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Role of glycogen synthase kinase-3 in insulin resistance and type 2 diabetes - Review of the evidence

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ONLINE ARTICLE

ARTICLE INFORMATION

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1. ABSTRACT

The analyzed publication is a narrative review that examined the potential role of glycogen synthase kinase-3, or GSK-3 (an enzyme that modifies other proteins), in skeletal muscle insulin resistance and type 2 diabetes. Based solely on the available abstract, the authors synthesized studies conducted on animal models, muscle cells, and people with type 2 diabetes. The review indicates that increased GSK-3 activity is associated with a reduced ability of insulin to promote glucose entry into muscle cells and its storage as glycogen.In paragraph 4.13, “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi uses this publication to argue that GSK-3 inhibition can improve post-receptor insulin signaling, increase GLUT4 availability on the cell membrane, promote peripheral glucose utilization, and reduce hepatic glucose production. Independent evidence convergently confirms the negative biological role of GSK-3 on the insulin pathway, especially in cells and rodents, and also shows an association in human muscle. However, an experimental model of glucocorticoid-induced insulin resistance did not show a recovery of muscle glucose uptake following acute GSK-3 inhibition. The most prudent conclusion is therefore mechanistic: GSK-3 contributes to the regulation of insulin sensitivity, but it has not been proven that its inhibition represents an effective treatment in humans.

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 question addressed by the publication was whether GSK-3 contributes to the defect in how skeletal muscle responds to insulin in obesity and type 2 diabetes. Under normal conditions, insulin promotes the entry of glucose into the muscle cell and encourages its storage as glycogen, an energy reserve. GSK-3 is an enzyme that, when it remains too active, can hinder certain steps of this response.The hypothesis synthesized by the authors is that the increased expression or activity of GSK-3 in muscle is linked to reduced activation of glucose transport by insulin and lower activity of glycogen synthase, the enzyme that builds glycogen. The relevance to paragraph 4.13 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns, above all, the post-receptor segment of the insulin pathway: after insulin has interacted with its receptor, GSK-3 can influence proteins that transmit the signal toward AKT and GLUT4.Since this is a review and the available material is only the abstract, the publication does not allow for the attribution of a single causal effect to a single experiment. Instead, it summarizes previous results and proposes GSK-3 as a possible biological target. It does not demonstrate that the inhibition of GSK-3 prevents or cures diabetes in people.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication subject to the Evidence Review is a narrative review of the scientific literature, not a clinical or experimental study with its own cohort of participants. The available abstract reports that the authors considered results obtained in obese and insulin-resistant animal models, in the muscle of people with type 2 diabetes, and in experiments with selective GSK-3 inhibitors.The topics described include glucose transport in muscle, glycogen synthase activity, GLUT4 translocation (movement of the glucose transporter to the cell membrane), post-receptor insulin signaling, and glucose production by the liver. The number of studies included, publication selection criteria, search strategy, participant characteristics, inhibitor dosages, statistical analyses, and a formal assessment of the risk of bias are not reported in the available material.Consequently, this publication can be read as an interpretive summary of the state of knowledge as of 2006. It does not allow for an accurate estimation of the average magnitude of the effect of GSK-3 inhibition, nor does it establish which results are generalizable to humans.

4. RESULTS

The abstract reports that in obese animal models and in obese individuals with type 2 diabetes, increased expression and activity of GSK-3 in skeletal muscle were associated with a reduced ability of insulin to promote glucose clearance from the blood and to activate glycogen synthase. In practical terms, the muscle was less efficient at both absorbing glucose and converting it into energy reserves.The review also reports that selective inhibition of GSK-3 in insulin-resistant muscle improved insulin-stimulated glucose transport. The authors interpret this result as likely linked to an improvement in downstream insulin receptor signaling and increased GLUT4 translocation. The abstract does not report absolute values, sample sizes, confidence intervals, or significance levels of the included studies; such information is not provided in the available material.A further synthesized result concerns the liver: GSK-3 inhibitors were associated with a reduction in hepatic glucose production, likely through lower expression of genes involved in gluconeogenesis, i.e., the production of glucose from non-carbohydrate precursors. The use of "likely" indicates that, in the abstract, this mechanism is presented as an interpretation rather than a complete demonstration of the causal chain.

5. INTERPRETATION

The central biological significance is that GSK-3 can act as a brake on the insulin response. When insulin is functioning correctly, the IRS-1–PI3K–AKT pathway (a sequence of proteins that transmits the insulin signal) reduces GSK-3 activity. If this brake is not applied effectively, GSK-3 can contribute to keeping the muscle in a condition that is less sensitive to insulin.The phase of the narrative documented by the analyzed publication is: GSK-3 hyperactivity in insulin-resistant muscle reduced signaling efficiency downstream of the insulin receptor decreased GLUT4 translocation and reduced glucose transport. The reference does not, by itself, demonstrate every step

described in the book's paragraph, particularly the direct phosphorylation of IRS-1 or the effects on specific organ complications. However, it supports the synthesis that GSK-3 is a negative regulator of the insulin response in muscle and that its inhibition can improve certain metabolic outcomes in experimental models.The most important point for the reader is to distinguish the mechanism from the therapy. An enzyme can participate in a disease without automatically being a useful and safe pharmacological target. The effects of GSK-3 inhibitors depend, in fact, on the tissue, the model of insulin resistance, and the selectivity of the molecule used.

