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Hyperinsulinemia and insulin receptor alterations in the cerebral endothelium

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1. ABSTRACT

The original study evaluated whether hyperinsulinemia, i.e., a persistent elevation of insulin, alters the behavior of the insulin receptor in the cells lining the small blood vessels of the brain. In hippocampal microvessels of mice fed a high-fat diet and in cultured murine and human cerebral endothelial cells, exposure to elevated insulin increased the total or membrane amount of the receptor, but reduced its autophosphorylation, the activation of the AKT protein, and internalization following insulin stimulation. The PTP1B inhibitor improved these signals in murine cells.The research contributes to the passage from "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, dedicated to the possibility that hyperinsulinemia modifies the function of the cerebral endothelial receptor and, potentially, the entry of insulin into the brain. Independent studies show that a high-fat diet and obesity can reduce insulin uptake or transport across the blood-brain barrier in animals. However, it remains controversial whether the insulin receptor is always essential for the passage of the hormone through this barrier. Overall, the confirmation is primarily mechanistic and preclinical.

ONLINE ARTICLE

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2. ANALYZED STUDY

The research question was whether hyperinsulinemia could modify how cerebral microvascular endothelial cells expose, activate, and internalize the insulin receptor. The hypothesis was that prolonged exposure to the hormone would reduce the efficiency of insulin signaling and receptor internalization, partly through the action of PTP1B (protein tyrosine phosphatase 1B, an enzyme that can remove phosphate groups and turn off cellular signals).This question is relevant to section 3.5 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi. The book describes a case in which the total number of receptors may increase while their function decreases: a larger portion remains on the cell membrane, but autophosphorylation and internalization are reduced. The analyzed study directly documents this cellular segment of the narrative. However, it cannot, on its own, prove that such alterations reduce insulin transport in the living brain or cause cerebral insulin resistance in humans.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors used three experimental models. The first included three cohorts of five male C57BL/6 mice per group, fed for six weeks with either a standard diet (10% of calories from fat) or a high-fat diet (54% of calories from fat). Hippocampal microvessels were isolated after four hours of Fasting, pooling tissue from five animals per sample. The microvessels were then exposed ex vivo to insulin or saline solution for 15 minutes.The second and third models were cell cultures: primary mouse brain microvascular endothelial cells and an immortalized human brain microvascular endothelial cell line. Experimental hyperinsulinemia was induced for 12 hours with 20 nM of insulin in murine cells and 5 nM in human cells. After this phase, the cells were acutely stimulated with insulin. In some experiments, the murine cells received Claramine, 10 µM for 30 minutes, a compound used as a selective PTP1B inhibitor.Proteins were measured using western blotting (a technique that allows for the comparison of the quantity and activation state of specific proteins). The insulin receptor, its phosphorylation on tyrosines 1150/1151, IRS-1 phosphorylated on serine, and AKT phosphorylated on serine 473 were analyzed. Phosphorylation is the addition of a small chemical group that, in this context, helps transmit the insulin signal. Receptor internalization was evaluated by labeling receptors exposed on the surface with biotin and subsequently distinguishing the portion remaining on the membrane from that which had entered the cell. The IR-A and IR-B RNA variants were analyzed using quantitative PCR. Data were evaluated primarily using t-tests, analysis of variance, and multiple comparisons; the significance threshold was P less than 0.05.

