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Saturated fatty acids induce insulin resistance in podocytes by inhibiting IRS1 through the activation of both IKKb and mTORC1 - Evidence review

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ONLINE ARTICLE

ARTICLE INFORMATION

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1. ABSTRACT

The analyzed study examined how palmitate, a saturated fatty acid, can reduce the insulin response in podocytes, specialized kidney cells that contribute to the glomerular filter. The authors combined experiments in cultured murine podocytes with observations in the glomeruli of db/db mice, a model of type 2 diabetes. Palmitate increased the activity of the IKKb and mTORC1/S6K1 pathways, increased the inhibitory phosphorylation of IRS-1, and reduced insulin-induced AKT activation. Inhibition of mTORC1 with rapamycin reduced this modification of IRS-1 and restored much of the AKT activation in cells exposed to palmitate.In Chapter 4 and Chapter 15 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the narrative that persistent hyperactivation of mTORC1/S6K1 can weaken IRS-1 and make the insulin signal directed to PI3K and AKT less efficient. Independent studies confirm this chain in cells, nutritional models, and human muscle. However, the original work does not directly demonstrate the phenomenon in humans or in Alzheimer's disease; it primarily documents an experimental mechanism in podocytes. The body of evidence therefore supports the shift at a mechanistic level, with significant limitations regarding clinical transferability.

MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

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.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The research question was whether saturated free fatty acids could make podocytes less responsive to insulin and through which molecular steps this effect occurred. Podocytes are cells that wrap around the capillaries of the glomerulus, the renal structure that filters blood; their proper functioning is essential to limit the loss of protein in the urine.The authors' hypothesis was that palmitate increased the phosphorylation of IRS-1 at serine 307. IRS-1 is a protein that transmits the signal from the insulin receptor to PI3K and AKT; phosphorylation at certain serine sites can reduce its function. The study also verified whether IKKb, a kinase linked to inflammatory signals, and mTORC1/S6K1, a pathway that integrates nutrient availability and cell growth, were involved.The reason for its relevance to section 4.8 and section 15.9 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is precise: the publication documents the mTORC1/S6K1 inhibitory phosphorylation of IRS-1 reduced activation of AKT by insulin segment. It does not demonstrate the entire pathophysiology of human insulin resistance, does not evaluate skeletal muscle, and does not study neurons or Alzheimer's disease. Instead, it shows a mechanism in murine podocytes and in the glomeruli of diabetic mice.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors used 25-week-old male db/db mice, which lack the leptin receptor and exhibit a diabetic phenotype, comparing them with non-diabetic db/dm animals. Renal function was assessed via the urinary albumin-to-creatinine ratio and glomerular filtration using labeled inulin clearance. The structure of the glomerulus, mesangial expansion, and proteins associated with kidney damage, including collagen IV and TGF-β, were also examined.To measure the insulin response in the kidney, the animals received intravenous insulin at 5 mU per gram of body weight; after 15 minutes, the glomeruli were isolated. In parallel, a line of differentiated murine podocytes was exposed for 24 hours to 25 µmol/L of albumin-bound palmitate, followed by insulin stimulation for five minutes. The authors measured IRS-1, AKT, IκBα, NF-κB, mTOR, and S6 using immunoblotting, a technique that detects proteins and their modifications.To verify the causal role of the pathways observed in the cells, IKK16 (an IKK complex inhibitor), rapamycin (an inhibitor primarily of mTORC1), and myriocin (an inhibitor of ceramide synthesis) were used. Ceramides are lipids that can accumulate when saturated fatty acids are abundant. Data are expressed as mean plus or minus standard deviation; unpaired t-tests or analysis of variance with Tukey's correction were applied. The main cellular experiments included four to six independent experiments; animal groups varied according to the endpoint, ranging from five to eleven animals. Detailed inclusion and exclusion criteria are not reported in the available material.

