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Modulation of muscle insulin resistance through selective GSK-3 inhibition in obese Zucker diabetic rats - Review of the evidence

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1. ABSTRACT

The analyzed study evaluated whether the selective pharmacological inhibition of GSK-3, an enzyme that can hinder certain insulin signals, improved glucose utilization in the muscle of Zucker Diabetic Fatty rats, an animal model of type 2 diabetes. In isolated muscles, the inhibitors increased insulin-stimulated glucose transport; after acute oral treatment, they reduced glucose and insulin responses to an oral glucose tolerance test.In section 4.13 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the narrative that GSK-3 hyperactivity may participate in the post-receptor insulin signaling defect. The available material directly documents the functional improvement of glucose transport and the increase of GLUT4 in the membrane, but does not report measurements of IRS-1, PI3K, or AKT. Independent studies support that GSK-3 can phosphorylate IRS-1 and that its inhibition improves IRS-1-dependent signals in the muscle of insulin-resistant rodents. Inconsistent results in other animal experiments necessitate caution: the confirmation is primarily mechanistic and preclinical, not clinical in humans.

ONLINE ARTICLE

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2. ANALYZED STUDY

The research question was whether selectively blocking GSK-3 (glycogen synthase kinase 3, an enzyme that can limit glycogen synthesis and modulate insulin signaling) could improve insulin action in insulin-resistant skeletal muscle. The hypothesis was that excessive GSK-3 activity contributes to the muscle's reduced ability to take up glucose when the insulin signal arrives.The research is relevant to section 4.13 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it verifies, in an animal model of diabetes, whether GSK-3 inhibition improves a functional consequence of post-receptor insulin signaling: glucose entry into the muscle. However, the study cannot demonstrate that GSK-3 necessarily acts through IRS-1 (insulin receptor substrate-1, an adapter protein that transmits the signal from the insulin receptor) because, in the only available abstract, measurements of IRS-1, PI3K, or AKT phosphorylation are not reported.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

An experimental animal model was used: Zucker Diabetic Fatty rats, described in the abstract as insulin-resistant. Two isolated skeletal muscles were studied: the epitrochlearis, predominantly type IIb, and the soleus, predominantly type I. The number of animals, sex, age, inclusion criteria, and the experimental period are not reported in the available material.In the isolated muscle preparations, the authors incubated the tissues with CT-98014, a selective GSK-3 inhibitor, and compared glycogen synthase activity and 2-deoxyglucose uptake, a molecule used to estimate glucose transport in cells. They also evaluated the amount of GLUT4 present on the cell surface; GLUT4 is the transporter that allows glucose to enter muscle fibers in response to insulin. Lithium, which can inhibit GSK-3 but has additional biological effects, was also examined.In a second experiment, the rats received CT-98023, another selective GSK-3 inhibitor, orally at a dose of 30 mg/kg twice. Subsequently, an oral glucose tolerance test was performed, which is a test that observes how glycemia and insulinemia change after glucose intake. Details of the statistical analyses, randomization, and any blinding of the evaluators are not reported in the available material.

4. RESULTS

In the muscles of Zucker Diabetic Fatty rats, CT-98014 increased glycogen synthase activity by 49% in the epitrochlearis and by 50% in the soleus, with $P < 0.05$. In simple terms, the treatment made the enzyme that promotes glucose storage in the form of glycogen more active. The inhibitor did not alter basal glucose uptake, meaning the entry of glucose when no insulin was added.The most relevant finding for the book's narrative is that CT-98014 increased insulin-stimulated glucose transport. In the epitrochlearis, the increase was 37% with submaximal insulin and 24% with maximal insulin; in the soleus, it was 43% and 26%, respectively. These increases were associated with a greater presence of GLUT4 on the cell surface. The result therefore indicates that, in the isolated muscle of these rats, GSK-3 inhibition increased the response to the insulin signal and the availability of the transporter necessary for glucose entry.After two oral doses of CT-98023, glucose and insulin responses during the oral glucose tolerance test decreased by 26% and 34%, respectively, compared to untreated animals. Thirty minutes after the last dose, insulin-stimulated glucose transport had increased by 57% in the epitrochlearis and by 43% in the soleus. Two hours after the last dose, the increase was still significant only in the soleus, at 26%.The abstract does not report absolute values, sample sizes, confidence intervals, or results regarding IRS-1 phosphorylation, PI3K activation, or AKT phosphorylation. Therefore, these specific molecular steps cannot be directly attributed to the analyzed study based on the available material.

