ABBREVIATIONS

A	=	amphetamine
ABC	=	avidin biotinylated horseradish peroxidase complex
ADHD	=	attention-deficit hyperactivity disorder
AM	=	ante meridiem
AMPA	=	α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate
ANOVA	=	one-way analysis of variance
°C	=	degree Celsius
Ca^{2+}	=	calcium ions
cm	=	centimeter
DAB	=	3, 3'–diaminobenzidine tetrahydrochloride
DAT	=	dopamine transporter
D1	=	dopamine receptors type 1
D2	=	dopamine receptors type 2
D3	=	dopamine receptors type 3
g	=	gram
GFAP	=	glial fibrillary acidic protein
h	=	hour
H^+	=	Hydrogen ion
H_2O_2	=	hydrogen peroxide
iGlu	=	ionotropic glutamate
IR	=	immunoreactive
K^+	=	Potassium ion
LTD	=	long-term depression
LTP	=	long-term potentiation
M	=	Molar
MAP2	=	microtubule-associated protein 2
MBP	=	myelin basic protein
METH	=	methamphetamine
Mg^{2+}	=	Magnesium ions
mg/kg	=	milligram per kilogram

ABBREVIATIONS (CONT.)

mGlu	=	metabotropic glutamate receptors
min	=	minute
ml/kg	=	milliliter per kilogram
µm	=	micrometer
n	=	number
Na^+	=	Sodium ion
NaCl	=	sodium chloride
NAS	=	nucleus accumbens
NMDA	=	*N*-methyl-D-aspartate
NMDAR	=	*N*-methyl-D-aspartate receptor
P	=	power
PBS	=	phosphate buffer saline
PCNA	=	proliferating cell nuclear antigen
pH	=	power of hydrogen ion concentration
p-value	=	Probability value
RMS	=	rostral migratory stream
ROI	=	region of interest
sec.	=	seconds
S.E.M	=	standard error of the mean
SGZ	=	subgranular zone
SVZ	=	subventricular zone
t	=	time
VMAT2	=	vesicular monoamine transporter 2
VTA	=	ventral tegmental area
w/v	=	weigh by volume
Zn^{2+}	=	Zinc ions

PUBLICATIONS

Poster presentation

Suksamrahn N, Duangto P, Thanoi S and Nudmamud-Thanoi S. The effects of *Bacopa Monnieri* extract on Glutamate/NMDA receptor subunit 1 induced by beta-amyloid peptide in rat temporal cortex. 34TH Annual conference of the Anatomy association of Thailand 2011.

Suksamrahn N, Duangto P, Thanoi S and Nudmamud-Thanoi S. The effects of *Bacopa Monnieri* extract on Glutamate/NMDA receptor subunit 1 induced by beta-amyloid peptide in rat temporal cortex. Medical Science Academic Annual Meeting (MSSAM) Naresuan University 2011.

Suksamrahn N, Thanoi S and Nudmamud-Thanoi S. The alterations of glial fibrillary acidic protein and myelin basic protein in rat cingulate cortex after escalating and binge doses methamphetamine administration. Medical Science Academic Annual Meeting (MSSAM) Naresuan University 2012.

Proceeding

Suksamrahn N, Thanoi S and Nudmamud-Thanoi S. Escalating and Binge Doses Methamphetamine Change the Behavioral Profile in Rats. 17th Naresuan Research conference 2011.

Suksamrahn N, Duangto P, Thanoi S and Nudmamud-Thanoi S. The effects of *Bacopa Monnieri* extract on Glutamate/NMDA receptor subunit 1 induced by beta-amyloid peptide in rat temporal cortex. 34TH Annual conference of the Anatomy association of Thailand 2011.

Oral presentation

Suksamrahn N, Thanoi S and Nudmamud-Thanoi S. Escalating and Binge Doses Methamphetamine Change the Behavioral Profile in Rats. 17th Naresuan Research conference 2011.

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การประชุมวิชาการสมาคมวิภาคศาสตร์แห่งประเทศไทย ครั้งที่ 34
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Effects of *Bacopa Monnieri* extract On the Alteration of Glutamate/NMDA Receptor Subunit 1 Induced by Beta-amyloid Peptide in Rat Temporal Cortex

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Abstract

Bacopa Monnieri Wettst. (Brahmi) is an Ayurvedic medicinal plant. It has a pharmacological properties and neuroprotective effect which has been used as a cognitive enhancer. The glutamate/*N*–methyl–*D*–aspartate (NMDA) receptor plays a critical role at excitatory synapses which is implicated in multiple functions such as synaptic plasticity, learning and memory. Therefore, the aim of this study was to investigate the neuroprotective effect of Brahmi extract on the alteration of NMDAR1 induced by beta-amyloid peptide. Male rats (200-250 g) were divided into 5 groups: Group I – rats were administered with vehicle; Group II–IV rats were administered by Brahmi extract at dose of 4, 40, 80 mg/kg/day before the treatment of beta–amyloid peptide (25–35), respectively; Group V– rats were administered by vehicle before the treatment of beta–amyloid peptide via intracerebroventricular administration. NMDAR1 immunoreactivity (NMDAR1–IR) was measured in temporal cortex by immunohistochemistry technique. NMDAR1–IR cells were significantly increased in beta–amyloid peptide group compared with control group. Moreover, NMDAR1–IR cells were significantly decreased in Brahmi group compared with beta–amyloid peptide group. The results of this study indicate that Brahmi extract has potential to protect the brain from neurotoxicity induced by beta-amyloid peptide.

Keyword: *Bacopa Monnieri* (Brahmi), beta-amyloid peptide, glutamate/*N*-methyl- *D*-aspartate (NMDA) receptor subunit 1 (NMDAR1)

Background

Bacopa Monnieri Wettst. (Brahmi) is a small herb with white flowers. It is a medicinal plant in Indian systems of medicine. It is an antioxidant to protect the brain (Sumathy et. al, 2002) and liver (Sumathy et. al, 2001). Moreover, it has a pharmacological properties and neuroprotective effect which has been used as a cognitive enhancer (Usbundit et. al, 2010). The intracerebroventricular (ICV) injection of beta–amyloid peptide to rodent can induce the alteration of learning and memory (Chen et. al, 2000) or neurodegeneration (LaFerla et. al, 1995).

