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Targeting the PI3K/AKT/GSK3b pathway in Parkinson's disease: a therapeutic plan - Evidence review

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1. ABSTRACT

The study analyzed is a narrative review examining the potential role of the PI3K/AKT/GSK3b pathway in Parkinson's disease. The authors describe a reduction in PI3K/AKT cellular signaling, generally associated with neuronal survival, and increased activity of GSK-3b, an enzyme involved in oxidative stress, inflammation, and programmed cell death. It does not present a new clinical trial or a new study on patients.In the narrative of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the passage suggesting that strategies capable of increasing AKT activity and reducing GSK-3b activity could restore cellular homeostasis in Parkinson's. Independent studies in animal and cellular models support the relevance of GSK-3b in the degeneration of dopaminergic neurons and show results consistent with the modulation of the AKT-GSK-3b axis. However, a clinical trial with pioglitazone did not demonstrate a modification of the progression of early-stage Parkinson's. The confirmation of the narrative is therefore primarily mechanistic and preclinical.

ONLINE ARTICLE

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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 the PI3K/AKT/GSK3b pathway could represent a useful target for reducing the biological processes associated with neuronal degeneration in Parkinson's disease. PI3K and AKT are proteins that transmit growth, adaptation, and survival signals within the cell. GSK-3b, on the other hand, is a kinase—an enzyme that modifies other proteins—whose excessive activity can promote conditions unfavorable to neuronal survival.The publication is relevant to section 4.12 because it discusses the final segment of the insulin cascade described in the book: AKT can phosphorylate GSK-3b at an inhibitory site, reducing its activity. In the context of Parkinson's, the authors propose that lower PI3K/AKT activity and higher GSK-3b activity contribute to oxidative stress, neuroinflammation, mitochondrial alterations, and apoptosis, which is programmed cell death.As a narrative review, the analyzed study can summarize and correlate previously published results, but it cannot demonstrate on its own that the pharmacological activation of AKT and the inhibition of GSK-3b slow down the disease in patients. Its contribution to the book is therefore primarily biological and mechanistic: it defines why the AKT-GSK-3b balance may be important for the survival of dopaminergic neurons.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is a literature review and not an experiment conducted directly by the authors on people, animals, or cells. The available text discusses preclinical studies, observations on post-mortem human samples, cellular models, and research on animals with characteristics that reproduce certain aspects of Parkinson's disease.The authors organized the discussion around the physiology of the PI3K/AKT/GSK3b pathway, its potential imbalance in Parkinson's disease, and molecules that could increase PI3K/AKT or reduce GSK-3b. Among others, metformin, pioglitazone, fenofibrate, statins, lithium, and tideglusib are discussed. The text does not report a reproducible bibliographic research strategy with queried databases, search dates, formal inclusion and exclusion criteria, standardized risk of bias assessment, or quantitative meta-analysis.Therefore, there is no overall number of participants attributable to the publication. This information is not applicable to a narrative review. There is no single control group, unified experimental intervention, common primary endpoint, or follow-up period specific to the study, as these elements belong to the individual works discussed.

4. RESULTS

The central finding of the review is a conceptual synthesis: in experimental Parkinson's disease, reduced PI3K/AKT activation is linked to a decreased ability of neurons to cope with metabolic and oxidative stress. In parallel, increased GSK-3b activity is associated with processes that can exacerbate inflammation, mitochondrial impairment, the accumulation of abnormal proteins, and apoptosis.For the passage covered in the book, the functional relationship between AKT and GSK-3b is particularly relevant. Under physiological cellular conditions, AKT can phosphorylate GSK-3b at serine 9; this modification tends to reduce the kinase's activity. In simple terms, AKT can act as a biological brake on GSK-3b. If this brake is reduced, GSK-3b may remain more active and promote signals unfavorable to neuronal survival.The authors also report that certain pharmacological or experimental interventions have shown, in preclinical models, an increase in AKT phosphorylation, greater inhibitory phosphorylation of GSK-3b, or a reduction in markers of neuronal damage. However, the results are derived from studies that vary significantly in terms of model, molecule, dose, and outcome. The review itself acknowledges that the benefits observed in cells and animals are not automatically transferable to patients with Parkinson's disease.The work does not provide a single quantitative estimate of the therapeutic effect of AKT activators or GSK-3b inhibitors. It therefore does not report a relative risk, a hazard ratio, or a combined measure of clinical efficacy. Its result is a plausible biological proposal, not the demonstration of an effective treatment.

5. INTERPRETATION

For a non-technical reader, the message is that dopaminergic neurons depend on survival signals and systems that limit harmful cellular responses. AKT

and GSK-3b represent two nodes of this balance: when AKT is active, it can reduce the activity of GSK-3b; when GSK-3b is excessively active, it can promote conditions associated with neuronal damage.In the book's paragraph, the publication is used to support the idea that in Parkinson's disease, the reduced activity of the PI3K/AKT pathway and the persistent hyperactivation of GSK-3b are biologically consistent with neuroinflammation, oxidative stress, and apoptosis. The segment directly documented by the review is therefore: reduction of PI3K/AKT signals and increased activity of GSK-3b as a possible unfavorable configuration for neuronal survival.The most solid part of the narrative concerns the experimental role of GSK-3b in the vulnerability of dopaminergic neurons. It is less proven that a dual pharmacological strategy—that is, one capable of simultaneously activating AKT and inhibiting GSK-3b—modifies the progression of Parkinson's in humans. The difference is important: a plausible biological mechanism does not yet equate to a clinically effective treatment.

