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ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

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STUDY ON THE MECHANISMS OF ANTICONVULSANT ACTIVITY OF
(N-HYDROXYMETHYL)-2-PROPYLPENTAMIDE



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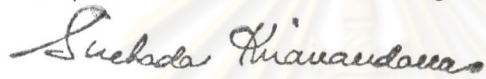
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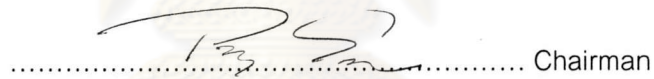
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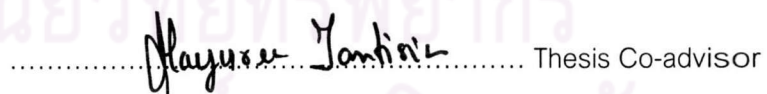


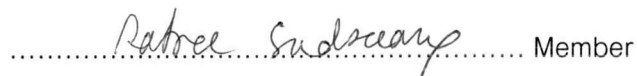
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การวิจัยนี้มีวัตถุประสงค์เพื่อศึกษาผลของ (เอ็น-ไฮดรอกซีเมทิล)-2-โพรพิลเพ็นทามายด์ ซึ่งเป็นอนุพันธ์ใหม่ของกรควาลโพรอิกที่มีฤทธิ์ต้านชัก ต่อระดับของสารสื่อประสาทที่เป็นกรดอะมิโนโนในเปลือกสมองของหนูแรท ในขณะที่ตื่น โดยวิธีไมโครไดอะลิสซิส กรดอะมิโนโนที่ทำการศึกษาเหล่านี้ได้แก่กลูตาเมต แอสพาร์เตต กลัยซีนและกาบารวมทั้งศึกษาฤทธิ์ของสารดังกล่าวที่มีต่อตัวรับชนิด กาบา เอ, โกลซีน และ เอ็นเอ็มดีเอ ในเซลล์ประสาทที่แยกได้ทันทีจากฮิปโปแคมปัสของหนูแรท และทำการศึกษาโดยการวัดกระแสทั้งหมดที่ไหลผ่านเยื่อหุ้มเซลล์ของเซลล์ประสาท

(เอ็น-ไฮดรอกซีเมทิล)-2-โพรพิลเพ็นทามายด์ ในขนาด 80 และ 160 มก/กก น้ำหนักตัว มีฤทธิ์ทำให้ระดับของกลูตาเมตในเปลือกสมองของหนูแรทในขณะที่ตื่นลดลงอย่างมีนัยสำคัญทางสถิติในขณะที่จะพบการลดของกลูตาเมตเฉพาะแต่ในกลุ่มของหนูแรทที่ได้รับกรควาลโพรอิกในขนาดสูง (440 มก/กก น้ำหนักตัว) เท่านั้น สารทดสอบนี้ไม่มีผลโดยตรงในการที่จะทำให้เกิดกระแสไหลผ่านเข้าเซลล์ประสาทปริามิดที่แยกได้ทันทีจากฮิปโปแคมปัสของหนูแรท และไม่มีผลต่อตัวรับชนิดกาบา เอ, โกลซีนและ เอ็นเอ็มดีเอ การลดของระดับกลูตาเมตซึ่งเป็นสารสื่อประสาทที่มีฤทธิ์กระตุ้น น่าจะเป็นกลไกปฐมภูมิในการออกฤทธิ์ต้านชักของสารทดสอบ

เมื่อเปรียบเทียบผลของสารทดสอบกับกรควาลโพรอิกในการทดลองนี้พบว่า กรควาลโพรอิกไม่มีฤทธิ์ต่อสารสื่อประสาทที่เป็นกรดอะมิโนชนิดอื่นใด นอกจากทำให้ระดับของกลูตาเมตลดลงหากให้กรควาลโพรอิกแก่หนูแรทในขนาดสูง 440 มก/กก น้ำหนักตัว อาจกล่าวได้ว่า (เอ็น-ไฮดรอกซีเมทิล)-2-โพรพิลเพ็นทามายด์ มีกลไกในการออกฤทธิ์ต้านชักไม่แตกต่างจากกรควาลโพรอิก แต่มีความแรงมากกว่า โดยที่มีกลไกปฐมภูมิเกี่ยวข้องกับการลดลงของกลูตาเมต อย่างไรก็ตาม ควรมีการศึกษาต่อไปถึงกลไกที่ทำให้ระดับของกลูตาเมตลดลง รวมทั้งกลไกในการออกฤทธิ์ต้านชักอื่น นอกเหนือจากที่รายงานไว้ในการวิจัยนี้

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ลายมือชื่อนิสิต.....
ลายมือชื่ออาจารย์ที่ปรึกษา.....
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

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SUMITTRA GOMONCHAREONSIRI: STUDY ON THE MECHANISMS OF ANTICONVULSANT ACTIVITY OF (N-HYDROXYMETHYL)-2-PROPYLPENTAMIDE. THESIS ADVISOR: ASSOCIATE PROFESSOR BOONYONG TANTISIRA, Ph.D. 96 pp. ISBN 974-17-3897-8.

