TIME: 95 年 3 月 18 日上午 9:00-11:00

**Taiwan Society of Pharmacology Annual Meeting - Graduate Student Paper Award Selection Speech**

**Inhibition of ICAM-1-Mediated Metastasis by Thalidomide in Human Lung Cancer**

**Authors:** Yi-Chu Lin*, Ching-Chow Chen#

**Presented by:** Yi-Chu Lin (Speaker), Ching-Chow Chen#

**Department of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan**

**Abstract:**

Our previous study demonstrated that intercellular adhesion molecule-1 (ICAM-1) expression induced by TNF-a not only increased monocyte adherence to A549 lung epithelial cells, but also elicited lung cancer cell invasion. In this report, we examined the role of ICAM-1 in carcinogenesis and the inhibitory effect of thalidomide. ICAM-1-overexpressing A549 cells induced in vitro cell invasion and in vivo tumor metastasis which were inhibited by thalidomide. The tumors grown in nude mice introduced by s.c. human lung cancer xenografts were detected to express ICAM-1, and attenuated by oral administration of thalidomide (200 mg/kg/day). Moreover, highly expressed ICAM-1 was found in the human specimens of lung cancer patients. The inhibitory effect of thalidomide on the TNF-a-induced protein and mRNA expressions of ICAM-1 was seen. This inhibition attributed to the reduced activity and binding of NF-kB to the ICAM-1 promoter, however, IkB-alpha degradation and translocation of NF-kB to the nucleus induced by TNF-a were not affected. These studies provide a framework that targeting ICAM-1 gene by thalidomide is a biologically based therapy for lung cancer.

TIME: 96 年 3 月 18 日上午 9:10-9:30

**Effects of Neonatal Dexamethasone Treatment on Hippocampal Synaptic Function**

**Authors:** Hsiao-Ju Lin*, Chiung-Chun Huang, Kuei-Sen Hsu#

**Presented by:** Hsiao-Ju Lin (Speaker), Chiung-Chun Huang, Kuei-Sen Hsu#

**Department of Pharmacology, College of Medicine, National Cheng Kung University, Tainan, Taiwan**

**Abstract:**

Our previous study demonstrated that intercellular adhesion molecule-1 (ICAM-1) expression induced by TNF-a not only increased monocyte adherence to A549 lung epithelial cells, but also elicited lung cancer cell invasion. In this report, we examined the role of ICAM-1 in carcinogenesis and the inhibitory effect of thalidomide. ICAM-1-overexpressing A549 cells induced in vitro cell invasion and in vivo tumor metastasis which were inhibited by thalidomide. The tumors grown in nude mice introduced by s.c. human lung cancer xenografts were detected to express ICAM-1, and attenuated by oral administration of thalidomide (200 mg/kg/day). Moreover, highly expressed ICAM-1 was found in the human specimens of lung cancer patients. The inhibitory effect of thalidomide on the TNF-a-induced protein and mRNA expressions of ICAM-1 was seen. This inhibition attributed to the reduced activity and binding of NF-kB to the ICAM-1 promoter, however, IkB-alpha degradation and translocation of NF-kB to the nucleus induced by TNF-a were not affected. These studies provide a framework that targeting ICAM-1 gene by thalidomide is a biologically based therapy for lung cancer.
The synthetic glucocorticoid dexamethasone (DEX) is frequently used to prevent or lessen the morbidity of chronic lung disease in premature infants. Surprisingly, little is known about the long-term neurodevelopmental outcomes of this therapy. Here, we use a protocol with tapering doses of DEX proportional to the one used to treat preterm human neonates to examine the consequences of neonatal DEX treatment on hippocampal synaptic plasticity and associative memory in later life. We found that neonatal DEX treatment switched the direction of synaptic plasticity, favoring low-frequency stimulation-induced long-term depression (LTD), and opposing the induction of long-term potentiation (LTP) by high-frequency stimulation in the adolescent (5-week-old), but these alterations disappeared in young adulthood (8-week-old). The effects of neonatal DEX treatment on LTP and LTD were correlated with an increase in the autophosphorylation of Ca\(^{2+}\)/calmodulin-dependent protein kinase II at threonine-286 and a decrease in the protein phosphatase 1 activity. Neonatal DEX treatment also induced a disruption of memory retention in 5-week-old rats subjected to a passive avoidance learning task, whereas 8-week-old rats exhibited normal memory retention. These results suggest that neonatal DEX treatment alters the hippocampal synaptic plasticity and contextual fear memory formation in later life; however, these impairments are not permanent.

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時間：95 年 3 月 18 日 上午 9：50-10：10

題目：HYPOXIA-INDUCIBLE FACTOR-1/HEME OXYGENASE-1 CASCADE ACTIVATES NITRIC-OXIDE SYNTHASE I/PROTEIN KINASE G SIGNALING PATHWAY AT ROSTRAL VENTROLATERAL MEDULLA DURING MEVINPHOS INTOXICATION IN THE RAT

作者：C.Y. Tsai\(^1\), Samuel H.H. Chan\(^1\), Alice Y.W. Chang\(^1\)

蔡靜宜（演講者）、陳慶鏗、張雅雯

演講單位：1Department of Biological Sciences, National Sun Yat-sen University
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1國立中山大學生物科學系
2國立中山大學神經科學研究中心

