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SPINALLY MEDIATED ANALGESIC INTERACTION BETWEEN γ-AMINOBUTYRIC ACID B RECEPTOR AGONIST AND GLUTAMATE RECEPTOR ANTAGONISTS IN RATS

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ABSTRACT
Background. Many mechanisms are involved in pain transmission in the spinal cord. Therefore, combination of drugs acting on different kinds of mechanisms might be useful for analgesia. We investigated the interaction between γ-aminobutyric acid （GABA）$_B$ receptor agonist, baclofen, and N-methyl-D-aspartate （NMDA） receptor antagonist, AP-5, or α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid （AMPA） receptor antagonist, YM-872, on analgesic effects in acute thermal and formalin induced pain models of rats. Methods. Male Sprague-Dawley rats implanted with lumbar intrathecal catheters were given intrathecal baclofen, AP-5, YM872 or combination of baclofen and AP-5 or YM872, then tail flick test or formalin test was performed. Fifty % effective doses of combinations were obtained and isobolographic analysis was done. Results. The combination of baclofen and AP-5 or YM872 showed dose dependent increases in tail flick latency and decreases in flinching response in the formalin test. In the tail flick test, ED50s of the combination of baclofen + AP-5 or YM872 were close to the additive points. In both phases of the formalin test, ED50s of the combination of baclofen + AP-5 or YM872 were significantly lower than additive points. Conclusions. For acute thermal pain, both AP-5 and YM872 had similar additive analgesic effects with baclofen. For chemical induced acute pain, both AP-5 and YM872 had similar synergistic analgesic effects with baclofen, but for facilitated pain, YM872 had stronger synergistic analgesic effects with baclofen than AP-5.

KEYWORDS: Analgesia, $GABA_B$ receptor, NMDA receptor, AMPA receptor, Spinal cord.

INTRODUCTION
Intrathecally administered AP-5 (2-amino-5-phosphonovaleic acid), a N-methyl-D-aspartate (NMDA) receptor antagonist, and YM872 ([2,3-Dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl] acetic acid, an α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist had analgesic effects in acute thermal and formalin induced acute and facilitated pain in the rat models in our previous study. [1]

Baclofen, a γ-aminobutyric acid $(GABA)_B$ receptor agonist had analgesic effects in acute pain, [2] and formalin induced pain [3] in the rat models. Baclofen is also clinically used as intrathecal administration to relieve neuropathic pain. [4]

There are many mechanisims concerning pain transmission in the spinal cord, therefore, combining the drugs acting on different mechanisms might be useful for analgesia. Intrathecal baclofen and ketamine, a NMDA receptor antagonist, had synergistic analgesia in rat model of neuropathic spinal cord injury pain. [5] However, the effects of $GABA_B$ receptor agonist in combination with NMDA or AMPA receptor antagonist on any other pain models have not been studied. Therefore, our present study was performed to investigate the interaction between $GABA_B$ receptor agonist, baclofen, and NMDA receptor antagonist, AP-5, or AMPA receptor antagonist, YM-872, on analgesic effects in basic acute thermal and formalin induced pain models of rats.

MATERIALS AND METHODS
After obtaining the approval of the Research Committee of the University of Tokyo, male Sprague-Dawley rats (280-300 g; Nippon Bio-Supply, Tokyo, Japan) were implanted with lumbar intrathecal catheters under halothane (2 %) anesthesia. The experiment procedures are the same as our previous study. [1] Briefly, an 8.5 cm polyethylene catheter (PE-10; Clay Adams, Parsippany,

NJ) was inserted caudally to the thoracolumbar level in the intrathecal space through atlanto-occipital membrane. The rostral part of the catheter was plugged with a 28-gauge steel wire and put through to the top of the skull. Only rats with normal motor function and behavior and increase in body weight seven days later were used for experiments. After the study, rats were euthanized under halothane 5% and the location of the catheter was confirmed anatomically and the data of the rats with mal location of the catheter was excluded and another rat was added to fill the number of each group.

