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Dexamethasone represses signaling through the mammalian target of rapamycin in muscle cells by increasing REDD1 expression - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether dexamethasone, a synthetic glucocorticoid, reduces mTOR signaling—a cellular pathway that promotes protein synthesis and growth—by increasing REDD1. In the experiments available in the abstract, the treatment increased REDD1 in rat skeletal muscle and in L6 myoblasts, which are muscle precursor cells cultured in the laboratory. In parallel, downstream mTOR signals associated with protein synthesis decreased.The research contributes to sections 4.17, 21.8, and 22.3 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, supporting the segment of the narrative in which glucocorticoids induce REDD1 and, through this mediator, reduce the anabolic activity of mTOR. Independent studies confirm the inhibitory role of REDD1 on mTOR, the relevance of the gene in muscle exposed to dexamethasone, and an analogous mechanism in lymphocytes. The evidence remains primarily cellular and animal-based; it does not allow for the demonstration that chronic stress or loneliness produce the same metabolic outcome in humans.

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2. ANALYZED STUDY

The research question was whether REDD1, a protein induced by cellular stress, is the mediator through which dexamethasone shuts down part of the mTOR pathway in muscle cells. mTOR functions as an integration system: when nutrients and growth signals are adequate, it promotes protein production; when stress signals prevail, its activity can decrease.The relevance to the book's sections is precise. The publication examines the pathway synthetic glucocorticoid increase in REDD1 reduction in mTOR signaling fewer signals compatible with protein synthesis. It does not directly evaluate endogenous cortisol during chronic stress, insulin resistance in humans, loneliness, or long-term clinical outcomes. Instead, it documents an experimental mechanism in muscle models.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract. The study used two models: rat skeletal muscle treated acutely in vivo and laboratory-cultured L6 myoblasts. Myoblasts are immature muscle cells, useful for observing cellular mechanisms under controlled conditions.The authors measured the expression of REDD1 and REDD2, a related protein, and evaluated mTOR signaling by observing the phosphorylation of S6K1 and 4E-BP1. Phosphorylation is a chemical modification that can indicate whether a signaling protein is active. They also reduced REDD1 using RNA interference, a technique that selectively decreases the amount of RNA from the target gene, and experimentally increased Rheb, an activator located upstream of mTOR.The number of animals and cultures, the exact dose and duration of dexamethasone, selection criteria, statistical procedures, P-values, absolute values, and experimental details are not reported in the available material.

4. RESULTS

The main finding is that dexamethasone markedly increased REDD1 messenger RNA, but not REDD2, in both rat skeletal muscle and L6 myoblasts. In simple terms, the glucocorticoid primarily activated the REDD1 gene in the muscle models examined.Simultaneously, dexamethasone reduced the phosphorylation of S6K1 and 4E-BP1, two downstream targets of mTOR. This reduction is consistent with a slowing of the signaling that normally supports the initiation of protein synthesis. The abstract does not report the numerical magnitude of the reduction nor the related statistical values.When REDD1 was reduced in myoblasts using interfering RNA, the inhibitory effect of dexamethasone on mTOR signaling was attenuated. Furthermore, silencing REDD1 altered the assembly of the regulatory complex formed by tuberin and hamartin, known as the TSC1/TSC2 complex. Experimental increase of Rheb counteracted the effect of dexamethasone on the phosphorylation of mTOR targets. Taken together, these data place REDD1 functionally upstream of the TSC complex and Rheb in the observed response.

5. INTERPRETATION

The biological significance is that, in muscle cells and rat muscle, a glucocorticoid can induce a resource-saving program: it increases REDD1 and reduces molecular signals associated with the synthesis of new proteins. REDD1 therefore appears to be more than just a marker of pharmacological stress, because reducing its expression limited the inhibition of mTOR caused by dexamethasone.The directly supported pathway is: dexamethasone REDD1 TSC/Rheb complex reduced phosphorylation of S6K1 and 4E-BP1. This is consistent with a reduction in anabolic signaling. However, the phosphorylation of these targets is a molecular indicator and does not, by itself, equate to measuring muscle mass loss, insulin resistance, or metabolic deterioration in the human body.The use of dexamethasone allows for the isolation of a glucocorticoid signal in a controlled manner, but it does not fully reproduce the physiology of circulating cortisol. Therefore, the study provides mechanistic evidence in the examined models, not a clinical demonstration of the consequences of chronic stress in people.

