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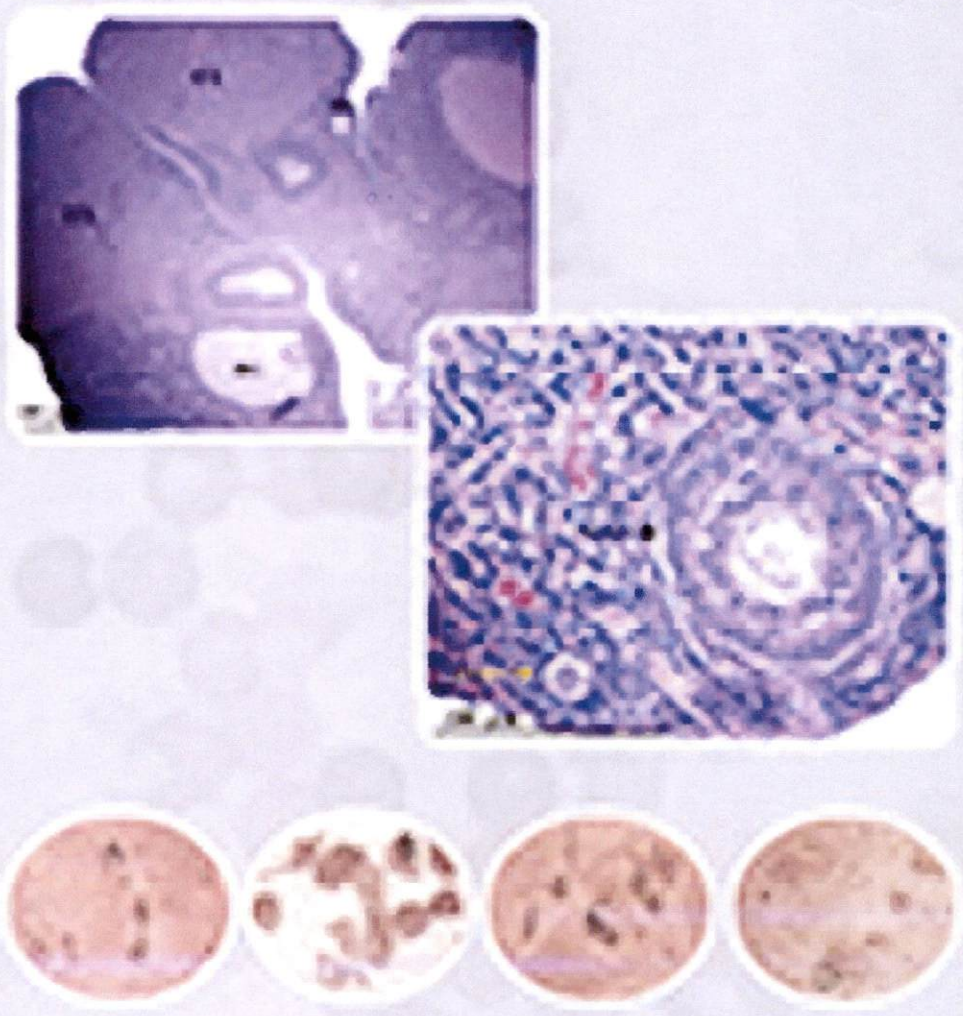

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The Effectiveness of GABA Agonist in Decreasing Expression of NR2B Subunit of *N*-Methyl-D-Aspartate (NMDA) Receptor in Neuropathic Mice by Partial Sciatic Nerve Ligation (PSNL) Method

(Efektivitas Agonis GABA terhadap Penurunan Ekspresi Reseptor *N-Methyl-D-Aspartate* (NMDA) Subunit NR2B pada Mencit Neuropati dengan Metode *Partial Sciatic Nerve Ligation* (PSNL))

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Abstract: Neuropathy pain is a pain that caused by nerves injury. Nowadays, treatment for neuropathic pain change to drugs that works as GABA agonist and cause reimbalance between excitatory and inhibitory neurotransmitter in central nervous system (CNS). The present study was designed to investigate the effectiveness of gabapentin and baclofen in decreasing N-Methyl-D-Aspartate (NMDA) receptor NR2B subunit activity in neuropathic pain. Fourty mice were divided into 8 groups i.e sham, negative control, gabapentin (10, 30, 100 nmol) and baclofen (1, 10, 30 nmol). Neuropathic pain was induced by ligation of sciatic nerve with Partial Sciatic Nerve Ligation (PSNL) method). Treatments were administrated intrathecally once a day for seven consecutive days, at a week after induction. On day 15th, mice were sacrified and the spinal cord were removed quickly. The expression of NMDA receptor NR2B subunit were examined with imunohistochemistry and data were analyzed by one way anova. The result from this research was gabapentin and baclofen administration significantly decrease expression of NMDA receptor NR2B subunit in mice compared to sham group. The higher the dose, the more effective to decrease the number of neuron that express NR2B. The conclusion of this research was gabapentin and baclofen treat neuropatic pain by decreased the number of NMDA receptor NR2B subunit.