The glutamatogic system especially *N*–methyl–*D*–aspartate (NMDA) receptor plays a critical role at excitatory synapses which is implicated in multiple functions such as synaptic plasticity, learning and memory. Moreover, the glutamate/NMDAR1 dysfunction has been implicates in neurodegenerative disease such as Alzheimer's disease (Ulas and Cotman, 1997). Therefore, the aim of this study was to investigate the neuroprotective effect of Brahmi extract on the alteration of NMDAR1 induced by beta-amyloid peptide.

Materials and Methods

Male Sprague–Dawley rats (200–250 g) were housed 5 per cage and maintained at 24±1°C under a 12-hour light/dark cycle with free access to water and food. Rats were divided into 5 groups: Group I – rats were orally administered with propylene glycol for 14 days; Group II–IV rats were orally administered by Brahmi extract at dose of 4, 40, 80 mg/kg/day before the treatment of beta–amyloid peptide (25–35), respectively; Group V– rats were orally administered by propylene glycol 14 days before the treatment of beta–amyloid peptide via ICV administration. Rats were sacrificed by cervical dislocation and brains were removed. NMDAR1 immunoreactivity (NMDAR1–IR) was measured in temporal cortex by immunohistochemistry technique.

Results, Discussion and Conclusion

The results showed that NMDAR1 immunoreactive (NMDAR1–IR) cells were significantly increased in the temporal cortex in beta–amyloid peptide induced neurodegeneration group when compared with control group ($p<0.01$). Moreover, NMDAR1–IR cells were significantly decreased in the temporal cortex in Brahmi treated group when compared with beta–amyloid peptide induced neurodegeneration group ($p<0.01$).

It has been reported that beta-amyloid peptide can induce cell damage by increasing glutamate release in cortical neurons. Therefore, an increase of NMDAR1 expression in this study may be a compensatory effect in response to glutamatogic cell death. Moreover, a decrease of NMDAR1 in Brahmi treated group may be

consequences of neuroprotective effects of Brahmi extract that can prevent glutamatergic cell death induced by beta-amyloid peptide (25–35).

In conclusion, the results of this study indicate that Brahmi extract has potential to protect the brain from neurotoxicity induced by beta-amyloid peptide (25–35).

Table 1 Expression of NMDAR1 immunoreactive cells in all layers of the temporal cortex of rats pretreated with Brahmi extract before received beta-amyloid peptide.

Treatment	Temporal cortex NMDAR1-IR cells density (% of control)		
	Layer II/III	Layer IV/V	Layer VI
control	100±29.72	100±24.14	100±39.76
Beta-amyloid peptide	230±34.15*	230±17.77*	225±29.79*
BM 4 mg/kg +AB	112±27.91#	127±31.44#	128±19.72#
BM 40 mg/kg +AB	130±12.58#	122±11.14#	115±7.25#
BM 80 mg/kg +AB	108±2.50#	125±9.29#	103±14.24#

AB = Beta-amyloid peptide, BM = Brahmi extract
Data were present as Mean ± SD. (n=4–6/group)
*p< 0.01 VS control
#p< 0.01 VS Beta-amyloid peptide
(ANOVA post hoc Dunnetts test.)

Acknowledgement:
This study was financially supported by the National Research Council of Thailand through the Annual Research Fund of Naresuan University.

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6. Ulas J, Cotman CW. Decreased expression of N-methyl-D-aspartate receptor 1 messenger RNA in select regions of Alzheimer brain. Neuroscience 1997,79 (4):973-82.

ผลของสารสกัดพรมมิต่อการเปลี่ยนแปลงของตัวรับกลูตาเมท NMDA subunit 1ที่ถูกเหนี่ยวนำด้วยเบตาอะไมลอยเปปไทด์ในสมองส่วน Temporal cortex

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บทคัดย่อ

สมุนไพรพรมมิเป็นพืชที่ใช้ในทางการรักษาของอินเดียที่มีสรรพคุณทางยาและมีผลต่อการป้องกันระบบประสาท การฉีดเบตาอะไมลอยเปปไทด์แก่สัตว์ทดลองทางโพรงสมองสามารถเหนี่ยวนำให้เกิดความเป็นพิษและการเปลี่ยนแปลงทางระบบประสาทได้ ตัวรับกลูตาเมท NMDA subunit 1(NMDAR1) มีบทบาทสำคัญกับ excitatory synapses ซึ่งเกี่ยวข้องกับหลายหน้าที่ เช่น synaptic plasticity ที่เกี่ยวข้องกับการเรียนรู้และความจำ เป็นต้น ดังนั้นการศึกษานี้จึงมีวัตถุประสงค์เพื่อศึกษาผลของสารสกัดสมุนไพรพรมมิต่อตัวรับกลูตาเมท NMDAR1 ที่ถูกเหนี่ยวนำด้วยเบตาอะไมลอยเปปไทด์ โดยแบ่งหนูเพศผู้ออกเป็น 5 กลุ่ม กลุ่มที่ 1 ได้รับตัวทำละลายเป็นเวลา 14 วัน กลุ่มที่ 2-4 ได้รับสารสกัดสมุนไพรพรมมิปริมาณ 4, 40, 80 มก./กก./วัน และตามด้วยเบตาอะไมลอยเปปไทด์ตามลำดับ กลุ่ม 5 ได้รับตัวทำละลายเป็นเวลา 14 วัน และตามด้วยเบตาอะไมลอยเปปไทด์ (25-35) ผ่านทางโพรงสมอง จากนั้นนำสมองของหนูส่วน temporal cortex มาทำการศึกษาการแสดงออกของ NMDAR1 โดยเทคนิคทาง immunohistochemistry จากการศึกษาพบว่าสารสกัดสมุนไพรพรมมิมีความสามารถในการป้องกันและลดความเป็นพิษต่อระบบประสาทแก่หนูที่ถูกเหนี่ยวนำด้วยเบตาอะไมลอยด์เปปไทด์(25-35)

Poster presentation: Proceedings of the Anatomy Association of Thailand April 27-29, 2011

The effects of *Bacopa Monnieri* extract on Glutamate/NMDA receptor subunit 1 induced by beta-amyloid peptide in rat temporal cortex

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Introduction

Bacopa Monnieri Wettst. (Brahmi) is a small herb with white flowers. It is a medicinal plant in Ayurvedic medicine. Brahmi has been reported in effect an antioxidant to protect the brain [1] and liver [2]. Moreover, it has a pharmacological properties and neuroprotective effect which has been used as a cognitive enhancer [3]. The intracerebroventricular (ICV) injection of beta–amyloid peptide to rodent can induce the alteration of learning and memory [4] or neurodegeneration [5].

