Activation of AMP-activated Protein Kinase by Propofol in Vascular Smooth Muscle

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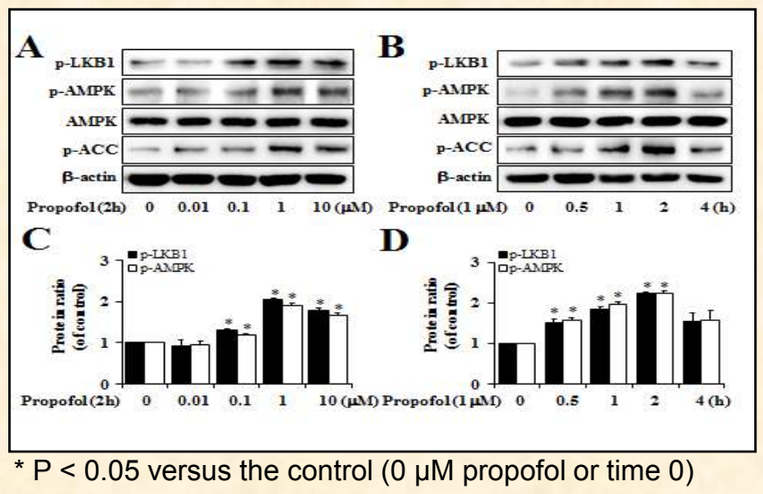
Background

Propofol induces vascular relaxation by increasing nitric oxide (NO) production and availability through endothelial protein kinase C (PKC) isoforms-mediated eNOS activation and decreasing cytoplasmic Ca^{2+} sensitivity in vascular smooth muscle cell (VSMC). **AMP-activated protein kinase (AMPK)** is a serine/threonine protein kinase involved in the **regulation of cellular energy homeostasis** by two major upstream kinase; liver kinase B1 (LKB1) and Ca^{2+}/calmodulin-dependent kinase kinase β (CaMKKβ) and also plays **an important role in the regulation of vasomotor tone in VSMC**. However, it has not established yet **whether energy metabolite-sensing signaling pathway is involved in propofol-induced vasodilation in VSMC**.

The purpose of this study was to investigate whether **propofol** attenuates phenylephrine (PE)-induced contraction through **AMPK activation** and to clarify **LKB1-signaling pathway** is involved in mediating propofol-induced AMPK activation in rat aortic VSMCs.

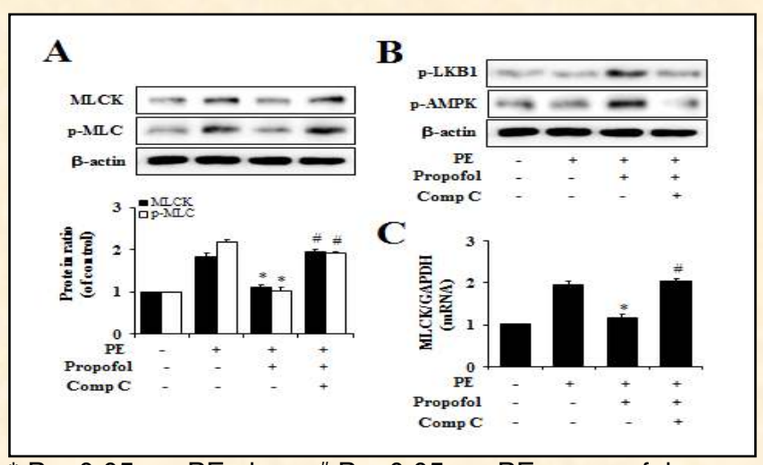
Methods and Result

Fig 1. Propofol phosphorylates AMPK, acetyl CoA carboxylase (ACC), and LKB1 in VSMCs (Western blot analysis).



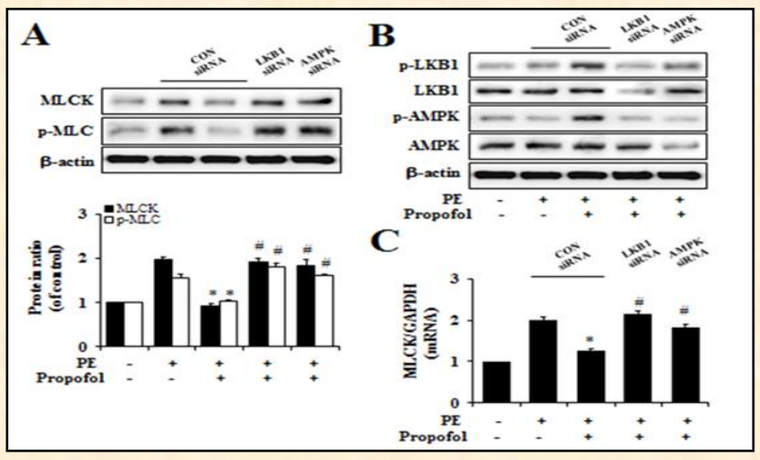
* P < 0.05 versus the control (0 μM propofol or time 0)

Fig 2. AMPK activation by propofol suppresses protein levels of myosin light-chain kinase (MLCK) and phosphorylated myosin light chain(p-MLC) in VSMC (Western blot analysis & q-PCR).