Drug preparation

Baclofen (a $GABA_B$ receptor agonist, Sigma, St. Louis, MO) and AP-5 (2-amino-5-phosphonovaleic acid, a NMDA receptor antagonist, Sigma, St. Louis, MO) were dissolved in normal saline to get the concentrations used in each test. YM872 ([2,3-Dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl] acetic acid, an AMPA receptor antagonist, Yamanouchi Pharmaceutical Co. Ltd., Tsukuba, Ibaraki, Japan) 10 mg was dissolved in 0.97 mL distilled water with 30 µL 1N NaOH added to adjust pH between 7.3 – 7.5, then dissolved in normal saline to get the concentrations used in each test.

Nociceptive test

According to our previous study, [1] we used the same two classic methods as nociceptive tests.

Tail-flick test

The tail-flick test was performed with the Tail-Flick Analgesia Meter (MK-330A; Muromachi Kikai Co. Ltd., Tokyo, Japan). Rats were placed in a clear plastic cage with their tails extending through a slot located of the rear of the cage. Thermal stimulation was given by a beam of high intensity light focused on the tail 2 to 3 cm proximal to the end. The time between the start of the stimulation and tail withdrawal response was measured as a tail-flick latency. The cut-off time in the absence of a response was set to 14 seconds to prevent tissue injury of the tail. The test was done at 5, 10, 15, 30, 60, 90, 120, 180, and 240 minutes after drug injection. The data were shown as the % of maximum possible effect (% MPE): % MPE = (post-drug latency – pre-drug latency at time 0) X 100 / (cut-off time (14 sec) – pre-drug latency at time 0.

Formalin test

The formalin test was performed 10 minutes after intrathecal drug injection. Fifty µL of 5 % formalin was injected subcutaneously into the dorsal surface of the right hind paw with a 30 G needle. Immediately after injection, the rat was placed in an open clear plastic chamber and their flinching or shaking paw response was observed for 60 minutes. The number of flinches was counted for 1 minute. Usually two phases were observed: phase 1, during 0 to 6 minutes after formalin injection; and phase 2, beginning about 10 minutes after injection with the interval of no flinches between both phases.

Side effects

Side effects were examined and judged as present or absent. Agitation was judged as spontaneous irritable movement, vocalization, or both. Allodynia-like behavior was judged as escape, vocalization, or both induced by lightly stroking the flank of the rat with a small probe. The placing or stepping reflex was evoked by drawing the dorsum of either hind paw across the edge of the table. Normal rats try to put the paw ahead into a position to walk. The righting reflex was assessed by placing the rat horizontally with its back on the table. Normally rats twist the body to an upright position immediately. Flaccidity was judged as muscle weakness by putting the forepaw 3 to 5 cm higher than the hind paw. Normal rats will walk up. Pinna or corneal reflex was examined with a paper string. When a string is put into the ear canal or touches the cornea, rats normally shake their heads. Behavioral side effects were checked simultaneously with the tail flick test.

Protocol

Each drug intrathecally administered was adjusted in 10 µL and after injection of the drug, the catheter was flushed with normal saline 10 µL to clear the dead space of the catheter.

Baclofen

Tail flick test was performed with intrathecal baclofen 0.1, 0.3, 1, and 3 µg / 10 µL, and 50 % effective dose (ED50) was calculated. Formalin test was performed with intrathecal baclofen 0.003, 0.03, 0.1, 0.3, and 1 µg / 10 µL, and ED50 was calculated. Normal saline was used as a control. In each test and each dose, 8 rats were used.

AP-5 and YM872

These two compounds were already studied in both tests. [1] In the present study, AP-5 1, 3, 10, and 30 µg / 10 µL, and YM872 0.3, 1, 3, 10, and 30 µL / 10 µL, each 3 rats were used in both tail flick test and formalin test. After we confirmed the similarity of the data with previous study, [1] these data were added to the previous data and recalculated ED50 from the data of 11 rats in each test to save rats.

