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The Role of Somatostatin in Nociceptive Processing of the Spinal Cord in Anesthetized Cats

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Somatostatin (SOM) is one of the major neuropeptides in dorsal root ganglion cells, but its role in spinal nociceptive process has not been well known. In present study we aimed to investigate the effect of SOM on the response of dorsal horn neurons to the various types of peripheral nociceptive stimuli in anesthetized cats. Using carbon-filament microelectrode, the single cell activities of wide dynamic range neurons were recorded from the lumbosacral enlargement after noxious mechanical (squeeze), thermal (radiant heat lamp) and cold (dry ice) stimulation to the receptive field. Sciatic nerve was stimulated electrically to evoke Aδ- and C-nociceptive responses. SOM analogue, octreotide (10 μg/kg), was applied intravenously and the results were compared with those of morphine (2 mg/kg, MOR). Systemic SOM decreased the cellular responses to the noxious heat and the mechanical stimulation, but increased those to the cold stimulation. In the responses to the electric stimuli of sciatic nerve, Aδ-nociceptive response was increased by SOM, while C-nociceptive response was decreased. On the other hand, MOR inhibited the dorsal horn cell responses to all the noxious stimuli. From the above results, it is concluded that SOM suppresses the transmission of nociceptive heat and mechanical stimuli, especially via C-fiber, while it facilitates those of nociceptive cold stimuli via Aδ-fiber.

Key Words: Somatostatin, Wide dynamic range (WDR) cell, Noxious stimulation, Aδ-fiber, C-fiber

INTRODUCTION

Somatostatin (SOM) has been well known to act as neuromodulator or neurotransmitter (Delfs et al, 1980), which inhibits neuronal activity and modulates neurotransmitter release (Pelton et al, 1986; Mulder et al, 1988; Betoin et al, 1994). This peptide is present in various regions modulating nociceptive information, such as small dorsal root ganglion (DRG) cells, small primary afferent fibers (Hökfelt et al, 1976), neurons of the substatia gelatinosa of spinal dorsal horn (Hunt et al, 1981) and neurons of the midbrain periaqueductal gray projecting to the medullary nucleus raphe magnus (Beitz et al, 1983). Since Terenius et al (1976) reported that SOM might play an important role on the process of nociceptive information, a number of studies have been investigated the role of SOM on pain control in spinal cord (Hökfelt et al, 1976; Basbaum et al, 1978; Hunt et al, 1981; Beitz et al, 1983). In order to acquire the information of the action mechanism of SOM in spinal cord, it is necessary for the study to be related with the role and distribution of neurotransmitter.

Calcitonin-gene-related-peptide (CGRP) and Substance P (SP) found in DRG are considered as neurotransmitter, which controls pain information. SOM also reported as major neurotransmitter in DRG (Hkö felt et al, 1976; Rang et al, 1994). SOM was found in medium or small sized DRG associated with nociception and contents of SOM were decreased like those of CGRP and SP after axotomy (Tessler et al, 1986). Recently, the analgesic effect of SOM on pain response and *c-fos* expression in spinal cord induced

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by SP was known as that of modulator of pain (Ruan et al, 1997).

These facts imply that SOM may play an important role on the pain control as CGRP and SP. Though SOM may exert its action on pain control through spinal mechanisms, however, the exact mechanism is still controversial. In view of the pain modulation, function of SOM could be largely classified as followings; 1) SOM might be involved in the transmission of nociceptive information from DRG to spinal dorsal horn neurons (Seybold et al, 1982; Kuraishi et al, 1985; Wisenfeld-Hallin, 1985; Kamei et al, 1993a). Such studies were conducted through agonist binding studies or behavioral studies such as tail flick or hot plate test. 2) SOM might have a suppressive effect on nociceptive neuronal responses and suppressed more effectively on heat pain (Randic et al, 1978; Sandkühler et al, 1990) or initial A δ-pain (Taddese et al, 1995). These results were acquired from extracellular recording study, clinical study or whole cell recordings. Although the role of SOM in spinal cord were complex and often confusing like these two contentions, all these experimental findings could imply the heterogeneous actions of SOM on nociceptive process. Thus, we assumed that all the above various experimental reports on SOM in nociceptive process and analgesic mechanisms are due to the contention that nociceptive processes itself may be diverse and specified to types of injury, nociceptors, analgesic drugs and routes of administration. Hence in present investigation we aimed to clarify the effects of SOM on the responses of spinal dorsal horn neurons to various peripheral noxious stimuli (heat, mechanical, cold and electrical stimuli).

