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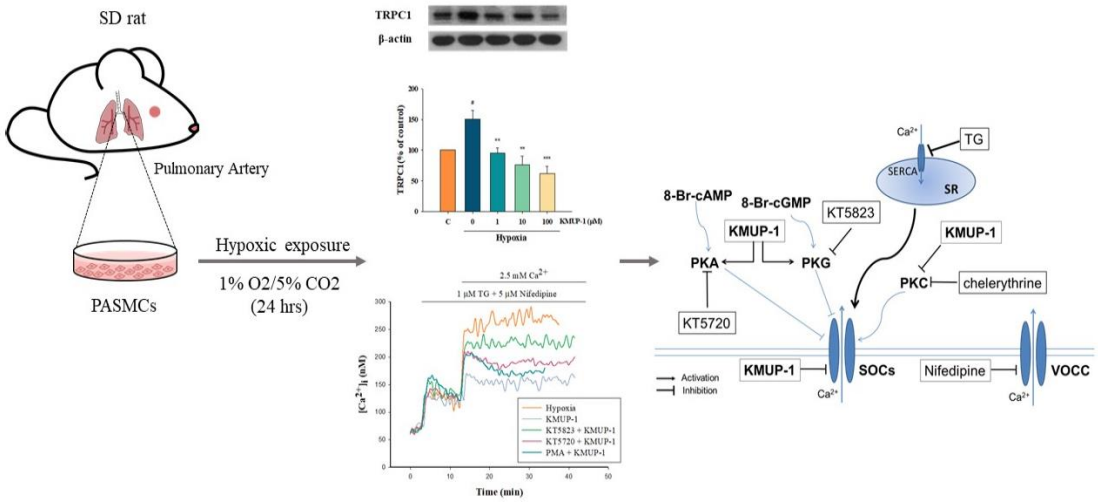
我們的團隊在 2024 年發表一篇很有意思的文章，發表於 Pharmaceuticals 2024, 17, 440。文章的標題為黃嘌呤衍生物 KMUP-1 抑制缺氧誘導肺動脈高壓透過調控 TRPC1 通道表現及鈣池調控鈣離子通道在肺動脈平滑肌細胞，其摘要如下所示：

暴露在缺氧（hypoxia）的情況之下會引起所謂的肺高壓。除此之外，肺動脈平滑肌細胞內鈣離子濃度的增加是引起肺血管的收縮及細胞增生的一個重要因子。本研究目的是探討 KMUP-1 能否抑制缺氧所導致的瞬時受體電位離子通道（canonical transient receptor potential channel; TRPC）的過度表現，其中所參與的機轉及 KMUP-1 能否調節藉由鈣池調控鈣離子通道(store-operated calcium channels; SOCs)進入的鈣離子濃度。犧牲 Spraque-Dawley 大鼠取出肺動脈初代培養肺動脈平滑肌細胞，將細胞置入含氧量為 1% O2/5% CO2 的可調節式細胞培養箱中 24 小時來誘導鈣池調控鈣離子通道的過度表現。KMUP-1（1 μM）可以抑制缺氧導致 TRPC 陽離子通道家族之蛋白質轉碼成鈣池調控鈣離子通道的過度表現，特別是 TRPC1 陽離子通道。而 KMUP-1 的抑制作用可以被 PKG 及 PKA 的抑制劑 KT5823（1 μM）、KT5720（1 μM）減弱，另外 KMUP-1 會抑制 PKC 的活化劑 PMA（1 μM）調控的 TRPC1 表現。所以 KMUP-1 的作用由實驗中可發現可能參與了活化 cGMP/PKG 和 cAMP/PKA 並且抑制 PKC 的路徑。除此之外，我們還利用 Fura-2/AM 測量缺氧誘導的肺動脈平滑肌細胞其儲存鈣離子的釋放以及經由鈣池調控鈣離子通道進入細胞的鈣離子。發現缺氧可以增加經由鈣池調控鈣離子通道之鈣離子。KMUP-1 可以減弱缺氧誘導肺動脈平滑肌細胞的鈣離子進入。

