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Calcium signaling in insulin action on striated muscle - A review of the evidence

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1. ABSTRACT

The analyzed publication is a narrative review examining how insulin modifies calcium signals in skeletal and cardiac muscle cells. The central point is that the hormone does not act solely through the classic PI3K/AKT metabolic pathway, but can also mobilize calcium from different sources: a rapid signal associated with the ryanodine receptor and a slower signal associated with the IP3 receptor.In section 5.4.2 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the narrative that insulin activates convergent intracellular calcium mobilization circuits. Available experimental evidence confirms that insulin can increase calcium near the membrane in muscle fibers and that calcium can contribute to the late stages of glucose uptake. Cellular studies also support a link between NADPH oxidase, reactive oxygen species, and IP3-mediated calcium release. However, these results are primarily derived from animal and cellular models; they do not directly demonstrate in humans the entire chain proposed in the book leading up to the activation of cPLA2a.

ONLINE ARTICLE

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MISSION

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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 question addressed by the publication is whether, in striated muscle cells, insulin also utilizes calcium signals in addition to the better-known metabolic cascade that promotes glucose uptake. The hypothesis discussed is that intracellular calcium—that is, the calcium present inside the cell—participates in the translocation of the GLUT4 transporter to the cell surface. GLUT4 is the protein that allows glucose to enter, primarily in muscle cells.The relevance to section 5.4.2 is specific. "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi cites this publication to argue that insulin can activate a dual convergent circuit of calcium mobilization. The review describes a rapid release of calcium associated with the ryanodine receptor, or RyR, and a relatively slower release through the inositol 1,4,5-trisphosphate receptor, or IP3R. The segment effectively supported is therefore: insulin activation of intracellular calcium channels increase in cytoplasmic calcium.As a narrative review, the publication synthesizes previous experimental results and does not constitute a new clinical or animal trial. It can therefore describe a plausible integration of mechanistic evidence, but it does not by itself prove that every step occurs simultaneously in the human body, nor that the insulin-induced increase in calcium directly determines the activation of cytosolic phospholipase A2 alpha, or cPLA2a.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The only material available is the abstract. From this, it appears that the article is a review dedicated to calcium signaling in the action of insulin on skeletal and cardiac muscle. The authors discuss studies that have examined the movement of GLUT4, the release of calcium from the sarcoplasmic-endoplasmic reticulum, the production of reactive oxygen species, and the involvement of RyR and IP3R receptors.The available material does not report a bibliographic search strategy, study selection criteria, number of included publications, preregistered protocol, systematic risk of bias assessment, or meta-analysis. Furthermore, no samples, sample sizes, dosages, duration of observation, quantitative endpoints, or original statistical analyses are reported, because the article does not present a single original experiment but rather a narrative synthesis of the literature.This characteristic is important for the reader: the review is useful for understanding how different results can be linked, but the strength of individual points must be verified by returning to the experimental studies that produced the data.

4. RESULTS

According to the abstract, insulin promotes glucose entry into muscle cells by stimulating the translocation of GLUT4, which is the movement of this transporter from internal compartments to the cell surface. Alongside the canonical pathway based on phosphorylation reactions, the review describes two modes of calcium mobilization.The first is rapid and involves skeletal muscle. Insulin is described as being capable of activating NADPH oxidase 2, or NOX2, an enzyme that produces low amounts of reactive oxygen species. These redox signals can modify the RyR through S-glutathionylation, a reversible chemical modification of certain components of the protein, promoting the release of calcium into the cytoplasm.The second mode is relatively slower. In skeletal muscle and cardiac cells, insulin is described as being capable of activating IP3R, a channel located in intracellular calcium stores. The calcium released through IP3R is indicated as necessary, in the models discussed, for a portion of GLUT4 translocation and the increase in glucose uptake. Furthermore, in skeletal muscle, the calcium released by IP3R can promote calcium entry into the mitochondria, the cellular structures that contribute to energy production.The abstract does not report quantitative values, experimental sample sizes, P-values, or confidence intervals related to the studies included in the review. Therefore, it does not allow for a precise estimation of the average magnitude of the calcium increase, nor for a quantitative comparison of the two described circuits.

5. INTERPRETATION

In simple terms, the publication suggests that insulin does not send just one message to the muscle. In addition to promoting the activation of PI3K and AKT, which are central proteins in the metabolic response to insulin, the hormone can generate small, localized calcium signals. These signals could contribute to the

steps by which GLUT4 reaches the cell membrane and glucose enters the muscle fiber.The connection to the book lies in the fact that calcium can act as a second intracellular signal. The text "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi places this increase in calcium within the chain that makes cPLA2a fully activatable, alongside phosphorylation mediated by MAPK/ERK. The reviewed study supports the initial segment of the chain—that is, the insulin-induced increase in calcium—and specifically the idea of multiple convergent pathways for calcium mobilization.However, it does not prove that RyR and IP3R always act with the same weight in every type of muscle, in every metabolic condition, or in humans. Furthermore, the presence of a calcium signal does not automatically equate to the activation of cPLA2a: to establish this latter connection, experiments would be needed that measure insulin, calcium, cPLA2a activation, and arachidonic acid mobilization in the same preparation.

