Effect of DA-9701 on Colorectal Distension-Induced Visceral Hypersensitivity in a Rat Model

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Background/Aims: DA-9701 is a newly developed drug made from the vegetal extracts of *Pharbitidis semen* and *Corydalis tuber*. The aim of this study was to evaluate the effect of DA-9701 on colorectal distension (CRD)-induced visceral hypersensitivity in a rat model. **Methods:** Male Sprague-Dawley rats were subjected to neonatal colon irritation (CI) using CRD at 1 week after birth (CI group). At 6 weeks after birth, CRD was applied to these rats with a pressure of 20 to 90 mm Hg, and changes in the mean arterial pressure (MAP) were measured at baseline (i.e., without any drug administration) and after the administration of different doses of DA-9701. **Results:** In the absence of DA-9701, the MAP changes after CRD were significantly higher in the CI group than in the control group at all applied pressures. In the control group, MAP changes after CRD were not significantly affected by the administration of DA-9701. In the CI group, however, the administration of DA-9701 resulted in a significant decrease in MAP changes after CRD. The administration of DA-9701 at a dose of 1.0 mg/kg produced a more significant decrease in MAP changes than the 0.3 mg/kg dose. **Conclusions:** The administration of DA-9701 resulted in a significant increase in pain threshold in rats with CRD-induced visceral hypersensitivity. **(Gut Liver 2014;8:388-393)**

INTRODUCTION

Despite significant advances in the recognition of etiological factors and pathological mechanism, the pathophysiology of functional gastrointestinal (GI) disorders is still not completely understood.[1] Visceral hypersensitivity is currently the leading hypothesis to explain functional GI disorders, such as irritable bowel syndrome (IBS).[2] Since Ritchie[3] first reported that IBS patients were more sensitive than normal subjects to balloon distension of the colon, many studies confirmed lower colonic pain thresholds in most of the patients with IBS.[4,5] Similarly, intolerance to gastric distension was documented in patients with functional dyspepsia.[6,7] Some attempts have already been made to pharmacologically decrease the visceral hypersensitivity of functional GI disorders, using a number of drugs.[8,9] However, the treatment was not satisfactory and the side effects could not be easily overcome.

DA-9701 is a newly formulated prokinetic agent obtained from the vegetal extracts of *Pharbitidis semen* and *Corydalis tuber*. These herbs have been used as a traditional treatment for their analgesic and antiulcer effects.[10] It was previously reported that administration of DA-9701 not only resulted in accelerated gastric emptying and GI transit in the normal rat, but also induced increase in gastric accommodation in Beagle dogs.[10-14] Moreover, binding assays for various receptors controlling GI motor functions, using several compounds isolated from DA-9701, showed the affinity for 5-hydroxytryptamine (5-HT) receptors.[13,14] 5-HT receptor ligands modify pain signaling from the gut.[15,16] Thus, the neuromodulator 5-HT, also known as serotonin, has been proposed to play a key role in GI functional disorders.[17] Based on these observations, we hypothesized that DA-9701 might show efficacy for treatment of IBS by ameliorating effect on visceral hypersensitivity.

The aim of this study was to evaluate in a rat model the effect of DA-9701 on colorectal distension (CRD)-induced visceral hypersensitivity.

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MATERIALS AND METHODS

1. Preparation of animals

We used a total of 24 adult male Sprague Dawley rats, weighing 250 to 350 g, that were obtained as preweaning (7-day-old) neonates from Orient Bio Inc., Seongnam, Korea; 18 rats received colon irritation (CI) in neonate (CI group), and six rats were kept untreated (control group). Rats were housed in plastic cages containing corn cob bedding, and maintained on a 12:12-hour light:dark cycle (lights on at 7 AM). The CI procedure and experimental testing were conducted during the light component of the cycle. We housed 10 neonates, with one mother, per cage until they were 25 days old. The adult female had access to food and water ad libitum. After separation from the mother, the young male rats were housed four per cage, with access to food and water ad libitum. The rats were observed daily, and their weights were measured at least once a week. The experimental protocol was summarized at Fig. 1.

All studies were approved by the Institutional Animal Care and Use Committee at the Dong-A ST, Co., Ltd., Research Center, in accordance with the guidelines provided by the National Institutes of Health, USA.

2. Neonatal colon irritation

We used the neonatal CI method, following that of Lin and Al-Chaer.[18] We used CRD to induce visceral hyperalgesia during postnatal development. We subjected all rats except those in the normal group to CI, once each at 8, 10, and 12 days old.