4. RESULTS

In db/db mice, kidney damage was already detectable at 25 weeks: compared to db/dm controls, there was greater albuminuria (i.e., urinary albumin loss), glomerular filtration, glomerular hypertrophy, mesangial expansion, and expression of collagen IV and TGF-b. These data confirm that the model exhibited alterations consistent with diabetic nephropathy, but they do not prove that palmitate was the sole cause of the kidney damage.The result most relevant to the book's narrative concerns insulin signaling. In the glomeruli of db/db mice, AKT phosphorylation following insulin stimulation was reduced compared to controls, while IRS-1 phosphorylation at serine 307 was increased. In cultured podocytes, palmitate reduced insulin-induced AKT phosphorylation by 75%, with $p<0.0001$. At the same time, it increased IRS-1 phosphorylation at serine 307 by 98%, with $p=0.008$, and abolished insulin-induced IRS-1 phosphorylation at tyrosine 608. In simple terms, palmitate made the transmission of the signal from insulin to AKT less efficient.Palmitate increased the phosphorylation of IkBa at serine 32/36, an indicator of IKKb activation, threefold. It also increased mTOR phosphorylation at serine 2448 by 74%, with $p=0.0082$, and that of the S6 protein, a downstream indicator of mTORC1/S6K1, by 90%. In the same cells, there was no increase in JNK signaling or the translocation of various PKC isoforms, two pathways that can contribute to insulin resistance in other contexts.By blocking IKK with IKK16, the authors eliminated the increase in IRS-1

phosphorylation at serine 307 and partially recovered, by 59%, the AKT response to insulin. By blocking ceramide synthesis with myriocin, they prevented IRS-1 phosphorylation and restored AKT activation to levels similar to cells not exposed to palmitate. Finally, rapamycin reduced IRS-1 phosphorylation at serine 307 by 87%, with p=0.0178, and recovered insulin-induced AKT phosphorylation by 90%. However, rapamycin did not prevent IKKb activation, suggesting that IKKb and mTORC1 acted as separate but convergent branches on IRS-1.

5. INTERPRETATION

The biological significance of these results is that an experimental excess of palmitate can activate cellular systems normally involved in nutrient and stress management, turning them into a brake on insulin signaling. The key point is not necessarily that IRS-1 disappears, but that a chemical modification of it increases, reducing its ability to transmit the signal. Consequently, AKT, a protein important for many insulin responses, is activated less effectively.The pathway documented directly by the study is: palmitate activation of mTORC1/S6K1 and IKKb increased phosphorylation of IRS-1 at serine 307 reduced phosphorylation of AKT following insulin. Experiments with rapamycin, IKK16, and myriocin strengthen the causal interpretation in the cellular model because blocking these pathways reduced the modification of IRS-1 and restored the AKT signal.This result provides a mechanistic basis for the sections of the book where persistent hyperactivation of mTORC1/S6K1 weakens IRS-1 and reduces the signal to PI3K/AKT. However, serine 307 in the mouse model corresponds to a site that may have different designations in the human protein; furthermore, IRS-1 phosphorylation depends on the site, cell type, and duration of the stimulus. Rapamycin corrected the defect in culture, but this does not prove that it is a safe or effective treatment for insulin resistance or diabetic nephropathy in humans.

