Title	ALTERATIONS OF HIPPOCAMPAL NEUROGENESIS AND BEHAVIORAL PROFILES IN AN ANIMAL MODEL OF METHAMPHETAMINE DEPENDENCE
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Academic Paper	Thesis M.S. in Anatomy, Naresuan University, 2012
Keywords	Methamphetamine, drug dependence, hippocampal neurogenesis, gliogenesis, cognitive function, proliferative cell nuclear antigen (PCNA), microtubule associated protein 2 (MAP2), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP)

ABSTRACT

Methamphetamine (METH) is an abused psychostimulant drug. METH has been reported to induce neurotoxicity and cause neuronal cells death leading to behavioral changes. METH can cause learning and memory impairments and diminish neurogenesis as well as neurodegeneration. Moreover, not only neurons have been affected following METH administration but the response of glial cells has also been demonstrated. Therefore, the aim of this study was to investigate the alterations of behavioral profiles and the alterations of proliferative cell nuclear antigen (PCNA), a marker of neuronal stem cells, microtubule associated protein 2 (MAP2), a marker of mature neurons, myelin basic protein (MBP), a marker of oligodendrocytes and glial fibrillary acidic protein (GFAP), a marker of astrocytes in the hippocampal neurogenesis in area of subgranular zone (SGZ) and subventricular zone (SVZ) after escalating and binge doses-METH administration. Adult male rats were divided into 4 groups: control group – rats were intraperitoneally administered with saline; acute dose-METH binge group (AB-METH) – rats were injected with saline and 4x6.0 mg/kg METH on day 15; escalating dose-METH group (ED-METH) – rats were injected with three doses of METH 0.1-4.0 mg/kg/day on day 1-14 and saline on day 15; escalating dose-METH binge group (ED-METH binge) – rats were injected as well as ED-METH group on day 1-14 and 4x6.0 mg/kg METH on day 15. At the last dose

of each day, the behaviors of animals were observed using behavioral rating scale and locomotor activity test, while novel object recognition test was observed on day 15-16. Rats were sacrificed and brains were removed. Expressions of all markers were measured by immunohistochemistry technique.

The results showed that the behavioral rating scale scores were significantly increased in all groups compared with control group. In addition, locomotor activity was significantly increased in ED-METH binge and ED-METH groups while in AB-METH was significantly decreased on day 15 compared with control group. Although, AB-METH group showed hypolocomotion while animal in AB-METH group showed behavior of drug dependence, such as oral stereotype and head movement. In addition, the novelty index of short-term memory in all groups was significantly decreased when compared with control group. In long-term memory, the novelty index was significantly decreased in ED-METH binge compared with control group.

A significantly decreased of PCNA immunoreactive (PCNA-IR) cell in SGZ was observed in ED-METH binge and ED-METH groups compared with control group. Moreover, PCNA-IR cells were significantly decreased in SVZ in all groups compared with control group. MAP2 immunoreactive (MAP2-IR) cells were significantly decreased in ED-METH binge and ED-METH groups in SGZ and in all groups in SVZ when compared with control group. GFAP immunoreactive (GFAP-IR) cells were significantly increased in ED-METH binge and AB-METH groups in SGZ and SVZ compared with control group. In addition, MBP-IR was significantly decreased in cingulate cortex in ED-METH binge and AB-METH compared with control group.

In conclusion, the results of this study indicate that escalating and binge doses-METH can increase behavioral responses such as hyperlocomotion and stereotypy and induce cognitive performance impairment. Moreover, METH can diminish neurogenesis and cause alteration of gliogenesis in SGZ and SVZ of hippocampus. The results of this study also provide evidence to support neurotoxicity of METH which not only it can induce neuronal and glial cell death, but it also induce originally neurogenesis and gliogenesis, leading to abnormalities of behaviors and cognitive functions.