

**Effects of buprenorphine on the memory acquisition and the nociceptin receptor expression in the hippocampus**Chen Ruei-Ching<sup>1</sup>, Huang Chieh-Liang<sup>1,3</sup>, Ho Ing-Kang<sup>1,2,4</sup>, **Chiang Yao-Chang**\*<sup>1,2</sup><sup>1</sup>Center for Drug Abuse and Addiction, China Medical University Hospital, Taichung, Taiwan<sup>2</sup>Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan<sup>3</sup>College of Medicine, China Medical University, Taichung, Taiwan<sup>4</sup>Neuropsychiatric Research Center, National Health Research Institutes, Zhunan, Miaoli County, Taiwan

**Abstract** Buprenorphine is an antinociceptive agent, which is usually used for treating pain in low doses, and also used for treating heroin addicts in higher doses recently. Buprenorphine can act on  $\mu$ -opioid receptor (MOR) and nociceptin receptor (NOPR) by a concentration-dependent manner. Lower doses of buprenorphine act on MOR, but both MOR and NOPR are activated in higher doses of buprenorphine administration. It is well known that chronic opioids (such as morphine or methadone) administration influences memory functions in human and animals. NOPR has been reported to involve in the regulation of glutamine system, which is an important neurotransmitter for memory development and formation. Although, buprenorphine exhibits several benefits for treating heroin addicts than methadone, chronic effects of buprenorphine on memory and glutamate system are unclear and needed further investigation. In our current results showed that buprenorphine treatment with low or high dose, acute or chronic, decreased the percentage of arm entry and time spent in the Novel arm as compared to vehicle control in Y maze model. The mRNA expression of MOR and NOPR were also showed the different expression patterns in the acute and chronic buprenorphine administration. The miRNA-seq was also performed to find the passible candidate of miRNA for regulating the receptors expression. Additionally, the cell model also exhibited that buprenorphine influences the Grin1 (glutamate NMDA receptor subunit zeta-1) gene expression with a time dependent manner. Therefore, in the current results might imply that both low and high doses of buprenorphine with acute or chronic treatment conditions changed the spatial memory acquisition of mice on Y maze model via influences of NOPR and glutamate systems.

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**Key words:** buprenorphine, nociceptin receptor, memory, glutamate, microRNA

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