The glutamategic system especially *N*–methyl– *D*–aspartate (NMDA) receptor plays a critical role at excitatory synapses which is implicated in multiple functions such as synaptic plasticity, learning and memory. Moreover, the glutamate/NMDAR1 dysfunction has been implicates in neurodegenerative disease such as Alzheimer's disease [6]. Therefore, the aim of this study was to investigate the neuroprotective effect of Brahmi extract on the alteration of NMDAR1 induced by beta-amyloid peptide.

Materials and Methods

Male Sprague–Dawley rats (200–250 g) were housed 5 per cage and maintained at 24±1°C under a 12-hour light/dark cycle with free access to water and food. Rats were divided into 5 groups: Group I – rats were orally administered with propylene glycol for 14 days; Group II–IV rats were orally administered by Brahmi extract at dose of 4, 40, 80 mg/kg/day before the treatment of beta–amyloid peptide (25–35), respectively; Group V – rats were orally administered by propylene glycol 14 days before the treatment of beta–amyloid peptide via ICV administration. Rats were sacrificed by cervical dislocation and brains were removed. NMDAR1 immunoreactivity (NMDAR1–IR) was measured in temporal cortex by immunohistochemistry technique.

Results

NMDAR1 immunoreactive (NMDAR1–IR) cells were significantly increased in the temporal cortex in beta–amyloid peptide induced neurodegeneration group when compared with control group ($p<0.01$). Moreover, NMDAR1–IR cells were significantly decreased in the temporal cortex in Brahmi treated group when compared with beta–amyloid peptide induced neurodegeneration group ($p<0.01$) (Fig 2).

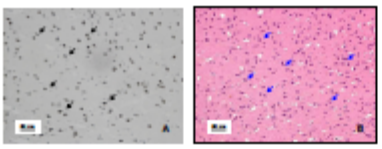

Fig 1 Expression of NMDAR1-IR cells (A) and H&E (B) of the temporal cortex of rats pretreated with Brahmi extract before received beta-amyloid peptide at 20x magnification. Black and blue arrows indicate NMDAR1-IR cells and pyramidal cells, respectively.

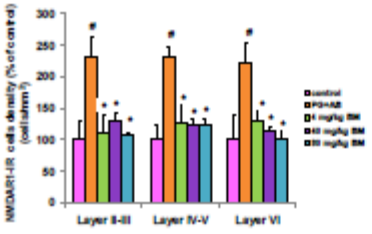

Fig 2 Expression of NMDAR1 immunoreactive cells in all layers of the temporal cortex of rats pretreated with Brahmi extract before received beta-amyloid peptide.

PG = propylene glycol , AB = Beta–amyloid peptide, BM = Brahmi extract
Data were present as Mean ± SD. (n=6–6/group)
* $p<0.01$ VS control
# $p<0.01$ VS Beta-amyloid peptide
(ANOVA post hoc Dunnette test.)

Discussion

It has been reported that beta-amyloid peptide can induce cell damage by increasing glutamate release in cortical neurons. Therefore, an increase of NMDAR1 expression in this study may be an effect in response to glutamategic neurotransmission overstimulation. Moreover, a decrease of NMDAR1 in Brahmi treated group may be consequences of neuroprotective effects of Brahmi extract that can prevent neurotoxicity induced by beta–amyloid peptide (25–35).

Conclusion

The results of this study indicate that Brahmi extract has potential to protect the brain from neurotoxicity induced by beta-amyloid peptide (25–35).

Acknowledgements

This study was financially supported by the National Research Council of Thailand through the Annual Research Fund of Naresuan University.

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Escalating and Binge Doses Methamphetamine Change the Behavioral Profile in Rats

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Abstract

Methamphetamine (METH), an N-methyl homolog of amphetamine, is an abused psychostimulant drug. METH can induce neurotoxic effects in several brain regions. Moreover, METH has been reported to induce long term behavioral changes including behavioral sensitization, tolerance and drug dependence. Therefore, the aim of this study was to investigate the effects of escalating binge, escalating and acute binge doses METH administrations on the alterations of behavioral rating scale. Adult male Sprague-Dawley rats (200-250 g) were divided into 4 groups: Control group – rats were injected with three doses of vehicle on day 1-14 and four doses on day 15; Acute binge dose-methamphetamine group (AB-METH) – rats were injected with three doses of vehicle on day 1-14 and four doses of 6.0 mg/kg METH on day 15; Escalating dose-methamphetamine group (ED-METH) – rats were injected increasing three doses of 2.0 mg/kg/day METH on day 1-13 and three doses of 4.0 mg/kg METH on day 14 and four doses saline on day 15; Escalating dose-methamphetamine binge group (ED-METH binge) – rats were injected increasing three doses of 2.0 mg/kg/day METH on day 1-13 and three doses of 4.0 mg/kg METH on day 14 and four doses of 6.0 mg/kg METH on day 15. At 30 min after the last dose injection of each day, the behaviors of all animals were observed for 30 min. The behavioral rating scale was significantly increased in ED-METH binge and ED-METH on day 1-15 when compared with control group. AB-METH group was significantly increased in behavioral rating scale on day 15 and 16 when compared with control group. The results of this study indicate that ED-METH binge, ED-METH, acute binge METH doses have effects to increase behavior of rats induced by METH dependence.

Keywords: behavior, methamphetamine, escalating dose-methamphetamine group (ED-METH), escalating dose-methamphetamine binge group (ED-METH binge), acute binge dose-methamphetamine group (AB-METH)

Introduction

Methamphetamine (METH) has an incident of increasing numbers of users worldwide. It has been reported that METH abusers increased in all ages especially in adult age between 18-25 in males and 12-17 in females (Winslow et al., 2007). METH, an N-methyl homolog of amphetamine, can abuse on several systems such as cardiovascular system (Yu et al., 2003), urinary system (Ishigami et al., 2003), enhance sexuality behavior, increase libido (Winslow et al., 2007) especially on central nervous system (CNS) and peripheral nervous system (PNS) (Dutta et al., 2006 and Johnson et al., 2007). METH has been reported to induce neurotoxic effects in several brain regions such as frontal cortex,

parietal cortex and hippocampus (Wahnschaffe and Esslen, 1985; Zhu et al., 2006; Lee et al., 2011). In addition, METH can increase neurodegeneration and neuronal cell death (Schmued and Bowyer, 1997 and Kuczenski et al., 2007; **Zhu et al., 2006** and Atianjoh et al., 2008) leading to behavioral changes (Suzuki et al., 2004). Moreover, METH can cause learning impairments and memory loss (Winslow et al., 2007 **and Lee** et al., 2011) as well as long term behavioral changes including behavioral sensitization (Suzuki et al., 2004), tolerance (Winslow et al., 2007 and Kuczenski et al., 2007) and drug dependence (Mandyam et al., 2007). Although, the effects of methamphetamine and its mechanism involved in neurotoxicity have been published, those studies have been focused mainly on different drug administrations such as self-administration (Mandyam et al., 2008 and Gancarz et al., 2011) or single dose administration (Kerdsan et al., 2009 and Xi et al., 2009). In this study, an animal model of drug dependence was designed relatively similar to methamphetamine taken by drug abusers. We hypothesized that escalating and binge doses of METH administration would alter behavioral responses. Therefore, the aim of this study was to investigate the effects of escalating, escalating binge and acute binge doses METH administrations on the alterations of behavioral rating scale in rats.