6. INDEPENDENT SUPPORTING EVIDENCE

Initial confirmation concerns the existence of an insulin-induced calcium signal in muscle fibers. In isolated mouse skeletal muscle fibers, Bruton and colleagues observed that insulin increased calcium near the cell membrane by approximately 70%, without increasing global calcium throughout the entire fiber. The response decreased in a low-calcium environment and with the use of L-type calcium channel blockers. This result directly confirms the part of the narrative suggesting that insulin can rapidly mobilize calcium in a specific cellular compartment; however, it does not prove the involvement of all the channels described in the review, nor does it demonstrate an effect in humans [1].A second study, conducted on single muscle fibers and isolated muscles from normal and ob/ob mice, linked the direction of the calcium signal to the metabolic response to insulin. Maneuvers that reduced calcium influx also reduced insulin-induced 2-deoxyglucose uptake; conversely, those that increased calcium influx were associated with greater insulin-stimulated glucose uptake. The interventions did not modify the insulin-induced activation of AKT or ERK1/2, suggesting an action at a different or later stage of the response. This provides functional support for the role of calcium, but the pharmacological tools do not definitively identify a single channel, and the model remains an animal one [2].Regarding the redox branch of the chain, a study on cultured rat myotubes found that insulin increased the production of reactive oxygen species and that the inhibition of NADPH oxidase or the reduction of p47phox, its regulatory subunit, reduced this signal. Inhibitors of NADPH oxidase, PI3K, and the IP3/IP3R system also reduced the increase in calcium caused by insulin. The work therefore supports, at the cellular level, the pathway: insulin NADPH oxidase/reactive oxygen species IP3R calcium increase. The main limitation is that the experiments were performed in cultured cells and do not directly demonstrate the contribution of this axis in intact human muscle [3].Taken together, these studies support a coherent network: insulin can increase calcium in specific cellular locations; the alteration of the calcium signal can modify glucose uptake; and in myotubes, a mechanism dependent on NADPH oxidase and IP3R contributes to the increase in calcium. However, the network does not prove that such a signal is universally indispensable for all insulin action.

7. CONFLICTING EVIDENCE

There are findings that require caution when interpreting calcium as an obligatory mediator of insulin action. In cultured L6 muscle cells, Klip and colleagues observed that insulin increased the uptake of 2-deoxy-D-glucose even in the absence of external calcium. Artificially increasing intracellular calcium with the ionophore A23187 did not increase hexose uptake, while chelation of intracellular calcium did not reduce the response to insulin under the experimental conditions tested. The authors concluded that, in that cell model, calcium did not appear to play the general role proposed for mediating the increase in glucose transport [4].This finding does not eliminate the correspondence between the analyzed review and the book's paragraph. Rather, it indicates that the contribution of calcium depends on the model, the site of the signal, the duration of the stimulus, and the specific phase of insulin action being examined. A local and transient increase near the membrane may not be detected by global calcium measurements; conversely, an intense and diffuse increase in calcium obtained artificially does not

necessarily reproduce the physiological signal. No directly conflicting evidence sufficiently relevant to the specific RyR-IP3R dual circuit described by the review 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 experimental research used to confirm or define the narrative of the book's chapter.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature on skeletal and cardiac muscle	Describes two insulin-mediated calcium mobilization circuits, associated with RyR and IP3R, integrated with metabolic signaling.	biologically consistent evidence	preliminary
[1]	Animal, isolated muscle fibers	Mouse skeletal muscle fibers	Insulin increases calcium near the membrane by approximately 70%, without increasing global fiber calcium.	direct confirmation	moderate
[2]	Animal, ex vivo	Isolated fibers and muscles from normal and ob/ob mice	Reducing calcium influx reduces insulin-induced glucose uptake; increasing it is associated with greater glucose uptake.	indirect confirmation	moderate
[3]	Cellular	Cultured rat skeletal myotubes	Inhibition of NADPH oxidase, PI3K, or IP3/IP3R reduces the insulin-induced increase in calcium.	direct confirmation	moderate
[4]	Cellular	Cultured L6 muscle cells	Insulin stimulates hexose transport even without external calcium; modifying calcium neither reproduces nor blocks the response under the tested conditions.	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The reviewed analysis consistently supports the idea that insulin can generate calcium signals in striated muscle through multiple pathways, including components associated with RyR, IP3R, and redox signals. Subsequent or parallel experimental studies confirm that calcium can increase near the muscle membrane and contribute to the metabolic response to insulin. The narrative is therefore supported at a mechanistic level.The strength of the inference decreases when the chain is extended to cPLA2a and arachidonic acid mobilization. The evaluated data do not directly demonstrate, in the same model and especially in humans, that insulin-mobilized calcium activates cPLA2a sufficiently to produce the pathophysiological consequence described in the chapter. This step requires further integrated validation.

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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