Combination

The combination of 1/2, 1/4, 1/8, 1/16, and 1/32 ED50s of AP-5 and baclofen in 10 µL and 1/2, 1/4, 1/8, and 1/16 ED50s of YM872 and baclofen in 10 µL were studied in the tail flick test. The combination of 1/2, 1/4, 1/8, and 1/16 ED50s of AP-5 or YM872 and baclofen in 10 µL were studied in the formalin test.

The ED50 was obtained using the maximum effects in the tail flick test and the area under the curve of the number of flinches in the formalin test. A total fractional dose value was calculated to describe the magnitude of the interaction as follows: (ED50 dose of drug 1 in combination) / (ED50 dose of drug 1 alone) + (ED50 dose of drug 2 in combination) / (ED50 dose of drug 2

alone). The value was normalized by assigning the ED50 value of each drug given alone as 1. Values near 1 suggest an additive interaction, values > 1 implies an antagonistic interaction, and values < 1 indicate a synergistic interaction. To compare the theoretical additive point with experimentally derived ED50, isobolographic analysis was used.

Data analysis

The data are shown as mean ± standard deviation or 95% confidential interval (CI). Statistical analysis was performed with the Student's t test to compare the calculated ED50 values with the theoretical additive values. A p value less than 0.05 was considered to be statistically significant.

RESULTS

Intrathecal baclofen showed dose dependent increases in tail flick latency and decreases in flinching response in both phases of the formalin test. The combination of baclofen and AP-5 or YM872 also showed dose dependent increases in tail flick latency and decreases in flinching response in the formalin test. The ED50s of each drug were shown in the Table 1. In both phases of the formalin test, ED50s of the combination of baclofen + AP-5 or YM872 were significantly lower than ED50s of each agent alone (Table 1). The isobolograms of each test were shown in figures 1 to 6. In the tail flick test, ED50s of the combination of baclofen + AP-5 or YM872 were close to the additive points (Fig1, 2). In both phases of the formalin test, ED50s of the combination of baclofen + AP-5 or YM872 were significantly lower than additive points (Fig. 3-6). The total fractional dose values were 0.75 (95% CI, 0.34 – 1.23) (AP-5 + baclofen, tail flick test), 0.84 (0.24 – 1.98) (YM872 + baclofen, tail flick test), 0.18 (0.012 -1.48) (AP-5 + baclofen, formalin test phase 1), 0.35 (0.06 - 1.87) (YM872 + baclofen, formalin test phase 1), 0.05 (0.002 - 1.64) (AP-5 + baclofen, formalin test phase 2), and 0.01 (0.009 – 0.78) (YM872 + baclofen, formalin test phase 2).

Side effects observed in each agent were not seen in each combination (Table 2).

Table 1: ED5095% confidence interval in the parenthesis, *: P < 0.05 vs. the value of each single drug.

	Tail flick	Formalin phase 1	Formalin phase 2
Baclofen (μg)	0.32 (0.25-0.4)	0.0062 (0.001-0.034)	0.013 (0.002-0.076)
AP-5 (μg)	5.5 (2.3-10.8)	7.5 (4.0-13.1)	1.5 (0.5-5.9)
YM872 (μg)	1.0 (0.4-2.8)	0.24 (0.08-0.75)	0.2 (0.07-0.7)
Baclofen + AP-			
Baclofen (μg)	0.13 (0.08-1.44)	0.001 (0.0004-0.026)*	0.0003 (0.0001-0.006)*
AP-5 (μg)	1.91 (1.47-2.48)	0.12 (0.005-1.93)*	0.04 (0.002-6.7)*
Baclofen + YM872			
Baclofen (μg)	0.14 (0.047-0.7)	0.001 (0.0007-0.002)*	0.0004 (0.0002-0.0007)*
YM872 (μg)	0.4 (0.35-0.55)	0.045 (0.03-0.07)*	0.016 (0.009-0.03)*

Table 2: Side effects The number of rats with each side effect. Total number of rats were 8 in baclofen and 11 in AP-5 and YM872.