Materials and methods

Animals

Adult male Sprague-Dawley rats (National Laboratory Animal Center, Mahidol University, Nakorn Pathom, Thailand) weigh between 200-250 g were used in this study. Rats were housed one per cage (7.5x11.5x5 inch) and maintained at room temperature about 24±1°C under light dark cycle 12:12, light on at 6:00 AM, with *ad libitum* access to food and water. All rats were habituated for 1 week. All rat procedures were carried out in compliance with Mahidol University code of practice and the National Institutes of Health (USA) Guidelines for treatment of laboratory animals. The research protocols for this study were approved by the Animal Research Committee of Naresuan University.

Drugs

D-methamphetamine hydrochloride (Alltech, Palatine & DC, Il, USA) with the permission of Ministry of Public Health was used in this experiment. The drug was dissolved in sterile saline (0.90% w/v of NaCl) and administered subcutaneously (2 ml/kg). Drug was made up freshly each day and all doses of drug injection were calculated based on body weight of animals.

Drug treatment

Drug doses for treatment of the animals were carried out according to Segal et al. (2003). Briefly, animals (total number = 21) were divided into four groups: control group (n = 8), acute binge dose-methamphetamine group (AB-METH) (n = 5), escalating dose-methamphetamine group (ED-METH) (n = 4) and escalating dose-methamphetamine binge group (ED-METH binge) (n = 4). At the phase of drug administration, the control group – rats were injected three doses of 2.0 mg/kg/day

saline on day 1-14 and four doses saline on day 15; the AB-METH group – rats were injected three doses of 2 mg/kg/day saline on day 1-14 and four doses of 6.0 mg/kg METH on day 15; the ED-METH group – rats were injected increasing three doses of 2.0 mg/kg/day METH on day 1-13 and three doses of 4.0 mg/kg METH on day 14 and four doses saline on day 15; the ED-METH binge group – rats were injected increasing three doses of 2.0 mg/kg/day METH on day 1-13 and three doses of 4.0 mg/kg METH on day 14 and four doses of 6.0 mg/kg METH on day 15. Rats were sacrificed and removed brain at 24 h after the last injection on day 15. Time-line of methamphetamine administration was shown in figure 1 and drug administration for ED-METH binge dose pretreatment schedule was shown in Table 1, respectively.

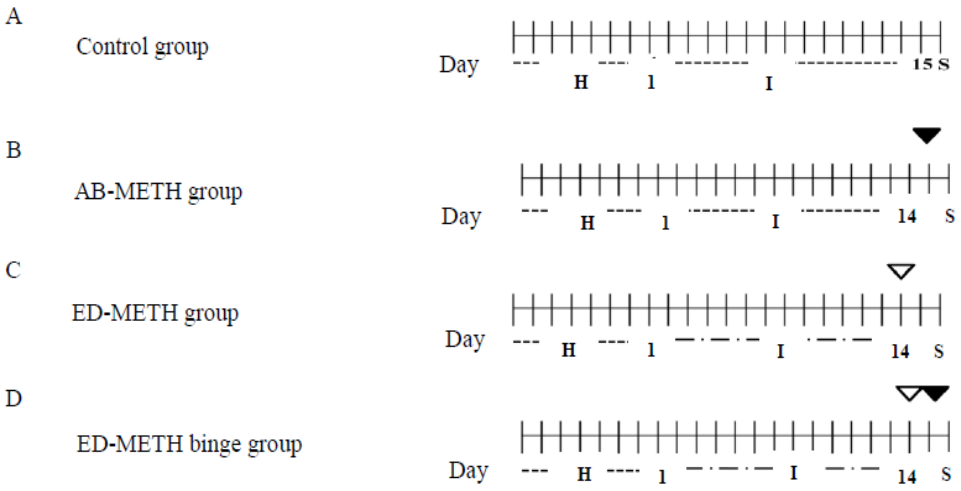

Figure 1 Time-line of methamphetamine administration

Each vertical line in A-D represents one day that corresponding to duration of treatment.

H=habituate, I=injection, S=sacrifice

····· = saline injection, ━ · ━ · = METH injection

▼ = Four doses of 6.0 mg/kg METH

▽ = Three doses of 4.0 mg/kg METH

Table 1 Escalating doses pretreatment methamphetamine schedule

Day	Methamphetamine dose (mg/kg)			
	07:30	10:30		13:30
1	0.1	0.2		0.3
2	0.4	0.5		0.6
3	0.7	0.8		0.9
4	1.0	1.1		1.2
5	1.3	1.4		1.5
6	1.6	1.7		1.8
7	1.9	2.0		2.1
8	2.2	2.3		2.4
9	2.5	2.6		2.7
10	2.8	2.9		3.0
11	3.1	3.2		3.3
12	3.4	3.5		3.6
13	3.7	3.8		3.9
14	4.0	4.0		4.0
Day	**07:30**	**09:30**	**11:30**	**13:30**
15	6.0	6.0	6.0	6.0

Source from: Segal et al., 2003

Behavioral Test

The behavioral tests were observed on day 0-16. On day 0, rats were taken to familiar in their home cage (30x19x13 cm) that used to observe behavioral tests. At 30 min after the last injection of each day, each group was observed behavior rating scale in their home cage for 30 min. Thereafter, rat behaviors were scored using the behavioral rating scale modified from Davidson et al. (2005) (Table 2). The data were collected at 5, 10, 15, 25, 30 min. Rats behaviors were also recorded using video recorder.