For CI, we used an angioplasty balloon (length, 20.0 mm; diameter, 3.0 mm; Advanced Polymers Inc., Carlstadt, NJ, USA), inserted rectally into the descending colon to a depth of 3 cm,

and distended for 1 minute with 0.3 mL of water at a pressure of 60 mm Hg (pressure was measured with a sphygmomanometer).

3. Electrophysiological preparations

1) Drug administration and animal preparation

The doses of the test drug, DA-9701, were 0.3 and 1 mg/kg. Eighteen rats received CI in neonate (CI group) were randomized into three groups: no medication group (n=6), DA-9701 (0.3 mg/kg) group, and DA-9701 (1 mg/kg) group.

Experiments were carried out on adult rats (6 weeks old). All drugs were administered orally. After 40 minutes, we induced anesthesia with intraperitoneal sodium pentobarbital 50 mg/kg.

A polyethylene catheter was inserted into and fixed to the carotid artery to measure mean arterial pressure (MAP). During the surgery and electrophysiological recording, we maintained the sodium pentobarbital, using the pedal reflex to check the depth of the anesthesia. We monitored and maintained body temperature at 37.8°C using a heating blanket.

#### 2) Colonic stimulation and blood pressure recording

We used a different distension balloon, and modified the colonic stimulation procedure, from the previous method by Lin and Al-Chaer.[18] We measured the blood pressure during each colonic simulation, obtaining results of 20 to 90 mm Hg. The balloon was 3 cm long and made of the finger of a latex glove. Prior to use, the balloon was left fully distended overnight for compliant distension. We attached the balloon to a polyethylene tube and tied it tightly to prevent any air leaking. After insertion into the anus to a depth of 4 cm, the tube was taped to the tail for fixation. The other end of the catheter was connected to a sphygmomanometer. We applied CRD by rapidly distending the balloon to the desired pressure, in serial increments of 20 mm Hg (i.e., 20, 40, 60, or 80 mm Hg), for a duration of 10 seconds.

The MAP was universally defined as the average arterial pressure during a single cardiac cycle and it was calculated as 1/3 systolic plus 2/3 diastolic pressure. In this study, we calculated the average of the MAP during five cardiac cycles at stable baseline response in each CRD. The MAP changes were subtracted basal MAP from MAP in each CRD.

To minimize the possible human factor bias, the format of stimulation was standardized for every rat. Colonic stimulation was accurately applied according to the pressure gauge, and the experimenter remained unaware of the response magnitude by not observing the oscilloscope or computerized record.

4. Data analysis

We measured the MAP changes to graded CRD for each animal after treatment. We compared the MAP changes in each CRD to that of either normal rats or neonatal CI rats not given DA-9701, using one-way analysis of variance.
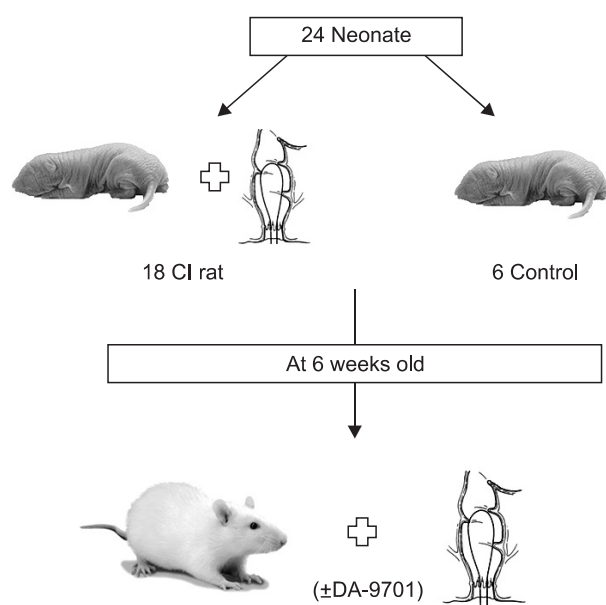
Fig. 1. The schematic diagram of the experimental protocol. CI, colon irritation.

A p<0.05 was considered as statistically significant.

RESULTS

### 1. Effect of neonatal CI on MAP response to graded CRD

As shown in Fig. 2, the MAP changes to graded CRD were significantly higher in the CI group than that in control group, in almost all applied pressures (p<0.05). In particular, the increase of the MAP changes was a significant at 20, 30, 40, and 60 mm Hg distension (p<0.001).