	Agitation/ Allodynia	Disturbance of Placing/Stepping reflex	Disturbance of Righting reflex	Flaccidity	Loss of corneal reflex	Loss of Pinna reflex
Baclofen 1μg	0	4	4	4	0	0
3μg	0	8	8	8	0	2
AP-5 10μg	1	2	2	0	1	0
30μg	2	2	3	0	1	0
YM872 10μg	0	4	4	3	0	0
30μg	0	5	5	6	0	0
Baclofen + AP-5	0	0	0	0	0	0
Baclofen + YM872	0	0	0	0	0	0

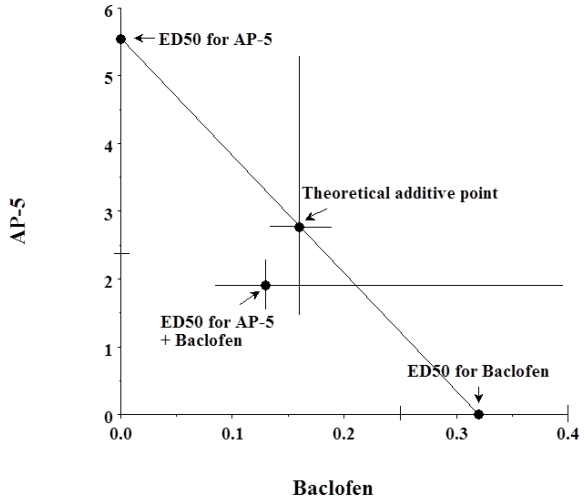

Figure 1: Isobolograph of the tail flick test with baclofen + AP-5.
X axis and Y axis are in µg. Bars indicate 95 % confidence interval.

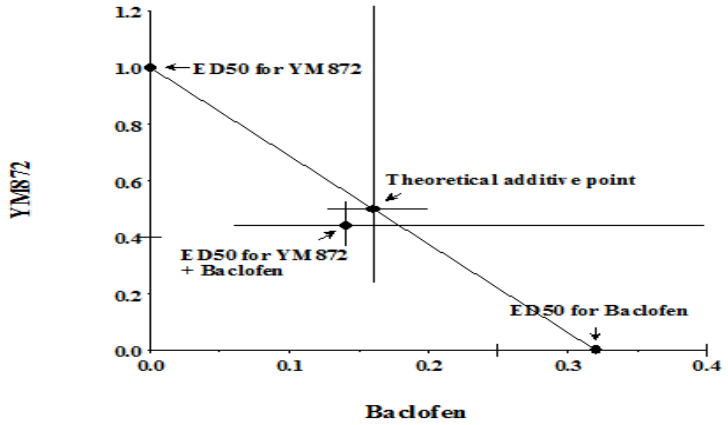

Figure 2: Isobolograph of the tail flick test with baclofen + YM872.
X axis and Y axis are in µg. Bars indicate 95 % confidence interval.

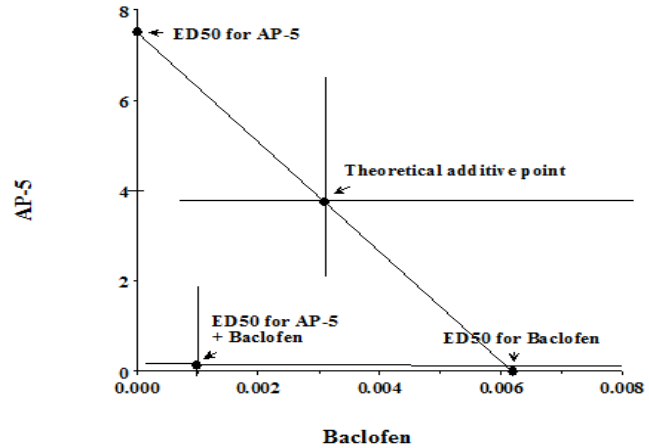

Fig.3

Figure 3: Isobolograph of the formalin test phase 1 with baclofen + AP-5.
X axis and Y axis are in µg. Bars indicate 95 % confidence interval.