Table 2 A modified versions of the Ellinwood and Blaster (1974) behavioral rating scale after methamphetamine administration

Score	Classification	Definition
1	Asleep	Lying down, eyes close
2	Almost asleep	Relax muscle, eyes partially shut
3	Dystonia	Abnormal posture, tense tendon
4	Inactive	Lying down, eyes open, infrequent sniffing
5	Grooming	Grooming of face, body or groin
6	Normal active movement	Investigation or sniffing of cage, rearing
7	Hyperactive	Running with rapid jerky positional changes
8	Slow pattern movement	Repetitive exploration
9	Fast pattern movement	Intense, rapid repetitive exploration of cage
10	Stereotype	In-place sniffing or grooming

Source from: Davidson et al., 2005

Data Analysis

All data of behavioral rating scale was expressed as median. Statistical analysis between groups was performed using one-way analysis of variance (ANOVA) with post-hoc Dunnette test, while ordinal data was performed using Kruskal–Wallis, a level of *p*-value less than 0.05 were considered statistically significant.

Results

Behavioral Test

The results showed that the behaviors of animals in all experiment groups were normal on day 0. On day 1, the animals in ED-METH binge and ED-METH groups showed sniffing of cage; rearing and walk around their home cage but in AB-METH and control groups were normal. On day 2-6, the animals in ED-METH binge and ED-METH groups showed hyperactivity and slow pattern of movement and always performed oral stereotype and head movement on day 7-15 and day 10-14, respectively. In contrast, animals in AB-METH group were normal on day 0-14 and performed oral stereotype and head movement on day 15. At the time for treatment of each day, rats in ED-METH binge and ED-METH groups were excited and alertness similar to those gets rewarded.

Behavioral rating scale

There were no significant differences in the behavioral observation before starting the experiment (day 0).

On day 1, the behavioral rating scale was significantly increased in METH-treated group when compared with saline-treated group ($p < 0.01$) (figure 2).

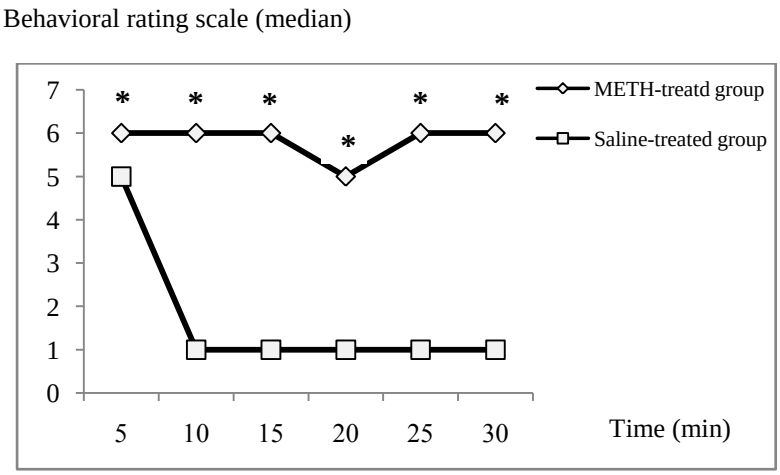

Figure 2 Behavioral rating scales (median) on day 1 of METH-treated group (n = 8) and saline-treated group (n = 13)

* $p < 0.01$ in comparison with saline group by Kruskal–Wallis test

On day 14, the behavioral rating scale was significantly increased in METH-treated group when compared with saline-treated group ($p < 0.01$) (figure 3).

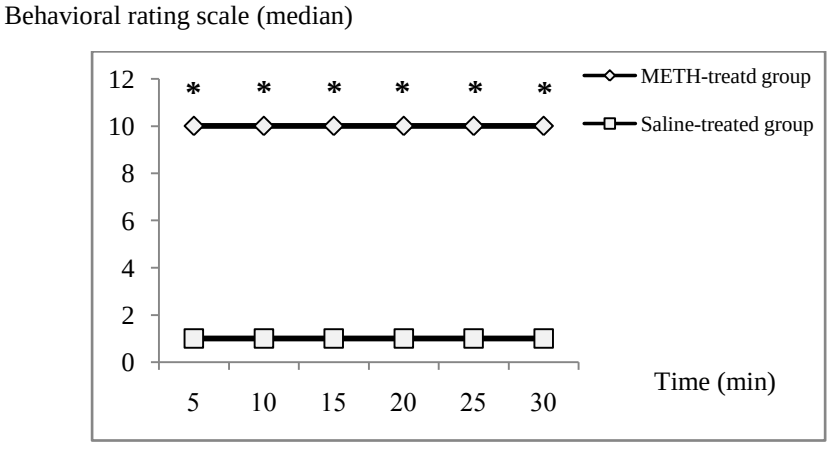

Figure 3 Behavioral rating scale (median) on day 14 of METH-treated group (n = 8) and saline-treated group (n = 13)

* $p < 0.01$ in comparison with saline group by Kruskal–Wallis test

The results showed that the behavioral rating scale on day 15 was significantly increased in both ED-METH binge and AB-METH groups when compared with control group ($p < 0.01$) (figure 4). Moreover, the behavioral rating scale was significantly increased in AB-METH groups when compared at day 14 (before binge doses treated) ($p < 0.01$) (figure 5A) but no significant differences in ED-METH binge group when compared at day 14 (figure 5B). The relationship between behavioral rating scales of each group that observed at the last dose of each day was shown in figure 7.

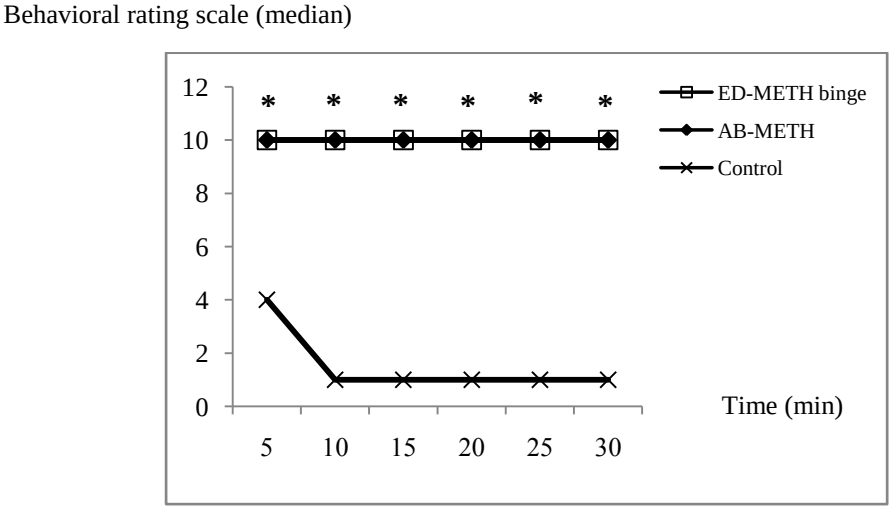

Figure 4 Behavioral rating scale (median) of all experimental groups on day 15. ED-METH binge = escalating dose-methamphetamine binge group (n = 4), AB-METH = Acute binge METH (n = 5) and control group (n = 8).

