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# GSK-3 inhibition and improvement of insulin signaling in insulin-resistant prediabetic rats

**M. Moscati**[1]

1 Italy

## 1. ABSTRACT

The analyzed study examined whether acutely blocking GSK-3 (glycogen synthase kinase-3, an enzyme that can inhibit certain metabolic signals) improves insulin action in the muscle of obese, prediabetic Zucker rats, an animal model of insulin resistance. In isolated muscles, the selective inhibitor CT118637 increased the insulin response of glucose transport and the pathway involving IRS-1, PI3K, and AKT. The available material is only the abstract, which is also incomplete in the final part; therefore, numerous quantitative details are not reported.In the narrative of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication contributes to the passage stating that GSK-3 hyperactivity primarily compromises post-receptor events of insulin signaling in skeletal muscle. Independent cellular experiments confirm that GSK-3 can modify IRS-1 in an inhibitory manner, while studies on human muscle cells support an improvement in metabolic response following the inhibition of the enzyme. However, murine genetic models indicate that preventing the normal insulin-mediated inactivation of GSK-3 does not necessarily lead to diabetes or glucose intolerance. The confirmation is therefore primarily mechanistic and does not equate to a clinical demonstration in humans.

ONLINE ARTICLE

ARTICLE INFORMATION

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## 2. ANALYZED STUDY

The research question was whether the selective inhibition of GSK-3 could improve the ability of insulin to transport glucose into insulin-resistant skeletal muscle and, most importantly, through which cellular signaling steps. The authors evaluated the hypothesis that excessive GSK-3 activity reduces the efficiency of the insulin pathway downstream of the receptor—that is, in the signals transmitted by IRS-1 (insulin receptor substrate, an adapter protein), PI3K (phosphatidylinositol-3-kinase, an enzyme that propagates the signal), and AKT (a protein that coordinates metabolic responses).The relevance to paragraph 4.13 is specific: the research discussed in the article does not demonstrate the entire biological history of GSK-3b, nor does it establish therapeutic effects in humans. Instead, it documents a segment of the chain described in the book: when GSK-3 is inhibited in insulin-resistant muscle, IRS-1-dependent signals and the insulin-induced glucose response increase. Since this involved isolated rat muscles treated in vitro, the work can support a cellular-muscular mechanism, but it does not demonstrate clinical benefits or the safety of inhibiting GSK-3 in people.

## 3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study is experimental, conducted *in vitro* on skeletal muscles isolated from female obese Zucker rats, described by the authors as insulin-resistant and prediabetic. The type I soleus muscle, rich in oxidative fibers, and the type IIb epitrochlearis muscle, with different metabolic characteristics, were analyzed.The tissues were incubated in the absence or presence of CT118637, a small selective GSK-3 inhibitor, at a concentration of 1 micromolar. The stated selectivity was high for the GSK-3a and GSK-3b isoforms, with an inhibition constant of less than 10 nanomolar. A maximal insulin stimulation of 5 mU/ml was then applied. The authors measured glucose transport, glycogen synthase activity, and several signals: tyrosine phosphorylation of the insulin receptor and IRS-1, association of IRS-1 with the p85 subunit of PI3K, phosphorylation of AKT, and phosphorylation of GSK-3.The number of animals, inclusion and exclusion criteria, breeding period, details of statistical analyses, and complete significance values are not reported in the available material. A direct measurement of GLUT4 translocation (the transporter that brings glucose into the muscle fiber) to the membrane is also not reported in the available material.

## 4. RESULTS

In simple terms, blocking GSK-3 made the insulin-resistant muscle more capable of responding to insulin. In the available abstract, inhibition with CT118637 increased insulin stimulation of glucose transport and the activity of glycogen synthase, the enzyme that helps store glucose in the form of glycogen.The effect relevant to the book's paragraph was localized after the insulin receptor. The inhibitor increased the tyrosine phosphorylation of IRS-1, a modification normally associated with signal transmission, and increased the association between IRS-1 and the p85 subunit of PI3K. Insulin-induced phosphorylation of AKT and GSK-3b also increased. Conversely, the abstract indicates that there was no direct improvement in insulin receptor phosphorylation.This direction of the results is important: the intervention does not seem to have acted by making the receptor more active, but by restoring part of the signaling located downstream of the receptor. The abstract received ends after the indication of initial statistical significance; the complete numerical differences, P-values for each comparison, and the quantitative comparison between the two muscle types are not reported in the available material.

## 5. INTERPRETATION

The biological significance is that GSK-3 can act as a brake on the insulin response in already insulin-resistant muscle. If this brake is reduced, IRS-1 can more easily reconnect to PI3K; from there, the signal can reach AKT and promote glucose utilization. In the studied model, the increase in glucose transport is consistent with this recovery of the signaling pathway.The segment directly documented by the publication is therefore: acute pharmacological inhibition of GSK-3  greater functionality of IRS-1 associated with PI3K and greater activation of AKT  increased insulin response of glucose transport in rat muscle. The absence of a direct effect on the insulin

receptor makes the book's statement regarding the prevalence of post-receptor events consistent.This interpretation does not prove that GSK-3 is the sole cause of insulin resistance, nor that GSK-3 inhibition produces the same effect in every tissue or in the human body. Furthermore, GSK-3 possesses many cellular functions; reducing its activity may generate consequences that an acute experiment on isolated muscle cannot evaluate.

