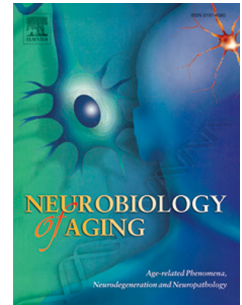


Accepted Manuscript

Atypical PKC, PKC λ /I, activates β -secretase and increases A β _{1–40/42} and phospho-tau in mouse brain and isolated neuronal cells, and may link hyperinsulinemia and other aPKC activators to development of pathological and memory abnormalities in Alzheimer's Disease.



Mini P. Sajan, Barbara C. Hansen, Margaret G. Higgs, C. Ron Kahn, Ursula Braun, Michael Leitges, Collin R. Park, David M. Diamond, Robert V. Farese

PII: S0197-4580(17)30294-4

DOI: [10.1016/j.neurobiolaging.2017.09.001](https://doi.org/10.1016/j.neurobiolaging.2017.09.001)

Reference: NBA 10021

To appear in: *Neurobiology of Aging*

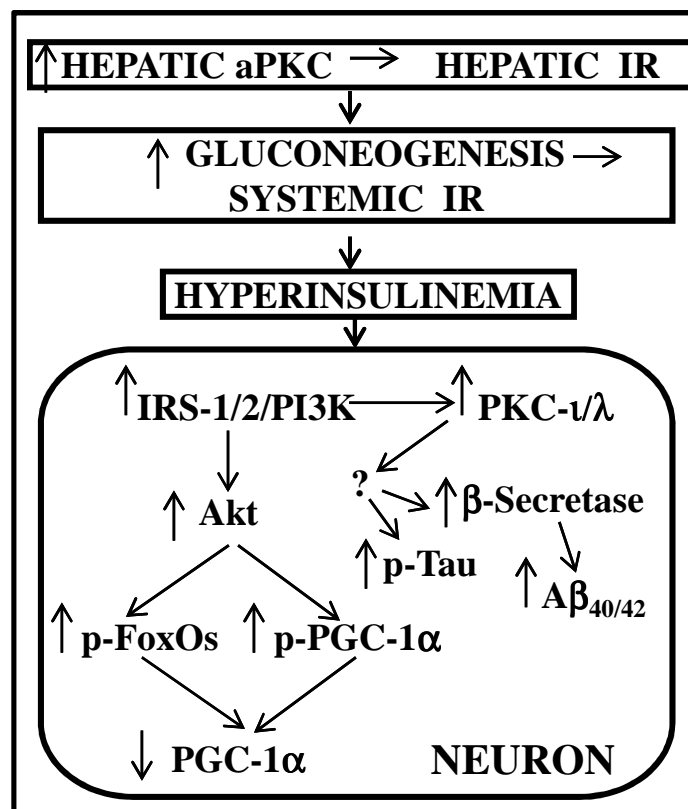
Received Date: 23 March 2017

Revised Date: 25 August 2017

Accepted Date: 3 September 2017

Please cite this article as: Sajan, M.P., Hansen, B.C., Higgs, M.G., Kahn, C.R., Braun, U., Leitges, M., Park, C.R., Diamond, D.M., Farese, R.V., Atypical PKC, PKC λ /I, activates β -secretase and increases A β _{1–40/42} and phospho-tau in mouse brain and isolated neuronal cells, and may link hyperinsulinemia and other aPKC activators to development of pathological and memory abnormalities in Alzheimer's Disease., *Neurobiology of Aging* (2017), doi: 10.1016/j.neurobiolaging.2017.09.001.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Schematic of pathogenesis of neuronal signaling abnormalities in insulin-resistant states that lead to production of factors that may abet development of Alzheimer's disease. In this scheme, diet-induced increases in hepatic aPKC activity lead to impaired Akt activation by insulin, i.e., hepatic insulin resistance (IR), increases in hepatic gluconeogenesis, systemic IR, and hyperinsulinemia, which persistently hyperactivates brain Akt and aPKC. Increases in brain Akt activity lead to phosphorylation and thus diminished activities of all FoxOs (1/3a/4/6), and decreased activity and expression of PGC-1 α (all needed for neuronal function and integrity). Increases in brain aPKC activity, either directly or indirectly, provoke increases in b-secretase activity, and levels of A $\beta_{1-40/42}$ and phospho-thr-231-tau, and thus abet plaque and tangle development.

Download English Version:

<https://daneshyari.com/en/article/6803213>

Download Persian Version:

<https://daneshyari.com/article/6803213>

[Daneshyari.com](https://daneshyari.com)