Bee Venom Exerts Neuroprotective Effects on Neuronal Cells and Astrocytes under Hypoxic Conditions Through MAPK Signaling Pathways

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Disclosure

- I have no relevant financial relationships to disclose or conflicts of interest to resolve
- I will not discuss any unapproved or off-label, experimental or investigational use of a product, drug or device.

Background

- **Hypoxia and ischemia**
  - Essential factors of neonatal hypoxic-ischemic encephalopathy.
  - Many biochemical changes
  - **Involvement of multiple signal transduction cascades**

Background

- **Hypoxia/Ischemia**
  - Involvement of signaling pathways for apoptosis
  - Its modification→ neuroprotection

- **Bee venom**
  - Anticancer mechanisms under hypoxia
  - Modification of signaling pathways for apoptosis

Bee venom (BV)

- Contains various peptides, enzymes and non-peptide components
- **BV peptides**; melittin, apamin, mast cell degranulation peptide and adolapin
- **Enzymes**; phospholipase A2, hyaluronidase, phosphomonoestrase, α-d-glucosidase and lypophospholipase
- **Non-peptide components**; histamine, dopamines, noradrenaline, carbohydrates and some lipids

Bee venom

- **Anti-inflammatory**, anti-neurotoxic, antibacterial, anti-allergic, and anti-hypertensive effects and regulatory functions in the autonomic nervous system *(Choi et al 2014, Lee et al 2012, Kwon et al 2001, Park et al 2008, Boman et al 1989)*
- Rheumatoid arthritis, Parkinson's disease, multiple sclerosis, neuro-muscular pain syndrome, skin disease and immune disease *(Wu 2014, Cho et al 2010)*

Background

BV and neuroprotection

- Bee Venom and Its Component Apamin as **Neuroprotective Agents** in a Parkinson Disease Mouse Model (Alvarez-Fischer, D., et al. (2013))
- A secretory phospholipase A2-mediated **neuroprotection** and anti-apoptosis(Armugam, A., et al. (2009))
- Bee Venom Phospholipase A2, a Novel Foxp3+ Regulatory T Cell Inducer, **Protects Dopaminergic Neurons** by Modulating Neuroinflammatory Responses in a Mouse Model of Parkinson's Disease(Chung, E. S., et al. (2015))
- Bee Venom **Protects** against Rotenone-Induced Cell Death in NSC34 **Motor Neuron Cells** (Jung, S. Y., et al. (2015))
- Apitoxin **protects rat pups brain** from propionic acid-induced oxidative stress: The expression pattern of Bcl-2 and Caspase-3 apoptotic genes (Khalil, S. R., et al. (2015))

Background

- **Anti-inflammatory effect of BV**
  - **Inhibiting NF-kB activation and modulating the expression of various inflammatory cytokines such as tumor necrosis factor alpha *(Choi et al 2014, Lee et al 2012)***
  - **Downregulates inducible nitric oxide synthase and cyclooxygenase-2, possibly through NF-kB and MAPK activation in neuronal and glial cells *(Lee et al 2012, Tu eat al 2011)***
  - **Melittin; decrease the expression of inflammatory cytokines through the regulation of NK-kB and MAPK signaling pathways *(Lee et al 2014)***

Background

- **MAPK pathways**
  - Mainly composed of key regulatory protein
  - Control **inflammation** and physiologic processes
  - Regulated by phosphorylation cascades
  - At least 3 distinct group MAPKs in mammals

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- **MAPK pathways**
  - Mainly composed of key regulatory protein
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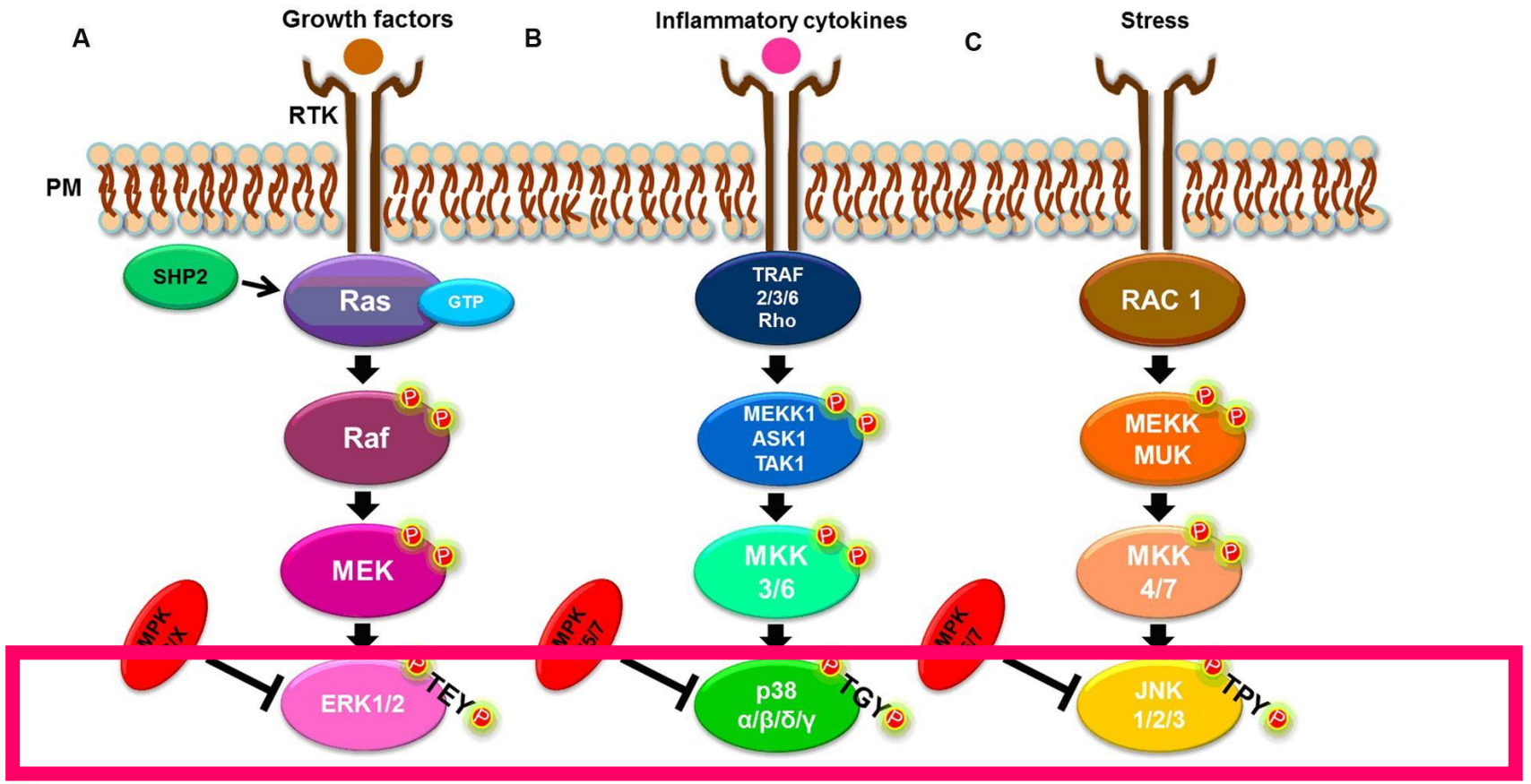
  - At least 3 distinct group MAPKs in mammals
    - Extracellular signal-regulated protein kinase 1/ 2 (ERK 1/ 2)
    - Stress-activated protein kinases (SAPK/JNK)
    - P38 kinases

