**[S8-4] [10/11/2003(Sat) 11:50-12:30/ Grand Ballroom 105]**

# Effects of Berberine on Morphine-induced Neurotoxicity in Mice

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Morphine is a potent analgesic and addictive substance. Morphine produces neurotoxicity such as rewarding effect, analgesic tolerance and physical dependence. It has been restricted to the use of morphine in patients because of these problems.

The present study was investigated the effect of berberine on the neurotoxicity of morphine. Repeated administration of morphine produced conditioned place preference (CPP) and behavioral sensitization in mice. Pretreatment with berberine significantly inhibited morphine-induced CPP and behavioral sensitization. In this experiment, pretreatment with berberine did not decrease postsynaptic dopamine receptor supersensitivity induced by apomorphine 24h after morphine CPP and sensitization, suggesting that inhibition by berberine of morphine-psychotoxicity is not related to the dopaminergic system. However, pretreatment with berberine significantly reduced morphine-induced NR2A and NR2B expression in the cortex and was tended to decrease morphine-induced NR1 expression, compared with the morphine-treated group. In addition, the administration of morphine significantly increased NADPH-diaphorase (NADPH-d) positive sells and nNOS expression in the striatum compared with the saline group. This result suggests a possible role of NOS system in the morphine reward process. Pretreatment with berberine significantly reduced NADPH-d positive cells and nNOS expression compared with the morphine group. Our finding suggests that NOS system in the striatum may play a role in control of rewarding effects of morphine.

Accumulating data suggest that immediately early genes (IEGs) are involved in the drugs of abuse. We, therefore, measured c-fos, p-CREB and Δfos-B expression in morphine CPP mouse brain. c-Fos, p-CREB and Δfos-B expression were increased in the cortex and striatum of morphine CPP mice. Pretreatment with berberine reduced the morphine-induced IEGs, c-fos, p-CREB and Δfos-B expression in various brain regions. These data indicate that the IEGs expression plays an important role in modulating of morphine-induced CPP and suggest that inhibitory effect by berberine of morphine-induced CPP are mediated by the inhibition of NOS system, NMDA receptors, and IEGs expressions.

In analgesic tolerance study, pretreatment with berberine inhibited development of morphine tolerance. Acute treatment with berberine did not reduce the morphine analgesia in mice. These results suggest that berberine can be used for the treatment and prevention of morphine tolerance.

Taken together, it is concluded that berberine may be useful for the preventive and treatment of morphine-induced neurotoxicity. (Supported by the Brain Korea 21 project in 2003)