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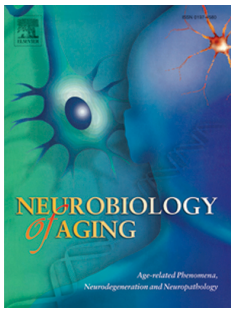

Atypical PKC, PKCλ/ι, activates β-secretase and increases $A\beta_{1-40/42}$ and phospho-tau in mouse brain and isolated neuronal cells, and may link hyperinsulinemia and other aPKC activators to development of pathological and memory abnormalities in Alzheimer's Disease.

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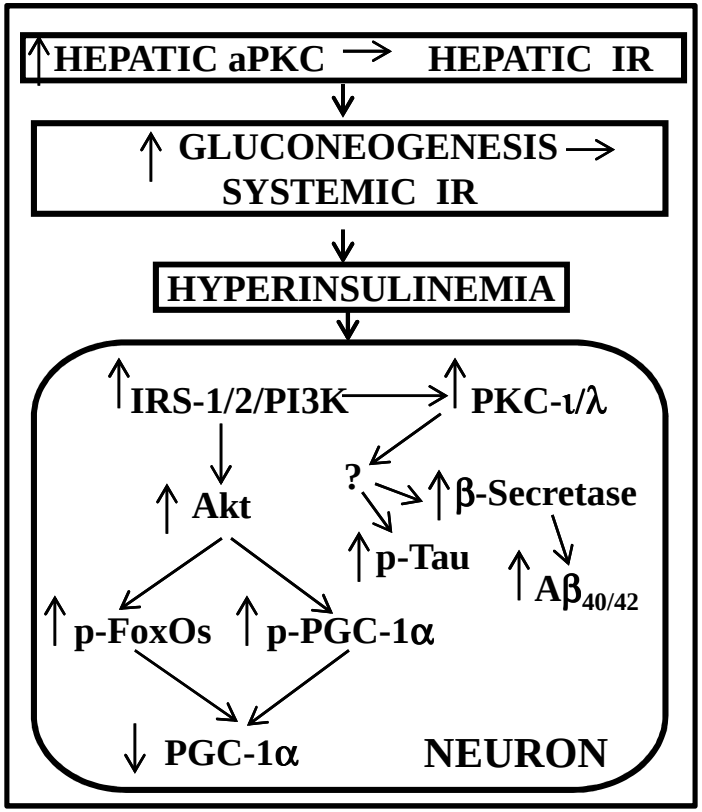

Schematic of pathogenesis of neuronal signaling abnormalities in insulin-resistant states that lead to production of factors that may abet development of Alzheimer's disease. In this scheme, diet-induced increases in hepatic aPKC activity lead to impaired Akt activation by insulin, i.e., hepatic insulin 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-1α (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 $A\beta_{1\text{-}40/42}$ and phospho-thr-231-tau, and thus abet plaque and tangle development.