METHODS

Preparation of animal

A total of thirty cats of either sex (body weight, 1.8~3.0 kg) were used. After treatment with atropine sulfate (0.2 mg/kg, s.c.) and ketamine hydrochloride (Ketalar, Yu-Han, Korea, 30 mg/kg, i.m.), the animal was anesthetized with a-chloralose (60 mg/kg, i.v.) and cannulated into trachea, femoral artery and vein. Pancuronium bromide (Mioblock, Organon, Netherland; initial dose 0.4 mg, maintenance dose 0.4 mg/hr) was administered to relax systemic musculature and the animal was ventilated artificially with end-expiratory carbon dioxide concentration maintained in the range of 3.5~4.5% (Normocap CO_2 & O_2 monitor, Datex, Finland). Rectal temperature was monitored and maintained within 37.5°C by an electrical blanket (Hoemothermic Blanket Control Unit, Harvard Apparatus, U.S.A). Arterial blood pressure was monitored and Hartmann solution was infused continuously.

Lumbosacral enlargement was exposed by a laminectomy done on L2-S3 vertebrae. After identifying the entry between L6 and S1 dorsal roots, several small pia holes were made for insertion of recording electrode. The left sciatic nerve was dissected and exposed after the skin incision of left leg.

After operation, the animal was transferred to a stereotaxic animal fixation apparatus. A warm mineral oil pool was made using skin flaps and the pool was maintained warm by a heating coil in which warm water circulated. Animal was recovered for an hour or longer before experiment.

Stimulation and recording

The responses of wide dynamic range (WDR) cell to the noxious mechanical, heat, cold and electrical stimuli (A δ- and C-intensity) applied to peripheral receptive field or sciatic nerve, were recorded with carbon-filament microelectrode of which tip resistance was 1~3 MΩ.

Signals picked up by recording electrode amplified by an AC amplifier (DAM 80, WPI, U.S.A.) and were fed into oscilloscopes and window discriminator. Through a laboratory interface (CED 1,401, Cambridge Electronic Design, U.K.) the signals were stored and analyzed by a personal computer.

The noxious mechanical stimuli were given by applying squeeze to receptive field with a serrated forceps manually and the noxious heat stimuli were applied into 55°C by radiant heat source with thermal electrode with a thermistor to monitor the surface temperature of receptive field. Dry ice was contacted with receptive field as noxious cold sitmuli, which dropped skin temperature to −20°C. The usage of dry ice is easy to manage in dropping skin temperature rapidly. After a platinum triple-polar electrode as placed at the exposed sciatic nerve as a stimulating electrode, A δ-intensity (1 mA intensity, 0.1 ms width) or C-intensity (10 mA intensity, 0.5 ms width) single or triple square pulses generated by stimulator (Pulse Master, A300, WPI) was applied to sciatic nerve.

Antidromic stimulation technique was used to determinate whether the recorded WDR cells were projecting cells or not. After a laminectomy at cervical vertebrae, a bipolar electrode was placed on the contralateral ventrolateral funiculus at C2 spinal cord segment. It was confirmed whether recorded cell is projecting based on (1) response of a constant latency (100 μA and 1 Hz), (2) ability of the spike to follow high-frequency stimulus trains (333 Hz, 3 pulses), and (3) collision between the antidromic spike and the orthodromic action potentials evoked by natural stimulation to the RF (Trevino et al, 1973).

Experimental procedure

When a single neuronal activity of sufficient amplitude was identified, the cell was characterized by responses to graded mechanical stimuli applied to the receptive field. Then its cellular responses to noxious mechanical, thermal and cold stimuli were characterized. Usually the depth of recording site was in 500~1,200 μm and 1,500~3,000 μm.