Keywords: Neuropathic pain, PSNL, baclofen, gabapentin, spinal cord.

Abstrak: Nyeri neuropati merupakan nyeri yang disebabkan oleh trauma atau cedera pada saraf. Saat ini, terapi untuk mengatasi nyeri neuropati beralih pada agonis GABA yang menyebabkan kembalinya keseimbangan antara neurotránsmitter eksitatori dan inhibitori di sistem saraf pusat (SSP). Penelitian ini bertujuan untuk membuktikan efektivitas dari gabapentin dan baclofen dalam menurunkan ekspresi dari reseptor *N-Methyl-D-Aspartate* (NMDA) subunit NR2B pada nyeri neuropati. Empat puluh mencit dibagi kedalam 8 kelompok yaitu: sham, kontrol negatif, gabapentin (10, 30, 100 nmol) dan baclofen (1, 10, 30 nmol). Nyeri neuropati diinduksi dengan ligasi pada saraf sciatic dengan metode *Partial Sciatic Nerve Ligation* (PSNL). Senyawa uji diberikan setiap hari selama tujuh hari, satu minggu setelah induksi. Pada hari ke-15, mencit dikorbankan dan diambil bagian *spinal cord*. Ekspresi reseptor NMDA subunit NR2B diamati dengan imunohistokimia dan data dianalisis menggunakan anova satu arah. Hasil dari penelitian ini menunjukkan gabapentin dan baclofen menurunkan ekspresi reseptor NMDA

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subunit NR2B (*dose dependent*) dibandingkan kelompok sham. Kesimpulan dari penelitian ini bahwa gabapentin dan baclofen dapat mengatasi nyeri neuropati melalui penurunan aktivitas reseptor NMDA subunit NR2B.

Kata kunci: nyeri neuropati, PSNL, gabapentin, baclofen, *spinal cord.*

INTRODUCTION

INTERNATIONAL Association Study of Pain defines that pain is an unpleasant sensory and emotional experience associated with actual or potential damage[1]. Many people think that pain is a simple condition, but pain without an appropriate treatment can cause a condition that is called chronic pain. Neuropathic pain, one of the condition that leads chronic pain condition, is a spontaneous pain and hypersensitivity to pain in association with damage or a lesion of a nervous system. Neuropathic pain included in chronic pain, pain with duration more than six month. Neuropathic pain, one of the condition that leads chronic pain condition, is a spontaneous pain and hypersensitivity to pain in association with damage or a lesion of a nervous system[2]. Until now, pathophysiology of neuropathic pain is still not properly understood, so an appropriate treatment for this condition is still be a challenge. Treatment for neuropathic pain is so important, because adverse effect of drugs that have been used as first line treatment and in the other hand the use of morphine is still debated.

Chronic pain was related to imbalance between neurotransmitter in brain. This proccess includes exitatory neurotransmitter (i.e glutamate) and Inhibitory neurotransmitter (i.e GABA). Glutamate and GABA are the important key in pathophysiology of chronic pain[3]. NR2B is one of the subunit receptor of NMDA that plays essensial role in dorsal horn of spinal cord, an important key for neuropathic pain[4]. Neuropathic pain always associated with increasing the expression of NMDA receptor subunit NR2B. Higher NR2B expression was reported in neuropathic condition[5]. So, increasing the activation of inhibitory neurotransmitter, GABA will appropriate as an alternative management therapy.

Gabapentin and Baclofen are drugs that have an action in GABA receptor. Both of them can induct the activation of GABA and then inhibit activation of NMDA subunit NR2B. Eventhough this drugs are not primary used in neuropathic pain, but hopefully because of their mechanism can give an explaination how both of them work in neuropathic patophysiology. In this research, we try to get an explanation how the action of Gabapentin and Baclofen in neuropathic especially in NMDA receptor subunit NR2B.

MATERIALS AND METHOD

MATERIALS. Male Balb-C mice (20-25 g) were obtained from Faculty of Pharmacy University of Airlangga Surabaya and maintained in room temperature with 12 h light/dark cycle. They had free access to food and water. Gabapentin and Baclofen were purchased from Sigma. Each of them was dissolved in 1 mL of normal saline. Gabapentin and baclofen was administration as a solution 5 µL by intrathecally.

