HKU Med LKS Faculty of Medicine
Department of Medicine
香港大學內科學系

CMF-019 elevates neuronal insulin sensitivity: an implication of therapeutic potential of Alzheimer's disease

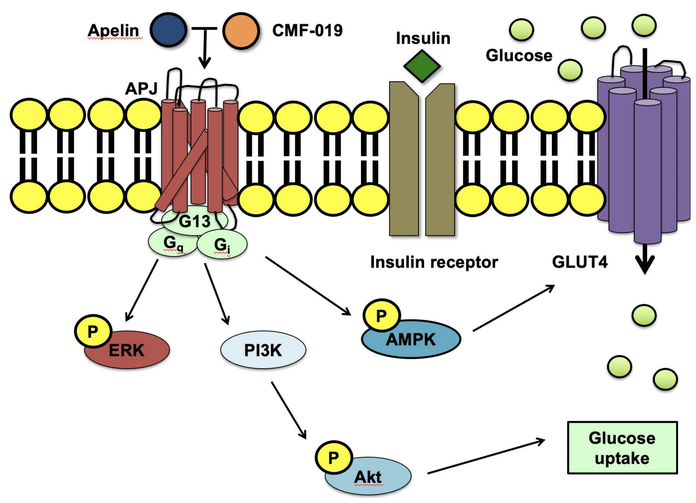
Ka-Fai Oscar MA*, Koon-Ho CHAN, Roy Chun-Laam NG
Department of Medicine, The University of Hong Kong, Laboratory Block, Hong Kong

*Correspondence: Mr. OKF MA, u3004636@connect.hku.hk

Introduction:

- Increasing evidence has demonstrated the association between neuronal insulin resistance and Alzheimer's Disease (AD) pathogenesis.
- Neuronal insulin resistance not only enhances the activity of γ-secretase, Aβ production and secretion, but also induces the activation of GSK3β, which could lead to Tau phosphorylation and aggregation.
- Reports have shown that Apelin can increase glucose uptake by promoting GLUT4 translocation and restore insulin sensitivity of TNFα-induced insulin resistance via activating PI3K/AKT and Erk1/2 signalling pathways.
- CMF-019 is a novel invented Apelin receptor (APJ) agonist with specific activity on $G\alpha_i$ pathway that enhances insulin signalling.
- We believe that CMF-019 can be a promising therapeutic drug for AD by enhancing neuronal insulin sensitivity through the activation of PI3K-AKT and Erk1/2 signalling.

Illustration:



We hypothesize that the activation of APJ, upon binding with Apelin or CMF-019, enhances the phosphorylation of insulin signaling molecules, such as AMPK, ERK and Akt, and further induces GLUT4 translocation to plasma membrane for glucose uptake.

Methods:

CMF-019 Treatment

HT22
Insulin-induced IR (100μM Insulin)
24 hr
CMF-019/Apelin
30 min
10mM insulin
30 min
WB: pAkt/Akt, Erk/pErk, AMPK/pAMPK

Pharmacokinetic study

Starve for 24 hr
Feed with 10mg/kg CMF-019 by oral gavage.
Harvest at 0, 0.5, 1hr
HPLC/MS/MS

Results:

