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Original Article :

Inhibition of the mitogen activated protein kinase (mapk) in the inflammatory pain like state using sb 203580 and pd 98059 in mice

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Abstract :

The therapeutic management of pain related inflammation is difficult to handle. The inflammatory process is mediated through the mitogen-activated protein kinase (MAPK) signal transduction pathway. Inhibition of this signal with specific inhibitors of p38 and Erk 1/2 MAPK pathway i.e. SB 203580 and PD 98059 has been reported. This study was aimed to assess the effectiveness of those specific inhibitors for inflammatory pain management in Balb-c mice. Inflammatory model was developed by intraplantar injection of Complete Freud's Adjuvant (CFA). PD 98059 and SB 203580 were dissolved in 30% DMSO to acquire concentration of 10.0 nmol, then was diluted to obtain doses of 0.1; 1.0 and 5.0 nmol. The intrathecally administered of SB 203580 and PD 98059 was injected once a day for 7 consecutive days at dose of 0.1, 1.0 and 5.0 mmol that was started from day 7 to day 13 after CFA injection. The control group received 10 µl 30% DMSO. Hyperalgesia was measured on day 0,1,3,5,7,8,10,12, and 14 following CFA injection. At dose of 5.0 nmol, PD 98059 increased mice's latency time to heat stimulation compared with placebo ($F(3.26)=6.881$; $p=0.001$). Also, SB 203580 at dose of 0.1, 1.0 and 5.0 showed similar results compared with placebo ($F(3.25)=4.394$; $p=0.002$, $p=0.001$ and $p=0.039$ for doses 0.1, 1.0 and 5.0 nmol respectively). MAPK inhibitors such as PD 98059 and SB 203580 can decrease hyperalgesia which is shown by increasing response time toward heat stimuli, so that MAPK inhibitors could have a place of therapy in the inflammatory pain like state due to its effectiveness in decreasing hyperalgesia.

Keyword :

Inflammatory pain, mitogen activated protein kinase, PD 98059, SB 203580, chronic pain,

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INHIBITION OF THE MITOGEN ACTIVATED PROTEIN KINASE (MAPK) IN THE INFLAMMATORY PAIN LIKE STATE USING SB 203580 AND PD 98059 IN MICE

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ABSTRACT

The therapeutic management of pain related inflammation is difficult to handle. The inflammatory process is mediated through the mitogen-activated protein kinase (MAPK) signal transduction pathway. Inhibition of this signal with specific inhibitors of p38 and Erk 1/2 MAPK pathway i.e. SB 203580 and PD 98059 has been reported. This study was aimed to assess the effectiveness of those specific inhibitors for inflammatory pain management in Balb-c mice. Inflammatory model was developed by intraplantar injection of Complete Freud's Adjuvant (CFA). PD 98059 and SB 203580 were dissolved in 30% DMSO to acquire concentration of 10.0 nmol, then was diluted to obtain doses of 0.1; 1.0 and 5.0 nmol. The intrathecally administered of SB 203580 and PD 98059 was injected once a day for 7 consecutive days at dose of 0.1, 1.0 and 5.0 mmol that was started from day 7 to day 13 after CFA injection. The control group received 10 µl 30% DMSO. Hyperalgesia was measured on day 0,1,3,5,7,8,10,12, and 14 following CFA injection. At dose of 5.0 nmol, PD 98059 increased mice's latency time to heat stimulation compared with placebo ($F_{(3.26)}$=6.881; p=0.001). Also, SB 203580 at dose of 0.1, 1.0 and 5.0 showed similar results compared with placebo ($F_{(3.25)}$=4.394; p=0.002, p=0.001 and p=0.039 for doses 0.1, 1.0 and 5.0 nmol respectively). MAPK inhibitors such as PD 98059 and SB 203580 can decrease hyperalgesia which is shown by increasing response time toward heat stimuli, so that MAPK inhibitors could have a place of therapy in the inflammatory pain like state due to its effectiveness in decreasing hyperalgesia.