6. INDEPENDENT CONFIRMING EVIDENCE

Independent confirmation of the general role of REDD1 as a brake on the mTOR pathway comes from cellular experiments conducted by Sofer and colleagues. In fibroblasts and cells lacking REDD1,

energy stress did not normally reduce the phosphorylation of S6K and 4E-BP1. Conversely, induced expression of REDD1 rapidly reduced these signals and decreased cell size. The authors also showed that the phenomenon required TSC2 and could be countered by increasing Rheb. This study confirms the central feature of the pathway, REDD1 TSC/Rheb mTOR inhibition, but concerns energy stress in cells rather than glucocorticoid treatment in muscle [1].In mouse skeletal muscle, Britto and colleagues provided a particularly relevant functional verification. After seven days of dexamethasone, normal mice showed a reduction in the weight of the tibialis anterior and gastrocnemius muscles and smaller fiber size; these changes were not observed in mice lacking REDD1. After a single administration, the absence of REDD1 also prevented the reduction in protein synthesis and mTORC1 signaling. The result reinforces the idea that REDD1 is necessary, in that animal model, for the glucocorticoid-induced reduction of muscle anabolic activity [2].Further confirmation extends the narrative to lymphocytes, without turning it into proof valid for all tissues. Molitoris and colleagues observed that dexamethasone increases REDD1 in a murine T-cell line and in mouse thymocytes. Silencing or the genetic absence of REDD1 attenuated mTOR inhibition and reduced autophagy, which is the process by which the cell recycles intracellular components. The work argues that the glucocorticoid REDD1 lower mTOR link can also operate in immune cells, but it also highlights that the final outcome depends on the cell type and the experimental context [3].

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance has been identified; this does not prove the absence of contrary results.However, there is an important mechanistic clarification. In the murine muscle model by Britto and colleagues, REDD1 was necessary for the effects of dexamethasone on mTORC1 and protein synthesis, but the authors did not attribute this effect to a modulation of the binding between TSC2 and 14-3-3. Instead, they highlighted a possible involvement of AKT and PRAS40, a regulatory protein of mTORC1. This does not contradict the general direction of REDD1 reduced mTOR signaling, but it indicates that the molecular detail may vary between models and should not be considered definitively resolved [2].Furthermore, in experiments on lymphocytes, autophagy induced by dexamethasone was only partially dependent on REDD1, and at higher doses of the drug, the dependence on REDD1 was lower. This limits a linear interpretation in which REDD1 would be the sole mediator of glucocorticoid effects [3].

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent evidence used to verify the steps of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal and cellular	Rat skeletal muscle and L6 myoblasts	Dexamethasone increases REDD1 and reduces S6K1 and 4E-BP1 phosphorylation; reducing REDD1 attenuates mTOR inhibition.	direct confirmation	moderate
[1]	Cellular and genetic	Fibroblasts, U2OS cells, and REDD1-deficient cells	Energy stress-induced REDD1 requires TSC2, acts upstream of Rheb, and reduces mTOR signaling.	indirect confirmation	moderate
[2]	Animal	Normal mice and REDD1-deficient mice treated with dexamethasone	The absence of REDD1 prevents the reduction in mTORC1 activity, protein synthesis, and muscle mass observed in normal mice.	direct confirmation	moderate
[3]	Cellular and animal	Murine T-cell line WEHI7.2 and mouse thymocytes	Dexamethasone increases REDD1; reducing or eliminating REDD1 attenuates mTOR inhibition and autophagy.	direct confirmation	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed pertinently supports the finding that dexamethasone can increase REDD1 in muscle and reduce downstream mTOR signaling. Independent confirmations make the mechanism quite well-supported in cells and animals, especially regarding the role of REDD1 in the catabolic response of muscle to glucocorticoids.However, the conclusion must remain proportionate: the data do not prove that cortisol from chronic stress automatically produces insulin resistance, muscle loss, or metabolic dysfunction in every person. The link is confirmed primarily at a mechanistic level and requires validation in properly designed human studies.

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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