Background



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Objectives

- 1) the effects of BV on cell viability following hypoxia with low glucose condition in neuronal cells and astrocytes
- 2) their neuroprotective mechanisms through expression of the activated MAPK pathways, including ERK, p38MAPK, and SAPK/JNK.

Methods

Neuronal Cells (E14)

Astrocytes(P1)

Normoxia (N)

Hypoxia
(1% O_2, 5% CO_2, 94% N_2)
Low glucose (H+lowG)

Hypoxia
(1% O_2, 5% CO_2, 94% N_2)
Low glucose+ BV
(H+lowG+BV)

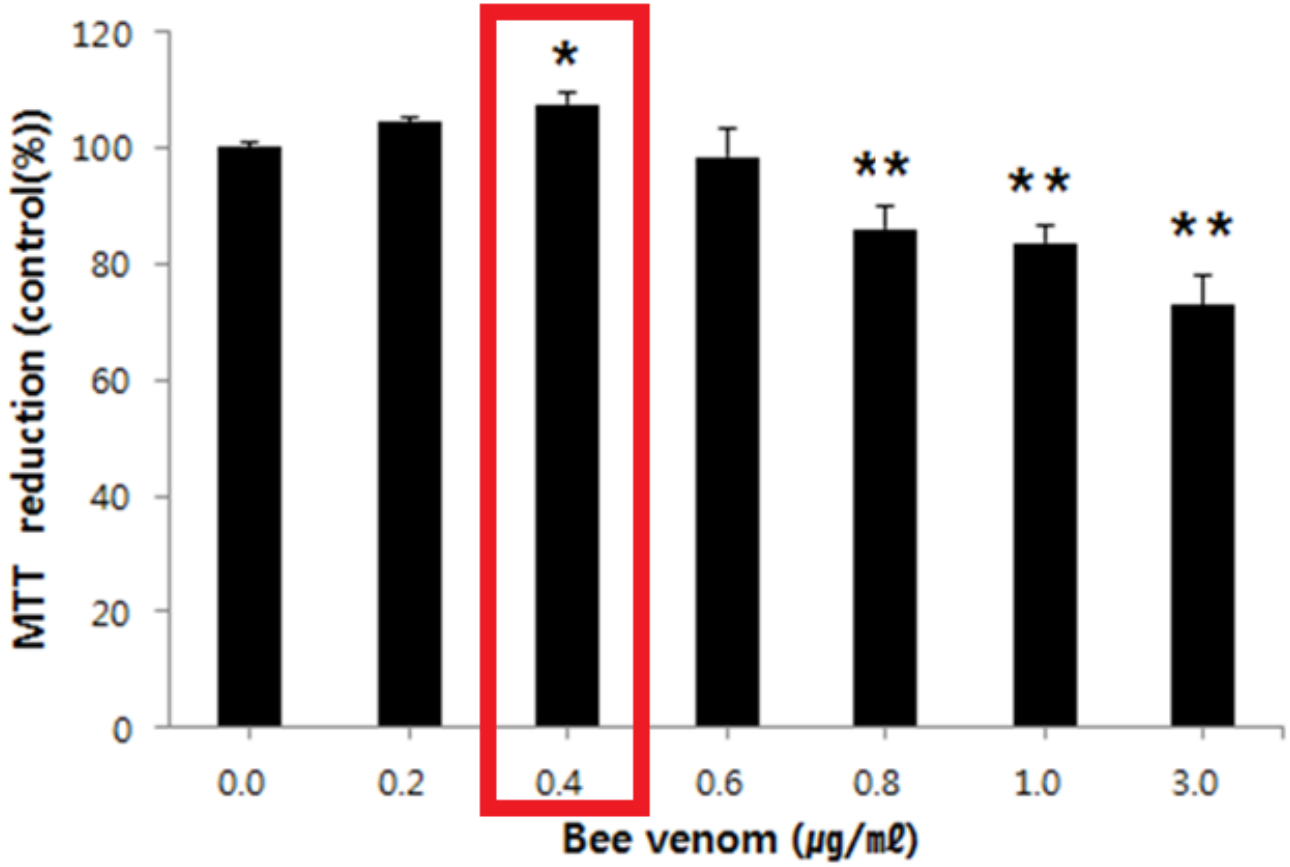
BV

ERK
P38
SAPK/JNK
Cell viability
0 hr
6 hr