* $p < 0.01$ in comparison with control group by Kruskal–Wallis one-way ANOVA on ranks with post hoc Dunn's test

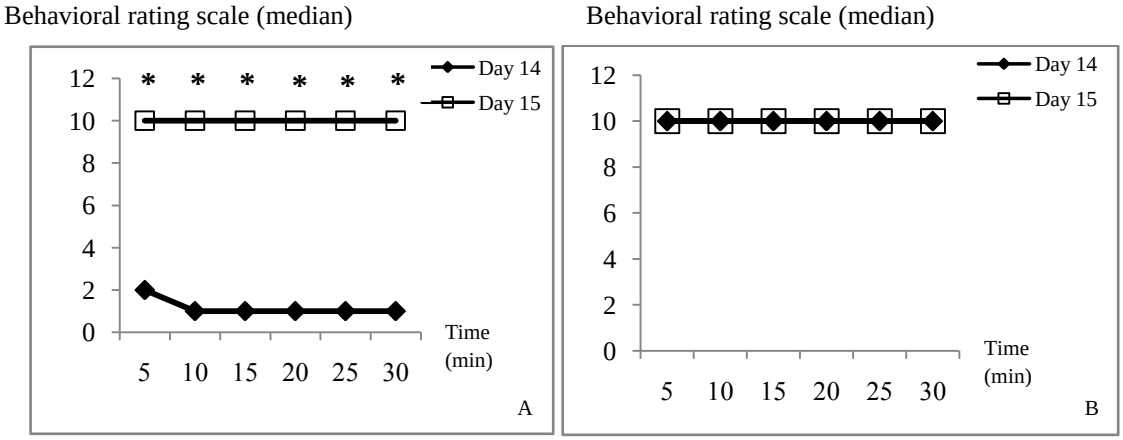

Figure 5 Behavioral rating scale (median) of AB-METH group (A) and ED-METH binge (after binge dose treated) (B) on day 14 and day 15.

* $p < 0.001$ in comparison with day 14 by Kruskal–Wallis test

Behavioral rating scale (total ambulation in 30 min)

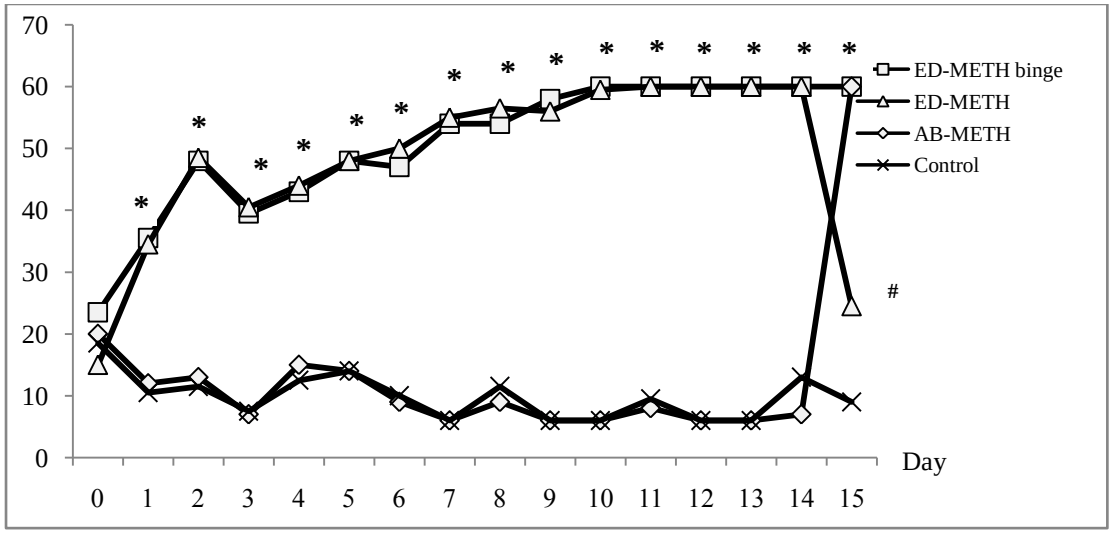

Figure 6 Behavioral rating scale (median) on day 0-15 of ED-METH binge, ED-METH and AB-METH groups. ED-METH binge = escalating dose-methamphetamine binge group (n = 4), ED-METH = escalating dose-methamphetamine group (n = 4), AB-METH = Acute binge METH (n = 5) and control group (n = 8)

$^{*,\#}p < 0.01$ in comparison with control group by one-way ANOVA post-hoc Dunnette test

Discussions

The present study demonstrated that the alterations of behavioral rating scale were significantly increased following METH administration in ED-METH binge and ED-METH on day 1-15 and AB-METH after on day15. The results of this study was in agreement with the previous reports that an increase of behavioral responses was found after escalating and binge METH administrations in rats (Segal et al., 2003 and Davidson et al., 2005). Early stage of METH abuse made to satisfaction and increasing drug dose for response to the needs of the mind because METH abuser resistance to drug (tolerance) (Winslow et al., 2007). METH dependence can be divided into two important components including physical dependence and psychological dependence. The psychological dependence is main factors to continue drug intake for maintaining a sense of well-being from the previous use. The physical dependence is a physical alteration of METH abuser who cannot stop drug taking for a long time.

Conclusion

The results of this study indicate that ED-METH binge, ED-METH, AB-METH doses had effects to increase behaviors of rats induced by METH dependence.