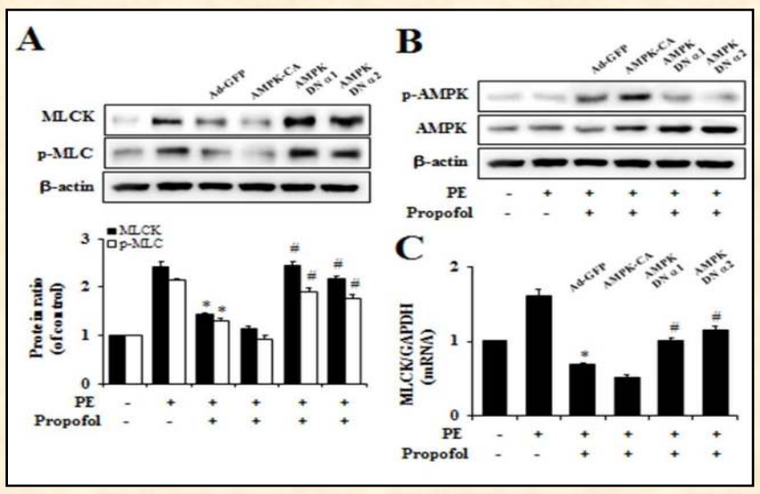
* P < 0.05 vs. PE alone, # P < 0.05 vs. PE + propofol
Comp C, Compound C ; nonspecific AMPK inhibitor

Fig 3. Propofol inhibits expressions of MLCK and p-MLC via a LKB1-AMPK-dependent mechanism in VSMCs (Western blot analysis & q-PCR).



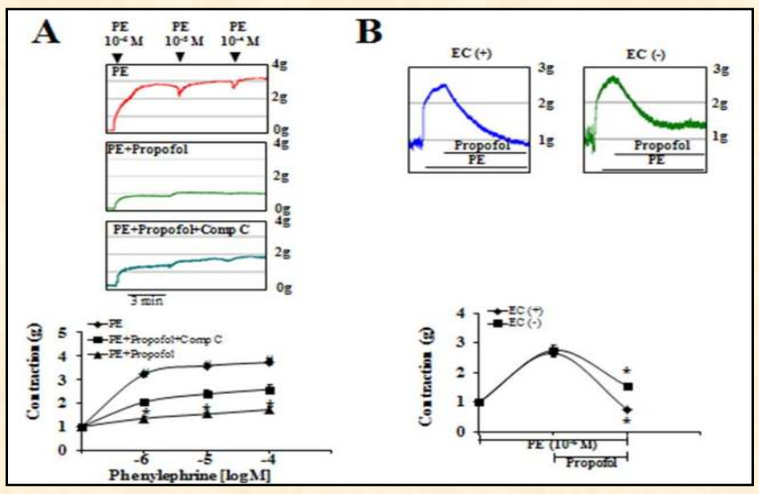
* P < 0.05 vs. PE alone, # P < 0.05 vs. control siRNA

Fig 4. Propofol regulates expressions of MLCK and p-MLC via AMPKα-dependent mechanism in VSMCs (Western blot analysis & q-PCR).



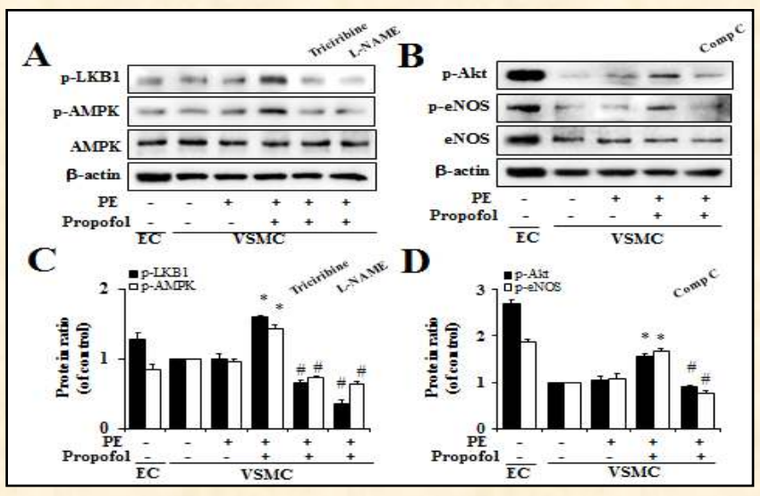
* P < 0.05 vs. PE alone, # P < 0.05 vs. adenovirus-GFP

Fig 5. Propofol attenuates phenylephrine-induced contractions in rat aorta (Isometric tension measurement).



* P < 0.05 versus PE, # P< 0.05 versus PE + propofol.
Comp C, Compound C ; nonspecific AMPK inhibitor

Fig 6. Propofol suppresses Protein kinase B (Akt) and endothelial nitric oxide synthase(eNOS) activation via a LKB1-AMPK-dependent mechanism in vascular smooth muscle cells (Western blot analysis).



* P < 0.05 vs. PE alone, # P < 0.05 vs. PE plus propofol
Triciribine; Akt inhibitor, L-NAME; eNOS inhibitor

Conclusion

Propofol activates AMPK via phosphorylation of LKB1, an upstream kinase, and subsequently attenuates phosphorylation of myosin light chain in phenylephrine-preconstricted aorta. Elucidating the AMPK activation mechanism of propofol in vasculature provides an additional explanation for the high incidence of hypotension observed in patients with vascular disease or metabolic syndrome during induction and maintenance of propofol anesthesia.

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