因此由實驗當中可以得知，KMUP-1 可以抑制缺氧誘導的肺動脈平滑肌細胞 TRPC1 蛋白質的表現並且可以減少經由鈣池調控鈣離子通道進入的鈣離子。



【具體成果】

審稿編輯：

1. Frontiers in Cardiovascular and Smooth Muscle Pharmacology
2. Frontiers in Clinical and Translational Physiology

副編輯：高雄醫學科學雜誌

【研究團隊】

團隊成員：王亮鈞、張毓秦

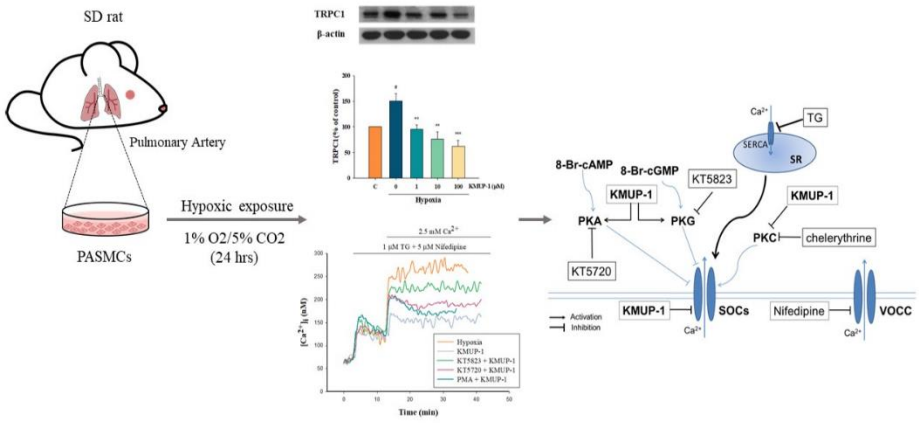
王亮鈞：博士後研究員

張毓秦：碩士級研究助理

團隊簡介：目前我們的研究團隊成員為一位博士後研究員，一位碩士級研究助理，兩位碩士班研究生以及一位博士班研究生。我們的團隊於每個星期五下午會舉行實驗室的會議，主要的目的是藉著會議分享每一位成員之研究進度及解決該週實驗碰到的問題。

研究聯繫 Email：binnan@kmu.edu.tw

Our team published an exciting paper in Pharmaceuticals 2024, 17, 440. The article entitled "The Xanthine Derivative KMUP-1 Inhibits Hypoxia-Induced TRPC1 Expression and Store-Operated Ca^{2+} Entry in Pulmonary Arterial Smooth Muscle Cells." The abstract is as follows. Exposure to hypoxia results in the development of pulmonary arterial hypertension (PAH). An increase in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in pulmonary artery smooth muscle cells (PASMCs) is a major trigger for pulmonary vasoconstriction and proliferation. This study investigated the mechanism by which KMUP-1, a xanthine derivative with phosphodiesterase inhibitory activity, inhibits hypoxia-induced canonical transient receptor potential channel 1 (TRPC1) protein overexpression and regulates $[Ca^{2+}]_i$ through store-operated calcium channels (SOCs). Ex vivo PASMCs were cultured from Sprague-Dawley rats in a modular incubator chamber under 1% O_2/5% CO_2 for 24 h to elucidate TRPC1 overexpression and observe the Ca^{2+} release and entry. KMUP-1 (1 μM) inhibited hypoxia-induced TRPC family protein encoded for SOC overexpression, particularly TRPC1. KMUP-1 inhibition of TRPC1 protein was restored by the protein kinase G (PKG) inhibitor KT5823 (1 μM) and the protein kinase A (PKA) inhibitor KT5720 (1 μM). KMUP-1 attenuated protein kinase C (PKC) activator phorbol 12-myristate 13-acetate (PMA, 1 μM)-upregulated TRPC1. We suggest that the effects of KMUP-1 on TRPC1 might involve activating the cyclic guanosine monophosphate (cGMP)/PKG and cyclic adenosine monophosphate (cAMP)/PKA pathways and inhibiting the PKC pathway. We also used Fura 2-acetoxymethyl ester (Fura 2-AM, 5 μM) to measure the stored calcium release from the sarcoplasmic reticulum (SR) and calcium entry through SOCs in hypoxic PASMCs under treatment with thapsigargin (1 μM) and nifedipine (5 μM). In hypoxic conditions, store-operated calcium entry (SOCE) activity was enhanced in PASMCs, and KMUP-1 diminished this activity. In conclusion, KMUP-1 inhibited the expression of TRPC1 protein and the activity of SOC-mediated Ca^{2+} entry upon SR Ca^{2+} depletion in hypoxic PASMCs.



【Concrete Results】

Reviewer Editor:

1. Frontiers in Cardiovascular and Smooth Muscle Pharmacology

2. Frontiers in Clinical and Translational Physiology

Associate Editor: The Kaohsiung Journal of Medical Sciences

【Research Team】

Team Members: Liang-Jun Wang、Yu-Chin Chang

Liang-Jun Wang: Postdoctoral fellowship

Yu-Chin Chang: Master research assistant

Research Team Introduction: So far, our research team has one postdoctoral fellow, one master research assistant, two master students, and one Ph.D. student. We routinely have a laboratory meeting each Friday afternoon. The principal purpose is to let each member share their research in progress and troubleshoot the experimental problem.

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