METHODS. Neuropathy induction by ligation. Mice were weighed and divided into 8 groups of each 5 animals: on day 0, each mice in group 1-7 (neuropathy group) will induce neuropathy with PSNL method. Mice were anasthetized with aether and tying 1/3-1/2 of dorsal portion of sciatic nerve on the left lumbar nerve of mice with 8-0 silk. In group 8 (Sham group), the sciatic nerve was exposed without ligation. On day 7-13, each group will receive different treatment one daily: negative control (normal saline), sham (normal saline), gabapentin groups (dose 10, 30 and 100 nmol) and baclofen groups (dose 1, 10 and 30 nmol) by intrathecal. On day 14th, all mice will sacrifice with decapitation and spinal organ of each mice was immediatelly removed. Each spinal cord was fixed in neutral buffer formalin (NBF) 10% for 24 hours.

Application of Drugs. All treatments were dissolved in normal saline. Intrathecal injection were administrated according to Hylden and Wilcox (1980). In brief, mice were restrained the left hand and the injection was performed in the right hand. Drugs were injected 5 µL into the spinal subarachinoid space between L5 and L6 using 30 gauge needle combine to 10 µL Hamilton syringe. The right placement of the drugs administration was demonstrated by a quick flicking motion of the mouse's tail upon entry of needle[6].

Immunohistochemistry. Tissue section from 3 mice were used for imunohistochemistry (IHC). Mice were sacrified with dislocation method and the spinal tissue were removed quickly. The IHC method that was used in this research was labelled-streptavidin biotin II (LSAB II), fixation samples with NBF 10% with paraffin block method and sliced of 3-4 µm. These samples were then routinely processed using imunohistochemistry with mouse NMDA receptor subunit NR2B antibody (1:100).

Statistical Analysis. Data are described as the mean ± SEM. The comparation of the number of cell that express NMDA receptor NR2B subunit between treatment groups were tested by one-way ANOVA followed by Tukey's HSD. Differences p value of less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

In neuropathy model, mice were inducted by PSNL method. According to Bridges, et al[7], PSNL was widely used because this method was analog with human condition. This method caused 60% hyperalgesia and allodynia that was usually seen by increasing the response of animal in noxious stimulus or non noxious stimulus. Neuropathy that was caused by PSNL contributed to neuronal damage, particularly at L4 and L5 of the spinal cord[8].

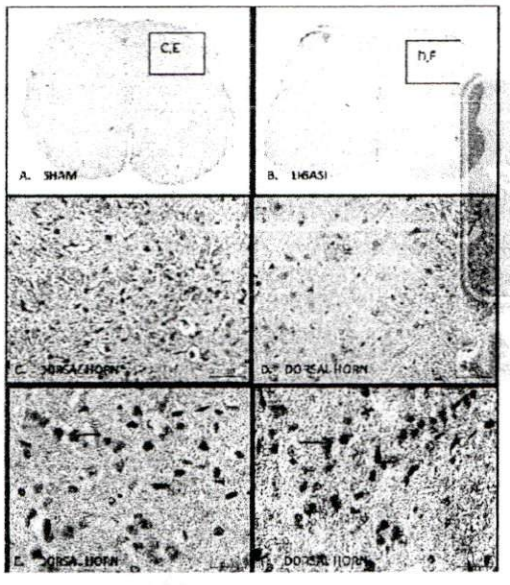

Figure 1. Imunohistochemistry of dorsal horn of mice with magnification of 40x (A,B), 400x (C,D) and 1000x (E,F). Red arrow show activity of NMDA receptor NR2B subunit.

Based on Figure 1, negative control (neuropathic group) had higher intensity of brown colour than sham group. Chronic pain induction by ligation caused higher intensity of brown colour in the cytoplasm of dorsal horn of mice. Higher intensity of brown colour indicated higher activity of NR2B subunit. According to Guo, *et al*[9], the increased activity of NR2B subunit was associated with tyrosine phosphorylation that was occurred in chronic pain conditions. Neuropathy causes signal transduction and followed by releasing of inflammatory mediators (such as prostaglandins, bradykinin, histamine and serotonine), results activation of nociceptor[10]. This process is followed by pain transmission by Aδ and C nerve fibers from dorsal horn of spinal cord to the brain, then induces release of excitatory neurotransmitter (i.e glutamate and substance P). Glutamate binds non NMDA receptors (i.e AMPA and kainite), whereas substance P binds to NK-1 receptors, causes depolarization. Continuous depolarization causes loss inhibition of Mg^{2+} blockade on NMDA receptor channel, resulting Ca^{2+} influx from extracellular to intracellular. Ion Ca^{2+} binds calcium calmodulin (CaM) and stimulates activation of calcium-stimulated signaling pathways. This process involves two pathways, adenylate cyclase and protein kinase, including calcium-calmodulin dependent protein kinase II (CaMKII) and mitogen-activated protein kinase (MAPK). All of the process increases activation of NMDA receptor by higher expression of NR2B subunit[11,12].