15 hr
24 hr

Results

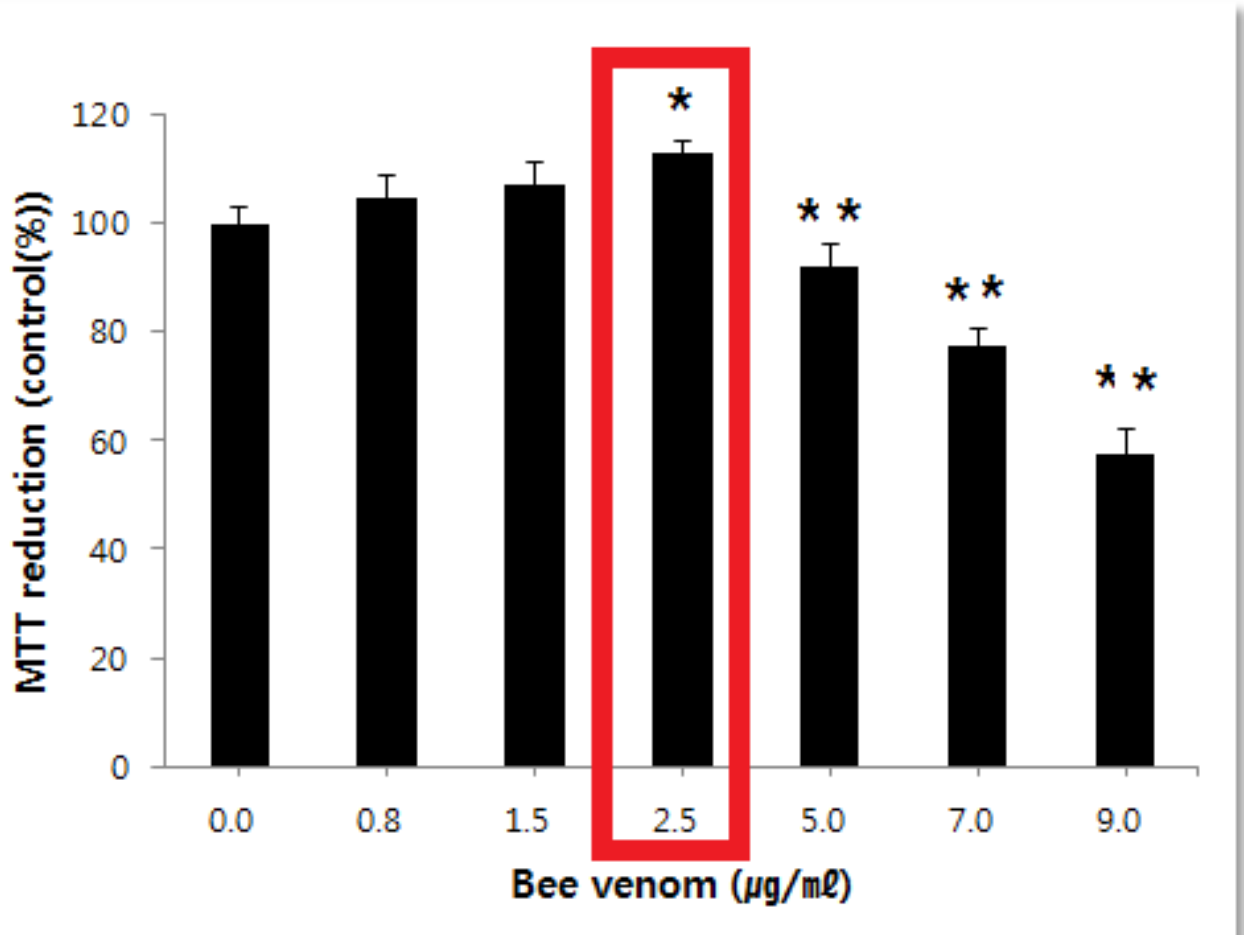
Optimal concentration of BV

Neuronal Cells



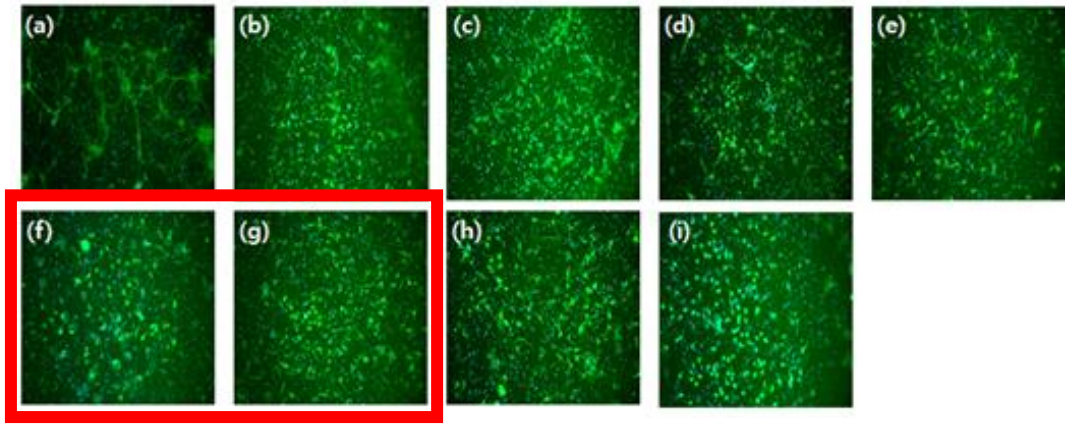
Optimal concentration of BV

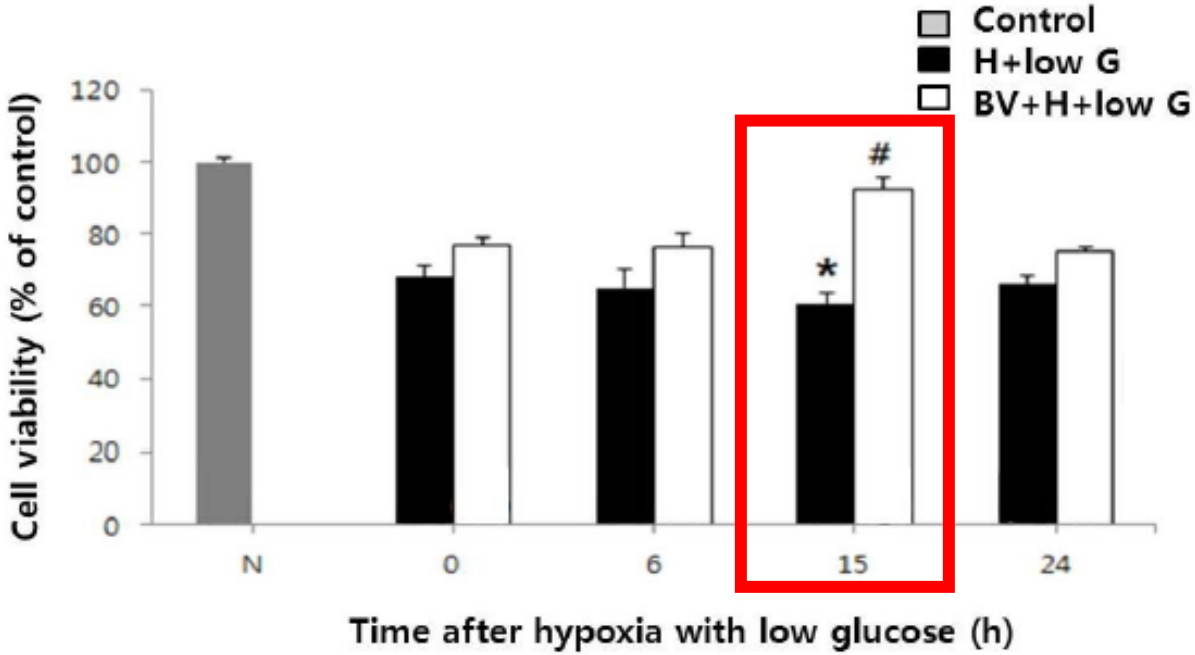
Astrocytes



Cell viability

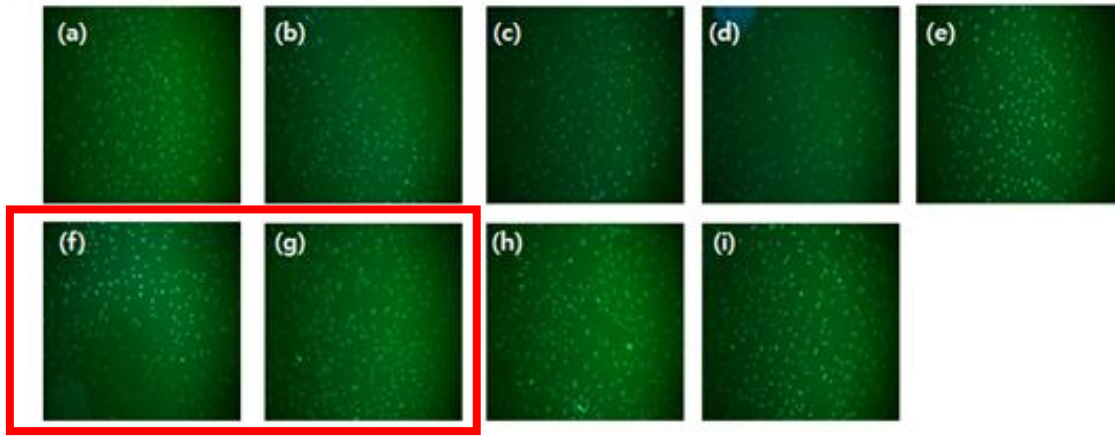
