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Reduced tyrosine and serine-632 phosphorylation of insulin receptor substrate 1 in the gastrocnemius muscle of obese Zucker rats - Evidence review

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1. ABSTRACT

The analyzed study examined how obesity alters the early steps of insulin signaling in the gastrocnemius muscle of obese Zucker rats, an animal model genetically predisposed to obesity, hyperinsulinemia, and insulin resistance. Compared to lean rats, the obese animals showed poorer glucose tolerance, lower levels of IRS-1, and a reduced ability of insulin to increase certain essential phosphorylations of the insulin receptor and IRS-1.The research contributes to the narrative of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it documents that IRS-1 is an essential link between the insulin receptor and intracellular signals. Independent studies in humans confirm that, in type 2 diabetes, tyrosine phosphorylation of IRS-1 and the activation of downstream pathways can be reduced. However, serine phosphorylations do not all have the same significance: some are associated with a reduced insulin response, while others may increase or decrease depending on the site studied and the biological context.

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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 obesity and insulin resistance alter the initial signals transmitted by the insulin receptor in the gastrocnemius muscle. Under normal conditions, insulin binds to its receptor on the surface of the muscle cell. The receptor then activates IRS-1 (insulin receptor substrate 1), an adapter protein that collects the signal and allows for the recruitment of other enzymes.The authors evaluated the hypothesis that, in obese Zucker rats, both the quantity of IRS-1 and some of its phosphorylation sites are altered. Phosphorylation is the addition of a phosphate group to a protein: depending on the position involved, it can promote, modulate, or hinder signal transmission. The connection to section 4.2 of the book lies primarily in the fact that the study shows IRS-1 as a functional step between the insulin receptor and intracellular pathways.The publication can demonstrate that specific modifications of IRS-1 and the insulin receptor are present in the muscle of this animal model and that the acute response to insulin is altered. It cannot demonstrate, on its own, that the same changes are identical in humans, nor can it attribute all the consequences of insulin resistance to a single phosphorylation.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study used 8–10-week-old obese female Zucker rats and lean rats of the same age as controls. In some additional experiments, KK-Ay/J mice were used, a mouse model with hyperglycemia, hyperinsulinemia, and reduced glucose tolerance, along with C57BL/6J control mice. Each group included 4–6 animals; six rats per group were used for the glucose tolerance test.After overnight Fasting, the rats received glucose intraperitoneally at a dose of 1.5 g/kg. Glycemia was measured before administration and after 15, 30, 60, and 120 minutes. The authors also calculated the area under the curve, which is an overall measure of the increase in glycemia over time.To study the muscular response to insulin, some animals received intraperitoneal insulin at a dose of 5 units/kg. Five minutes later, the gastrocnemius muscle was harvested. Muscle proteins were analyzed using immunoprecipitation and immunoblotting, techniques that allow for the isolation of a protein and the measurement of its quantity or chemical modifications. IRS-1, the beta subunit of the insulin receptor, the tyrosine phosphorylation of both proteins, and the phosphorylation of IRS-1 at serine 632 were evaluated.The results were expressed as mean ± standard error of the mean. Comparisons between groups were performed using two-way analysis of variance and Dunnett's post hoc test. The authors considered a P value of less than 0.05 to be statistically significant.

4. RESULTS

The first finding indicates that obese rats managed glucose less effectively. Baseline glycemia was higher in obese Zucker rats compared to lean rats, 7.0 versus 5.3 mmol/L. After the glucose load, the glycemia of the obese animals remained significantly higher at 15, 30, 60, and 120 minutes. The area under the curve was also greater, with $P < 0.01$, indicating reduced glucose tolerance.In the gastrocnemius muscle of obese rats, the amount of IRS-1 was reduced to approximately 55% of the value observed in lean rats, with $P < 0.01$. In KK-Ay/J mice, the amount of IRS-1 was approximately 65% of that of the controls, also with $P < 0.01$. Conversely, the total amount of the insulin receptor beta subunit was not significantly different between obese and lean rats. In practical terms, the observed defect did not simply concern the number of receptors, but primarily the way the signal was transmitted after receptor activation.In lean rats, insulin increased the tyrosine phosphorylation of the insulin receptor by at least four times. In obese rats, basal receptor phosphorylation was approximately double that of the lean ones, but insulin injection did not significantly increase it further. The authors interpret this data as a receptor response that is already abnormal and poorly reactive to further insulin stimulation.For IRS-1, in lean rats, insulin produced an approximately three-fold increase in tyrosine phosphorylation. In obese rats, the ratio of tyrosine-phosphorylated IRS-1 to total IRS-1 appeared elevated under basal conditions, primarily because the total amount of IRS-1 was decreased. After insulin, however, this ratio was reduced compared to stimulated lean rats and compared to unstimulated obese rats. This is the data most relevant to the book's paragraph: the insulin signal failed to activate IRS-1 in

the way normally observed in lean muscle.Phosphorylation of serine 632 of IRS-1 was three times lower in the muscle of obese rats compared to lean ones, with $P < 0.005$. In lean rats, insulin increased it at least five-fold. In obese rats, the increase after insulin was slight, and the level remained lower than that of stimulated lean rats. This result shows an altered regulation of the Ser632 site in the animal model, but it does not demonstrate that all serine phosphorylations are necessarily inhibitory.