Keyword: *Inflammatory pain, mitogen activated protein kinase, PD 98059, SB 203580, chronic pain*

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INTRODUCTION

Pain is a subjective unpleasant sensation associated with actual or potential tissue damage (Siddal & Cousins 1998, Page et al 2002). Chronic pain can be caused by inflammation (inflammatory pain state) or nerve cell damage either peripherally or centrally (neuropathic pain state). The presence of peripheral tissue damage will release pain mediators and inflammation which will increase the sensitivity of C and A-delta nerve fibers toward stimuli. Furthermore, persistent inflammation will be develop into chronic pain and subsequently become a neuropathic pain. At this situation, the stimuli that is normally cannot cause pain will be perceived as a pain (allodynia) or an excessive response to pain (hyperalgesia) for normal pain stimuli (Harden 2005).

More than 90% diseases is usually accompanied by pain where 40% of this will be developed into chronic pain or neuropathic pain. In the developed countries, this problem produces health problems due to the decreasing quality of life, medical costs and decreased productivity (Bowsher 1991, Harden 2005, Von Kroff et al 1990). Today the prevalence of chronic pain is increasing. In 2003 it was reported that in the United States about 2 million people suffer from chronic pain and increased to 3.75 million in 2005 (Foley 2003, Harden 2005). The increasing prevalence of chronic pain is very influential on the amount of budget used for the treatment of pain. It is estimated that an additional of U.S. $ 100 billion annually is needed. Another factor which contributes to the increased prevalence of chronic pain is the tendency of increasing life expectancy in which the elderly is more susceptible to chronic pain of various etiology. Based on UK Data in 2002, it is shown that chronic pain occurs in 10.6% elderly (> 75 years) (Mallen 2005). Chronic pain is associated with various diseases either infectious diseases such as HIV/AIDS or Herpes Zoster and degenerative diseases such as diabetes, cancer and some diseases caused by immune system disorders.

One of the underlying mechanism of the chronic pain is an increase release of glutamate and aspartate from pre synapse and increase in post sinaptic quantity of NMDA (N-Methyl D-aspartate) and non-NMDA including AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors. The persistent release of glutamate as a pain mediator for a long period of time

and activation of non-NMDA receptors as well as neurokinin receptors could stimulate the NMDA receptor to be in a ready state for activation. This activation resulted in removal of Mg2+ ions which is normally it blocks the sodium and calcium channels and inhibits the entry of Ca2+ ions. And thus, removal of Mg2+ ions caused the entry of Ca2+ ions that activate Nitric oxide synthetase (NOS) and phospholipase C. These compounds will activate second messengers (Kuno 1995, Siddall & Cousins 1998). Ca2+ ions will activate five enzymes that are two phospholipase enzyme membranes (phospholipase C/PLC and phospholipase A2/PLA 2) and three cytosolic enzymes (calpain, protein kinase C and calmodulin-dependent kinase). Ca2+ in the micromolar is able to stimulate PLC directly. Calpain is activated by Ca2+, in which its proteolytics action will produce various cellular mechanisms such as modulating protein kinase C (PKC) (Kuno 1995). Phosphorylated Protein kinase C will activate MAP kinase pathway (MAPK) (Tsuda 2004). MAPK is a family of the serine/threonine kinases which involve in the transmition of the extracellular stimuli. This stimulus affects the change in gene expression, proliferation and differentiation. This gene expression could indirectly affect the post sinaptic electrical activity for long period of time (Purves et al 1997).

In mammals there are three MAPK which can be activated i.e. extracelluler signal regulated kinases 1 and 2 (ERK 1/2), p38 and c-jun N terminal kinase (JNK)/stress-activated protein kinase (SAPK). ERK 1/2 is activated by growth factor, stress activates JNK and p38, while extracellular stimulation will increase the activity of protein kinases by phosphorylation of the threonine and tirosine (Nieminen et al 2005). In the development of pain, either noxious and unoxious pain will stimulate production of cytokines and other substances that facilitate the transmission of pain (Karim et al 2006). Activation of MAPK (Erk1/2 - Extracellular regulated kinase and P38) will facilitate the upregulation of COX-2 (Cyclo oxygenase) expression and prostaglandin production (PGE2) in which both factors are very influential in the development of inflammation (Nieminen 2005). The inhibition on MAPK will subsequently inhibit cyclooxyenase, lipo oxygenase dan cytokine biosynthesis. Several studies have reported that the use of MAPK inhibitors could inhibit arachidonic metabolism and platelet activation (Haubold et al 1998). It is expected that the provision of MAPK inhibitors during chronic pain development could inhibit inflammatory pain process.