Neuronal cells

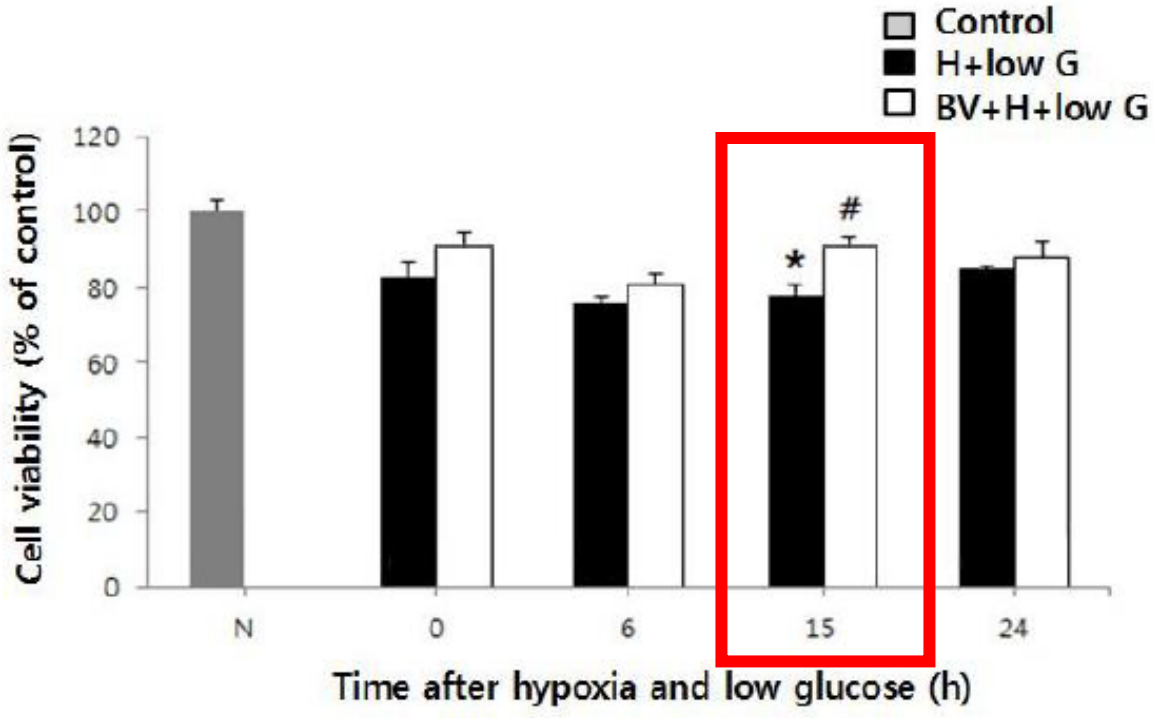




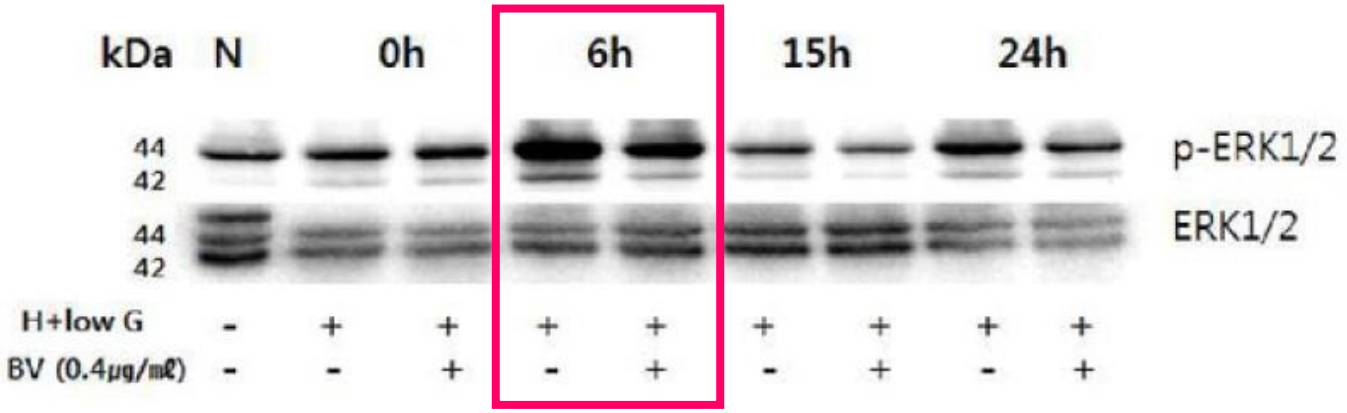
Cell viability

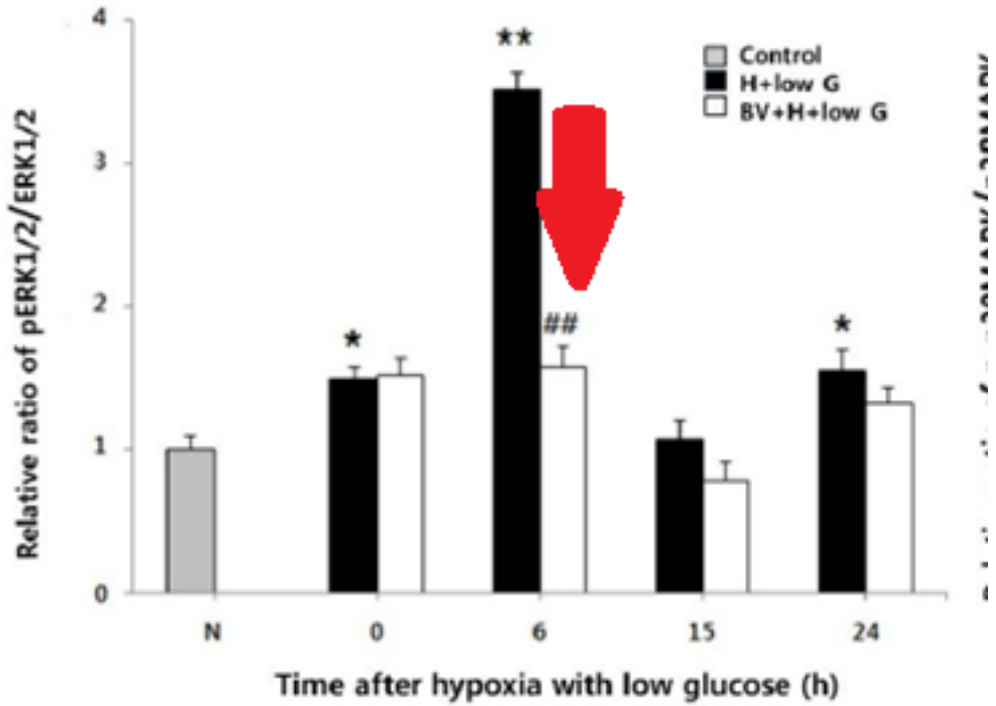
Astrocytes





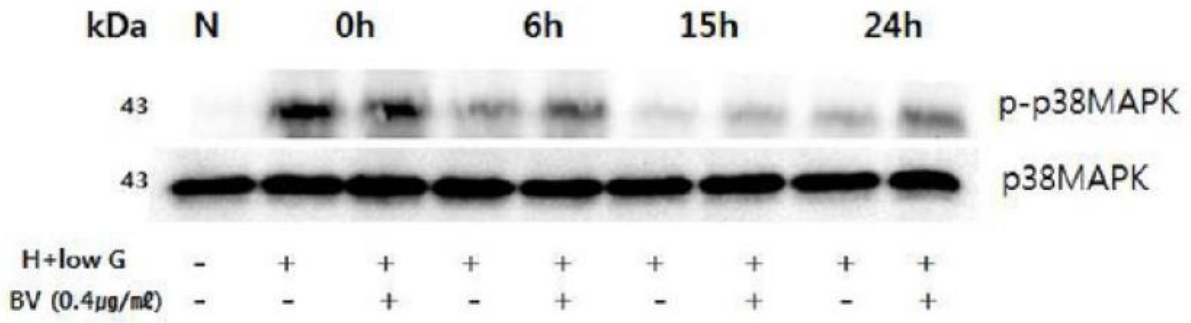
ERK

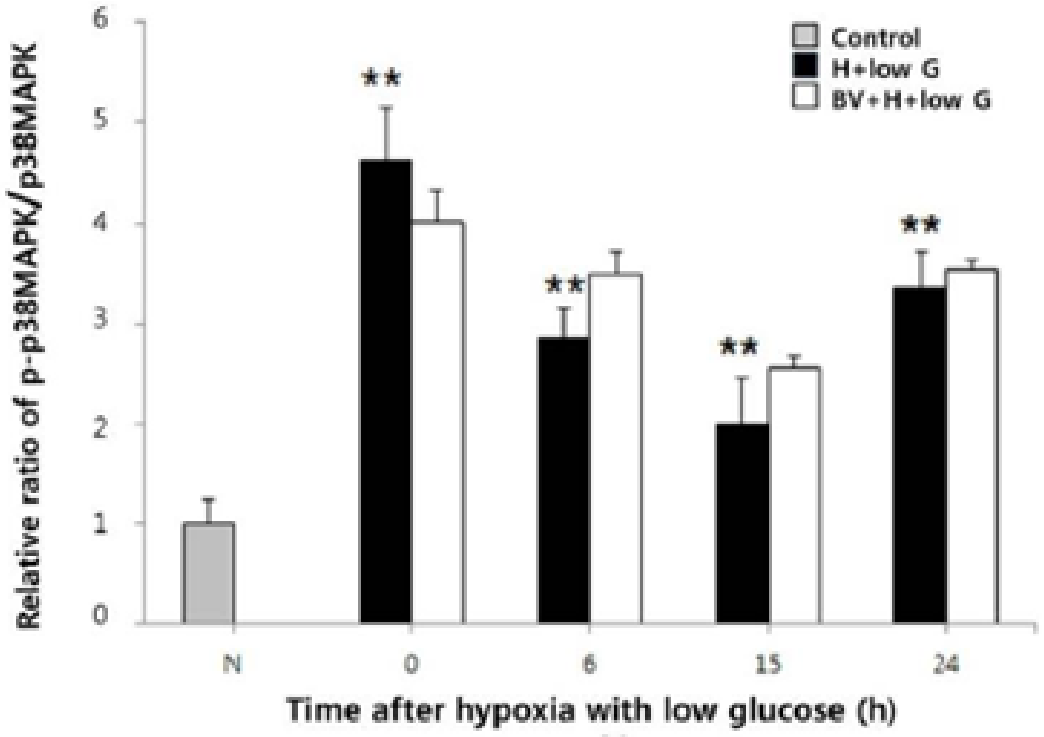




Neuronal Cells

p38