After identifying a wide dynamic range (WDR) neuronal activity, natural noxious stimuli (mechanical, heat and cold) were applied before and after intravenous application (Eschalier et al, 1991) of octreotide acetate (Sandoz, Pharmaceuticals Corp. Switzerland; 10 μg/kg), a SOM analogue, and MOR (2 mg/kg). The results were analyzed by compiling single pass time histograms. To correlate the effect of SOM on the natural nociception with the type of peripheral nerve, electrical stimuli were applied to sciatic nerve. Fiber activities were considered as A δ- or C- responses in view of their specific velocity to electrical stimuli.

Statistical analysis of data

Efficacy of SOM was analyzed as change of neuronal responses to noxious stimuli (percent of the control); suppression to 85% or less of the control was considered to be effective. To compare this suppressive effect of SOM with that of morphine (MOR) in the same cell, MOR (2 mg/cc/kg) was administered systemically after the effect of SOM disappeared and cellular activity had recovered.

At the end of experiment, all animals were euthanized with anesthetics. All the data were expressed as mean$\pm$S.E.M and the statistical significance was determined from Students' t-test as $p<0.05$.

RESULTS

Distribution of WDR cell in spinal cord

The responses of 73 WDR cell were extracellularly recorded in 30 cats. The cells were typical WDR cells, which had the gradual responses from innocunous to noxious stimuli. All of them had the excitatory receptive fields at one or more toes of the ipsilateral hindpaw or footpad. The distribution of them is illustrated at Fig. 1. They located in the dorsal horn at depths from 1,000 to 3,000 mm (mean$\pm$S.E.M, 1805.1$\pm$63.6; N=73; laminae IV-VI of Rexed).

Effect of SOM on natural noxious stimuli

In Fig. 2, the effects of systemically administered SOM (10 μg/cc/kg) on the responses of WDR cell to peripheral noxious stimuli (heat, mechanical) are shown. Fig. 2A shows the time course of SOM effect on the response of WDR cell to noxious mechanical stimuli. Five of 8 neurons were inhibited by SOM, and 2 neurons were activated. Fig. 2B illustrated the

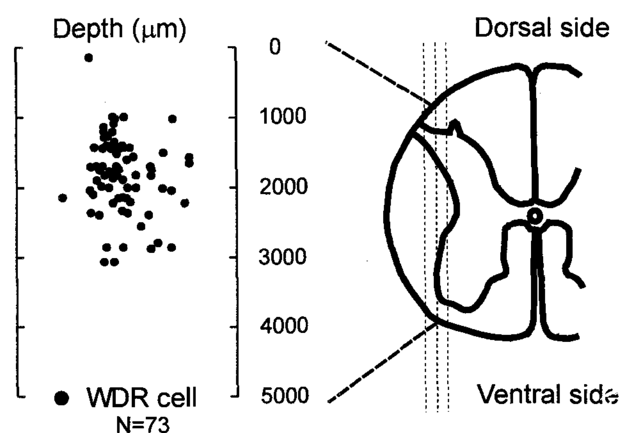

Fig. 1. Distribution of recording electrode depths for WDR cell having receptive fields. The lumbosacral segment cross-section with electrode track is on the right column. All cells were isolated in the lateral gray matter and had receptive field in hind paw of left leg. (A) shows the locations of 73 WDR cells. Most cells distributed at 1,000~3,000 mm (mean$\pm$S.E.M, 1805.1$\pm$63.6; N=73; laminae IV-VI of Rexed). All of them had the excitatory receptive fields at one or more toes of the ipsilateral hindpaw or footpad. The filled circle (•) shows each WDR cell and middle axis indicates the depth from dorsal surface.