6. INDEPENDENT CONFIRMING EVIDENCE

The molecular basis of the step involving IRS-1 was documented independently by Eldar-Finkelman and Krebs. In biochemical experiments and in Chinese hamster ovary cells expressing the insulin receptor and IRS-1, GSK-3 phosphorylated IRS-1 on serine residues; this modification reduced the subsequent phosphorylation of IRS-1 by the insulin receptor and attenuated the signal. The authors also observed that IRS-1 modified in this way could inhibit the tyrosine kinase activity of the receptor in vitro. This directly confirms the molecular step GSK-3 IRS-1 reduced insulin signaling, but the cellular model alone does not prove that the same mechanism explains human insulin resistance [1].Confirmation in humans comes from biopsies of the vastus lateralis muscle collected from people with type 2 diabetes and non-diabetic controls. In the muscle of people with diabetes, GSK-3a and GSK-3b proteins were increased by approximately 30% compared to lean controls and non-diabetic obese controls, while total GSK-3 activity was approximately double. A higher amount of GSK-3 was associated with lower insulin-stimulated glucose disposal and lower glycogen synthase activity. This is an observational association, so it does not establish that GSK-3 is the sole cause of the metabolic defect, but it confirms the direction of the relationship described in the book in human tissue [2].In Zucker Diabetic Fatty rats, a model of obesity with type 2 diabetes, Henriksen and colleagues tested selective GSK-3 inhibitors in isolated muscle and after oral administration. In the muscle, the inhibitor CT-98014 increased glycogen synthase activity by 49% in the epitrochlearis muscle and by 50% in the soleus. It also increased insulin-stimulated glucose transport at both submaximal and maximal concentrations, with increases ranging from 24% to 43% depending on the muscle type and insulin concentration; the effect was accompanied by a greater presence of GLUT4 on the cell surface. After oral treatment, during the oral glucose tolerance test, glucose and insulin responses were reduced by 26% and 34%, respectively. These experimental data confirm the part of the chain GSK-3 GLUT4 increased glucose uptake, but these remain data in rats and not therapeutic proof in humans [3].Taken together, these studies form a coherent chain: a molecular modification of IRS-1 can attenuate insulin signaling; in human muscle with diabetes, GSK-3 is more abundant and more active; in insulin-resistant rats, its inhibition increases glucose transport and GLUT4 availability. The convergence is biologically sound, but the most complete causal evidence is experimental and not clinical.

7. CONFLICTING EVIDENCE

A relevant but not overlapping result comes from Wistar rats treated for 12 days with dexamethasone, a glucocorticoid that induces insulin resistance. In this model, the selective GSK-3 inhibitor CHIR-637 increased the fractional activity of glycogen synthase in the soleus muscles, but did not restore insulin-stimulated glucose uptake. The result indicates that blocking GSK-3 can improve one branch of the insulin response, glycogen synthesis, without necessarily correcting glucose transport [4].This evidence does not contradict the existence of the GSK-3–IRS-1 mechanism, but it reduces the possibility of automatically generalizing the effects observed in Zucker Diabetic Fatty rats to all forms of insulin resistance. The difference may depend on the cause of the insulin resistance, the muscle type, the compound used, the duration of the treatment, or additional alterations induced by glucocorticoids. No directly conflicting evidence sufficiently relevant to the molecular relationship between GSK-3 and IRS-1 has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from the independent research used to verify the individual steps of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Previous studies on human muscle, animal models, and cells	Synthesizes that GSK-3 hyperactivity is associated with muscle insulin resistance and that its inhibition can improve glucose transport and glycogen synthase activity.	biologically consistent evidence	moderate
[1]	Cellular and biochemical	Recombinant proteins and CHO cells with insulin receptor and IRS-1	Phosphorylation of IRS-1 by GSK-3 reduces insulin-stimulated phosphorylation of IRS-1 and attenuates the signal.	direct confirmation	moderate
[2]	Observational with muscle biopsies	People with type 2 diabetes and non-diabetic controls	In type 2 diabetes, muscle GSK-3 is increased and inversely associated with insulin-stimulated glucose disposal.	indirect confirmation	moderate
[3]	Experimental animal	Zucker Diabetic Fatty rats and isolated muscles	GSK-3 inhibition increases GLUT4 on the membrane, insulin-stimulated glucose transport, and glycogen synthase activity.	direct confirmation	moderate
[4]	Experimental animal	Muscles of Wistar rats with dexamethasone-induced insulin resistance	GSK-3 inhibition increases glycogen synthase activity but does not restore insulin-stimulated glucose uptake.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the role of GSK-3 as a negative regulator of insulin sensitivity, particularly in skeletal muscle. Independent evidence confirms that GSK-3 can modify IRS-1, that its increased activity is associated with a reduced insulin response in human muscle with type 2 diabetes, and that its inhibition improves glucose transport in specific animal models.The narrative is well-supported at a mechanistic level. However, it remains necessary to distinguish between the recovery of certain cellular signals and a demonstrated therapeutic benefit: an animal model of glucocorticoid-induced insulin resistance did not show a restoration of glucose uptake. Controlled clinical validations with selective and safe molecules are therefore required before considering GSK-3 inhibition a consolidated therapeutic strategy.

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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