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*Commentary*

# Phosphatidylserine Purity and Neuronal Resilience: Linking Formulation to SIRT1–PGC-1α Signaling

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## Abstract

Aging and Alzheimer's disease are associated with progressive loss of neuronal resilience, driven in part by mitochondrial dysfunction and oxidative stress. In this context, SIRT1 and PGC-1α are important because they link metabolic state, stress adaptation, and mitochondrial maintenance. Jeon et al., show that higher-purity Phosphatidylserine (PS) is associated with stronger activation of the SIRT1-PGC-1α pathway in human cortical neurons, along with reduced oxidative stress and improved resistance to Aβ42-associated injury. The study suggests that PS may act as a formulation-dependent regulator of neuronal stress resistance.

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## Description

A major challenge in brain aging is the gradual loss of neuronal resilience. Neurons are highly dependent on mitochondrial health; when mitochondrial function declines, oxidative stress rises and vulnerability to neurodegenerative injury increases. This is especially relevant in Alzheimer's disease, where mitochondrial dysfunction and redox imbalance have been repeatedly linked to progressive neuronal injury and cognitive decline [1,2].

Among these, the SIRT1-PGC-1α axis stands out as particularly compelling. SIRT1 has been linked to memory and synaptic plasticity, [3] while PGC-1α is a major regulator of mitochondrial respiration, oxidative stress defense, and neuronal survival [4]. Together, these proteins provide a biologically plausible framework for understanding neuronal resilience in aging and Alzheimer's-associated stress. For that reason, interventions that preserve or enhance this pathway are naturally of interest in the aging brain [3,4].

Here, phosphatidylserine becomes especially relevant. PS is not simply a structural membrane lipid. In the brain, it contributes to membrane organization, synaptic signaling, and the function of membrane-associated proteins [5]. It has also been explored clinically as a supplement for memory-related outcomes, although the underlying mechanisms and the consistency of benefit remain less clear [6]. That combination makes PS intriguing: it has clear biological plausibility in neural tissue, but its formulation-dependent activity has not been well defined [5].

Given this background, the recent study by Jeon et al. becomes worth highlighting. Rather than asking only whether PS is generally helpful, the authors ask whether different PS preparations differ in their effects on neuronal signaling. Using human embryonic stem cell-derived cortical neurons, they report that higher nominal PS purity is associated with progressively stronger induction of SIRT1 and PGC-1α [1]. They further connect this to an Aβ42-associated stress context, in which higher-purity PS was associated with reduced neuronal death, lower mitochondrial oxidative stress, and improved mitochondrial dynamics-related markers [1]. The significance of the study, therefore, lies not only in the finding that PS appears beneficial, but also in the possibility that it may act in a formulation-dependent manner on a pathway already strongly linked to mitochondrial resilience [1,4]

That is the key conceptual advance of the study. Phosphatidylserine has often been discussed broadly as a supportive membrane-associated compound, but Jeon et al. suggest that its bioactivity may depend meaningfully on formulation [1,5]. In other words, not all PS preparations should necessarily be expected to behave identically, even when administered at the same nominal concentration [1]. In the context of neurodegeneration research, this is important because the paper places PS within a defined neuronal stress-response pathway rather than treating it as a nonspecific supportive factor. This interpretation is strengthened by the authors' mechanistic findings that PS-associated PGC-1α upregulation was SIRT1-dependent, as supported by both SIRT1 knockdown and promoter activity assays. Taken together, these results frame PS as a modulator of SIRT1-PGC-1α signaling and mitochondrial stress resistance, rather than simply as a broadly beneficial lipid intervention.

The results highlight that the strongest effect was observed with the 80% phosphatidylserine preparation and outlines the proposed sequence in which higher-purity PS is associated with increased SIRT1, SIRT1-dependent upregulation of PGC-1α, improved mitochondrial homeostasis, reduced Aβ42-induced stress, enhanced neuronal survival, and reduced neuronal death. In doing so, it also captures the paper's major downstream mitochondrial findings, including reduced oxidative stress and partial normalization of fission-fusion-related markers. Authors also emphasize the broader interpretive point that PS bioactivity may depend on formulation-related properties. The caveat that the 80% preparation was obtained from a different manufacturer is included to ensure that the findings are accurately represented and not attributed solely to purity [1,5].

Even with these limitations, Jeon et al. make an important contribution. The study shifts the discussion from asking whether phosphatidylserine is simply helpful to asking how its composition influences neuronal signaling and mitochondrial stress responses [1]. That reframing opens the door to more mechanistically focused follow-up work. Future studies should identify which compositional features of PS preparations are biologically meaningful, determine whether these differences persist in more complex neural systems or *in vivo*, and test whether the reductions in mitochondrial superoxide and the partial normalization of fission-fusion markers observed here can be reproduced in broader models of neuronal stress.

The human cortical neuron system is a strength of the study because it provides a more relevant neuronal context than many simpler models, but it does not establish whether the same pathway effects would persist in more complex neural systems or *in vivo*. Clarifying which features of PS preparations drive these differences will therefore be essential for determining whether the effects observed in cultured neurons extend to broader settings of mitochondrial stress and neurodegenerative vulnerability [1,5].

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