Figure 1

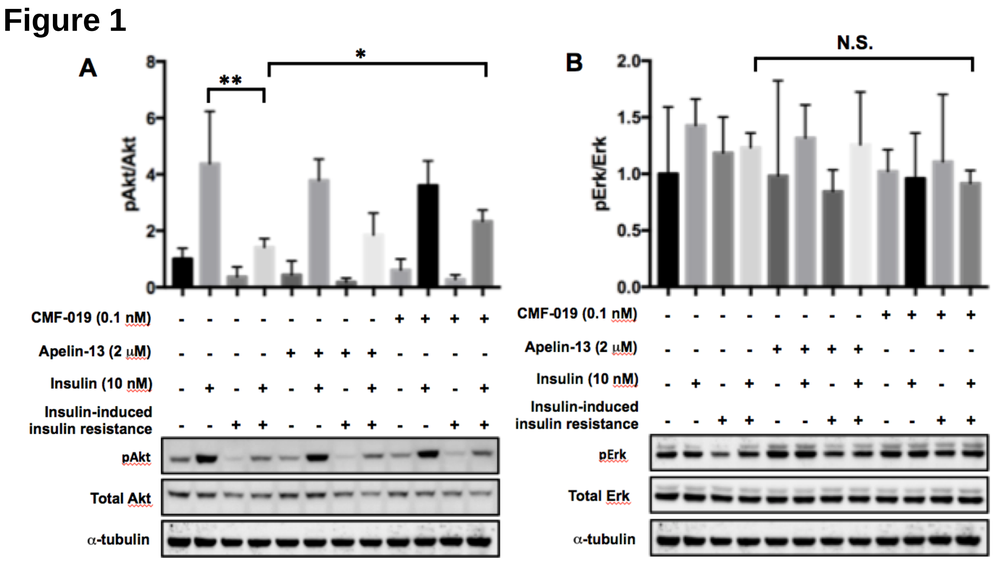


Figure 1. CMF-019 elevates insulin sensitivity via PI3K/Akt signaling pathway, but not MAPK-ERK signaling pathway
(A) Insulin resistance HT-22 ($HT\text{-}22_{IR}$) had decreased Akt phosphorylation upon 10 nM insulin induction compared with control HT22 ($p<0.01$). CMF-019 pre-treatment can improve insulin sensitization in $HT\text{-}22_{IR}$ cells by retrieving the Akt phosphorylation levels compared the control HT22 cells ($p<0.05$). (B) Neither insulin-induced insulin resistance nor CMF-019 / Apelin treatment has altered the phosphorylation level of Erk 2/3 in HT22 cells ($p>0.05$).

Figure 2

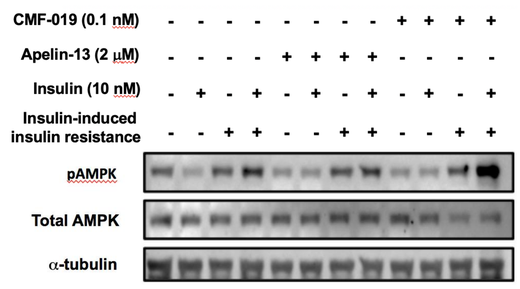


Figure 2. CMF-019 enhances AMPK phosphorylation in $HT\text{-}22_{IR}$ neurons
Representative western blot image indicates CMF-019 increases insulin-induced AMPK phosphorylation in $HT\text{-}22_{IR}$ hippocampal neurons.

Figure 3

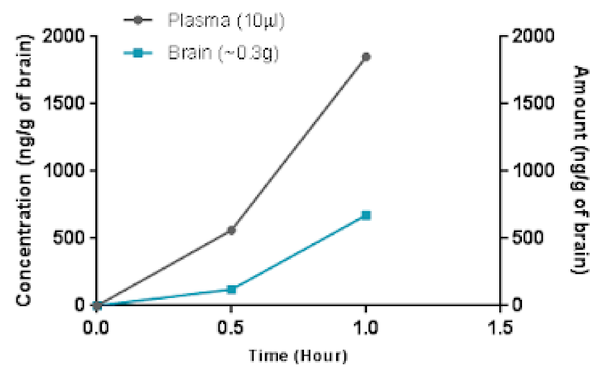


Figure 3. Pharmacokinetic studies of CMF-019 between brain and plasma detected by LC-MS/MS analysis
Pharmacokinetic studies of CMF-019 between brain and plasma detected by LC-MS/MS analysis.

Conclusions:

- CMF-019 pretreatment alleviated the insulin sensitivity by increasing higher level of Akt phosphorylation in the HT22 cells. However, there is no significant difference between CMF-019-treated, Apelin-13-treated and untreated $HT22_{IR}$ cells on the level of pErk1/2, suggesting that CMF-019 enhances insulin sensitivity through PI3K/Akt pathway instead of Erk signalling pathway.
- AMPK also plays a role in increasing glucose uptake by accelerating GLUT4 translocation. Upon insulin stimulation, the level of AMPK phosphorylation is enhanced in $HT\text{-}22_{IR}$ cells when compare to that of HT-22.
- LC-MS/MS analysis indicated that CMF-019 may cross the blood brain barrier.

References:
1) RCL Ng. et al. (2020) Mol Psychiatry
2) J Min et al. (2019) J Neuroinflammation 16(1):110
3) RCL Ng. et al. (2016) Mol Neurodegener 11(1):71

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