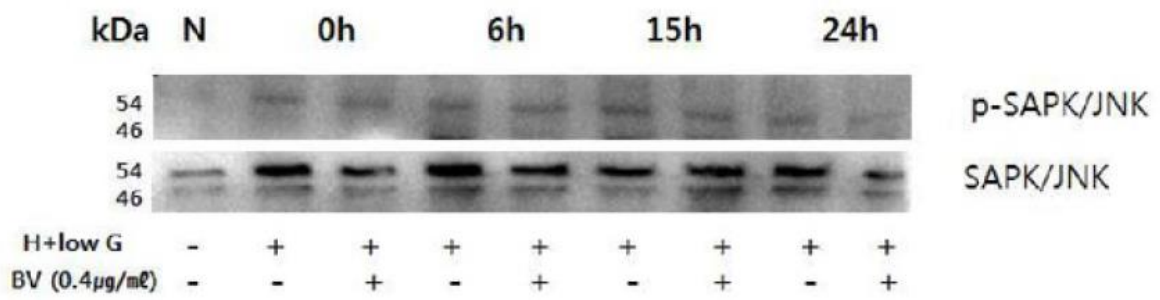


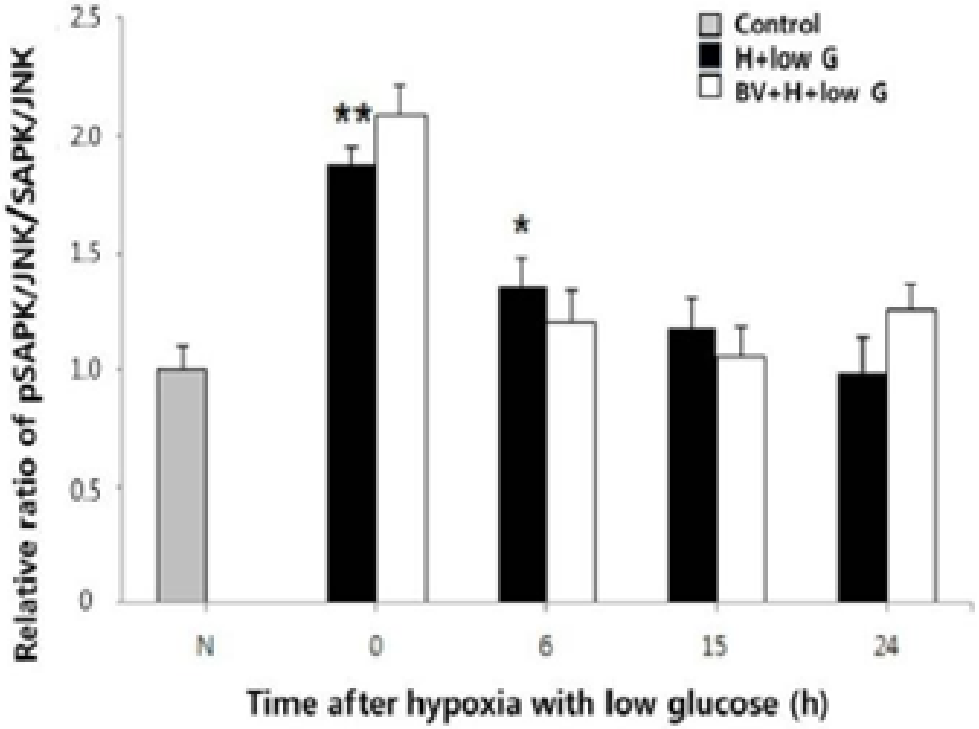


Gomgomi & Friends

Neuronal Cells

SAPK/JNK

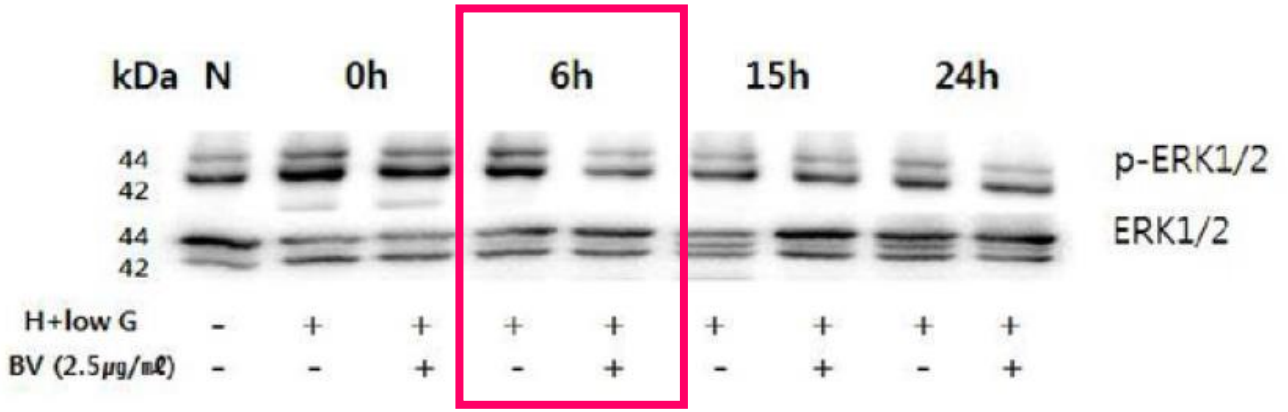


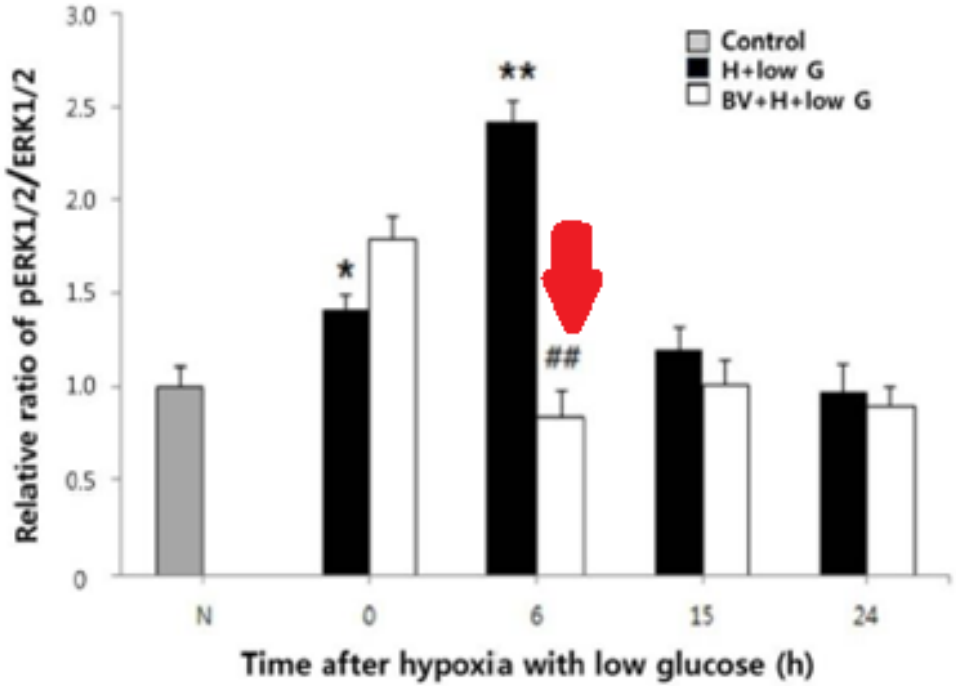


Gomgomi & Friends

Neuronal Cells

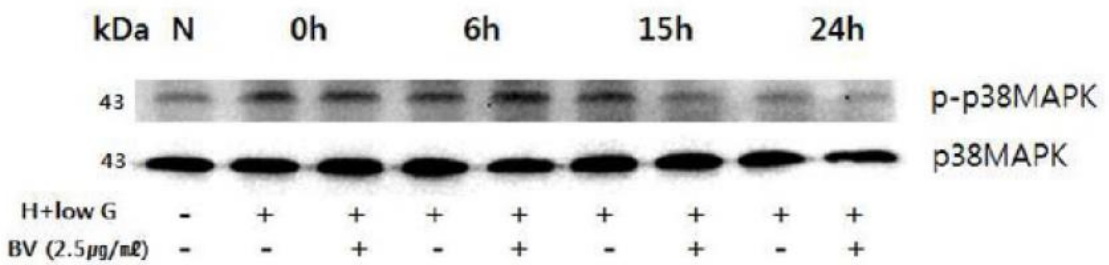
ERK

