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Insulin stimulates hypoxia-inducible factor 1 through a phosphatidylinositol 3-kinase/mammalian target of rapamycin-dependent signaling pathway - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether insulin can increase the activity of HIF-1, a transcription factor that helps cells modify gene expression in response to environmental conditions. In the retinal epithelial cell model, insulin increased the amount of the HIF-1a subunit, HIF-1 activity, and the expression of VEGF, a protein involved in blood vessel formation. The authors identified PI3K and mTOR as relevant components of the signaling pathway.The research contributes to the sections dedicated to the relationship between insulin, mTOR, and HIF-1a in "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi. The specific point supported is that HIF-1a can integrate metabolic and nutritional signals even when oxygen levels are normal, and that insulin can increase its availability primarily by regulating protein synthesis. Independent studies confirm this link in various cell models, but also show that the mechanism is not identical in all cell types. The confirmation is therefore primarily mechanistic, not a direct demonstration of effects in the human brain or in Alzheimer's disease.

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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.

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2. ANALYZED STUDY

The research question was whether insulin, beyond its well-known role in facilitating the entry and utilization of nutrients, could modify the activity of HIF-1. HIF-1 is a transcription factor, meaning it is a protein that helps determine which genes a cell should activate. Its regulatory component, HIF-1α, is usually rapidly eliminated when oxygen is available; when it increases, it can contribute to the activation of genes involved in glucose metabolism, cellular adaptation, and VEGF production.The hypothesis evaluated was that insulin increases HIF-1α through the PI3K/mTOR pathway. PI3K, phosphoinositide 3-kinase, is an enzyme that transmits signals received by the cell; mTOR, the mammalian target of rapamycin, is a regulator of protein synthesis and cell growth. The precise reason why this publication is relevant to the text "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is that it documents a segment of the chain: insulin PI3K/mTOR increase in HIF-1α greater transcriptional activity of HIF-1.The study can demonstrate an experimental effect of insulin in cultured cells and verify whether this effect depends on specific molecular pathways. However, it cannot demonstrate that the same mechanism occurs in all tissues, in the human brain, in people with Alzheimer's, or during insulin therapy.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract; therefore, any information not explicitly stated in the abstract is not included in the available material. The authors used retinal epithelial cells. The precise origin of the cells, the number of experiments, selection criteria, insulin concentrations, composition of the culture media, and the number of biological replicates are not reported in the available material.The cells were exposed to insulin, and the quantity of the HIF-1α protein, the binding of HIF-1 to DNA, and the activation of a HIF-1-dependent reporter gene were evaluated. A reporter gene is an experimental tool that produces a measurable signal when a specific transcription pathway is active. The authors also compared the HIF-1α mRNA—the molecule containing the instructions for producing the protein—with the quantity of the HIF-1α protein.To explore the mechanism, inhibitors of PI3K, the MAPK (mitogen-activated protein kinase) pathway, and TOR/mTOR were used. An active form of protein kinase B, now more commonly called AKT—a protein that acts downstream of PI3K—was also expressed. Details regarding the individual compounds, doses, statistical analyses, P-values, and the criteria used to interpret the differences are not reported in the available material.

4. RESULTS

In simple terms, insulin increased a protein within the cells that makes HIF-1 more available to activate adaptation genes. Specifically, insulin increased HIF-1α in a dose- and time-dependent manner, with a peak observed within six hours. The increase in HIF-1α was accompanied by a greater ability of HIF-1 to bind to DNA and increased activity of the HIF-1-controlled reporter gene.The most relevant step for the book's section concerns the origin of this increase. The abstract reports that insulin did not appear to increase HIF-1α mRNA transcription. The authors therefore interpreted the result as being primarily consistent with an increase in translation—that is, the production of protein from already available mRNA—rather than increased transcription of the HIF1A gene. This distinction is important: producing more protein and preventing the degradation of existing protein are two different biological mechanisms.Experiments with the active form of AKT and with inhibitors indicated that PI3K was primarily necessary for the insulin-induced increase in HIF-1α, and that TOR/mTOR contributed to a lesser extent. HIF-1 activity and the increase in VEGF expression also depended on PI3K/TOR signaling. Quantitative values for the variations, confidence intervals, or P-values are not reported in the available material; therefore, it is not possible to indicate the numerical magnitude of the effects or the statistical precision of the estimates.

5. INTERPRETATION

The biological significance of the result is that HIF-1α is not regulated exclusively by oxygen scarcity. In this cell model, a nutritional and hormonal signal—insulin—also increased the amount of the protein and the transcriptional activity of HIF-1. This is consistent with the idea that the cell integrates

nutrient availability and environmental conditions before modifying its genetic programs.The segment directly documented by the research is insulin PI3K/AKT and TOR/mTOR increased production of HIF-1α increased activity of HIF-1 and VEGF. The most specific finding is the apparent lack of variation in HIF-1α mRNA, along with the dependence on a protein translation pathway. This observation supports the hypothesis of post-transcriptional control, that is, occurring after the production of mRNA.The result does not prove that insulin stabilizes HIF-1α in every context. Nor does it prove that mTOR always acts with the same relative weight compared to PI3K, AKT, or other pathways. The book correctly describes a broader framework, provided that one distinguishes what was directly observed in retinal cells from what derives from the convergence of studies conducted in other cell types and from more general pathophysiological interpretations.