Until now, the pain therapeutic management only focuses on the classical blockade of ligand-receptor binding. Recently, the therapeutic management of pain has focused on molecular mechanism that is the drug development that regulates gene expression and selectively modifies expression of the specific receptor involved in nociceptive transmission and neuropathy (Siddall & Cousins 1998). In addition, the treatment of chronic pain using NSAIDs (Non steroidal anti Inflamatory Drugs) and opioids do not provide a good response as well as in acute pain (Harden 2005). Even the repeated use of opioids will lead to tolerance and dependence. Up to now, many available drugs used for chronic pain is a combination of analgesics or NSAIDs with a drug indicated for other diseases such as anticonvulsants, antidepressants, epilepsy or cardiac arrhythmia. Based on the above mentioned reasons, a new strategy is required in the treatment of chronic pain especially inflammatory pain like state. A drug that has a mechanism on the inhibition of MAPK pathway such as SB 203580 and PD 98059 could be developed to manage inflammatory pain like state.

MATERIAL AND METHODS

This study used 62 mice Balb-C divided randomly into 8 groups. Mice were placed in a cage with constant room temperature 25 ±1°C. Food and water was given ad libitum. Before the treatment, mice were allowed to adapt to the environment for one week. Inflammatory pain-like state model using mice was done by Complete Freund's Adjuvant (CFA) injection. Before surgery, mice were given diethyl ether, placed on a surgical board and were given 0.05 mL of CFA injection on the left and the right mice's intraplantar. Syringe needle was carefully injected into the space between the skin and muscles. Injection must not injure any tissues under the skin to prevent the entry of CFA into the blood vessels (systemic effects). In the control group, normal saline injection was given.

PD 98059 and SB 203580 were dissolved in 30% DMSO to acquire concentration of 10.0 nmol. This solution then was diluted to obtain doses of 0.1; 1.0 and 5.0 nmol of either PD 98059 or SB 203580. Both compounds were injected intrathecally based on Hylden and Wilcox procedure (1980). The needle was inserted in the space between 5 and 6 of the lumbar spinal cord. A quick tail flick would be observed if the needle was iserted in the correct space. PD 98059 or SB 203580 was injected on day 7, 8, 9, 10, 11, 12 and 13 after induction of CFA. 10 µl injections were carried out using 30G injection needle. The control group received 10 µl 30% DMSO.

Evaluation of pain conducted by hiperalgesia was measured using the Hot Plate Test methods. In these methods, hyperalgesia was observed by looking at the

mice's movement when constant plate temperature (51 ± 0.5°C) was given to mice's plantar. A 30 seconds was used as the cut-off time. Measurements were performed at day 0 (baseline), and day 1, 3, 5, 7, 8, 10, 12, 14 and 21. A two way ANOVA was used to compare between groups. Also, a paired sample t-test was used to compare data from the same group whereas independent sample t-test was used to compare different groups. A statistical different of $p<0.05$ was then followed by Least Square Design (LSD).

RESULTS

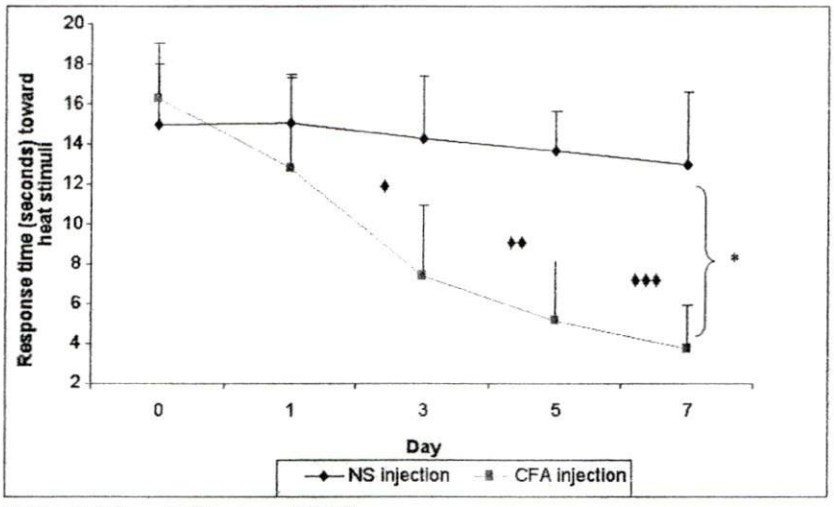
The development of inflammatory pain was observed by measuring the response time of mice toward heat stimuli (hyperalgesia). The control group of 10 mice received normal saline (NS) injection while 52 mice received intraplantar CFA injection in the ipsilateral side.

