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ORIGINAL RESEARCH

Insulin resistance induced by hyperinsulinemia coincides with a persistent alteration of the tyrosine kinase domain of the insulin receptor - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether prolonged exposure to insulin can reduce the insulin receptor's ability to respond to new stimulation. In rat liver cells and hamster ovary cells modified to express the human receptor, continuous exposure to the hormone reduced receptor autophosphorylation, which is the initial internal signal that allows the cell to respond to insulin. This reduction was not explained by a lower overall amount of receptor or its disappearance from the cell membrane.The research contributes to the section of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi dedicated to the idea that prolonged hyperinsulinemia may promote progressive insulin desensitization. Independent evidence in humans, muscle cells, and cellular models confirms that persistent excess insulin can attenuate the insulin response and modify initial components of the signaling pathway. However, the specific "molecular memory" of the receptor described in the original study has not been directly demonstrated in humans, and responses remain dependent on the tissue and the signal considered.

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2. ANALYZED STUDY

The research question was whether prolonged exposure to high concentrations of insulin could make the insulin receptor less capable of responding to subsequent exposure to the hormone. The insulin receptor is a protein located on the cell surface: when it binds to insulin, it activates a sequence of signals that contributes, among other things, to the entry and utilization of glucose.The hypothesis evaluated was that chronic hyperinsulinemia could induce a form of refractory state, i.e., a weakened response to new stimulation, by acting directly on the receptor or in its immediate molecular environment. This is the reason for its relevance to section 3.5 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi: the publication examines the initial segment of the chain proposed in the book, namely prolonged exposure to insulin reduced receptor activation reduced ability to transmit the signal.The study can demonstrate an experimental effect in cell cultures, under the conditions and at the concentrations used by the authors. However, it cannot establish that the same structural alteration occurs in human muscle, liver, or adipose tissue, nor can it quantify its contribution to the onset of diabetes in the body.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors primarily used rat hepatoma cells modified to express the human insulin receptor and Chinese hamster ovary cells. The cells were serum-starved for four hours and then exposed to recombinant insulin at different times and concentrations. The main concentrations were 5 nM, 17 nM, and 170 nM; nM stands for nanomolar, a unit expressing a very low concentration of a substance.Receptor activation was measured by assessing its phosphorylation, which is the addition of phosphate groups that acts as an activation signal. The authors used western blotting and ELISA (a laboratory test based on the recognition of proteins by antibodies). They specifically analyzed the tyrosine sites Y972 and Y1162/1163 of the receptor, which are important for initiating the signaling cascade.To verify whether the receptor moved from the membrane into the cell, fluorescence microscopy was used on cells with the receptor tagged with YFP, a fluorescent protein. To explore possible changes near the tyrosine kinase domain, the part of the receptor that transfers signals through chemical reactions, FRET (a technique that measures the relative proximity between two fluorescent markers and can signal a conformational or molecular environment change) was employed.Data were reported as mean ± standard deviation. Comparisons were performed using one-way analysis of variance and Tukey's post-hoc test; the authors considered a P-value of less than 0.05 to be statistically significant. No inclusion or exclusion criteria are reported, as this is not a study involving human participants.

4. RESULTS

Under short-term stimulation conditions, insulin rapidly increased receptor autophosphorylation at all concentrations examined. After longer exposures, phosphorylation at the Y972 and Y1162/1163 sites decreased compared to the initial peak, with differences reported as statistically significant. In simple terms, the receptor initially activated, but during prolonged contact with the hormone, it lost some of its ability to maintain that activation.The total amount of receptor did not change in the western blots. Furthermore, in fluorescently labeled cells, the amount of receptor localized to the membrane was not reduced after prolonged exposure to 17 nM of insulin. This data indicates that, in this model, the reduction in signal was not primarily explained by the loss of the receptor from the cell surface.After 120 minutes of exposure to 17 or 170 nM of insulin, a ten-minute wash rapidly reduced residual phosphorylation. However, a second short stimulation returned Y972 and Y1162/1163 only to the reduced level typical of the refractory state, rather than reproducing the intense response observed during the first short stimulation. This phenomenon did not appear after an initial exposure of only two minutes.FRET did not change after ten minutes of insulin, but it increased after 120 minutes. Since an increase in FRET signals that the fluorescent markers have changed their relative proximity, the result is consistent with a change in the conformation of the tyrosine kinase domain or in the environment of the proteins near it. After a short wash, this FRET alteration persisted; after 180 minutes of washing, it returned to baseline levels, but was rapidly

re-established with a new exposure to insulin.Downstream pathways did not all respond in the same way. Phosphorylation of ERK, a protein linked to growth signals and cellular response, was intense and transient, then decreased rapidly. In contrast, phosphorylation of AKT and GSK3 did not decrease within 120 minutes. This shows that desensitization was not uniform across all measured intracellular pathways.