4. RESULTS

In the hippocampal microvessels of mice fed a high-fat diet, the total amount of insulin receptor was 117% ± 37% higher than in standard-diet controls (P = 0.0333). However, after insulin stimulation, AKT activation was lower: the authors quantified a 132% ± 34% decrease in the pAKT/AKT ratio compared to stimulated control microvessels (P = 0.0176). In simple terms, there were more receptors present, but the signal transmitted after the arrival of insulin was weaker.In murine brain endothelial cells exposed to high insulin for 12 hours, the total receptor increased by 263% ± 78% (P = 0.0028) and serine phosphorylation of IRS-1 increased by 281% ± 92% (P = 0.0067). Serine phosphorylation of IRS-1 is commonly associated with reduced efficiency of the insulin cascade. In immortalized human cells, the total receptor increased by 288% ± 135% (P = 0.0491) and IRS-1 phosphorylation increased by 171% ± 49% (P = 0.0044). These experiments show that high insulin was sufficient to induce similar alterations in two cell models, but they do not equate to a demonstration in humans.In the mouse model, hyperinsulinemia reduced the RNA of the IR-A variant by 89% ± 36% and reduced the ratio of IR-A to the total of the two variants by 19% ± 7%. No significant difference was observed for IR-B. After insulin stimulation, cells conditioned by hyperinsulinemia did not show clear receptor internalization at the times examined, whereas control cells internalized a significant portion at 15 and 30 minutes.The portion of receptor localized on the membrane was 384% ± 162% higher in cells with hyperinsulinemia (P = 0.0352). Despite this greater presence on the surface, after insulin stimulation, receptor phosphorylation decreased by 117% ± 29% (P =

0.0011) and AKT phosphorylation decreased by 106% ± 48% (P = 0.0492), according to the authors' normalized quantifications. The biological significance is consistent with receptors that are more numerous but less capable of initiating their signal and entering the cell.With Claramine, in hyperinsulinemic murine cells, PTP1B levels decreased by 22% ± 6% (P = 0.0092). In parallel, receptor phosphorylation increased by 35% ± 14% (P = 0.0452) and AKT phosphorylation increased by 103% ± 46% (P = 0.0329). Internalization increased compared to untreated hyperinsulinemic cells. This result supports the hypothesis that PTP1B contributes to the reduced signaling observed in the model, but it does not prove that PTP1B inhibition is effective or safe in the human brain.

5. INTERPRETATION

The central finding is apparently counterintuitive but biologically plausible: having more insulin receptors does not necessarily mean responding better to insulin. A receptor must, in fact, be in the appropriate location, bind the hormone, autophosphorylate, and activate internal proteins to correctly transmit the message. In the study analyzed, hyperinsulinemia increased the amount of receptor exposed on the membrane but reduced both autophosphorylation and the signal to AKT, a protein involved in the metabolic and vascular response to insulin.The segment of the chain directly documented is: chronic exposure to high insulin reduced phosphorylation of the receptor and of AKT reduced receptor internalization in cerebral endothelial cells. The data also suggest a contribution from the IR-A variant and PTP1B. However, the relationship between these changes and the complete passage of insulin from circulation to brain tissue remains a reasonable interpretation, not a direct measurement from the study.The main limitation is that the more detailed functional results are derived from cell cultures and small experimental groups. Furthermore, the microvessels isolated from mice also contain components other than the endothelium, such as pericytes and astrocyte end-feet. The high-fat diet model associates hyperinsulinemia with other metabolic changes; therefore, it does not allow for attributing all the observed alterations exclusively to high insulin. Cellular experiments better isolate the role of insulin, but they do not reproduce the entire blood-brain barrier in a living organism.