Acknowledgments

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การเพิ่มขนาดและจำนวนการได้รับเมทแอมเฟตามีนก่อให้เกิดการเปลี่ยนแปลงทางพฤติกรรมของสัตว์ทดลอง

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บทคัดย่อ

เมทแอมเฟตามีนหรือยาบ้าเป็นอนุพันธ์ของแอมเฟตามีน จัด เป็นสารเสพติดที่มีฤทธิ์ในการกระตุ้นระบบจิตประสาทและสามารถเหนี่ยวนำให้เกิดความเป็นพิษต่อสมองหลายส่วนด้วยกัน นอกจากนี้ยังพบว่ายาบ้าสามารถเหนี่ยวนำให้เกิดการเปลี่ยนแปลงทางพฤติกรรมประกอบด้วย การทนต่อยาและการติดยา ดังนั้น การศึกษานี้จึงมีวัตถุประสงค์เพื่อศึกษาถึงผลของการเพิ่มขนาดและจำนวนการได้รับยาบ้า (escalating และ binge dose-methamphetamine) ต่อการเปลี่ยนแปลงทางพฤติกรรมของสัตว์ทดลอง โดยแบ่งหนูเพศผู้ออกเป็น 4 กลุ่ม กลุ่มที่ 1 ได้รับตัวทำละลาย 3 ครั้ง/วัน ในวันที่ 1-14 และ 4 ครั้ง/วัน ในวันที่ 15 กลุ่มที่ 2 ได้รับตัวทำละลาย 3 ครั้ง/วัน ในวันที่ 1-14 และยาบ้าขนาด 6.0 มก./กก. จำนวน 4 ครั้ง/วัน ในวันที่ 15 กลุ่มที่ 3 ได้รับยาบ้าแบบเพิ่มขนาดจำนวน 3 ครั้ง/วัน ที่ขนาด 2.0 มก./กก. ในวันที่ 1-13 และยาบ้าขนาด 4.0 มก./กก. จำนวน 3 ครั้ง/วัน ในวันที่ 14 และตัวทำละลาย 4 ครั้ง/วัน ในวันที่ 15 ตามลำดับ กลุ่มที่ 4 ได้รับยาบ้าแบบเพิ่มขนาดจำนวน 3 ครั้ง/วัน ที่ขนาด 2.0 มก./กก. ในวันที่ 1-13 และ ยาบ้าขนาด 4.0 มก./กก. จำนวน 3 ครั้ง/วัน ในวันที่ 14 และขนาด 6.0 มก./กก. จำนวน 4 ครั้ง/วัน ในวันที่ 15 ตามลำดับ 30 นาที หลังจากได้รับยาบ้าครั้งสุดท้ายของแต่ละวัน (0-15) หนูแต่ละกลุ่มถูกทดสอบการสังเกตพฤติกรรมเป็นเวลา 30 นาที จากการศึกษาพบว่าการเพิ่มขนาดและจำนวนการได้รับยาบ้ามีผลต่อการเพิ่มการแสดงออกทางพฤติกรรมของหนูทดลองที่ถูกเหนี่ยวนำให้ติดยาบ้า

คำสำคัญ: พฤติกรรม, ยาบ้า, การเพิ่มขนาดและจำนวนของยาบ้า

Abstract: Medical Science Academic Annual Meeting 2011, 6-7th March 2011

The effects of *Bacopa Monnieri* extract on Glutamate/NMDA receptor subunit 1 induced by beta-amyloid peptide in rat temporal cortex

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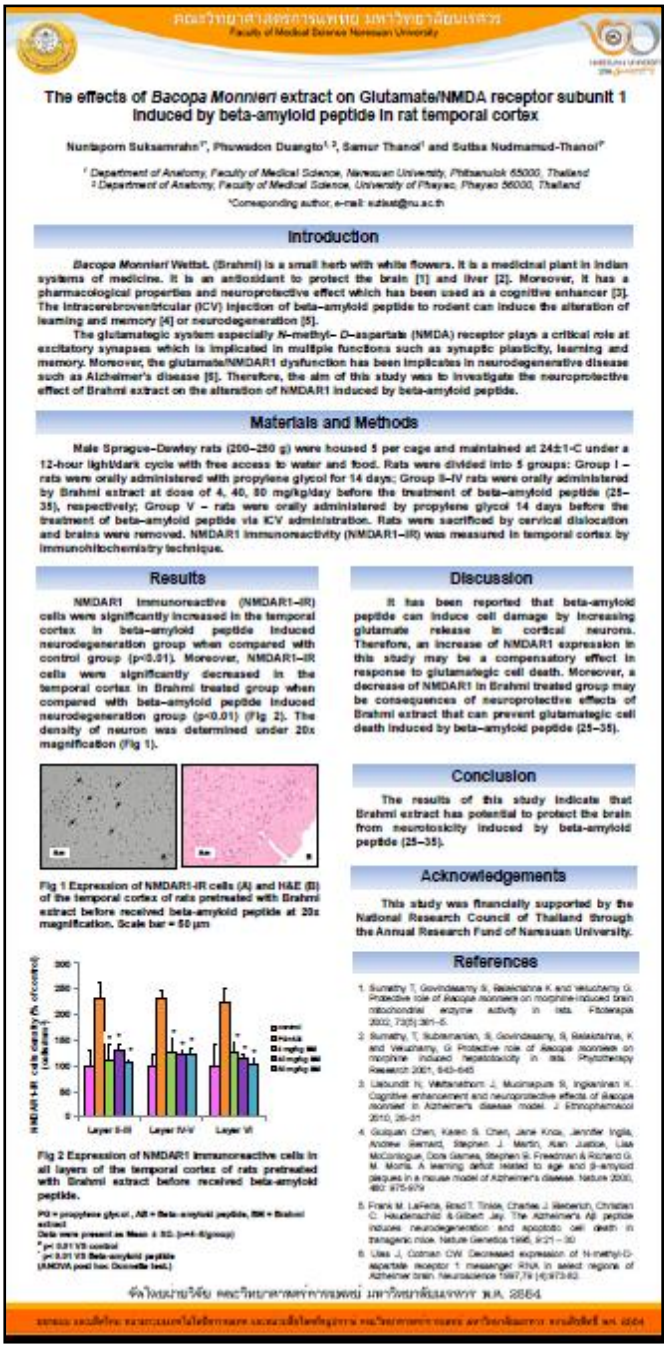
Abstract

Bacopa Monnieri Wettst. (Brahmi) is an Ayurvedic medicinal plant. It has a pharmacological properties and neuroprotective effect which has been used as a cognitive enhancer. The intracerebroventricular (ICV) injection of beta-amyloid peptide to rodent can induce neurotoxicity and neurodegeneration. The glutamate/*N*–methyl– *D*–aspartate (NMDA) receptor plays a critical role at excitatory synapses which is implicated in multiple functions such as synaptic plasticity, learning and memory. Therefore, the aim of this study was to investigate the neuroprotective effect of Brahmi extract on the alteration of NMDAR1 induced by beta-amyloid peptide. Male rats (200–250 g) were divided into 5 groups: Group I – rats were orally administered with vehicle for 14 days; Group II–IV rats were orally administered by Brahmi extract at dose of 4, 40, 80 mg/kg/day before the treatment of beta–amyloid peptide, respectively; Group V– rats were orally administered by vehicle 14 days before the treatment of beta–amyloid peptide (25–35) via ICV administration. Rats were sacrificed and brains were removed. NMDAR1 immunoreactivity was measured in temporal cortex by immunohistochemistry technique. The results of this study indicate that Brahmi extract has potential to protect the brain from neurotoxicity induced by beta-amyloid peptide (25–35).

