LIFE Science Hub
JOURNAL OF SCIENCE
EXPANDING KNOWLEDGE ABOUT NUTRITION AND HEALTH

ORIGINAL RESEARCH
ISSN 2845-7501

Phosphorylation of insulin receptor substrate 1 by glycogen synthase kinase 3 impairs insulin action - A review of the evidence

Dott. A. Colonnese[1]

1 Nutritional Biologist, Italy

1. ABSTRACT

The analyzed study evaluated whether glycogen synthase kinase 3 (GSK-3, an enzyme that adds phosphate groups to other proteins) can reduce the efficiency of insulin signaling by acting on IRS-1, a protein that transmits the signal from the insulin receptor inside the cell. In test-tube experiments and in Chinese hamster ovary cells modified to produce IRS-1 and the insulin receptor, increased GSK-3 activity enhanced serine phosphorylation of IRS-1 and reduced insulin-induced phosphorylation of IRS-1 and the receptor.The research contributes to the narrative of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, according to which persistent GSK-3 activity can weaken insulin signaling through IRS-1. Independent studies in humans show an association between higher muscle GSK-3 activity and lower glucose utilization; studies in insulin-resistant rats indicate that inhibition of the enzyme improves downstream signaling of IRS-1 and glucose transport. However, complete causal demonstration in humans remains limited.

ONLINE ARTICLE

ARTICLE INFORMATION

Published: November 19, 2026
Updated: November 19, 2026

DOI 10.5281/zenodo.24363476

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 GSK-3 could directly interfere with IRS-1, the primary initial adapter for insulin signaling. Under normal conditions, the insulin receptor adds phosphate groups to specific tyrosine residues of IRS-1; this modification allows the cell to transmit the insulin message to the systems that regulate glucose use. The authors hypothesized that the phosphorylation of IRS-1 on serine or threonine by GSK-3 could hinder this process.The relevance to paragraph 4.13 is precise: the publication documents the segment GSK-3 modification of IRS-1 attenuation of insulin receptor signaling. It does not directly evaluate obesity, type 2 diabetes, or insulin sensitivity in the human body. Furthermore, in the available material, GSK-3 is indicated without a separate demonstration of the beta isoform; the specific attribution to GSK-3b in the book's text is biologically consistent with subsequent literature, but it is not independently demonstrated by the available abstract of the original study.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study included in vitro biochemical experiments and CHO cells, i.e., Chinese hamster ovary cells cultured in the laboratory, in which IRS-1 and the insulin receptor were expressed. The authors evaluated the ability of GSK-3 to phosphorylate IRS-1 and compared the expression of the normal form of the enzyme with that of an S9A mutant, described as unregulated.The main variables observed were the serine phosphorylation of IRS-1, the insulin-induced tyrosine phosphorylation of IRS-1, and the tyrosine kinase activity of the insulin receptor, i.e., the receptor's ability to initiate signaling through phosphorylation. The number of experiments, inclusion criteria, number of biological replicates, concentrations used, detailed analytical procedures, and statistical analyses are not reported in the available material.

4. RESULTS

The central finding is that GSK-3 phosphorylated IRS-1 in vitro. In simple terms, the enzyme modified the protein that normally helps the insulin receptor transmit its message. Following this modification, IRS-1 became capable of inhibiting the tyrosine kinase activity of the insulin receptor in test-tube experiments.In CHO cells expressing IRS-1 and the insulin receptor, the expression of both normal GSK-3 and the S9A mutant increased the serine phosphorylation of IRS-1. Under the same conditions, the insulin-induced tyrosine phosphorylation of IRS-1 and the receptor was markedly suppressed. The abstract does not report percentages, P-values, confidence intervals, sample sizes, or absolute measurements; therefore, such data cannot be added.The most relevant finding for the book is directional: greater experimental activity or expression of GSK-3 is associated with lower activation of the insulin receptor and IRS-1 following insulin stimulation. This demonstrates a possible molecular brake on the signal, but it does not prove that this same mechanism is the predominant cause of insulin resistance in obesity or type 2 diabetes.

5. INTERPRETATION

The biological significance is that IRS-1 is not merely a passive step in the insulin pathway: certain chemical modifications can transform it into an obstacle to signal propagation. The proposed chain is simple: when GSK-3 adds phosphate groups to regulatory sites on IRS-1, IRS-1 responds less effectively to the receptor, and the insulin signal decreases.From a technical standpoint, the study links the phosphorylation of IRS-1 on serine or threonine to a reduction in the tyrosine phosphorylation of IRS-1 and the insulin receptor. Tyrosine phosphorylation is the signal that promotes insulin transduction; its reduction indicates a less efficient initial signal. The authors therefore proposed that GSK-3 may contribute to insulin resistance.This interpretation is consistent with the passage in the book, but it requires caution. The work demonstrates a cellular mechanism in an artificial model with protein overexpression. It cannot establish how much this mechanism weighs in different human tissues, nor can it demonstrate that GSK-3 inhibition is an effective or safe treatment for diabetes.