Table 1. Number of cells that express the activity of NR2B subunit on dorsal horn of spinal cord mice with neuropathic pain.

Groups	Treatment	Average number of cell (= SEM)
Sham	*Normal saline*	$11 = 2^{a)}$
Ligation	*Normal saline*	$38 = 2^{b)}$
	Baclofen 1 nmol	$27 = 3^{c)}$
	Baclofen 10 nmol	$18 = 1^{d)}$
	Baclofen 30 nmol	$13 = 1^{a)}$
	Gabapentin 10 nmol	$25 = 3^{c)}$
	Gabapentin 30 nmol	$16 = 1^{a)}$
	Gabapentin 100 nmol	$16 = 2^{a)}$

Note:
Different letter show significantly of average number of cell that express NR2B subunit activity in each treatment with one way anova analysis, followed by tukey HSD ($p<0.05$).

Influence of gabapentin and baclofen administration to the activity of NR2B subunit in neuropathic pain were analyzed by brown colour as positive marker of NR2B subunit activities. This action was showed at Fig 2 and 3.

Figure 2 dan 3 showed that brown colour intensity decreased by the administration of gabapentin and baclofen. The number of neuron that expressed the activity of NMDA receptor NR2B subunit in dorsal horn was showed at Table 1. Gabapentin and baclofen administration decreased activity of NR2B subunit, that was characterized by decreasing the intensity of brown colour. Higher doses indicates lower activity of NR2B subunit. Neuropathy causes imbalance between inhibitory neurotransmitter (GABA) and excitatory neurotransmitter (Glutamate) and leads to neuronal

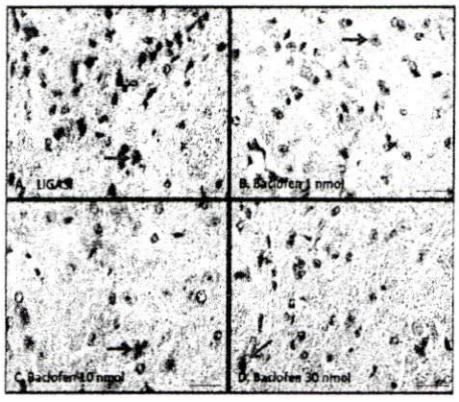

Fig 2. Imunohistochemistry of dorsal horn from spinal cord of mice with NR2B subunit antibody, neuropathic group (A), baclofen groups: 1 nmol (B), 10 nmol (B) and 30 nmol (C), observed at 1000 magnification. Red arrow show activity of NMDA receptor NR2B subunit.

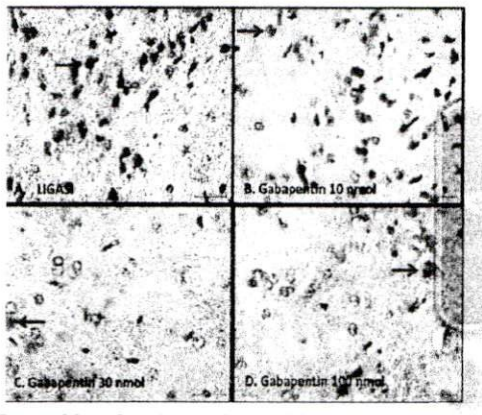

Fig 3. Imunohistochemistry of dorsal horn from spinal cord of mice with NR2B subunit antibody, neuropathic group (A), gabapentin groups: 10 nmol (B), 30 nmol (B) and 100 nmol (C), observed at 1000 magnification. Red arrow show activity of NMDA receptor NR2B subunit.

damaging. Gabapentin and baclofen have been known as GABA agonist, drugs that increasing activity of GABA receptor with two different mechanism. Gabapentin binds to $\alpha_2\delta_1$ subunit in Ca^{2+} canal and inhibits glutamate released[13,14].

The other side, baclofen is a $GABA_B$ agonist receptor that stimulates hyperpolarization by increases K^+ influx and decreases Ca^{2+} influx and inhibit glutamate released[15,16]. Higher activation of GABA leads increasing of GABA release and causes hyperpolarization. This process will inhibit release of excitatory neurotransmitter (i.e glutamate and substance P), decreases Ca^{2+} influx, resulting decreases activity of NR2B subunit and lowering pain sensitization[17]. By this research, dose gabapentin 100 nmol and baclofen 30 nmol give the biggest improvement in neuropathic pain.

CONCLUSIONS

Gabapentin and Baclofen decrease the activity of NMDA receptor NR2B subunit in mice with neuropathic pain.

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