2. Effect of DA-9701 to graded CRD

In control group, the MAP changes to graded CRD were not
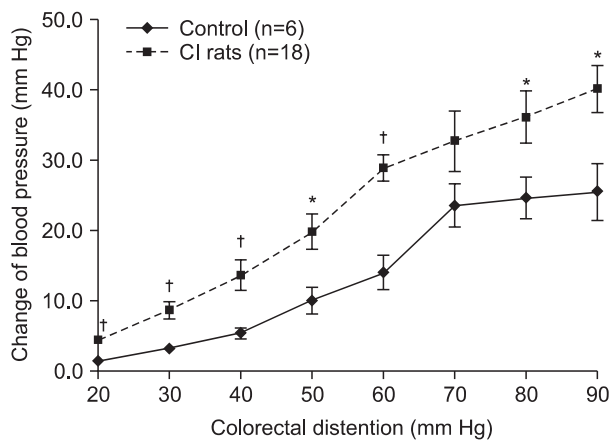
Fig. 2. Induction of visceral hypersensitivity during postneonatal period in rats by colon irritation using colorectal distension. The mean arterial pressure (MAP) changes were measured during colorectal distension, which was applied to the rats by inflating a balloon with a pressure of 20 to 90 mm Hg. Rats in the neonatal colon irritation group (CI group) were more susceptible to colorectal distension than normal rats. The MAP changes in response to graded colorectal distension were significantly increased in the neonatal CI group at almost all applied pressures. *p<0.05; †p<0.01.
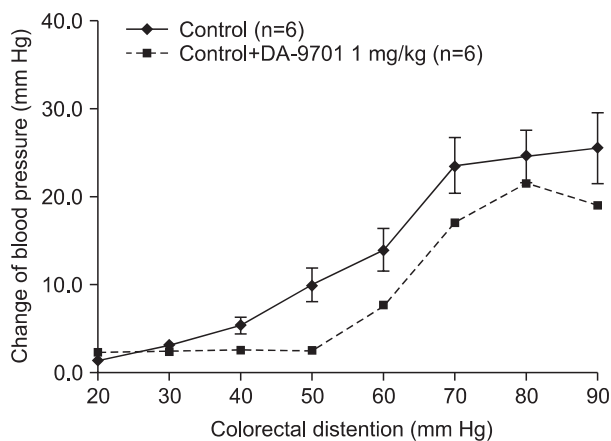
Fig. 3. The effect of DA-9701 in normal rats. In normal rats, the mean arterial pressure changes in response to graded colorectal distension tended to be reduced after the administration of DA-9701, although the difference was not statistically significant.

significantly different after administration of DA-9701 in all applied pressure (Fig. 3).

On the other hand, in the CI group, administration of DA-9701 resulted in significant decrease in the MAP changes to graded CRD in all applied pressures (p<0.05). DA-9701 produced dose-dependent reduction in distension-mediated MAP changes over a range of pressures. After 0.3 mg/kg DA-9701 administration, a significant reduction of the MAP changes was showed at 30 and 90 mm Hg distension (p=0.005 and p=0.003). Administration of DA-9701 at 1.0 mg/kg dose showed more significant decrease in the MAP changes, compared with the dose of 0.3 mg/kg in almost all applied pressures (p<0.01 in 1.0 mg/kg of DA-9701 and p<0.05 in 0.3 mg/kg of DA-9701, respectively), as presented in Fig. 4.

The cumulative percentage showed the total number of rats whose MAP changes were over 10 mm Hg in each CRD (Fig. 5). The 67% of the neonatal CI rats not given DA-9701 showed a significant increase in MAP change at 40 mm Hg distension. However, at the same distension, none CI rats administered DA-9701 showed significant increase in MAP changes. Also, all (100%) of neonatal CI rats not given DA-9701 showed significant increase in MAP changes at 50 mm Hg distension. However, 67% of neonatal CI rats administered 1 mg/kg of DA-9701 didn't significantly increase the MAP pressure even at 90 mm Hg distension.