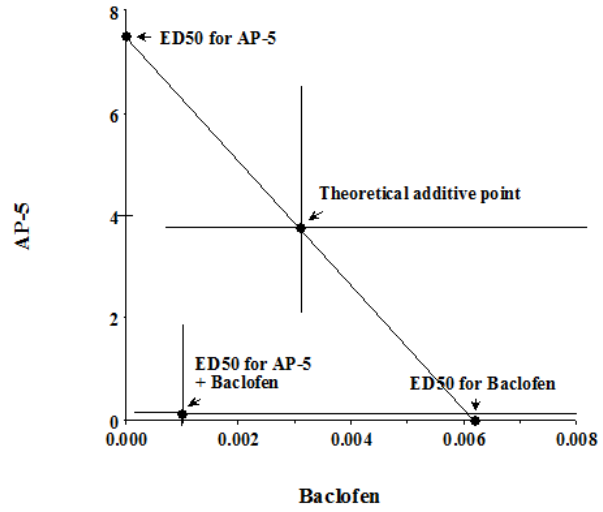

Figure 4: Isobolograph of the formalin test phase 2 with baclofen + AP-5. X axis and Y axis are in µg. Bars indicate 95 % confidence interval.

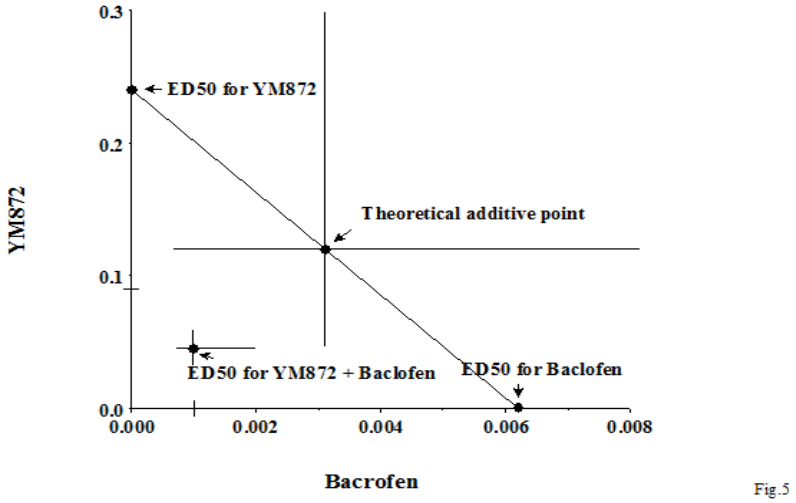

Figure 5: Isobolograph of the formalin test phase 1 with baclofen + YM872. X axis and Y axis are in µg. Bars indicate 95 % confidence interval.

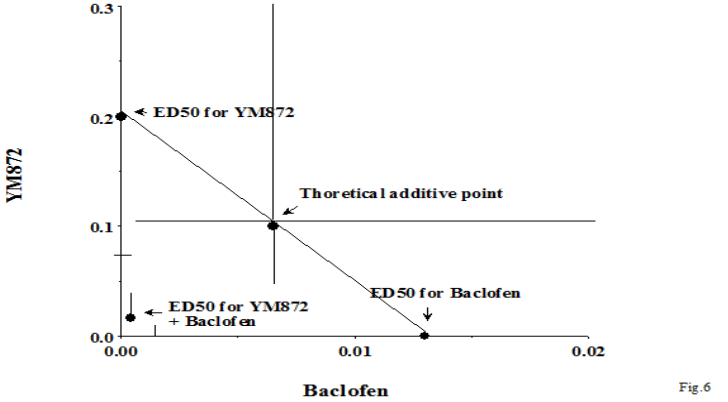

Figure 6: Isobolograph of the formalin test phase 2 with baclofen + YM872. X axis and Y axis are in µg. Bars indicate 95 % confidence interval.

DISCUSSION

This study showed that baclofen and AP-5 or YM872 had synergistic analgesia in both phases of the formalin test and additive analgesia in the tail flick test. The combinations decreased side effects we tested.