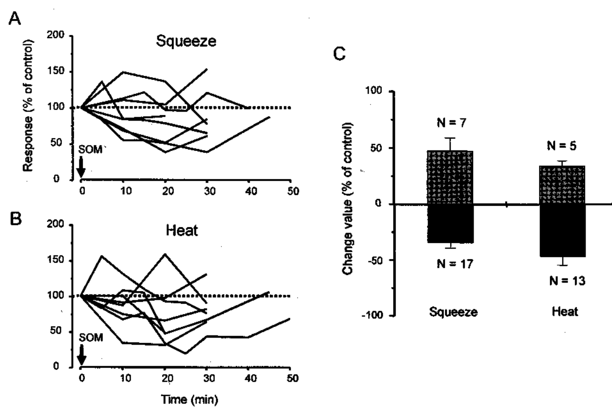

Fig. 2. Time course of the effects of SOM (10 μg/kg) on the response of dorsal horn WDR cells (n=8) to peripheral noxious stimuli (A, squeeze; B, heat). The responses were expressed as a percentile changes from control values and plotted by time after intravenous administration. (A) Individual responses of eight WDR neurons to noxious mechanical stimulation (squeeze). Five WDR neuronal responses to squeeze were decreased by SOM, but some neuronal responses produce facilitation after SOM injection (N=2). (B) Individual response of eight WDR neurons to noxious heat stimulation. Five WDR neuronal responses to heat were decreased by SOM, but two neuronal responses were excited by SOM. Effects of SOM on WDR neuronal activities maximized at 20~30 minutes for squeeze and heat stimuli. (C) Effects of SOM on the responses to mechanically or heat-stimuli are shown as mean percentile value. Control value is '0%', (+) expresses increment of response, and (−) indicates decrement of response by SOM. The numbers above or below the columns indicate the numbers of cells examined.

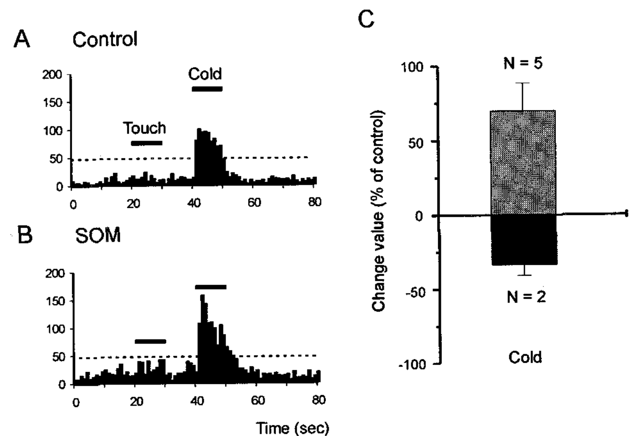

Fig. 3. Effects of systemic administered SOM on the response of WDR cell to peripheral noxious cold stimuli. Single cell activity was recorded in the lumbosacral area using extracellular electrode. The cell was identified as a typical WDR cell and showed marked nociceptive responses to noxious cold stimuli for 10 sec and innocuous touch for 10 sec. (A) After systemic application of SOM, the response of WDR neurons to noxious cold stimuli was enhanced (129.1%). However, SOM induced no significant change of touch response. (C) Effects of SOM on the responses to cold-stimuli are shown as mean percentile value. Control value is '0%', (+) expresses increment of response, and (−) indicates decrement of response by SOM. The numbers above or below the columns indicate the numbers of cells examined.

time course of SOM effect on the response of WDR cell to noxious heat stimuli. Here, 5 of 8 neurons were inhibited, and 2 neurons were activated. Also these maximal effects were observed at around twenty minutes following noxious heat or mechanical stimuli. Thus, SOM effects on the response to various noxious stimuli were analyzed at twenty minutes after intravenous SOM application.

In Fig. 2C, SOM suppressed noxious heat stimuli-evoked responses up to 52.9±7.7% of control value (mean±S.E.M, 13 of 20 cells, $p<0.05$) and noxious mechanical stimuli-evoked responses to 65.5±4.6% (17 of 27 cells, $p<0.05$). In a few cells, however, SOM had no effect or even increased the responses to peripheral noxious stimuli (heat stimuli-evoked response, 134.0±4.2%, 5 of 20 cells, $p<0.05$; mechanical stimuli-evoked response, 147.6±11.3%, 7 of 27 cells, $p<0.05$).