DISCUSSION

In the present study, conducted in rats with neonatal CI using CRD, administration of DA-9701 resulted in a significant
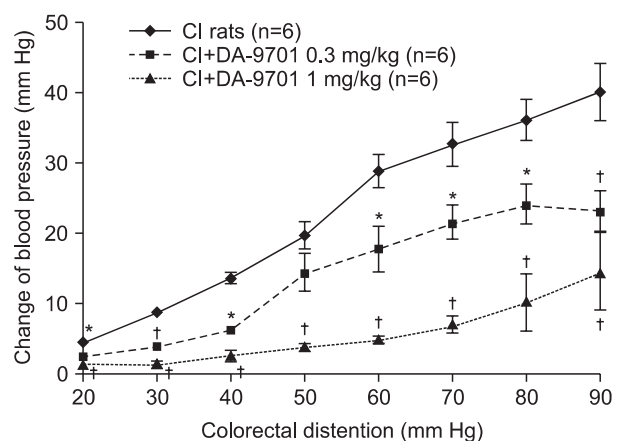
Fig. 4. The effect of DA-9701 in rats with visceral hypersensitivity-induced colon irritation (CI). In the CI group, the administration of DA-9701 produced a significant decrease in mean arterial pressure (MAP) changes in response to graded colorectal distension at all applied pressures (p<0.05). DA-9701 produced a dose-dependent reduction in the MAP changes in response to various extents of balloon distension. The dose of 1.0 mg/kg DA-9701 decreased the MAP changes to a greater extent than the dose of 0.3 mg/kg. *p<0.05; †p<0.01.
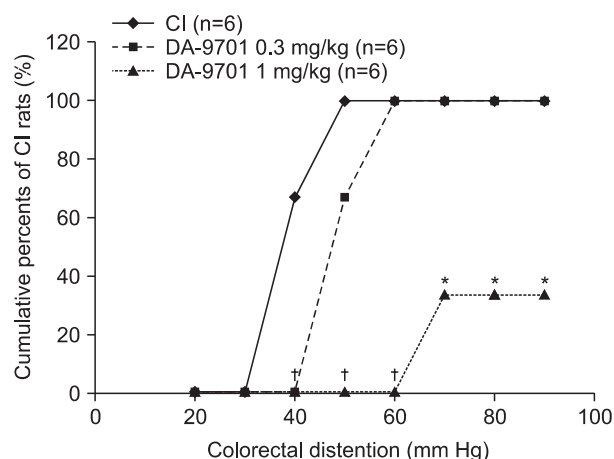
Fig. 5. Cumulative percentage of total colon irritation (CI) rats showing increases in the mean arterial pressure (MAP) changes. All of the neonatal CI rats not given DA-9701 showed a significant increase in MAP changes at a distension of 50 mm Hg. In contrast, 67% of the neonatal CI rats given 1 mg/kg DA-9701 did not show significant increases in MAP pressure even at a distension of 90 mm Hg. *p<0.05; †p<0.01.

decrease in MAP changes to graded CRD, producing a dose-dependent effect on CRD-induced visceral hypersensitivity. This indicates that administration of DA-9701 could significantly increase the pain threshold in rats with CRD-induced visceral hypersensitivity.

Visceral hypersensitivity is currently accepted as a major pathophysiologic mechanism, responsible for triggering both motility disturbances and abdominal pain in patients with functional GI disorders.[19] Although the pathogenesis of visceral hypersensitivity is not fully understood, several mechanisms have been proposed, including inflammatory injury in the GI tract, changes in the intraluminal milieu, psychosocial factors, and altered sensorimotor function of the gut.[2] Among the various mechanisms of visceral hypersensitivity, a major component is considered to be central and peripheral sensitization of visceral afferent neuronal pathways.[2] Visceral stimuli from the GI tract are transmitted to the brain via afferent nerves through the vagus or spinal cord.[2,20] Sensations such as pain are perceived in the brain, and altered perception of visceral stimuli may play an important role in visceral hypersensitivity. The peripheral sensitization of visceral nociceptors may also contribute to visceral hypersensitivity. In the accumulation of knowledge about the molecular mechanisms involved in peripheral sensitization, remarkable progress has been made in the identification of key mediators and receptors through animal studies.[21] Among the numerous receptors and neurotransmitters involved in peripheral sensitization, 5-HT is well known to regulate gut motility and visceral sensation through actions on several receptor subtypes, and 5-HT receptors are widely distributed in both the central nervous system and the GI tract.[1,22,23] Previous studies showed that 5-HT concentration in chronic visceral hypersensitivity (CVH) rats was significantly higher than in normal rats, indicat-

ing that 5-HT was involved in the mechanism of visceral hypersensitivity in the rat IBS model.[24,25] Moskwa *et al.*[26] showed that fasting blood serotonin concentration was increased, and 5-hydroxyindoleacetic acid (metabolite of serotonin) in the urine was decreased, in IBS patients. Another interesting study demonstrated that intraluminal infusion of 5-HT significantly attenuated visceromotor response to CRD in rats.[27] Moreover, there is evidence suggesting an interplay between the hypothalamic-pituitary-adrenal axis and the serotonergic system, especially in stressful situations.[28] In genetically stress-susceptible Wistar Kyoto (WKY) rats with altered HPA axes, visceral hypersensitivity was attenuated to both peripheral and central administration of RS 127445, a blocker of central 5-HT receptors.[29]

