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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 reimplalance 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. Forty 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 15\textsuperscript{th}, mice were sacrificed and the spinal cord were removed quickly. The expression of NMDA receptor NR2B subunit were examined with immunohistochemistry 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 neuropathic pain by decreased the number of NMDA receptor NR2B subunit.

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

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

Kata kunci: nyeri neuropati, PSNL, gabapentin, bacoefen, spinal cord.

INTRODUCTION

INTERNATIONAL Association Study of Pain defines that pain is an unpleasant sensory and emotional experience associated with actual or potential damage. 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. Until now, pathophysiology of neuropathic pain is still not properly understood, so an appropriate treatment for this condition is still 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 process includes excitatory neurotransmitter (i.e glutamate) and inhibitory neurotransmitter (i.e GABA). Glutamate and GABA are the important key in pathophysiology of chronic pain. NR2B is one of the subunit receptor of NMDA that plays essential role in dorsal horn of spinal cord, an important key for neuropathic pain. Neuropathic pain always associated with increasing the expression of NMDA receptor subunit NR2B. Higher NR2B expression was reported in neuropathic condition. So, increasing the activation of inhibitory neurotransmitter, GABA will appropriate as an alternative management therapy.

Gabapentin and Bacoefen 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. Even though this drugs are not primary used in neuropathic pain, but hopefully because of their mechanism can give an explanation how both of them work in neuropathic pathophysiology. In this research, we try to get an explanation how the action of Gabapentin and Bacoefen 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 Bacoefen were purchased from Sigma. Each of them was dissolved in 1 mL of normal saline. Gabapentin and bacoefen 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 bacoefen groups (dose 1, 10 and 30 nmol) by intrathecal. On day 14, all mice will sacrifice with decapitation and spinal organ of each mice was immediately 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 Hylton 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 subarachnoid 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.

Immunohistochemistry. Tissue section from 3 mice were used for immunohistochemistry (IHC). Mice were sacrificed 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 immunohistochemistry with mouse NMDA receptor subunit NR2B antibody (1:100).
Statistical Analysis. Data are described as the mean ± SEM. The comparison 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., 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.

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

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>Average number of cell (±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>Normal saline</td>
<td>11 ± 2^a</td>
</tr>
<tr>
<td></td>
<td>Normal saline</td>
<td>38 ± 2^b</td>
</tr>
<tr>
<td></td>
<td>Baclofen 1 nmol</td>
<td>27 ± 3^c</td>
</tr>
<tr>
<td></td>
<td>Baclofen 10 nmol</td>
<td>18 ± 1^d</td>
</tr>
<tr>
<td>Ligation</td>
<td>Baclofen 30 nmol</td>
<td>13 ± 1^e</td>
</tr>
<tr>
<td></td>
<td>Gabapentin 10 nmol</td>
<td>25 ± 3^f</td>
</tr>
<tr>
<td></td>
<td>Gabapentin 30 nmol</td>
<td>16 ± 1^g</td>
</tr>
<tr>
<td></td>
<td>Gabapentin 100 nmol</td>
<td>16 ± 2^h</td>
</tr>
</tbody>
</table>

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...
CONCLUSIONS

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

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