CHARPTER I

INTRODUCTION

Rationale and significance of the study

Methamphetamine had been increased an incident to use in worldwide, for example, Hawaiian (2.2%), two or more races (1.9%), American (1.7%), White (0.7%), Hispanic (0.5%), Black (0.1%) and Asian (0.2%), during 2002 to 2004 (Winslow, et al., 2007). In Thailand, between 2008 and 2010, the number of methamphetamine abusers had been increased by approximately 244.98% (Office of The Narcotics Control Board; 2011). Methamphetamine abusers have been reported to increase in all ages especially 8-14 years in Thailand (Office of The Narcotics Control Board; 2011). Methamphetamine abuse is a serious public health, social and economic problem leading to national crisis.

Methamphetamine, an N-methyl homolog of amphetamine, is an abuse psychostimulant drug of phenethylamine and amphetamine class that produces effects on several systems especially on central nervous system (CNS) and peripheral nervous system (PNS) (Dutta, et al., 2006; Bankole, et al., 2007). It has been reported that methamphetamine can induce neurotoxic effects in several brain regions such as frontal cortex, parietal cortex and hippocampus (Zhu, et al., 2006; Lee, et al., 2011). Methamphetamine causes increased levels of extracellular glutamate in several brain regions (Tzschentke and Schmidt, 2003; Raudensky and Yamamoto, 2007). High concentrations of glutamate in synaptic cleft may activate glutamate receptors and mediate excitotoxicity leading to apoptosis (Zhao, et al., 2006) and neuronal cell death. Moreover, it can increase neurodegeneration (Zhu, et al., 2006; Kuczenski, et al., 2007; Atianjoh, et al., 2008) leading to behavioral changes (Suzuki, et al., 2004). Methamphetamine can induce long term behavioral changes including behavioral sensitization (Suzuki, et al., 2004), tolerance (Winslow, et al., 2007; Kuczenski, et al., 2007) and drug dependence (Mandyam, et al., 2007) such as an increase of alertness, hyperlocomotion, euphoria, automatic jerking movement, repetitive behaviors, and stereotype. Methamphetamine can also

cause learning impairments and memory loss (Winslow, et al., 2007; Lee, et al., 2011). In addition, neurotoxic effects of methamphetamine can induce diminish neurogenesis and gliogenesis which lead to decrease mature neurons and glial cells such as astrocytes and oligodendrocytes (Mandyam, et al., 2008; Schaefers, et al., 2009) in striatum (Zhu, et al., 2006), medial prefrontal cortex and hippocampus (Kadota and Kadota, 2004; Mandyam, et al., 2008).

Neurogenesis is a process of generating new neuronal cells that occur in brain and spinal cord during development especially prenatal and early postnatal development (Jacobs, 2002; Balu and Lucki, 2009; Whitman and Greer, 2009). The regions of neurogenesis have been reported to occur in several brain regions such as posterior parietal cortex, (Magavi and Macklis, 2002), temporal cortex (Magavi and Macklis, 2002; Takemura, 2005), olfactory bulb (Yamada, et al., 2004) and hippocampus (Jacobs, 2002; Huang and Herbert, 2006; Verret, et al., 2007). Predominant regions of neurogenesis are subgranular zone of hippocampal dentate gyrus (Mandyam, et al., 2007; Mandyam, et al., 2008; Arisi, et al., 2011) and subventricular zone (Pencea, et al., 2001; Luca and Paolo, 2007; So, et al., 2008; Lai, et al., 2010).

Previous studies have been reported a decrease of neurogenesis related aging (Christina, et al., 2007; Cowen, et al., 2008), stress (Coe, et al., 2003), depression (Jacobs, et al., 2002; Henn and Vollmayr, 2004; Sahay, et al., 2007) and drug abuse such as cocaine (Lloyd, et al., 2010; Brown, et al., 2010), morphine (Eisch, et al., 2002), alcohol (McClain, et al., 2010) as well as methamphetamine (Mandyam, et al., 2008; Schaefers, et al., 2009). As mentioned above, drug abuse may cause neurotoxicity and neuronal degeneration leading to neuronal cells death. Although, the effects of methamphetamine and its mechanism involved in neurotoxicity have been published, those studies have focused on different drug administrations such as self-administration (Mandyam, et al., 2008; Gancarz, et al., 2011), and a single dose administration (Kerdsan, et al., 2009; Xi, et al., 2009). Actually, methamphetamine has been taken increasingly in drug abusers. It is interesting to use an animal model of drug dependence that is quite similar to methamphetamine taken in human. Moreover, several studies have reported neuronal cell death following methamphetamine administration but a few studies

have been conducted on the effects of methamphetamine on neurogenesis. Taken together, the aim of this study is to determine the effect of methamphetamine dependence using an imitation model of drug dependence in human on alterations of neurogenesis and gliogenesis in rat hippocampus. Moreover, behavioral profiles and cognitive performance have also been observed.

Purpose of the study

A general experiment objective

This experiment is designed to evaluate the alterations of hippocampal neurogenesis and gliogenesis in escalating and binge doses methamphetamine dependence.

Specific objectives

1. To determine the alterations of behavioral profiles and cognitive performance after escalating and binge doses methamphetamine administration in rats.

2. To determine the alterations of neuronal stem cells, oligodendrocytes, astrocytes and mature neurons in the subgranular, subventricular zones, cingulate cortex, and whiter matter nearby after escalating and binge doses methamphetamine administration in rats.

Hypotheses

A general hypothesis

Alterations of behavioral profiles, cognitive performance, and hippocampal neurogenesis and gliogenesis are related with methamphetamine dependence.

Specific hypotheses

1. Escalating and binge doses of methamphetamine administration to animals induce change in cognitive performance and behavioral profiles.

2. There are alterations of neuronal stem cells, oligodendrocytes, astrocytes and mature neurons in area of subgranular zone and/or subventricular zone and methamphetamine dependence.

Scope of this study

An animal model of methamphetamine dependence was used for determination of alterations of hippocampal neurogenesis and gliogenesis, behavioral profiles and cognitive performance using immunohistochemistry technique, behavioral observation, locomotor test and novel object recognition test.

Key words

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)

Anticipated outcome

1. To provide an information about the cognitive performance in escalating and binge doses methamphetamine dependence.

2. To provide an information about the possible alterations of hippocampal neurogenesis in area of subgranular zone and subventricular zone in escalating and binge doses methamphetamine dependence.