The binding assays for various receptors, using several compounds isolated from DA-9701, offered a possible explanation for the DA-9701 effect on visceral hypersensitivity. THB (5,8,13,13a-tetrahydro-9,10-dimethoxy-6H-benzo[g]-1,3-benzodioxolo[5,6-α]quinolizine) is an isoquinoline alkaloid with a micromolar affinity for dopamine D_2 (pKi 6.08) and 5-HT$_{1A}$ (pKi 5.38) receptors.[13] In a previous animal study, THB restored the delayed gastric emptying caused by apomorphine, a dopamine agonist; therefore, its action might be mediated by an antidopaminergic effect.[10] Furthermore, in rats stressed by repeated restraint, a significantly higher shift in the pressure-volume curve was produced by THB, and this effect was inhibited by WAY-100635 (a 5-HT$_{1A}$ antagonist) and L-NAME (a NOS inhibitor).[13] Similarly, CTE (another compound extracted from DA-9701) showed moderate affinity for D_2, 5-HT$_{1B}$, and 5-HT$_4$ receptors (Ki=0.2, 6.3, and 7.6 μg/mL, respectively).[14] CTE also improved the delayed gastric emptying induced by apomorphine. Taken together, these data suggest that the action mechanism of DA-9701 may be related to serotonergic and dopaminergic activity.

This possible serotonergic activity of DA-9710 may have a strong effect on visceral hypersensitivity. The 5-HT$_{1A}$ receptor is known to play a pivotal role in the serotonergic mechanism associated with the etiology of stress-related disorders.[30] In previous studies, 5-HT$_{1A}$ receptor knockout mice showed an increase in anxiety-like behaviors,[31] whereas mice overexpressing the 5-HT$_{1A}$ receptor displayed reduced anxiety-like behaviors.[32] Maternal separation changed the expression of the 5-HT$_{1A}$ receptor in the amygdala, hippocampus, and prefrontal cortex.[33-35] Buspirone, a 5-HT$_{1A}$ receptor partial agonist, attenuated the colorectal disension-induced changes in MAP and abdominal withdrawal response, in anesthetized and conscious rats, respectively.[36] Moreover, in another study, sumatriptan suppressed both inflammatory and noninflammatory visceral pain, most likely through peripheral 5HT$_{1B/D}$ receptors.[37] Thus, microinjection of sumatriptan into the rostral ventromedial medulla (RVM), which is an essential component of the descending pain control system, increased the mechanical threshold in the colonic hypersensitivity model. Concurrent microinjection of the 5HT$_{1B}$ antagonist isamoltane blocked the effect of RVM sumatriptan. In

contrast, concurrent microinjection into the RVM of the $5HT_{1D}$ antagonist BRL15722 did not block the effect of the sumatriptan.[37]

We observed no DA-9701-induced adverse effects during our experiments. In fact, repeated dose toxicity testing in rats, using much higher doses than were effective, revealed that DA9701 had no toxic effects at all, even at a dose of 1 g/kg.

Several limitations of this study have to be considered. In the present study, we measured only blood pressure as the surrogate of visceral pain during CRD. Changes in cardiovascular response such as blood pressure and heart rate can be less specific because it could be triggered by a variety of conditions including anticipating pain, other forms of stress, and respiratory changes that may not be directly associated with pain. Hence, we selected anesthetized rats for visceral pain model. Although analgesics attenuate distension-induced hypertensive response in conscious animals, our results showed a definite changes by DA-9701administration. And, according to report of Sivarao et al.,[36] the myoelectrical response was different between the WKY rats and the SD strain, but the cardiovascular changes to distension were about the same in each strain.

In conclusion, the current study demonstrated that DA-9701 has a significant dose-dependent effect on visceral hypersensitivity in colonic sensitized rats. Results from the current and previous studies, demonstrating the effect of DA-9701 on GI motor function,[10,13,14] suggest that DA-9701 has therapeutic potential, and may therefore be a good candidate for the treatment of patients with heterogeneous, functional GI disorders.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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