Based on Hot Plate Test, no inflammation occurred in the control group which was shown by no significant change in response time toward heat stimuli. On the other hand, the treatment group receiving CFA showed a statisctically significant decrease in response time toward heat stimuli on day 3 after CFA injection ($F_{(1,22)}$ =13.668; p=0.001). A decreased in response time toward heat stimuli is associated with hyperalgesia. Hyperalgesia is a sign of chronic pain development. Following inflammation on the CFA groups, mice were treated with once daily 0.1, 1.0 or 5.0 nmol of either PD 98059 or SB 203580 intrathecally starting on day 7 after CFA injection until day 13. Pain evaluation was measured on day 8, 10, 12 and 14.

Table 1. Response time toward heat stimuli in mice after intraplantar injection of CFA

Groups	Hyperalgesia (seconds) in mice after CFA injection				
	0	1	3	5	7
NS injection (n=10)	14.99±3.05	15.03±2.48	14.28±3.15	13.69±1.94	12.97±3.68
CFA injection (n=24)	16.23±2.84	12.79±4.53	7.43±3.52	5.17±3.09	3.77±2.11

NS = Normal Saline; CFA=Complete Freud's Adjuvant



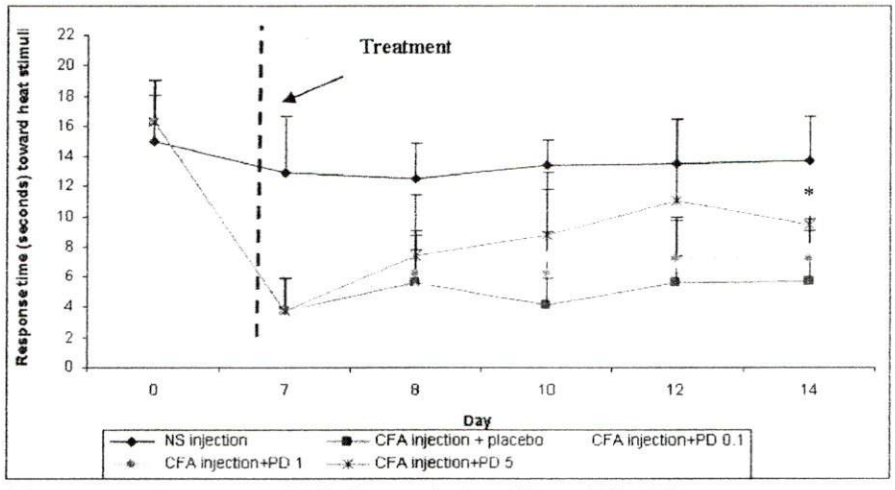
* F(1,22) =13.668 ; p=0.001 two way ANOVA
♦ p = 0.001 independent sample t-test on day 3
♦♦ p =0.001 independent sample t-test on day 5
♦♦♦ p=0.001 independent sample t-test on day 7

Figure 1. Development of inflammatory pain in mice injected with CFA with parameter of response time to heat stimuli

Table 2. Response time (seconds) toward heat stimuli following intrathecal injection of PD 98059 in mice suffering inflammation

day	Response time (seconds) toward heat stimuli after PD 98059 injection						
Group	0	7	Treatment	8	10	12	14
NS (n=10)	14.99 ± 3.05	12.97 ± 3.68	NS	12.57±2.28	13.42±1.63	13.47±3.00	13.76±2.92
			Placebo	5.65±2.18	4.19±1.75	5.61±1.75	5.76±4.07
CFA (n=24)	16.23 ± 2.84	3.77 ± 2.11	PD 0.1 nmol	5.35±3.43	7.40±4.42	6.93±3.04	7.93±2.60
			PD 1.0 nmol	6.18±2.93	6.18±2.81	7.23±2.55	7.16±1.91
			PD 5.0 nmol	7.35±4.08	8.81±4.07	11.07±5.40	9.45±2.39

NS = Normal saline injection; CFA= Complete Freund's Adjuvant injection; PD= PD 98059 injection



