Effect of nitric oxide synthase inhibitor on methamphetamine-induced dopaminergic neurotoxicity in rats

Kazue Kikuchi-Utsumi, Masahiko Watabe, Nobuko Matsumura, Toshio Nakaki

Department of Pharmacology, Teikyo University, School of Medicine, Japan

Methamphetamine (METH) is a psychostimulatory drug with addictive potential. This activity is associated primarily with the stimulation of dopamine release. METH is most harmful to dopaminergic neuron, and its administration to rodents causes long-term damage to dopaminergic terminals in the striatum. We previously demonstrated that BMY7378, α 1D-adrenoceptor antagonist, is completely abolished the METH-induced neurotoxicity without alteration of the striatal extracellular level of dopamine, suggesting an essential role for α 1D-adrenoceptor to the METH neurotoxicity in rats. A functional interaction between glutamate and nitric oxide (NO) has been implicated in the METH-induced neurotoxicity; however, this issue still remains controversial. This study was designed to investigate on the relationship between the neuroprotective effects of BMY 7378 and the striatal NO and glutamate levels in METH-injected rats.

The rats were intraperitoneally injected with METH (6 mg/kg), 4 consecutive times at 2-h intervals. Pretreatment with α 1-adrenoceptor antagonist (prazosin, BMY7378) or S-methyl-L-thiocitrulline (SMTC), NO synthase inhibitor, was administered intraperitoneally 30 min before each METH injection. METH-induced hyperthermia, one of the exacerbating factors of this neurotoxicity, was monitored 1 h after each METH injection with a rectal thermistor probe. Extracellular levels of dopamine, glutamate, and citrulline (an indirect marker for NO synthesis) in the striatum during METH administration was analyzed by *in vivo* microdialysis. Five days after METH administration, striatal dopamine level was quantified by HPLC.

METH treatments induced hyperthermia and a decrease in the striatal dopamine level. *In-vivo* microdialysis analysis revealed that METH led to an increase in extracellular citrullin and glutamate levels in the striatum. Pretreatment with prazosin (non-selective α 1-adrenoceptor antagonist), or BMY7378 was completely abolished the METH neurotoxicity with a partial reduction of the hyperthermia. These antagonists also strongly prevented increases in extracellular levels of citrulline and glutamate. On the other hand, pretreatment with SMTC did not affect METH-induced hyperthermia. Although this inhibitor exhibited complete inhibition of increases in extracellular glutamate and citrulline levels, the METH-induced neurotoxicity was not ameliorated.

These results suggest that METH-induced NO production is not directly associated with METH-induced dopaminergic neurotoxicity in rat striatum.