LIFE Science Hub
JOURNAL OF SCIENCE
EXPANDING KNOWLEDGE ABOUT NUTRITION AND HEALTH

ORIGINAL RESEARCH
ISSN 2845-7501

GSK-3 in the phosphatidylinositol 3-kinase/Akt cell survival pathway

M. Moscati[1]

1 Italy

1. ABSTRACT

The analyzed study evaluated whether glycogen synthase kinase-3 (GSK-3), a protein that can influence many cellular functions, participates in survival controlled by the PI3K/Akt pathway. In the available material, consisting only of the abstract, the authors report that artificially increasing GSK-3 activity induced apoptosis in Rat-1 and PC12 cells, while an inactive form of the protein protected cells from death caused by PI3K inhibition.The contribution to the narrative of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi therefore concerns the segment of the chain in which AKT promotes cell survival by also keeping GSK-3b inactive. Independent studies in neuronal and cellular models have confirmed that GSK-3b activation can promote apoptosis and that its inhibition can attenuate death caused by the blockage of PI3K/Akt. However, other evidence shows that GSK-3b is not essential in every form of cell death: the mechanism is biologically consistent, but depends on the cell type and the damaging stimulus.

ONLINE ARTICLE

ARTICLE INFORMATION

Published: November 22, 2026
Updated: November 22, 2026

DOI 10.5281/zenodo.24446812

MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

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 research question was whether GSK-3 plays an actual role in cell survival regulated by phosphatidylinositol 3-kinase, or PI3K (an enzyme that initiates intracellular growth and survival signals), and by AKT (a protein that transmits some of these signals). The hypothesis was that AKT does not promote survival solely through a general association with PI3K, but also by reducing the activity of GSK-3, a kinase, which is a protein capable of modifying other proteins through phosphorylation.This question is relevant to section 4.12 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because the book describes GSK-3b as a molecular target whose inactivation contributes to the survival function of AKT. The publication subject to the Evidence Review addresses precisely the PI3K/AKT GSK-3 apoptosis segment. However, it does not evaluate the entire insulin cascade in the organism, nor does it demonstrate clinical, metabolic, or therapeutic effects in humans.Since only the abstract is available, the description must remain limited to the information reported by the authors. The abstract uses the name GSK-3; it does not provide sufficient details to reconstruct with certainty all the experimental characteristics of the isoform studied, the genetic constructs, or the individual laboratory tests.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study is a preclinical experiment conducted in cell culture. The authors used Rat-1 and PC12 cells. Rat-1 cells are rat fibroblasts, which are connective tissue cells adapted for culture; PC12 cells are derived from a rat pheochromocytoma and are commonly used as a cell model with neuronal characteristics.The authors artificially increased the expression of a catalytically active form of GSK-3, meaning it is capable of maintaining its enzymatic function. They also expressed a dominant-negative form of GSK-3, designed to hinder the function of the endogenous protein present in the cell. To verify the relationship with PI3K, they inhibited this pathway and observed the effect on programmed cell death.The primary endpoint reported in the available material is apoptosis, which is an orderly process of cell elimination. The abstract does not report sample sizes, the number of independent experiments, quantitative criteria for assessing apoptosis, doses and duration of PI3K inhibition, the type of inhibitor used, statistical methods, P-values, or confidence intervals. This information is not provided in the available material.

4. RESULTS

The main result is that making GSK-3 artificially more active induced apoptosis in both Rat-1 and PC12 cells. In simple terms, when this kinase was pushed toward a state of high activity, programmed cell death increased in the two models examined.Conversely, the expression of a dominant-negative form of GSK-3 prevented apoptosis following PI3K inhibition. This result indicates that, under the experimental conditions used, the loss of the PI3K signal did not lead to cell death in a way that was completely independent of GSK-3: reducing GSK-3 function attenuated the pro-apoptotic effect of blocking PI3K.The finding most relevant to the book is therefore directional and functional: higher GSK-3 activity is experimentally associated with an increase in apoptosis, while interfering with GSK-3 reduces the apoptosis induced by PI3K inhibition. The abstract does not report percentages of apoptotic cells, absolute values, quantitative comparisons between Rat-1 and PC12, P-values, or direct measurements of AKT and GSK-3 phosphorylation. These data are not reported in the available material.

5. INTERPRETATION

The biological significance of this work is that AKT can promote cell survival not only by activating protective signals, but also by limiting the action of a protein that, if kept active in these models, promotes apoptosis. In this interpretation, GSK-3 represents a potential brake on survival: when PI3K and AKT are functioning, the brake is reduced; when PI3K is blocked, GSK-3 can contribute more significantly to cell death.The scientific detail is that AKT can phosphorylate GSK-3 at inhibitory sites. Phosphorylation is the addition of a small chemical group to a protein; in the case of GSK-3b, this modification can reduce its activity. The chain segment supported by the publication is therefore PI3K/AKT functional inactivation of GSK-3 lower propensity for apoptosis.This does not equate to

proving that GSK-3b is the only mechanism by which AKT protects cells. AKT acts on many targets, and apoptosis depends on the cell type, available growth signals, the stress experienced, and the observation time. The connection with "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is therefore clearly identifiable at a cellular and mechanistic level, not as direct proof of clinical effects or disease prevention in humans.