As shown in Fig. 3A, however, noxious cold-evoked response of WDR cell was enhanced up to 129.1%, from 810 bins/ 10 sec to 1,046 bins/ 10 sec. This cell was located at 1,807 μm below the dorsal surface. As a whole, SOM enhanced the cold stimuli-evoked cellular activities (162.4±20.2%, 5 of 7 cells, $p<0.05$, Fig. 3C). In a portion of WDR cells, SOM had decreased the responses to peripheral noxious stimuli (66.4±7.1%, 2 of 7 cells, $p<0.05$). The results of WDR cells identified as STT-like projecting were similar to those of the other cells. SOM inhibited both heat and mechanical stimuli- evoked cellular activity (N=5 and N=4, respectively), while enhanced cold stimuli-evoked response (N=2).

Effect of SOM on electrical stimuli

In Fig. 4, we observed the effect of SOM on dorsal horn neuronal responses to electrical stimulation

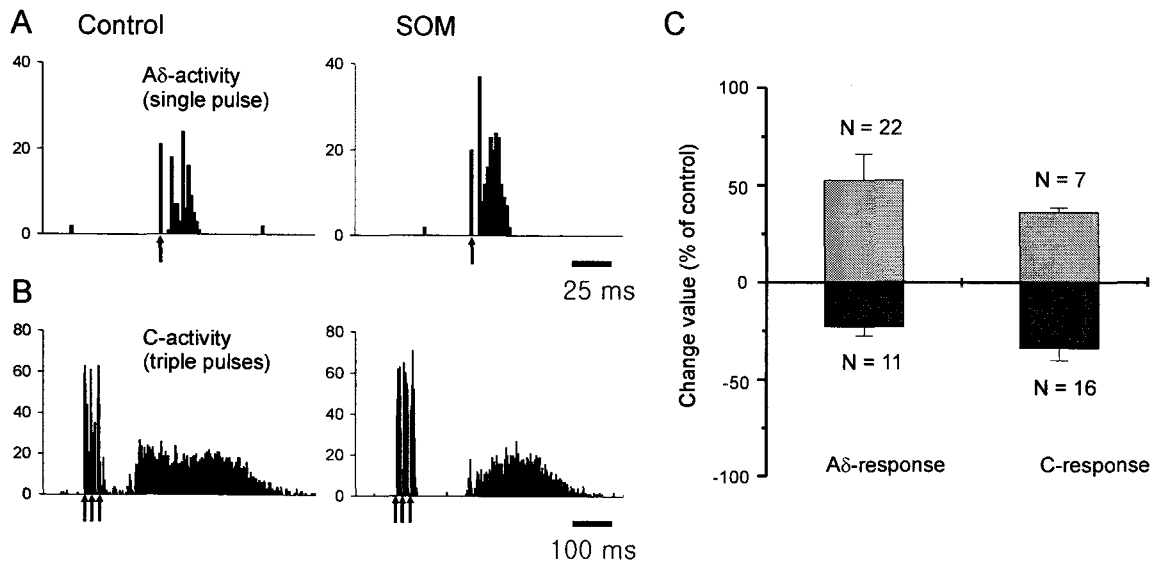

Fig. 4. The effects of SOM on the responses of WDR cells to noxious electrical stimulation of the peripheral nerve. Stimuli were applied to the sciatic nerve with A δ - strength (1 mA with 0.1 ms width) or C- strength (10 mA with 0.5 ms width) single (↑) or triple (↑ ↑ ↑) square pulses at 500 ms. Evoked responses were expressed as total number of impulses and twenty sweeps were compiled as a peristimulus time histogram (bin width; 2 ms, 20 sweeps). Cellular response following electrical stimuli are A δ -fiber response and later waves (>150 ms) are C-fiber response. After SOM was intravenously administered, A δ -response increased (A), while C-response markedly decreased (B) in the same cell. (A δ -activity, the response of WDR cell to electrical stimuli via A δ -fibers; C-activity, the response of WDR cell to electrical stimuli via C-fibers). (C) Effects of SOM on the responses to electrical stimuli (A δ - and C-fiber activation) are shown as mean percentile value. Control value is '0%', (+) expresses increment of response, and (−) indicates decrement of response by SOM. The numbers above or below the columns indicate the numbers of cells examined.