5. INTERPRETATION

The primary biological significance is that GSK-3 does not appear to be linked solely to glycogen production: in the model studied, its inhibition increased the muscle's response to insulin and promoted the appearance of GLUT4 on the cell membrane. In practice, when insulin was present, the treated muscle allowed more glucose to enter compared to the untreated muscle.The chain segment documented by the publication is therefore: GSK-3 inhibition increased insulin action on muscle glucose transport

more GLUT4 on the cell surface. This is consistent with the idea that high GSK-3 activity contributes to a post-receptor defect, that is, one located after the insulin receptor.The interpretation that the improvement specifically depends on the recovery of IRS-1 phosphorylation and the subsequent reactivation of PI3K-AKT is plausible within the overall framework of the literature, but it is not a measurement reported in the abstract of the original study. Furthermore, the results come from rats and isolated muscles: they do not demonstrate that a GSK-3 inhibitor is effective or safe for preventing or treating insulin resistance in humans.

6. INDEPENDENT CONFIRMING EVIDENCE

Confirmation of the upstream molecular pathway comes from biochemical and cellular experiments by Eldar-Finkelman and Krebs. The authors showed that GSK-3 can phosphorylate IRS-1 on serine and threonine residues. This modification reduced the subsequent phosphorylation of IRS-1 by the insulin receptor; in cells with higher GSK-3 expression, insulin-induced receptor phosphorylation was also reduced. The study therefore supports the pathway: activated GSK-3 lower IRS-1 efficiency attenuation of insulin signaling [1]. However, this is primarily a cellular demonstration and not evidence in humans.Functional validation in a distinct animal model was obtained in prediabetic obese Zucker rats treated for ten days with CT118637, a selective GSK-3 inhibitor. Compared to vehicle-treated controls, the animals showed an 18% reduction in the glycemic response to the oral test, a 28% increase in whole-body insulin sensitivity, and a greater response of muscle glucose transport to insulin, ranging between 32% and 60%. In the plantaris muscle, IRS-1 tyrosine phosphorylation, relative to fasting plasma insulin, increased by 50%, and PI3K activity associated with IRS-1 increased by 79% [2]. This study confirms, more directly than the previously analyzed publication, the link between GSK-3 inhibition, improved IRS-1 function, and greater insulin action in muscle. Nevertheless, it remains a study in rodents, using a specific pharmacological compound and a genetic model of obesity, rather than a clinical trial.

7. CONFLICTING EVIDENCE

A partially conflicting result emerged from a study also conducted on Zucker Diabetic Fatty rats. After treatment with GSK-3 inhibitors, the oral glucose tolerance test improved and fasting glycemia decreased; however, during the euglycemic-hyperinsulinemic clamp—an experimental procedure that measures glucose management under standardized insulin conditions—no significant increase in muscle glucose uptake or muscle glycogen synthesis was observed. The overall improvement was attributed primarily to an increase in glycogen synthesis in the liver [3].This difference does not invalidate the results of the analyzed study, but it indicates that the effects of GSK-3 inhibition may depend on the compound used, the duration of treatment, the specific muscle examined, the severity of the diabetes, and the method used to evaluate glucose metabolism. Furthermore, the absence of an increase in muscle uptake during the clamp does not exclude the possibility that local improvements in insulin signaling may occur in specific muscle preparations. No further directly conflicting evidence of sufficient relevance was identified; this does not prove the absence of contradictory results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent research used to confirm or define the narrative of the book's paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal, isolated muscles and acute oral treatment	Zucker Diabetic Fatty rats; soleus and epitrochlearis muscles	GSK-3 inhibition increased insulin-stimulated glucose transport and membrane GLUT4.	direct confirmation	moderate
[1]	Cellular and biochemical	Purified IRS-1 and CHO cells with insulin receptor and IRS-1	GSK-3 phosphorylated IRS-1 and reduced insulin phosphorylation of IRS-1 and the receptor.	direct confirmation	moderate
[2]	Animal, chronic pharmacological treatment	Pre-diabetic obese Zucker rats	GSK-3 inhibition increased IRS-1/PI3K signaling, insulin sensitivity, and muscle glucose transport.	direct confirmation	moderate
[3]	Animal, pharmacological treatment and metabolic clamp	Zucker Diabetic Fatty rats	Treatment improved oral glucose tolerance without significantly increasing muscle uptake in the clamp.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study shows that selective inhibition of GSK-3 can increase muscle insulin response and glucose transport in Zucker Diabetic Fatty rats. This finding supports the role of GSK-3 as a negative regulator of post-receptor insulin action.Independent evidence makes the chain linking GSK-3 activity to reduced IRS-1 function and, consequently, lower muscle glucose utilization, plausible and moderately well-supported. Confirmation remains primarily mechanistic and based on animal models. Differences between studies indicate that metabolic effects may vary between the liver and muscle, depending on the experimental model and treatment. Therefore, it is not possible to translate these results into human therapy without further clinical studies.

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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