6. INDEPENDENT CONFIRMATORY EVIDENCE

Particularly relevant confirmation of the link between nutrients, S6K1, and IRS-1 comes from Tremblay and colleagues. In cellular experiments, in mice, and in human skeletal muscle following amino acid infusion, the authors identified serine 1101 of human IRS-1 as a target of S6K1. Increased phosphorylation at this site was associated with a nutrient-induced reduction in insulin sensitivity. While this result does not concern podocytes or palmitate, it confirms in an insulin-sensitive human tissue the principle that nutritional activation of S6K1 can modify IRS-1 in an inhibitory manner [1].Harrington and colleagues studied mouse embryonic fibroblasts lacking TSC2, a regulator that normally limits the activity of the mTOR/S6K cascade. In these cells, S6K hyperactivation reduced IRS-1 expression, increased its phosphorylation, and decreased the association of IRS-1 with both the insulin receptor and PI3K. Rapamycin or experimental reduction of S6K restored, at least in part, the PKB/AKT response. This research supports both the acute brake exerted by phosphorylation and the more lasting effect on IRS-1 availability; the limitation is the use of murine cells with an extreme genetic perturbation [2].Independent work by Shah and colleagues obtained convergent results in cells lacking TSC1 or TSC2 and in cells overexpressing Rheb, an mTOR activator. Constitutive activation of the Rheb/mTOR/S6K cascade reduced IRS-1 and IRS-2 and rendered AKT unresponsive to insulin or IGF-1, while it remained activatable by signals that do not depend on IRS. This finding localizes the defect upstream of PI3K and AKT, consistent with the chain described in the book's chapters. Here, too, the evidence is cellular, not clinical [3].In the renal context, Gödel and colleagues showed that increased mTORC1 activity is present in the podocytes of diabetic human kidneys and in mouse models of diabetic nephropathy. However, they also observed that genetically deleting mTORC1 in podocytes causes proteinuria and progressive glomerulosclerosis. This result does not negate the damage caused by hyperactivation: rather, it indicates that mTOR is necessary at physiological levels and that both excess and complete inhibition can damage the renal filter [4].

7. CONFLICTING EVIDENCE

No directly conflicting evidence sufficiently relevant to the fact that persistent activation of mTORC1/S6K may impair IRS-1 function has been identified. However, there are significant limitations to the generalization of this narrative. The phosphorylation

sites of IRS-1 are not equivalent across species and can have different consequences depending on the cell type, stimulus, and duration of exposure.The most important evidence of context-dependency is renal: in podocytes, mTORC1 is not simply a pathway to be suppressed. Its genetic loss has caused proteinuria and progressive glomerulosclerosis, while hyperactivation has been associated with damage in diabetes [4]. Therefore, the observation that rapamycin restores AKT in podocytes treated with palmitate does not authorize the deduction that prolonged or complete inhibition of mTORC1 is beneficial in the human kidney.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent evidence used to verify the mTORC1/S6K1 → IRS-1 → PI3K/AKT chain.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal and cellular	db/db mice and murine podocytes exposed to palmitate	Palmitate: increase in mTORC1/S6K1 and IRS-1 Ser307; reduction in insulin-induced AKT; recovery with rapamycin.	direct confirmation	moderate
[1]	Cellular, animal, and human metabolic intervention	Cells, obese mice, and human skeletal muscle after amino acids	S6K1 phosphorylated IRS-1 at Ser1101; nutrient availability was associated with lower insulin sensitivity.	direct confirmation	moderate
[2]	Cellular and molecular	TSC2-deficient murine embryonic fibroblasts	S6K hyperactivation: increased phosphorylation and decreased expression of IRS-1; reduction in PI3K/AKT signaling, recoverable with rapamycin or S6K inhibition.	direct confirmation	moderate
[3]	Cellular and genetic	Cells with TSC1/TSC2 loss or Rheb overexpression	Constitutive activation of mTOR/S6K: reduction of IRS-1/2 and loss of AKT response to insulin and IGF-1.	direct confirmation	moderate

[4]	Animal, human tissue, and genetic	Murine podocytes, murine models of diabetes, and human diabetic kidneys	Increased mTORC1 accompanies diabetic nephropathy, but its deletion in podocytes causes proteinuria and glomerulosclerosis.	conflicting evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed convincingly demonstrates, within its experimental model, that palmitate reduces the insulin response of podocytes through two convergent pathways, IKKb and mTORC1/S6K1, which increase the inhibitory phosphorylation of IRS-1. The effect of rapamycin on the recovery of AKT supports the role of mTORC1 in this cellular sequence.

Independent evidence contributes to supporting the general idea that persistent activation of mTOR/S6K can inhibit IRS-1 function and reduce signaling toward PI3K/AKT. The link is particularly robust at a mechanistic level. However, it remains to be validated in which human tissues, under which metabolic conditions, and with what clinical consequences the mechanism carries the same weight observed in experimental models. Furthermore, the balance of mTOR in podocytes is delicate: both hyperactivation and complete inhibition can be harmful.

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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