5. INTERPRETATION

The most immediate biological significance is that continuous insulin stimulation can make the receptor's initial response to a new exposure to the hormone less prompt. The result most relevant to the book is not the demonstration of systemic insulin resistance, but the cellular segment showing that persistent excess insulin can weaken the autophosphorylation of its own receptor without necessarily requiring a reduction in the number of receptors on the membrane.The publication suggests a possible molecular memory of chronic exposure: after washing, some measurements returned toward baseline, but the reduced response reappeared immediately upon new stimulation. FRET makes a change in the tyrosine kinase domain or its interactions biologically plausible. However, FRET does not identify which molecular modification is responsible, nor does it prove that the detected change is the direct cause of the refractory state.The experimental model has an important limitation: it uses genetically modified cell lines and insulin concentrations that do not fully replicate the natural alternation of human insulin secretion. Furthermore, the absence of receptor reduction on the membrane observed here does not contradict studies that, in other tissues or after longer exposures, have detected a decrease in receptor expression. Rather, it indicates that the mechanisms of desensitization can vary depending on the context.

6. INDEPENDENT SUPPORTING EVIDENCE

The evidence most closely supporting the book's general narrative comes from a controlled clinical study of 15 healthy young adults. Physiological hyperinsulinemia maintained for 72–96 hours, with normal or slightly elevated glycemia, reduced insulin sensitivity. The defect primarily concerned the non-oxidative use of glucose—that is, its transformation and storage as glycogen—while the suppression of hepatic glucose production remained intact. This result supports the idea in humans that prolonged hyperinsulinemia may directly contribute to peripheral insulin resistance; however, it does not identify a molecular memory of the receptor [1].A second study cultured human myoblasts for three weeks with elevated insulin. After subsequent brief stimulation, cells chronically exposed to insulin showed no further increase in the phosphorylation of the receptor, IRS-1, PI3K, and AKT, nor in glucose transport, whereas these signals increased in control cells. IRS-1 is a protein that transmits the signal from the receptor; PI3K and AKT participate in subsequent steps. The research therefore confirms, in human muscle-derived cells, an attenuated response to new insulin exposure, consistent with the refractory state observed in the original study [2].An independent transcriptomic analysis integrated three datasets of human skeletal muscle totaling 488 samples and an experimental model of murine myotubes. In human samples, higher fasting insulin levels were associated with lower expression of INSR, the insulin receptor gene. In myotubes exposed to insulin for 16 hours, Insr RNA, total protein, and surface receptor protein decreased; after acute stimulation, AKT and ERK signals and glucose uptake were also attenuated. The study expands on the book's chain of evidence by showing that, in other models, hyperinsulinemia can decrease not only the functionality but also the availability of the receptor [3].

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance has been identified regarding the possibility that prolonged insulin exposure induces a reduced insulin response. However, there are findings that require caution in describing the phenomenon as a uniform loss of all insulin signaling.In adipocytes chronically exposed to insulin, GLUT4-dependent glucose transport was reduced, while the nuclear exclusion of FoxO1, a regulator of gene expression, remained largely preserved. The authors defined this scenario as selective insulin resistance: some cell functions become less responsive, while others remain sensitive because they require different levels of PI3K/AKT signaling. The result does not refute the

desensitization described in the book, but shows that its extent depends on the tissue and the specific branch of the cascade being analyzed [4].

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent research used to confirm or contextualize the passage in the book.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Experimental cellular	Rat hepatoma cells and hamster ovary cells with human insulin receptor	Prolonged insulin exposure reduced receptor reactivation without necessarily reducing its total or membrane presence.	direct confirmation	preliminary
[1]	Experimental clinical study	15 healthy young adults subjected to 72–96 hours of hyperinsulinemia	Prolonged physiological hyperinsulinemia reduced insulin sensitivity and non-oxidative glycogen synthesis.	indirect confirmation	moderate
[2]	Cellular	Human myoblasts cultured for three weeks with high insulin	After restimulation, the response of IR, IRS-1, PI3K, AKT, and glucose transport decreased.	indirect confirmation	moderate
[3]	Observational and cellular	488 human muscle samples and murine myotubes	High insulin was associated with lower human INSR; chronic insulin reduced the receptor and acute response in myotubes.	biologically consistent evidence	moderate
[4]	Cellular	Adipocytes in a chronic hyperinsulinemia model	GLUT4 was less responsive, while nuclear exclusion of FoxO1 remained largely preserved.	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study supports the idea at a cellular level that prolonged exposure to insulin can reduce subsequent insulin receptor activation without necessarily causing a loss of the receptor from the membrane. This observation is consistent with the book's narrative regarding a possible feedback loop between hyperinsulinemia and insulin resistance.Independent evidence moderately confirms that persistent excess insulin can attenuate the insulin response in peripheral tissues and muscle cells. However, the hypothesis that a specific conformational change in the receptor constitutes a stable and clinically relevant molecular memory in humans remains preliminary. The response appears to be dependent on the cell type, the duration of exposure, and the specific signaling pathway studied.

Aggiornato al 17/11/2026. 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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