*$F_{(3,26)}$ =6.881; p=0.001 two way ANOVA between placebo and 5.0 nmol PD 98059

Figure 2. Response time (seconds) toward heat stimuli following intrathecal injection of PD 98059 in mice suffering from inflammation

Table 3. p value of PD 98059 on day 8, 10, 12, and 14 (one way ANOVA)

	Day after CFA injection			
	day 8		Day 10	
	p	Meaning	*P*	Meaning
P vs PD 0.1 nmol	0.856	Not significant	0.082	Not significant
P vs PD 1.0 nmol	0.754	Not significant	0.217	Not significant
P vs PD 5.0 nmol	0.334	Not significant	0.018	significant
PD 1.0 nmol vs 5.0 nmol	0.491	Not significant	0.152	Not significant

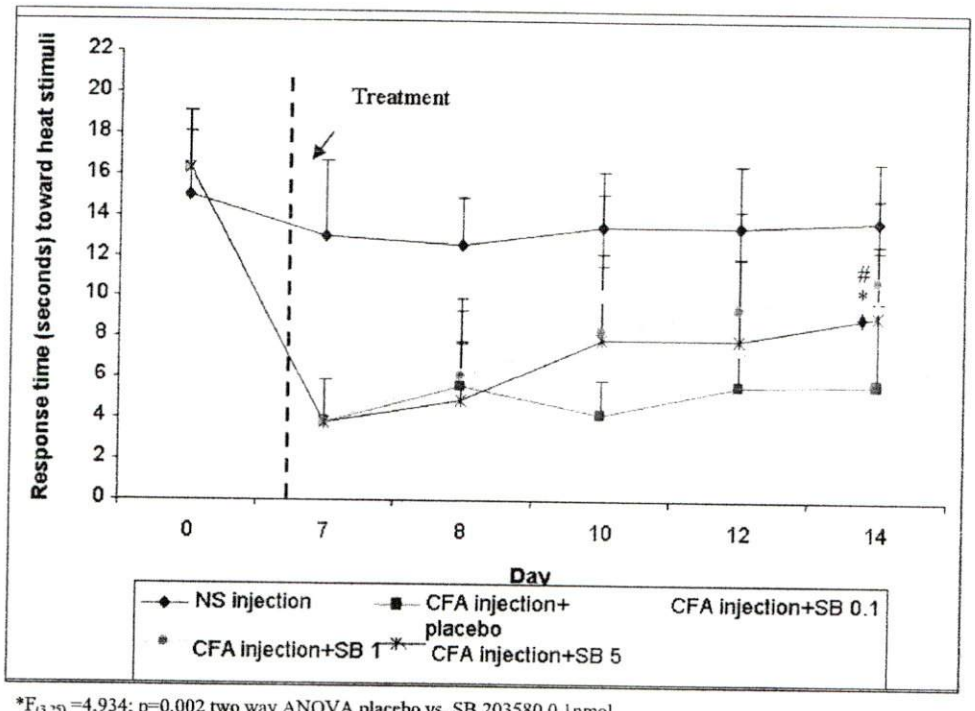
	Day after CFA injection			
	Day 12		Day 14	
	p	Meaning	*P*	Meaning
P vs PD 0.1 nmol	0.461	Not significant	0.150	Not significant
P vs PD 1.0 nmol	0.371	Not significant	0.344	Not significant
P vs PD 5.0 nmol	0.006	significant	0.021	significant
PD 1.0 nmol vs 5.0 nmol	0.039	significant	0.129	Not significant

P=Placebo injection; PD=PD 98059 injection

Table 4. Response time (seconds) toward heat stimuli following intrathecal injection of SB 203580 in mice suffering inflammation

Day	Response time (seconds) toward heat stimuli after SB 203580 injection						
Group	0	7	Treatment	8	10	12	14
NS (n=10)	14.99 ± 3.05	12.97 ± 3.68	NS	12.57±2.28	13.42±1.63	13.47±3.00	13.76±2.92
			Placebo	6.65±2.18	4.19±1.75	5.61±1.75	5.76±4.07
CFA (n=24)	16.23 ± 2.84	3.77 ± 2.11	SB 0.1 nmol	6.26±3.10	10.16±6.06	7.57±4.42	9.74±2.91
			SB 1.0 nmol	6.17±3.75	8.29±3.28	9.40±4.89	10.89±4.00
			SB 5.0 nmol	4.95±2.79	7.95±4.22	7.91±4.03	9.11±3.27