## 6. INDEPENDENT SUPPORTING EVIDENCE

Confirmation of the upstream molecular pathway comes from an independent cellular study that identified IRS-1 as a target of GSK-3. In hamster cells expressing the insulin receptor, the substitution of serines 332 and 336 of IRS-1 with alanine, which prevented GSK-3-mediated phosphorylation, increased insulin-stimulated tyrosine phosphorylation of IRS-1 and AKT activation compared to unmodified IRS-1. Lithium, a non-selective inhibitor of GSK-3, reduced IRS-1 phosphorylation at serine 332; conversely, GSK-3 overexpression increased it. The study therefore supports the pathway: GSK-3 activation inhibitory modification of IRS-1 reduced insulin signaling transmission, but it remains an experiment on engineered cells and does not measure insulin resistance in humans [1].A second study verified the relationship between GSK-3 and glucose metabolism in cultured human muscle cells. Pharmacological inhibition of GSK-3 rapidly increased glycogen synthase activity; after prolonged treatment, it increased both basal and insulin-stimulated transport. The increase in insulin-stimulated transport was accompanied by a approximately 3.5-fold increase in the amount of IRS-1, while the maximum insulin-induced AKT phosphorylation did not change. This evidence confirms that GSK-3 inhibition can improve certain metabolic outcomes in human muscle cells, but it also indicates that not all nodes of the IRS-1–AKT pathway respond in the same way and under the same experimental conditions [2].Overall, the two independent publications build a convergent chain with the original study: GSK-3 can modify IRS-1 in a way that is unfavorable to signal transmission, and its inhibition can improve the metabolic response of muscle. Confirmation in humans, however, is limited to cultured cells and not clinical trials on patients with insulin resistance.

## 7. CONFLICTING EVIDENCE

Important contextual evidence comes from genetically modified mice in which GSK-3a and/or GSK-3b could not be inactivated by the phosphorylation normally induced by AKT. In the muscle of these animals, insulin failed to inhibit the mutated forms of GSK-3 and did not stimulate glycogen synthase as it did in the controls. Despite this, the single and double knock-in mice maintained normal circulating glucose and insulin levels and did not show glucose intolerance at 20 weeks [3].This result does not directly contradict the observation that acute inhibition of GSK-3 improves insulin signaling in rat muscle. However, it scales back the idea that the failure to inactivate GSK-3 alone is sufficient to cause diabetes in the whole organism. The authors pointed to possible compensatory mechanisms in development, the liver, or other tissues. The GSK-3–IRS-1 relationship therefore remains dependent on the model, the isoform considered, the duration of the alteration, and the tissue analyzed.

## 8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from the independent research used to evaluate the same narrative passage.

### Quadro comparativo

| Reference | Study type | Population or model | Main result | Direction of evidence | Strength of evidence |
|---|---|---|---|---|---|
| Original study | Animal, isolated muscles in vitro | Soleus and epitrochlearis muscles from prediabetic female obese Zucker rats | Acute inhibition of GSK-3 increased post-receptor insulin signaling and glucose transport. | direct confirmation | moderate |
| [1] | Cellular and molecular | Hamster cells with experimentally expressed insulin receptor and IRS-1 | Preventing GSK-3-mediated IRS-1 phosphorylation increased IRS-1 tyrosine phosphorylation and AKT activation. | direct confirmation | moderate |
| [2] | Cellular | Cultured human skeletal muscle cells | GSK-3 inhibition increased glucose transport and the amount of IRS-1 after prolonged exposure. | indirect confirmation | moderate |
| [3] | Genetic animal | Knock-in mice with GSK-3 resistant to insulin-induced inactivation | Failure to inactivate GSK-3 impaired muscle glycogen synthase activation without causing glucose intolerance. | discordant evidence | moderate |

## 9. SINTESI EDITORIALE E CONCLUSIONI

### CONCLUSIONS

The study analyzed specifically supports the idea that, in the insulin-resistant skeletal muscle of prediabetic rats, GSK-3 acts primarily as a negative regulator of insulin signaling downstream of the receptor. Acute inhibition of the enzyme increased signals associated with IRS-1, PI3K, and AKT and improved glucose transport.The narrative is confirmed at a mechanistic level by studies identifying IRS-1 as an inhibitory target of GSK-3 and by results in human muscle cells. However, the evidence does not prove that GSK-3 is the sole determinant of insulin resistance, nor that its inhibition constitutes a proven treatment in humans. Clinical validation is necessary, given the differences between tissues, enzyme isoforms, and experimental models.

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.

## 11. RIFERIMENTI BIBLIOGRAFICI

[1] **Serine 332 Phosphorylation of Insulin Receptor Substrate-1 by Glycogen Synthase Kinase-3 Attenuates Insulin Signaling**
Liberman et al., 2005
*Journal of Biological Chemistry*
DOI: https://doi.org/10.1074/jbc.M410610200

[2] **Inhibition of Glycogen Synthase Kinase 3 Improves Insulin Action and Glucose Metabolism in Human Skeletal Muscle**
Nikoulina et al., 2002
*Diabetes*
DOI: https://doi.org/10.2337/diabetes.51.7.2190

[3] **Role that phosphorylation of GSK3 plays in insulin and Wnt signalling defined by knockin analysis**
McManus et al., 2005
*The EMBO Journal*
DOI: https://doi.org/10.1038/sj.emboj.7600633