Keyword: *Bacopa Monnieri* (Brahmi), beta-amyloid peptide, glutamate/*N*-methyl- *D*-aspartate (NMDA) receptor subunit 1 (NMDAR1)

Poster presentation: Medical Science Academic Annual Meeting 2011, 6-7th March 2011, Faculty of Medical Science, Naresuan U., Phitsanulok



Faculty of Medical Science Naresuan University

The effects of *Bacopa Monnieri* extract on Glutamate/NMDA receptor subunit 1 induced by beta-amyloid peptide in rat temporal cortex

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Introduction

Bacopa Monnieri Wettst. (Brahmi) is a small herb with white flowers. It is a medicinal plant in Indian systems of medicine. It is an antioxidant to protect the brain [1] and liver [2]. Moreover, it has a pharmacological properties and neuroprotective effect which has been used as a cognitive enhancer [3]. The intracerebroventricular (ICV) injection of beta-amyloid peptide to rodent can induce the alteration of learning and memory [4] or neurodegeneration [5].

The glutamategic system especially *N*-methyl- *D*-aspartate (NMDA) receptor plays a critical role at excitatory synapses which is implicated in multiple functions such as synaptic plasticity, learning and memory. Moreover, the glutamate/NMDAR1 dysfunction has been implicates in neurodegenerative disease such as Alzheimer's disease [6]. Therefore, the aim of this study was to investigate the neuroprotective effect of Brahmi extract on the alteration of NMDAR1 induced by beta-amyloid peptide.

Materials and Methods

Male Sprague–Dawley rats (200–250 g) were housed 5 per cage and maintained at 24±1◦C under a 12-hour light/dark cycle with free access to water and food. Rats were divided into 5 groups: Group I – rats were orally administered with propylene glycol for 14 days; Group II–IV rats were orally administered by Brahmi extract at dose of 4, 40, 80 mg/kg/day before the treatment of beta–amyloid peptide (25–35), respectively; Group V – rats were orally administered by propylene glycol 14 days before the treatment of beta–amyloid peptide via ICV administration. Rats were sacrificed by cervical dislocation and brains were removed. NMDAR1 immunoreactivity (NMDAR1–IR) was measured in temporal cortex by immunohistochemistry technique.

Results

NMDAR1 immunoreactive (NMDAR1–IR) cells were significantly increased in the temporal cortex in beta–amyloid peptide induced neurodegeneration group when compared with control group ($p<0.01$). Moreover, NMDAR1–IR cells were significantly decreased in the temporal cortex in Brahmi treated group when compared with beta–amyloid peptide induced neurodegeneration group ($p<0.01$) (Fig 2). The density of neuron was determined under 20x magnification (Fig 1).

Fig 1 Expression of NMDAR1-IR cells (A) and H&E (B) of the temporal cortex of rats pretreated with Brahmi extract before received beta-amyloid peptide at 20x magnification. Scale bar = 50 µm

Fig 2 Expression of NMDAR1 immunoreactive cells in all layers of the temporal cortex of rats pretreated with Brahmi extract before received beta-amyloid peptide.

PG = propylene glycol , Aβ = Beta-amyloid peptide, BM = Brahmi extract
Data were present as Mean ± SD. (n=4-6/group)
* $p< 0.01$ VS control
# $p< 0.01$ VS Beta-amyloid peptide
(ANOVA post hoc Duncan's test.)

Discussion

It has been reported that beta-amyloid peptide can induce cell damage by increasing glutamate release in cortical neurons. Therefore, an increase of NMDAR1 expression in this study may be a compensatory effect in response to glutamategic cell death. Moreover, a decrease of NMDAR1 in Brahmi treated group may be consequences of neuroprotective effects of Brahmi extract that can prevent glutamategic cell death induced by beta–amyloid peptide (25–35).

Conclusion

The results of this study indicate that Brahmi extract has potential to protect the brain from neurotoxicity induced by beta-amyloid peptide (25–35).

Acknowledgements

This study was financially supported by the National Research Council of Thailand through the Annual Research Fund of Naresuan University.

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Abstract: Medical Science Academic Annual Meeting2012, 5-6th March 2012, Faculty of Medical Science, Naresuan U., Phitsanulok

The alterations of glial fibrillary acidic protein and myelin basic protein in rat cingulate cortex after escalating and binge doses methamphetamine administration

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Abstract

Methamphetamine (METH) is an abused psychostimulant drug. METH has been reported to induce neurotoxicity and cause neuronal cells death. 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 effects of METH administrations on the expression of glial fibrillary acidic protein (GFAP) and myelin basic protein (MBP) which are markers of astrocytes and oligodendrocytes, respectively. Adult male rats were divided into 4 groups: control group – rats were intraperitoneally administered with saline; acute dose-METH binge group (AB-METH binge) – rats were injected with saline and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15; escalating dose-METH group (ED-METH) – rats were injected gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and three doses of 4.0 mg/kg METH on day 14 and saline on day 15; escalating dose-METH binge group (ED-METH binge) – rats were injected as same as ED-METH group on day 1-14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15. The GFAP immunoreactivity (GFAP-IR) and MBP immunoreactivity (MBP-IR) were measured in cingulate cortex and white matter by immunohistochemistry technique. In cingulate cortex, GFAP-IR cells were significantly increased in AB-METH binge when compared with control group. Moreover, MBP-IR was significantly decreased in both ED-METH binge and AB-METH binge when compared with control group. However, no significant differences of MBP-IR were observed in white matter in all experimental groups. The results of this study indicate that acute high dose of METH can induce an elevation of astrocyte immediately for maintaining brain homeostasis. However, acute high dose-METH administration may cause neurodegeneration or neuronal cells death and lead to diminish of myelin sheaths that envelop around the axon of the neurons.

Keywords: escalating, binge, methamphetamine, astrocyte, oligodendrocyte

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