NS = Normal saline injection; CFA=Complete Freund's Adjuvant injection; SB= SB 203580 injection



*$F_{(3,25)}$ =4.934; p=0.002 two way ANOVA placebo vs. SB 203580 0.1nmol
#$F_{(3,25)}$=4.934; p=0.001 two way ANOVA placebo vs. SB 203580 1.0 nmol
♦$F_{(3,25)}$=4.934; p=0.039 two way ANOVA placebo vs. SB 203580 5.0 nmol

Figure 3. Response time (seconds) toward heat stimuli following intrathecal injection of PD 98059 in mice suffering from inflammation

Table 5. p value of SB 203580 on day 8, 10, 12, and 14 (one way ANOVA)

	Day after CFA injection			
	Day 8		Day 10	
	p	Meaning	p	Meaning
P vs SB 0.1nmol	0.706	Not significant	0.011	Significant
P vs SB 1.0 nmol	0.746	Not significant	0.071	Not significant
P vs SB 5.0 nmol	0.681	Not significant	0.119	Not significant
SB 1.0 nmol vs 5.0 nmol	0.466	Not significant	0.883	Not significant

	Day after CFA injection			
	Day 12		Day 14	
	p	Meaning	p	Meaning
P vs SB 0.1nmol	0.355	Not significant	0.043	Significant
P vs SB 1.0 nmol	0.081	Not significant	0.011	Significant
P vs SB 5.0 nmol	0.313	Not significant	0.106	Not significant
SB 1.0 nmol vs 5.0 nmol	0.501	Not significant	0.372	Not significant

P=Placebo injection; SB=SB 203580 injection

No statistically significant difference was found between 0.1 and 1.0 nmol PD 98059 and placebo in the CFA group (p=0.059 for 0.1 nmol dose of PD and p= 0.101 for 1.0 nmol dose of PD) whereas a statistical significant difference was found with a dose of 5.0 nmol of PD (p=0.001). Similarly, a result of significant difference was also found for 1.0 nmol vs. 5.0 nmol PD (p=0.004). Statistical analysis were carried out also to for day 8, 10, 12 and 14 using one way ANOVA and showed the starting day of MAP kinase inhibitor's effectiveness (Table 3).

The injection of SB 203580 with dose of 0.1, 1.0 and 5.0 nmol in the CFA group showed a significant statistical difference compared with placebo (p=0.002 with 0.1 nmol; p= 0.001 with 1.0 nmol and p=0.039 with 5.0 nmol). But, there was no statistical difference between 1.0 nmol vs. 5.0 nmol dose of SB 203580 in the increased response time toward heat stimuli (p=0.238). A one way ANOVA was also carried out to compare the effectiveness of SB 203580 on day 8, 10, 12, and 14 (Table 5).

DISCUSSION

CFA injection has successfully developed an inflammation like state by activating cellular or humoral antibody response. In this condition, macrophage is the most active immune system. It comes from monocyte's bone marrow production and distributed via blood circulation. Macrophage has the ability to phagocyte in response to inflammation. During inflammation, inflammatory mediators such as cytokines, IL-1 and TNF-α will be released. The initial process of inflammation is started following a chemotactic and phagocytotic process. A phospholiphase will be released from cell membrane and induce the arachidonic acid pathway. Arachidonic acid metabolism via cyclooxygenase willl release prostaglandin and tromboxane. Several studies reported the main inflammation mediators are PGE2 dan PGI2 (Simmons 2004). This inflammation also resulted in extravasation and deposition of plasma protein, and thus oedema will be occurred. Other symptoms include redness, increasing local temperature and hyperalgesia (Katzung 2002, Ji et al 2002).