6. INDEPENDENT SUPPORTING EVIDENCE

Initial independent confirmation concerns the fact that insulin can activate genetic programs typically associated with HIF-1 even in the absence of hypoxia. Zelzer and colleagues studied various cell models and observed that insulin and insulin-like growth factor 1 increased the formation of the HIF-1a/ARNT complex, where ARNT is the partner subunit necessary for HIF-1 to act on DNA. In cells with defective ARNT, both basal and insulin-induced expression of GLUT1, GLUT3, glycolysis enzymes, and VEGF decreased. This study confirms the narrative that HIF-1 can link insulin signaling to the regulation of metabolic and vascular genes; however, it does not fully define the role of mTOR [1].A verification closer to the mechanism of the original study was obtained by Doronzo and colleagues in human and rat aortic smooth muscle cells maintained in normoxia, i.e., with normal oxygen availability. Insulin increased HIF-1a in the cytoplasm and nucleus and enhanced the binding of HIF-1 to the DNA region that regulates VEGF. The effect was reduced by the protein synthesis inhibitor cycloheximide, by PI3K inhibition, and by rapamycin, which inhibits mTOR. In cells from insulin-resistant obese Zucker rats, the insulin-induced increase was reduced. This reinforces the idea that HIF-1a availability may depend on protein synthesis and multiple branches of insulin signaling; it remains an experiment on cultured cells, not a clinical demonstration [2].Hudson and colleagues examined the relationship between mTOR and HIF-1 in PC-3 prostate carcinoma cells subjected to hypoxia or cobalt chloride, a substance that simulates some aspects of hypoxic signaling. Rapamycin reduced HIF-1a accumulation and HIF-1-dependent transcription, while the experimental increase of mTOR amplified the response. The study does not concern insulin, but it confirms a necessary step in the chain described in the book: mTOR can act upstream of HIF-1a and its transcriptional function. Since the model is tumor-based and the stimulus is hypoxic or pseudo-hypoxic, it represents an indirect mechanistic confirmation, not a complete replication of the original study [3].

7. CONFLICTING EVIDENCE

A study by Yim and colleagues demonstrates why this chain should not be considered universal. In 3T3 and HeLa cells, the authors observed that insulin and hypoxia could increase certain common target genes through regulatory elements dependent on ARNT and PI3K. However, in their model, insulin did not stabilize HIF-1α and did not prevent the hydroxylation of the protein, a process that normally promotes its degradation in the presence of oxygen. The authors therefore proposed that insulin might use ARNT partners other than HIF-1α [4].This result does not invalidate the observation of the analyzed study, which had indicated an increase in HIF-1α synthesis rather than protein stabilization. However, it shows that the activation of genes common to both insulin and hypoxia can depend on the cell type, culture medium, metabolic state, and the experimental tools used. Consequently, the concept of HIF-1α as an integrator of metabolic signals is biologically consistent, but the molecular detail is not identical in every model.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent evidence used to evaluate the same biological narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Experimental cellular	Retinal epithelial cells	Insulin increases HIF-1a, HIF-1 activity, and VEGF; PI3K and TOR/mTOR contribute to the phenomenon.	direct confirmation	moderate
[1]	Experimental cellular	Various cell types with experimental ARNT alteration	Insulin induces HIF-1a/ARNT activity; defective ARNT reduces insulin-induced GLUT1, GLUT3, and VEGF.	direct confirmation	moderate
[2]	Experimental cellular	Human and rat aortic smooth muscle cells	Insulin increases HIF-1a and activity on the VEGF promoter; protein synthesis, PI3K, and mTOR contribute to the effect.	direct confirmation	moderate
[3]	Experimental cellular	PC-3 prostate carcinoma cells	mTOR inhibition reduces HIF-1a and HIF-1-dependent transcription during hypoxia or pseudo-hypoxic stimulation.	indirect confirmation	moderate
[4]	Experimental cellular	3T3 and HeLa cells	Insulin induces genes shared with hypoxia but does not stabilize HIF-1a in the studied model.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study directly supports a specific part of the narrative: in retinal epithelial cells, insulin can increase HIF-1a and HIF-1 activity through signaling that depends primarily on PI3K and, in part, on mTOR. This finding is consistent with the idea that HIF-1a integrates oxygen and metabolic signals.Independent evidence confirms that insulin signaling can activate transcriptional programs linked to HIF-1 and that mTOR can regulate the availability or activity of HIF-1a. However, this relationship is primarily supported at the cellular level and depends on the cell type and the stimulus. It has not been proven that this mechanism directly explains brain alterations in Alzheimer's disease, nor that it has a uniform clinical significance in humans.

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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