supramaximal for the activation of A δ- or C-fibers applied to sciatic nerve. A δ-response appeared 5~30 ms and C-response, 200~300 ms after electrical stimuli in PSTH (peristimulus time histogram). As shown in SOM-induced inhibition of heat and mechanical stimuli-evoked response, SOM inhibited C-fiber response from 2,906 to 1,759 impulses (Fig. 4Ab). The mean decrease in C-fiber response was 65.8±6.0% (16 of 26 cells, $p<0.05$) of control. However, the Ad-fiber response of the same cell was enhanced from 123 to 215 impulses (Fig. 4Aa). Among the 37 cells recorded for A δ-responses, 22 cells excited to 152.9±13.3% of control value ($p<0.05$), 11 cells were inhibited to 76.9±4.4% ($p<0.05$) and 4 cells had no change after intravenous SOM injection (Fig. 4C). In three WDR cells, SOM facilitated the responses to noxious cold stimuli as well as the A δ-fiber responses.

Results identified as projecting cells also were similar to those of the other cells unidentified as the projection neurons. C-fiber responses of projection neurons (2 of 2 cells) were inhibited by SOM, and A δ-responses (4 of 4 cells) were enhanced. Especially, in three WDR cells, SOM facilitated the responses to noxious cold stimuli as well as the A δ -fiber responses. Also two cells of these were identified as STT-like projecting cells.

Fig. 5 summarizes all the results. Each vertical bar presents individual cell and vertical axis indicates percentile of control response of each cell.

We investigated whether these effects of SOM differ from effects of MOR in the same cells. Fig. 6 shows that MOR decreased the majority of cellular responses to all noxious stimuli, whereas SOM suppressed heat and mechanical stimuli-evoked cellular responses and C-response but increased cold evoked cellular response and A δ-response. Although SOM suppressed some responses to noxious stimuli (heat-evoked response and C-response) like MOR, others responses inhibited by MOR were enhanced by

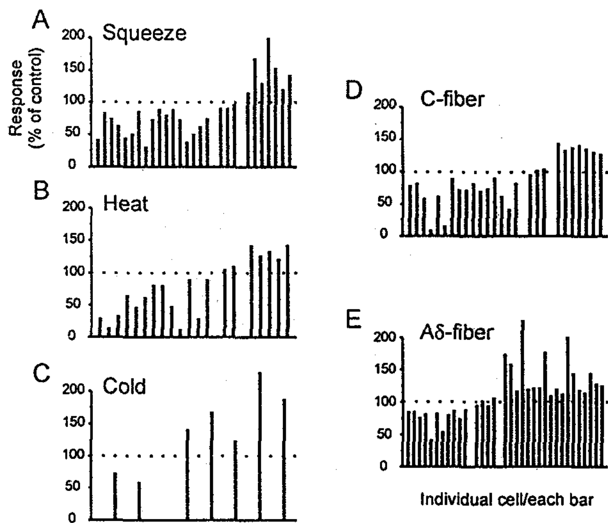

Fig. 5. Effects of SOM on the response of WDR neuron to various noxious stimuli (A, squeeze; B, heat; C, cold; D, C-fiber; E, A δ-fiber). (A) Most mechanically evoked WDR neuronal activities were decreased by SOM (mean ±S.E.M, 65.5±4.6%; n=17). Some WDR neuronal activity was increased by SOM (147.6±11.3%; n=7) (B) Most heat-evoked WDR neuronal activities were decreased by SOM (52.9±7.7%; n=13) and in a little population responses was increased (133.9±4.2%; n=5). (C) Cold-evoked neuronal activities were increased in many WDR neuron by SOM (170.2±18.4%; n=5), while two neuronal activities were decreased. (D) C-response of WDR neuron to electrical stimulation of peripheral nerve was markedly decreased by application of SOM (65.8± 5.9%; n=16). (E) A δ-response was increased by SOM (152.9±13.2%; n=22).