$GABA_B$ receptors are located at both presynaptic and postsynaptic compartments. $GABA_B$ receptor mediated regulation of neuronal excitability and neurotransmitter release might modulate pain transmission in the spinal dorsal horn.[6] Intrathecal baclofen significantly increased response latency in thermal pain.[7] Baclofen has antinociceptive effects in acute pain and inhibits allodynia and hyperalgesia in chronic neuropathic pain.[8] These results are consistent with our present results in the tail flick test and formalin test with intrathecal baclofen.

NMDA receptors in the spinal cord have a role in the development of central sensitization and neuropathic pain after nerve injury[9] and after formalin injection,[10] play a role in the initial induction of inflammatory pain, but the NMDA receptor activity in the spinal dorsal horn is not required for the maintenance of chronic inflammatory pain. [11] Presynaptic NMDA receptor activity at the spinal cord is increased in several neuropathic pain but not in chronic inflammatory pain. Increased presynaptic NMDA receptor activity can potentiate glutamate release from primary afferent terminals to spinal dorsal horn neurons.[12] Our previous study[1] showed that intrathecal AP-5, a NMDA receptor antagonist, had analgesic effects on acute thermal and formalin induced acute and facilitated pain.

The dorsal horn of the spinal cord has a high density of Ca^{2+}-permeable AMPA receptors, particularly in the superficial laminae, where primary afferents carrying pain and thermoreceptive inputs terminate and synapse on spinal second-order neurons.[13] Spinal AMPA receptors have a role in the mechanism of both acute and persistent inflammatory pain.[14, 15] Our previous study and this additional data showed that spinally administered YM872, an AMPA receptor antagonist, had analgesic effects on acute thermal and formalin induced acute ad facilitated pain in the rat models.[16]

AMPA complexes are physically coupled with NMDA receptors in the dorsal horn.[17] During inflammation, AMPA receptor/NMDA receptor ratio increased, but AMPA mediated currents did not increase and NMDA mediated currents decreased.[18] Therefore, for inflammatory pain, AMPA receptor antagonists might be more useful than NMDA receptor antagonists. In our study, the ratio of ED50 of YM872 / AP-5 was smaller in both phases of the formalin test than in the tail flick test, which was consistent with the results of the study by Vikman et al.[18] The total fractional dose value was significantly lower in YM872 than AP-5 in phase 2 of the formalin test.

NMDA receptors and AMPA receptors are modulated directly and indirectly by $GABA_B$ receptors.[19] NMDA receptors are present on GABAergic terminals in the superficial dorsal horn of the spinal cord.[20] Activation of presynaptic $GABA_B$ receptors decreases synaptic glutamate release in the spinal dorsal horn. [21] Activation of postsynaptic $GABA_B$ receptors suppresses Ca^{2+} permeability of NMDA receptors and reduces NMDA receptor activity.[22] Baclofen inhibits NMDA activated current in the primary sensory neurons.[23] and suppressed the expression of NR2B, a subunit of NMDA receptor, then decreased neuropathic pain.[24] Activation of NMDA receptors leads to down regulation and degradation of $GABA_B1$ and $GABA_B2$ subunits,[19] and also regulated trafficking and surface expression of $GABA_B$ receptors.[25] Therefore, $GABA_B$ receptor agonist, baclofen and NMDA receptor antagonist, AP-5 might have strong interaction, suggesting additive or synergistic analgesic effects as shown in the present study. AMPA receptors regulate GABA release in the spinal cord dorsal horn.[26] Therefore, AMPA receptor antagonist, YM872 had additive or synergistic effects with baclofen in this study. Activation of both NMDA and AMPA receptors is required for down regulation of $GABA_B$ receptors.[27] However, which receptors, NMDA or AMPA, have stronger interaction with $GABA_B$ receptors in different pain stimuli, has not been shown.

In our present study, for acute thermal pain, both NMDA receptor antagonist and AMPA receptor antagonist had similar additive effects with $GABA_B$ receptor agonist. For chemical induced acute pain, both NMDA receptor antagonist and AMPA receptor antagonist had similar synergistic effects with $GABA_B$ receptor agonist, but for facilitated pain, AMPA receptor antagonist had stronger synergistic effects with $GABA_B$ receptor agonist than NMDA receptor antagonist.

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