The purposes of the present study were to study the anticonvulsant mechanisms of N-Hydroxymethyl-2-propylpentamide (HPP), a newly synthesized valproic analogue with anticonvulsant activity, on the level of brain amino acid neurotransmitters of freely moving rats. Changes of brain amino acid namely, glutamate, aspartate, glycine and GABA (gamma-aminobutyric acid) were investigated by microdialysis technique. Furthermore, the effects of this compound on GABA_A, glycine and NMDA (N-methyl-D-aspartate) receptors in acutely dissociated rat hippocampal neurons using the whole-cell application of the patch-clamp techniques was also investigated.

Significant decreases in the level of cortical glutamate, an excitatory amino acid neurotransmitter, was noted in both of HPP-treated groups whereas a reduction of glutamate was observed only in rats receiving high dose (440 mg/kg B.W.) of VPA. However, HPP did not directly elicit inward currents in acutely dissociated rat hippocampal neurons. Additionally, GABA_A, glycine and NMDA currents were unaltered by HPP. Thus it is highly likely that a decrease in brain glutamate could primarily account for anticonvulsant effect of HPP observed in rats.

Based on our finding that VPA in the dose of 440 but not 220 mg/kg B.W. exclusively decreased the level of brain glutamate, it could be concluded hereby that HPP possessed the same mechanism of anticonvulsant activity as that exhibited by VPA but much stronger. A decrease in cortical glutamate seemed to be a primary anticonvulsant mechanism of HPP. Some mechanisms other than that demonstrated in the present study should be further investigated.

Inter-departmental Physiology
Field of study Physiology
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List of Abbreviations

α	=	alpha
δ	=	delta
ϵ	=	epsilon
γ	=	gamma
%	=	percent
θ	=	theta
β	=	beta
Ω	=	omega
π	=	pi
ρ	=	rho
μm	=	micrometre
μM	=	micromolar
$^{\circ}\text{C}$	=	degree Celcius
a.m.	=	ante meridian (before noon)
aCSF	=	artificial cerebrospinal fluid
AEDs	=	antiepileptic drug
AP-5	=	DL-2-amino-5-phosphonopentanoic acid
ATP	=	adenosine 5'-triphosphate
B.W.	=	body weight
BMC	=	bicuculline methochloride
BZ	=	benzodiazepine
Ca^{++}	=	calcium ion
CBZ	=	carbamazepine
Cl^{-}	=	chloride ion
Cm	=	centimeter
CNS	=	central nervous system
CSF	=	cerebrospinal fluid
DMSO	=	dimethyl sulfoxide

List of Abbreviations (cont.)

DZP	=	diazepam
e.g.	=	Exempli gratia (for example)
ED ₅₀	=	median effective dose
EEG	=	electroencephalogram
ESM	=	ethosuximide
et al.	=	et alii (and others)
etc.	=	et cetera (and so on)
FBM	=	felbamate
g	=	gram
GABA	=	gamma-aminobutyric acid
GABA-T	=	gamma-aminobutyric acid transaminase
GBP	=	gabapentin
Gly	=	glycine
HPLC	=	high performance liquid chromatography
HPP	=	N-hydroxymethyl-2-propylpentamide
Hr	=	hour
i.p	=	intraperitoneal
ILAE	=	International League Against Epilepsy
IP ₃	=	inositol-1, 4, 5,-triphosphate
K ⁺	=	potassium ion
LD ₅₀	=	median lethal dose
LEV	=	levetiracetam
LTG	=	lamotrigine
MES	=	maximal electroshock seizure
Mg ⁺⁺	=	magnesium ion
min	=	minute
ml	=	milliliter

List of Abbreviations (cont.)

mm	=	millimeter
mM	=	millimolar
ms	=	millisecond
mV	=	millivolt
Na ⁺	=	sodium ion
NMDA	=	N-methyl-D-aspartate
NSS	=	normal saline solution
OPA	=	ortho -phthaldialdehyde
OXC	=	oxcarbazepine
p.m.	=	post meridian (afternoon)
pA	=	picoampere
PB	=	pentobarbital sodium
PEG400	=	polyethylene glycol 400
PHT	=	phenytoin
PSS	=	physiological salt solution
PTX	=	picrotoxinin
PTZ	=	pentylenetetrazole
S.E.M.	=	standard error of the mean
sec	=	second
STR	=	strychnine
TGB	=	tiagabine
TPM	=	topiramate
v/v	=	volume by volume
VGB	=	vigabatrin
VPA	=	valproic acid
w/v	=	weight by volume
Zn ⁺⁺	=	zinc ion
ZNS	=	zonisamide