5. INTERPRETATION

The primary biological significance is that, in obese and insulin-resistant muscle, the insulin signal can weaken immediately after the receptor. IRS-1 acts as a molecular platform: when properly activated, it allows for the docking of proteins that propagate the signal toward glucose utilization. If IRS-1 is less abundant or responds poorly to insulin, the entire chain can become less efficient.In the studied model, the documented segment is: insulin insulin receptor IRS-1 tyrosine phosphorylation of IRS-1. The reduced response of IRS-1 to insulin stimulation is consistent with a lower capacity to activate the intracellular pathways that contribute to glucose transport. However, downstream proteins, such as PI3K, AKT, and GLUT4, were not directly measured in this work; their involvement therefore remains a physiologically plausible interpretation, not a direct experimental result of the study.The data regarding serine 632 requires particular caution. The chapter from “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi correctly describes that aberrant phosphorylation can hinder the insulin signal. But “aberrant” does not just mean increased: it can be reduced, excessive, delayed, or located at a site with a different function. The analyzed study observed a reduction in Ser632 phosphorylation, while other studies have observed an increase in other serine sites associated with insulin resistance.

6. INDEPENDENT CONFIRMATORY EVIDENCE

Independent confirmation of the central role of IRS-1 comes from a study on isolated skeletal muscle from people with type 2 diabetes and well-matched controls. In the muscle of participants with type 2 diabetes, IRS-1 phosphorylation, the activity of phosphoinositide 3-kinase or PI3K (an enzyme that receives signals from IRS-1), and glucose transport were reduced following insulin stimulation. Insulin receptor phosphorylation, however, was not altered. This result confirms in humans the step where IRS-1 is not a passive element: its insufficient activation can be accompanied by reduced signal transmission and lower glucose uptake in the muscle [1].A second study cultured myotubes, i.e., differentiated muscle cells, obtained from people with type 2 diabetes and controls. Cells from people with diabetes showed lower tyrosine phosphorylation of IRS-1 after insulin, less association between IRS-1 and PI3K, and lower PI3K activation. The authors also detected more than double the basal phosphorylation at Ser636, which corresponds in humans to the site near Ser632 in rats. This result supports the part of the narrative regarding the possibility that inappropriate modifications of IRS-1 interfere with signal propagation; however, it remains a cellular study, which cannot completely separate the effects of the donors' metabolic history from those intrinsic to the cells [2].Taken together, these independent studies converge on an essential point of the paragraph: IRS-1 functions as a connection node between the insulin receptor and intracellular pathways. When IRS-1 tyrosine activation decreases, PI3K recruitment and the muscle's metabolic response also decrease. The convergence is particularly relevant because it includes both directly examined human muscle and primary human muscle cells [1,2].

7. CONFLICTING EVIDENCE

Conflicting evidence does not negate the role of IRS-1, but rather shows that the regulation of serine and threonine phosphorylation is more complex than a simple distinction between "good" and "bad" sites. In a mass spectrometry study on vastus lateralis muscle biopsies from lean individuals, obese individuals without diabetes, and people with type 2 diabetes, some IRS-1 sites were found to be more phosphorylated in diabetes, while others were less phosphorylated. Furthermore, insulin retained the ability to increase or decrease certain phosphorylations even under conditions of insulin resistance [3].This picture is relevant to the result of the study analyzed regarding Ser632: the decrease of a single serine site in the obese Zucker rat does not automatically contradict studies that observe increases

in other serine sites in humans. The consequences depend on the precise position of the site, the active kinases, the type of muscle, the species, the duration of insulin exposure, and the metabolic context. No directly conflicting evidence sufficiently relevant to the reduction of the specific Ser632 in the gastrocnemius of the Zucker rat has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent research used to evaluate 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, experimental	Obese and lean Zucker rats; additional experiments in KK-Ay/J mice	IRS-1 was reduced and the insulin response of IRS-1 and the insulin receptor was impaired in the obese gastrocnemius.	direct confirmation	moderate
[1]	Ex vivo human experimental study	Isolated skeletal muscle from people with type 2 diabetes and controls	Insulin-induced IRS-1 phosphorylation, PI3K activity, and glucose transport were reduced in type 2 diabetes.	direct confirmation	moderate
[2]	Human cellular	Primary myotubes from people with type 2 diabetes and controls	Reduced IRS-1 tyrosine phosphorylation and PI3K activation; increased basal Ser636 phosphorylation.	indirect confirmation	moderate
[3]	Physiological observational with muscle biopsies	Lean people, obese people without diabetes, and people with type 2 diabetes	IRS-1 phosphorylations increased or decreased depending on the site; some insulin responses were preserved.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study convincingly supports, in the obese Zucker rat model, that IRS-1 represents a vulnerable point in insulin signaling within skeletal muscle. The reduction in the amount of IRS-1 and the decreased insulin response of its tyrosine phosphorylation are consistent with less efficient signal transmission.Independent evidence confirms that in human muscle with type 2 diabetes, reduced IRS-1 activation can be associated with lower activation of intracellular pathways and reduced glucose transport. Conversely, it is necessary to avoid a simplistic interpretation of serine phosphorylations: some are associated with signal inhibition, but their direction and function depend on the specific site studied and the metabolic conditions. The book's narrative is moderately supported and well-defined at

a mechanistic level.

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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