6. INDEPENDENT SUPPORTING EVIDENCE

Particularly relevant confirmation comes from an independent experiment on isolated rat brain endothelial cells and an in vitro blood-brain barrier model. Gray and colleagues observed that, at physiological concentrations, the insulin receptor facilitates the hormone's entry into brain endothelial cells through a vesicular process. In rats fed a high-fat diet for four weeks, insulin uptake by isolated endothelial cells decreased, without a measurable reduction in the quantity of the receptor. This finding directly confirms the central idea of the book's paragraph: a diet associated with obesity and insulin resistance can impair endothelial function and insulin uptake without necessarily requiring a numerical decrease in receptors [1]. The limitation is that cellular uptake does not automatically coincide with complete transport into the brain.A second animal study examined the downstream result of the chain: the amount of insulin reaching the cerebrospinal fluid after peripheral administration. In male rats with obesity induced by 22 weeks of a high-fat diet, insulin in the cerebrospinal fluid did not increase after the peripheral bolus, unlike in lean controls. Switching from a high-fat diet to a low-fat diet for eight weeks restored the increase of insulin in the cerebrospinal fluid and the behavioral response to centrally administered insulin [2]. The study therefore confirms the direction of the narrative, i.e., a reduction in insulin access to the central nervous system in obesity, but it does not identify the single molecular defect described in the original study.The involvement of PTP1B in receptor regulation is also supported by independent cellular work. In CHO cells expressing the insulin receptor, selective inhibition of PTP1B or its silencing with small interfering RNAs increased, in a dose-dependent manner, receptor phosphorylation and its persistence in the endocytic recycling compartment, which is the cellular site where internalized receptors can be reused or returned to the surface [3]. This evidence is consistent with the recovery of phosphorylation and internalization observed with Claramine in the original study. However, it is a general mechanistic confirmation, obtained in a non-brain cell line and not in a living organism.

7. CONFLICTING EVIDENCE

There is directly relevant evidence that limits the interpretation that insulin receptor-mediated internalization is necessarily the mandatory step for the hormone's transport across the blood-brain barrier. In mice with endothelial insulin receptor reduction and in mice treated with the S961 antagonist, Rhea and colleagues observed a decrease in insulin binding to the cerebral endothelium, but not a significant reduction in the rate of insulin transport from the blood to the brain [4].This result does not contradict the cellular observations of the analyzed study regarding reduced receptor autophosphorylation and internalization. However, it reduces the certainty of the subsequent step proposed in the book: the receptor defect could contribute to endothelial dysfunction and cerebral insulin resistance, but it does not, by itself, prove a reduction in net insulin transport into the brain. The authors of the conflicting study also point out that the endothelial deletion of the receptor might not be complete; nevertheless, the parallel use of the pharmacological antagonist reinforces the need for caution.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the cellular evidence of the original study from independent confirmations and the main evidence that limits the hypothesis regarding transport across the blood-brain barrier.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal and cellular	Mouse hippocampal microvessels; murine and human brain endothelial cells	Hyperinsulinemia increases membrane receptors but reduces autophosphorylation, AKT, and internalization; Claramine improves cellular signaling.	direct confirmation	moderate
[1]	Animal and cellular	Rats on a high-fat diet; isolated brain endothelial cells and co-culture with astrocytes	High-fat diet reduces endothelial insulin uptake; the receptor facilitates uptake under physiological conditions.	direct confirmation	moderate
[2]	Animal	Male Long-Evans rats with diet-induced obesity	In obesity, peripheral insulin does not increase in the cerebrospinal fluid; returning to a low-fat diet restores the response.	indirect confirmation	moderate
[3]	Cellular	CHO cells expressing the insulin receptor	Inhibition or silencing of PTP1B increases phosphorylation and intracellular retention of the receptor.	biologically consistent evidence	preliminary

[4]	Animal	Mice with endothelial insulin receptor reduction or pharmacological antagonism	Loss or inhibition of the receptor reduces endothelial binding but not overall insulin transport across the barrier.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study clearly supports the idea that experimental hyperinsulinemia can alter the insulin receptor in cerebral microvascular endothelial cells. The increased presence of the receptor on the membrane did not correspond to more efficient signaling: autophosphorylation, AKT activation, and internalization were found to be reduced. Independent evidence confirms that obesity and a high-fat diet can impair insulin uptake or access to the central nervous system in animals.The most robust part of the narrative therefore concerns the molecular and cellular desensitization of the cerebral endothelium. The possible effect on insulin transport across the blood-brain barrier is biologically plausible and moderately supported at the preclinical level, but requires validation because animal studies indicate that transport can persist even when the endothelial insulin receptor is inactivated. There is insufficient evidence to translate this mechanism into a clinical conclusion 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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