摘要：

The organophosphate poison mevinphos (Mev) induces its sympathoexcitatory phase (Phase I) of cardiovascular responses via nitric oxide (NO) produced by NO synthase I (NOS I) in the rostral ventrolateral medulla (RVLM), the origin of sympathetic vasomotor tone. This study evaluated the regulatory role of heme oxygenase-1 (HO-1) and its key transcription factor, hypoxia-inducible factor-1 (HIF-1), in this process. In Sprague-Dawley rats anesthetized with propofol, microinjection bilaterally of Mev (10 nmol) into the RVLM elicited significant hypoxia, along with nuclear translocation of HIF-1, in this medullary site. HO-1, heat shock protein 70 (HSP70), NOS I or protein kinase G (PKG) expression in the RVLM was also upregulated during Phase I Mev intoxication. Pretreatment by microinjection of anti-HO-1 antiserum or antisense ho-1 oligonucleotide bilaterally into the RVLM significantly blunted the augmented expression of HSP70, NOS I or PKG exhibited during this phase of Mev-induced increase in sympathetic...
vasomotor activities. Pretreatment with HO-2 antiseraum or antisense ho-2 oligonucleotide, however, was ineffective. We conclude that HIF-1/HO-1 cascade regulates NOS I/PKG signaling via activation of HSP70 in the RVLM during the sympathoexcitatory phase of Mev intoxication.

THALIPORPHINE INCREASES SURVIVAL RATE AND ATTENUATES MULTIPLE ORGAN INJURY IN LPS-INDUCED ENDOTOXAEMIA

題目：THALIPORPHINE INCREASES SURVIVAL RATE AND ATTENUATES MULTIPLE ORGAN INJURY IN LPS-INDUCED ENDOTOXAEMIA

作者：Chin-Wei Chiao1*, Shoei-Sheng Lee2, Chin-Chen Wu3, Ming-Jai Su1#

演講者單位：1Institute of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan
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3Department of Pharmacology, National Defense Medical Center, Taipei, Taiwan

摘要：This study addressed the question of whether thaliporphine, a phenolic aporphine alkaloid obtained from Chinese herbs and possessing antioxidant and α1 adrenoceptor antagonistic activity, has protective effects in endotoxaemic rats and we attempted to elucidate the mechanisms contributing to such protective effects. Injection of rats with endotoxin (lipopolysaccharide, LPS) induced severe hypotension and tachycardia as well as vascular hyporeactivity to NE. Pretreatment of LPS-treated rats with thaliporphine attenuated the delayed hypotension and decreased LPS-induced tachycardia. LPS increased NO and O2· levels that were reduced by pretreatment with thaliporphine. A peak at 60 min of serum TNF-α level and the late-phase decrease of blood glucose in endotoxaemia were both attenuated by thaliporphine. Endotoxaemia induced multiple organ injury, as indicated by increases of GOT, GPT, CRE, LDH and CKMB levels in serum. These increases of biochemical markers and inflammatory cell infiltration into injured tissues were reduced significantly by treatment with thaliporphine. In addition, thaliporphine increased the survival rate of LPS-treated mice dose-dependently. In conclusion, our results suggest that thaliporphine could be a novel agent for attenuating endotoxin-induced circulatory failure and multiple organ injury and may increase the survival rate. These beneficial effects of thaliporphine may be attributed to the suppression of TNF-α, NO and O2· production.

INSULIN STIMULATES POSTSYNAPTIC DENSITY-95 PROTEIN TRANSLATION VIA THE PHOSPHOINOSITIDE 3-KINASE-Akt-MAMMALIAN TARGET OF
RAPAMYCIN SIGNALING PATHWAY

作者：Cheng-Che Lee¹²*, Chiung-Chun Huang¹, Mei-Ying Wu¹, Kuei-Sen Hsu¹²#

演講者：李政哲*(演講者)、黃瓊君、吳美瑩、許桂森#

演講者單位：¹Department of Pharmacology, College of Medicine, National Cheng Kung University, Tainan 701, Taiwan
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摘要：Insulin receptors are highly enriched at neuronal synapses, but whose function remains unclear. Here we present evidence that brief incubations of rat hippocampal slices with insulin resulted in an increased protein expression of dendritic scaffolding protein postsynaptic density-95 (PSD-95) in area CA1. This insulin-induced increase in the PSD-95 protein expression was inhibited by the tyrosine kinase inhibitor, AG1024, phosphatidylinositol 3-kinase (PI3K) inhibitors, LY294002 and wortmannin, translational inhibitors, anisomycin and rapamycin, but not by LY303511 (an inactive analogue of LY294002), and transcriptional inhibitor, actinomycin D, suggesting that insulin regulates the translation of PSD-95 by activating the receptor tyrosine kinase-PI3K-mammalian target of rapamycin (mTOR) signaling pathway. A similar insulin-induced increase in the PSD-95 protein expression was detected after stimulation of the synaptic fractions isolated from the hippocampal neurons. Furthermore, insulin treatment did not affect the PSD-95 mRNA levels. In agreement, insulin rapidly induced the phosphorylation of 3-phosphoinositide-dependent protein kinase-1 (PDK1), protein kinase B (Akt), and mTOR, effects that were prevented by the AG1024 and LY294002. We also show that insulin stimulated the phosphorylation of 4E-binding protein 1 (4EBP1) and p70S6 kinase (p70S6K) in a mTOR-dependent manner. Finally, we demonstrate the constitutive expression of PSD-95 mRNA in the synaptic fractions isolated from hippocampal neurons. Taken together, these findings suggest that activation of the PI3K-Akt-mTOR signaling pathway is essential for the insulin-induced up-regulation of local PSD-95 protein synthesis in neuronal dendrites and indicate a new molecular mechanism that may contribute to the modulation of synaptic function by insulin in hippocampal area CA1.