6. INDEPENDENT CONFIRMING EVIDENCE

A necessary first step in this narrative is to verify that AKT can truly inactivate GSK-3 in response to insulin. In a previous and independent experimental study, insulin activated protein kinase B, also known as PKB or AKT, and this activation was associated with the inhibitory phosphorylation of GSK-3. PI3K inhibitors prevented both the activation of AKT and the inhibition of GSK-3. The study therefore provides direct confirmation of the upstream link PI3K AKT GSK-3 inhibition, although it did not directly measure cell survival as a primary outcome [1].The relationship between GSK-3b activity and programmed cell death was then evaluated in cultured rat cortical neurons. The withdrawal of trophic factors—external signals necessary for neuronal survival—or treatment with PI3K inhibitors increased GSK-3b activity prior to apoptosis. Conversely, a GSK-3b inhibitory protein or a dominant-negative form of the kinase reduced apoptosis; furthermore, overexpression of GSK-3b increased it. These results confirm, in a distinct neuronal model, the direction of the effect described in the original study: higher GSK-3b activity is associated with more apoptosis, while hindering it reduces apoptosis under specific experimental conditions [2].A further study on rat sympathetic neurons verified the relationship with PI3K and AKT particularly closely. Nerve growth factor produced PI3K-dependent phosphorylation of GSK-3b and reduced its activity. When PI3K or AKT were inhibited, a biological inhibitor of GSK-3b, called Frat1, or a kinase-dead form of GSK-3b reduced neuronal death. The result therefore supports the step whereby GSK-3b participates in death caused by the artificial interruption of the PI3K/AKT signal [3].Overall, the independent evidence builds a convergent chain: insulin or other survival signals can activate PI3K and AKT; AKT can inhibit GSK-3; in various cell models, the reduction of GSK-3b activity attenuates certain forms of apoptosis. However, all these data remain preclinical: they come from biochemical systems and cell cultures, not from clinical trials.

7. CONFLICTING EVIDENCE

The same research conducted on sympathetic neurons identified an important limitation. Although the functional blockade of GSK-3b reduced cell death caused by the inhibition of PI3K or AKT, it did not prevent death induced by the withdrawal of nerve growth factor. In other words, GSK-3b was relevant when the PI3K/AKT pathway was blocked directly, but it was not sufficient to explain all the apoptosis resulting from the loss of the natural trophic signal [3].This evidence does not contradict the step supported by the original study. Instead, it defines its scope: GSK-3b can be an important mediator of survival controlled by PI3K/AKT, without constituting a universal switch for cell death. Parallel pathways, other AKT targets, and specific neuron characteristics can modify the outcome. No directly conflicting evidence sufficiently relevant beyond this context-dependency has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from the independent research used to verify the PI3K/AKT → GSK-3b → apoptosis segment.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Experimental cellular	Rat-1 and PC12 cells	Active GSK-3 induced apoptosis; the dominant-negative form reduced apoptosis following PI3K inhibition.	direct confirmation	moderate
[1]	Experimental cellular and biochemical	Insulin-stimulated cell models	Insulin activated AKT and reduced GSK-3 activity; PI3K inhibitors blocked both steps.	direct confirmation	moderate
[2]	Experimental cellular	Cultured rat cortical neurons	Increased GSK-3b activity preceded or increased apoptosis; its inhibition reduced it.	direct confirmation	moderate
[3]	Experimental cellular	Cultured rat sympathetic neurons	GSK-3b inhibition reduced death from PI3K/Akt blockade, but not from NGF withdrawal.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports, in the cell models examined, that GSK-3 activity contributes to apoptosis and that its reduction can protect against death caused by PI3K blockade. Independent evidence makes the mechanism quite well-supported at the cellular and molecular level.The most prudent conclusion is that AKT can promote cell survival by also inactivating GSK-3b, but the relative importance of this step changes according to the cell type and the stimulus inducing death. It is not possible to automatically extend these results to clinical effects, treatments, or all human diseases.

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.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **Role of Glycogen Synthase Kinase-3b in Neuronal Apoptosis Induced by Trophic Withdrawal**
Hetman et al., 2000
The Journal of Neuroscience
DOI: https://doi.org/10.1523/JNEUROSCI.20-07-02567.2000

[2] **Glycogen Synthase Kinase-3b Activity Is Critical for Neuronal Death Caused by Inhibiting Phosphatidylinositol 3-Kinase or Akt but Not for Death Caused by Nerve Growth Factor Withdrawal**
Crowder et al., 2000
Journal of Biological Chemistry
DOI: https://doi.org/10.1074/jbc.M006160200

[3] **Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B**
Cross et al., 1995
Nature
DOI: https://doi.org/10.1038/378785a0