6. INDEPENDENT CONFIRMING EVIDENCE

Initial confirmation of the pathophysiological context comes from a study on vastus lateralis muscle biopsies from people with type 2 diabetes, lean people without

diabetes, and people with obesity without diabetes. In the muscle of people with type 2 diabetes, the amounts of the alpha and beta isoforms of GSK-3 were approximately 30% higher, and the total enzyme activity was about double compared to the groups without diabetes. Furthermore, higher levels of GSK-3 were associated with lower insulin-stimulated glucose disposal. This is an observational association: it confirms that GSK-3 is linked to a reduced insulin response in humans, but it does not prove that it is the cause [1].A second line of evidence comes from Zucker Diabetic Fatty rats, an animal model of obesity and type 2 diabetes. Selective inhibition of GSK-3 increased insulin-stimulated glucose transport in the soleus and epitrochlearis muscles by 43% and 26%, respectively, after acute oral treatment, while the glycemic and insulin response to the oral glucose tolerance test was reduced by 26% and 34%. The effect was accompanied by an increase in GLUT4 on the cell surface, the transporter that allows glucose to enter the muscle. This study confirms that reducing GSK-3 activity can improve insulin action in an insulin-resistant organism, although it remains an animal model [2].A third study, conducted on isolated muscle from pre-diabetic Zucker obese rats, delves into the post-receptor segment of the chain. Acute and selective inhibition of GSK-3 increased the tyrosine phosphorylation of IRS-1, the association of IRS-1 with PI3K, and the phosphorylation of AKT, a protein that participates in the metabolic response to insulin. It did not, however, increase the phosphorylation of the insulin receptor. This result is particularly consistent with the idea that GSK-3 primarily affects the efficiency of IRS-1 and subsequent signals, not necessarily the initial activation of the receptor [3].Taken together, these independent studies build a convergent chain: higher GSK-3 in human muscle is associated with a lower insulin response; in insulin-resistant rodents, GSK-3 inhibition improves IRS-1-dependent signaling and glucose entry into the muscle. The most direct confirmation of the specific phosphorylation of IRS-1 by GSK-3, however, remains primarily experimental and cellular.

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance has been identified; this does not prove the absence of contrary results.However, there are limitations that reduce the generalizability of this narrative. The available inhibition studies primarily concern the skeletal muscle of rodents and experimental compounds; effects may vary depending on the tissue, enzyme isoform, duration of exposure, and metabolic state. Furthermore, in the human observational study, increased GSK-3 activity could be a consequence of insulin resistance rather than its initial causal factor. These elements mean that results obtained in cells or animals should not be automatically extrapolated to human patients.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the mechanism demonstrated in the original study from the independent evidence available in human and animal models.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and biochemical	In vitro experiments and CHO cells with IRS-1 and insulin receptor	GSK-3 increased serine phosphorylation of IRS-1 and reduced insulin-induced phosphorylation of IRS-1 and the receptor.	direct confirmation	preliminary
[1]	Observational on human tissue	Vastus lateralis muscle biopsies in people with type 2 diabetes and controls	GSK-3 was more abundant and more active in type 2 diabetes; higher levels were associated with lower insulin-stimulated glucose clearance.	indirect confirmation	moderate
[2]	Experimental animal	Zucker Diabetic Fatty rats with insulin resistance	Selective inhibition of GSK-3 increased insulin-stimulated muscle glucose transport and reduced glycemic and insulin responses to oral load.	biologically consistent evidence	moderate
[3]	Ex vivo experimental animal	Isolated muscle from prediabetic Zucker obese rats	GSK-3 inhibition increased IRS-1 phosphorylation, IRS-1/PI3K association, and AKT phosphorylation without increasing receptor phosphorylation.	indirect confirmation	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study directly supports a cellular mechanism: GSK-3 can phosphorylate IRS-1 and reduce the efficiency of insulin signaling. Independent evidence makes this narrative quite well-supported in animal models and biologically consistent with observations in human muscle. However, validation in humans is still needed to clarify causality, the relevance of different isoforms, and potential effects in various tissues.

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] **Modulation of muscle insulin resistance by selective inhibition of GSK-3 in Zucker diabetic fatty rats**
Henriksen et al., 2003
American Journal of Physiology-Endocrinology and Metabolism
DOI: https://doi.org/10.1152/ajpendo.00346.2002

[2] **Acute selective glycogen synthase kinase-3 inhibition enhances insulin signaling in prediabetic insulin-resistant rat skeletal muscle**
Dokken et al., 2005
American Journal of Physiology-Endocrinology and Metabolism
DOI: https://doi.org/10.1152/ajpendo.00547.2004

[3] **Potential role of glycogen synthase kinase-3 in skeletal muscle insulin resistance of type 2 diabetes.**
Nikoulina et al., 2000
Diabetes
DOI: https://doi.org/10.2337/diabetes.49.2.263