Futhermore, inflammatory like state by CFA injection will subsequently release pain mediators that will interact with receptors in spinal cord so that it will increase pain sensation and hyperexcitability of the membrane (Woolf 2004). Likewise, these will activate afferent nerve that induce glutamate, natrium and kalium release. The release of the excitatory neurotransmitter such as glutamate will activate NMDA receptor which then induces neuropeptide release such as subtance P and neurokinin. This receptor activation will activate other second messegers such as MAP kinase (Siddals & cousins 1998). MAP kinase is a family of serine/threonine kinase that connects a signal transmision in response to inflammation and other extracellular signal such as gene expression. There are three type of MAP kinase which are p38, extraceullar signal-regulated kinase 1 and 2 (Erk1/2) and c-Jun N-terminal kinase (JNK) (Nieminen 2005). Activation of the MAPK Erk1/2 and MAPK p38 will upregulate COX-2 expression and prostaglandin production (Haulbold 1998). Some studies also reported that peripheral inflammation also activates Erk in dorsal horn. Such activation has great contribution to some gene such as prodinorfin dan neurokinin-1. Both genes has great influence in inflammatory pain hypersensitisation (Ji et al 2002).

On day 7 after CFA injection, a hot plate test was performed to asses the effectiveness of MAP kinase inhibitors to inhibit pain development. PD 98059 or SB 203580 was used to evaluate CFA groups. A once daily dose of 0.1, 1.0 and 5.0 nmol intrathecally of both subtance was given for 7 consecutive days. Statistical analysis with Two Way ANOVA showed that 0.1 and 1.0 nmol of PD 98059 did not significantly increase response time toward heat stimuli compared with placebo receiving CFA injection (p=0.059 for dose of 0.1 nmol and p= 0.101 for dose of 1.0 nmol). But, at dose of 5.0 nmol PD 98059 showed increase significant response toward heat stimuli compared with placebo ($F_{(3.26)}$=6.881; p=0.001) as shown in Figure 2. With similar analysis, 1.0 nmol and 5.0 nmol PD 98059 showed significant increase in response time toward

heat stimuli ($F_{(3.26)}$=6.881; p=0.004). Moreover, the Two Way ANOVA for SB 203580 showed that at dose 0.1, 1.0 and 5.0 nmol of SB in CFA injection group resulted in significant different compared with placebo ($F_{(3.25)}$=4.934; p=0.002 for 0.1 nmol SB; p=0.001 for 1.0 nmol SB and p= 0.039 for 5.0 nmol SB).

The increase in response time toward heat stimuli shows that the provision of MAP kinase inhibitor either PD 98059 or SB 203580 could inhibit the development of inflammatory pain. This is because either PD 98059 or SB 203580 can spesifically inhibit p38 and Erk 1/2 in the MAP kinase pathway. As a result, this inhibition can decrease the arachidonic acid concentration and thus subsequently inhibit tromboxane production. Several studies also reported that these can reversibelly inhibit COX-1 and COX-2 (Haulbold 1998). SB 203580 has great potential properties as anti inflammatory drug as it can inhibit cyclooxygenase, lipooxygenase and biosynthesis of inflammatory mediator cytokine. SB 203580 specifically inhibits p38 in the MAP kinase pathway and also inhibits mRNA expression in the synthesis of prostaglandin E2. Also, SB 203580 inhibits nitric oxyde synthesis and release. Nitric oxyde can induce the increase of glutamate and subtance P release. It also has its role on activating the macrophage and polymorphonuclear nucleuoside (PMN) involved in the pathogenesis of chronic inflammation (Chen & Wang 1999, Hudspith et al 2003). PD 98059 is a spesific inhibitor of Erk 1/2 that can suppres IL-1. IL-1 can induce COX-2 and prostaglandin E2 expression. This effect is dependent on the dose. PD 98059 also affects the inhibitory COX-2 activity (Nieminen 2005).

The provision of MAP kinase inhibitors either PD 98059 or SB 203580 could not inhibit inflammatory pain like state completely. In other words, the effect of both substances toward inflammatory pain is partial. Figure 2 and Figure 3 showed that the response time toward heat stimuli can not be restored into normal condition compared with the group of mice not suffering from inflamation (control group). It is reasonable that the inflammatory pain like state is complex and involves some other mechanism of inflammatory pain development. Also, MAP kinase has three activation pathway in which PD 98059 inhibit MAPK Erk 1/2 and SB 203580 inhibit MAPK p38 so that the pain inhibition is partial (Nieminen 2005).

CONCLUSION

Mitogen-Activated Protein (MAP) Kinase has a role in the development of inflammatory pain in which MAP kinase inhibitors such as PD 98059 and SB 203580 can decrease hyperalgesia which is shown by increasing response time toward heat stimuli.

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