6. INDEPENDENT CONFIRMING EVIDENCE

Initial independent confirmation concerns the finding that increased GSK-3b activity may contribute to the loss of dopaminergic neurons. In mice treated with MPTP, a neurotoxin used to replicate certain aspects of Parkinson's disease, Wang and colleagues observed GSK-3b activation accompanied by a reduction in inhibitory phosphorylation at serine 9. Two GSK-3b inhibitors reduced dopaminergic neuron apoptosis, attenuated the decrease in striatal dopamine, and improved toxin-induced behavioral deficits [1]. The result is consistent with the direction proposed in the book, but the MPTP model does not coincide with human Parkinson's disease.Li and colleagues provided a more selective verification using mice in which the Gsk3b gene was deleted only in dopaminergic neurons. After exposure to MPTP, the loss of tyrosine hydroxylase-positive cell bodies, a marker for dopaminergic neurons, was 24.7% in mice with neuronal Gsk3b deletion compared to 47.7% in controls. Nissl staining counts also showed less cell loss. Deletion of Gsk3a did not produce equivalent protection; furthermore, tideglusib showed neuroprotection only at higher doses in the mouse model [2]. This study provides causal support, albeit limited to animals, for the specific relevance of GSK-3b.A third study evaluated both sides of the axis described in the book together. In primary cortical neurons exposed to MPP+ and in mice treated with MPTP, tovophyllin A increased cell viability, attenuated the loss of dopaminergic neurons, and improved certain behavioral deficits. In the brain tissues of the treated mice, the molecule increased AKT phosphorylation at serine 473 and increased the inhibitory phosphorylation of GSK-3b at serine 9 [3]. This result is biologically consistent with the sequence: active AKT less active GSK-3b greater neuronal survival. However, the authors themselves specify that the causal link between the modulation of the axis and neuroprotection required further experiments with specific inhibitors.Taken together, these independent studies primarily support the experimental consistency of the cascade. They show that reducing GSK-3b, or accompanying the increase in AKT with the inactivation of GSK-3b, is associated with reduced neurotoxicity in Parkinson's models. They do not demonstrate that metformin, pioglitazone, fenofibrate, or statins produce the same clinical effect in patients through this precise molecular pathway.

7. CONFLICTING EVIDENCE

The main conflicting evidence of relevance concerns the transition from preclinical mechanisms to human therapy. In the multicenter, randomized, double-blind, placebo-controlled NET-PD FS-ZONE trial, 210 people with early-stage Parkinson's were assigned to 15 mg of pioglitazone per day, 45 mg of pioglitazone per day, or a placebo for 44 weeks. The mean change in the total UPDRS score, where higher values indicate greater clinical worsening, was 4.42 with 15 mg, 5.13 with 45 mg, and 6.25 with placebo [4].Despite the numerical difference favoring the placebo as a reference, the futility design indicated that the 45 mg dose was unlikely to be a disease-modifying therapy; sensitivity analyses suggested futility for the 15 mg dose as well. The authors concluded that, at the doses studied, pioglitazone is unlikely to modify the progression of early-stage Parkinson's [4]. This does not refute the biological role of AKT and GSK-3b, nor does it prove that every modulator of the pathway is ineffective. However, it shows that preclinical or indirect effects attributed to a drug do not guarantee clinical

benefit.No directly conflicting evidence sufficiently relevant to the experimental role of GSK-3b in MPTP-induced neurotoxicity was identified; this does not prove the absence of contrary results. Translation to humans remains limited by dependence on the experimental model, the incomplete selectivity of the drugs, and the possible difference between preventing acute toxic damage in animals and modifying a progressive neurodegenerative disease in patients.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent evidence used to verify the narrative in the book's section.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature on Parkinson's, experimental models, and clinical data discussed by the authors	Proposes that reduced PI3K/AKT and increased GSK-3b contribute to neurodegeneration and are potential therapeutic targets	biologically consistent evidence	preliminary
[1]	Animal and cellular	MPTP/MPP+ models of parkinsonism	GSK-3b inhibition reduced dopaminergic apoptosis, dopamine loss, and MPTP-induced behavioral deficits	direct confirmation	moderate
[2]	Animal with conditional knockout and pharmacological intervention	Mice with Gsk3b deletion in dopaminergic neurons, MPTP model	Gsk3b deletion reduced dopaminergic neuron loss; tideglusib provided protection only at higher doses	direct confirmation	moderate
[3]	Cellular and animal	Primary neurons exposed to MPP+ and mice treated with MPTP	Tovophyllin A increased AKT phosphorylation and inhibitory GSK-3b phosphorylation, with less dopaminergic damage	indirect confirmation	preliminary
[4]	Phase 2 RCT	210 people with early-stage Parkinson's	Pioglitazone did not appear to be a disease-modifying therapy at the doses studied	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the reason it is cited in the book's paragraph: AKT and GSK-3b form an important regulatory axis for cell survival, and an imbalance characterized by lower AKT activity and higher GSK-3b activity is plausibly linked to neuronal vulnerability in Parkinson's disease.Independent evidence confirms that GSK-3b contributes to neurodegeneration in toxin-induced Parkinson's models and that its reduction can attenuate neuronal loss and motor deficits in animals. The combined strategy of increasing AKT and inhibiting GSK-3b is supported at a mechanistic level, but requires clinical validation. It is therefore not possible to consider it a proven treatment for people with Parkinson's.

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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