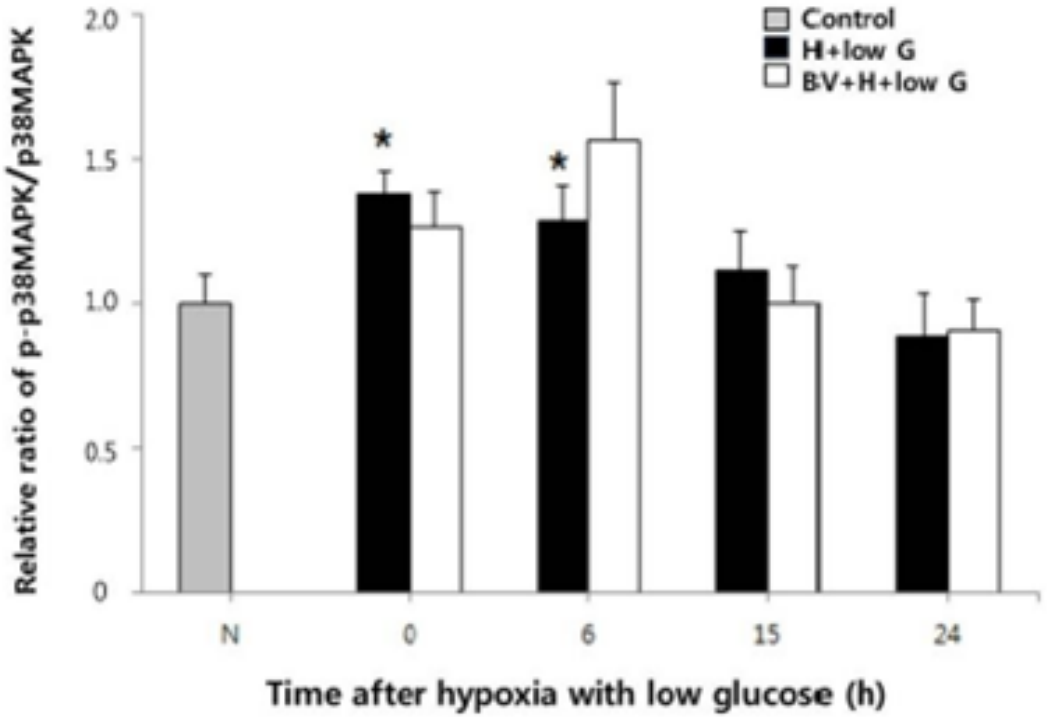




Astrocytes

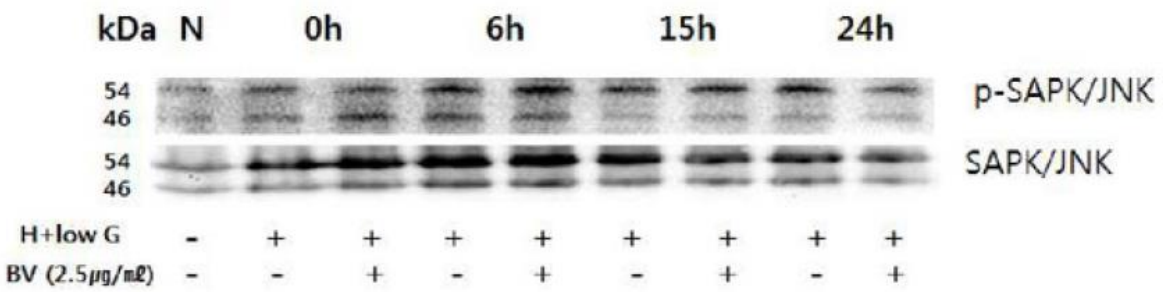
p38

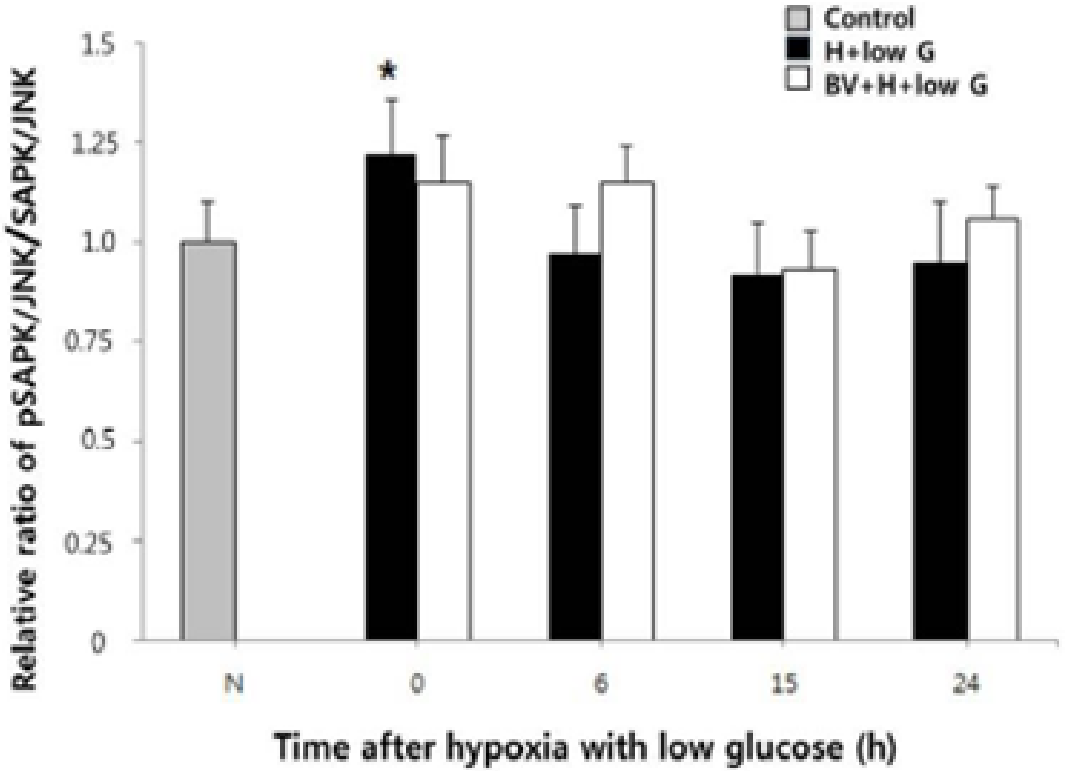




Astrocytes

SAPK/JNK





Astrocytes

Conclusion

- Phosphorylation of all MAPKs and reduction of cell survival after hypoxia and low G condition.
- Improved cell viability with BV pretreatment
- Inhibition of phosphorylation of ERK1/2 in BV pretreated neuronal cells and the astrocytes following H+low G condition
- No effects on p38MAPK and SAPK/JNK with BV pretreatment
- BV has neuroprotective effect through ERK1/2 mediated mechanism.

Acknowledgement