation. This helps to understand the concept of selective insulin resistance observed in animal models: some insulin signals may be attenuated, while lipogenic ones may be preserved.The pathway documented by the publication is insulin PI3K/AKT mTORC1 transcriptional induction of SREBP-1c. The experimental demonstration is strong within the models used because rapamycin reduced the induction of SREBP-1c without eliminating the repression of PEPCK. However, a pharmacological inhibitor alone does not identify all the molecular targets involved and does not prove that mTORC1 is the sole regulator of SREBP-1c.Regarding the narrative of “The Choice to Live in Health or Illness” by Dr. A.

Colonnese and R. Panzironi, the study precisely supports the idea that lipogenesis represents a functionally distinguishable branch of insulin signaling and that mTORC1 is indispensable for the insulin-induced expression of SREBP-1c in the rodent liver. It does not directly demonstrate the subsequent step toward inflammatory lipid mediators nor the effects of chronic insulin stimulation in humans.

6. INDEPENDENT CONFIRMING EVIDENCE

Particularly relevant independent verification was obtained in primary murine hepatocytes and mice. Yecies and colleagues observed that rapamycin reduced the insulin-induced increase of Srebp1c and Fasn, a gene essential for fatty acid synthesis, while increasing certain upstream AKT signals. After fasting and refeeding, rapamycin also reduced SREBP-1 activation in the liver. These data directly confirm that mTORC1 is necessary for the normal insulin-induced expression of SREBP-1c and hepatic lipogenesis in rodents [1].The same study also clarified an important limitation of the linear chain. In mice with hepatic deletion of Tsc1, a genetic modification that keeps mTORC1 constitutively active, SREBP-1c and lipogenesis were not adequately activated. The authors proposed that AKT also contributes through the reduction of Insig2a, a regulator that hinders SREBP-1c activation. mTORC1 therefore appears necessary, but not sufficient on its own [1].Owen and colleagues investigated a second level of regulation, namely the proteolytic maturation of SREBP-1c. This maturation allows the active form of the protein to reach the nucleus. In transgenic rat hepatocytes, insulin required mTORC1 and S6 kinase to increase SREBP-1c processing. This confirms that mTORC1 can control not only the amount of SREBP-1c messenger RNA, but also the availability of the active protein; the mechanism, however, concerns a different level than the transcriptional one examined in the original study [2].In a non-hepatic cell model and in the fruit fly, Porstmann and colleagues showed that AKT activation requires mTORC1 to support SREBP-dependent lipogenesis. Silencing SREBP reduced AKT-induced lipogenesis and attenuated the increase in cell size. This result does not demonstrate an effect in the human liver, but it reinforces the biological coherence of the AKT mTORC1 SREBP lipid synthesis sequence [3].

7. CONFLICTING EVIDENCE

The evidence does not contradict the fact that mTORC1 is required for the acute induction of SREBP-1c by insulin in the models studied. However, it shows that the relationship is not linear and depends on the context. Kenerson and colleagues deleted Tsc1 specifically in mouse hepatocytes, producing persistent activation of mTORC1. Contrary to the hypothesis that more mTORC1 automatically leads to more fat in the liver, these animals showed a lower tendency for diet-induced lipid accumulation and a slight reduction in hepatic SREBP-1c expression during fasting [4].This result is biologically consistent with the existence of feedback loops: an artificially maintained mTORC1 signal can reduce AKT and alter other factors essential for SREBP-1c. The conflicting evidence therefore limits the interpretation that mTORC1 activation is, by itself, sufficient to produce lipogenesis or steatosis. It does not eliminate the scientific correspondence between the original study and the book's paragraph, which instead concerns the necessity of mTORC1 in the acute response to insulin.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study subject to the Evidence Review from independent publications that confirm or define the scope of the narrative passage.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and animal	Rat hepatocytes; rat and mouse liver	Rapamycin blocks insulin-induced SREBP-1c, but not PEPCK repression.	direct confirmation	moderate
[1]	Animal and cellular	Primary murine hepatocytes and mice with hepatic Tsc1 alterations	mTORC1 is required for insulin-induced SREBP-1c, but its isolated activation is not sufficient.	direct confirmation	moderate
[2]	Cellular and animal	Transgenic rat hepatocytes	mTORC1 and S6 kinase are required for insulin-mediated SREBP-1c processing.	indirect confirmation	moderate
[3]	Cellular and animal	Cultured cells and Drosophila	mTORC1 and SREBP support AKT-dependent lipogenesis and growth.	biologically consistent evidence	low
[4]	Animal	Mice with hepatic Tsc1 deletion and high-fat diet	Persistent mTORC1 activation does not automatically increase SREBP-1c or hepatic lipid accumulation.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed clearly supports that, in the rodent liver, insulin signaling diverges after PI3K and AKT: mTORC1 is necessary for the increase of SREBP-1c and for the lipogenic program, but not for the repression of PEPCK. This conclusion is confirmed by independent experiments in cells and animals.The evidence is solid at a mechanistic level, but must be interpreted within its context. SREBP-1c also depends on parallel pathways and feedback circuits; therefore, mTORC1 activation alone is not sufficient to explain fat accumulation in the liver. The link with chronic hyperinsulinemia and human clinical outcomes requires further validation.

Aggiornato al 24/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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