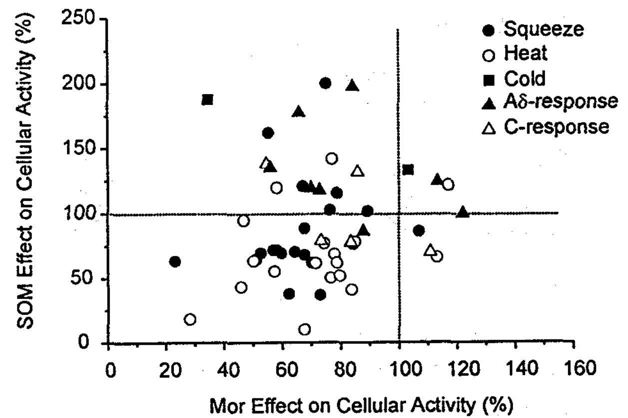

Fig. 6. Comparison effect of SOM to that of MOR on responses of the same WDR cell to noxious stimuli. Vertical axis is effect of SOM (% of control value) and horizontal axis is effect of MOR. Each point represents the response of one WDR cell and the each symbol indicated type of noxious stimuli(●, squeeze; ○, heat; ■, cold; ▲, A δ-response; △, C-response). MOR decreased the majority of cellular responses to all noxious stimuli. SOM has enhancement and suppression of response of WDR cell. Majority of mechanical and heat-evoked response and C-response were suppressed by SOM. The Ad-response and the cold response suppressed by MOR, however, were increased by SOM.

SOM. For example, SOM excited all A δ-responses, which were suppressed by MOR. This fact indicated that the effects of SOM on the cellular response to noxious stimuli differ from those of MOR.

DISCUSSION

This study shows that systemic injection of SOM has selective analgesic effects on the responses of WDR dorsal horn neurons to some noxious stimuli (heat, mechanical stimuli and C-fiber response). The new finding in the present result is that the cold-evoked response and A δ-response were increased by SOM. That is, SOM has dual effect on pain control, namely, selective inhibitory action or excitatory action. Thus, it suggested that SOM found in 5~15% of DRG neurons (Hökfelt et al, 1976; Rang et al, 1994) seems to play an important role in pain control of the spinal cord.

The peptide SOM is thought to penetrate the blood-brain barrier poorly because SOM has the hydrophilic properties, very short half-life time in circulation (2~3 min) and large molecular weight (MW 1638). Thus it is questioned whether the systemic injection of SOM affects the spinal cord or CNS (Banks et al, 1990). When SOM was administered systemically in clinical study, however, it has shown to be analgesic in-patients (Sicuteri et al, 1984; Penn et al 1992; Mollenholt et al, 1994). Recently, some studies revealed that RC-160 (D-Phe-Cys-Tyr-D-Trp-Lys-Val--Cys-Trp-NH_2), vapreotide and octreotide, analogues of SOM, are capable of penetrating the blood-brain barrier. That is, SOM has a diffusion route across the membranes that comprise the blood-brain barrier rather than a saturation of transporter (Banks et al, 1990). And octreotide has longer half-life time, 72~98 min, than SOM (Katz & Erstad, 1989). Consequently, systemic effects of SOM have been attributed to metabolites with a better capability of penetrating the blood-brain barrier, as has been shown for vapreotide, an analogue of SOM

(Helmchen et al, 1995). In addition, Eschalier et al (1991) observed the long-lasting analgesic effect after systemic injections of RC-160 (16, 64, 256, 1,024 μg/kg) in mice and rats. Thus, based on these evidences octreotide acetate, a SOM analogue was used with 10 μg/kg concentration in present experiment.

The present study has contradictions to some reports. For example it was stated that SOM was released at primary afferent nerve terminal by noxious heat stimuli and substance P, by noxious mechanical stimuli (Kuraishi et al, 1989; Morton et al, 1989; Kamei et al, 1991, 1993a) and that intrathecal SOM induced pain in rats (Wiesenfeld-Hallin, 1985). Also SOM was involved in nociception through immunohistochemistry or pharmacological study (Hökfelt et al, 1976; Tessler et al, 1986). Whereas it was reported that SOM may inhibit the transmission of nociceptive information. Randic and Miletic reported that nociceptive neuron in spinal cord of cats were inhibited by iontophoretic application of SOM (Randic & Miletic, 1978). Also SOM was used as analgesics in patients (Sicuteri et al, 1984) and Sankühler et al. investigated the cat spinal cord superfused with SOM by using an extracellular single-cell recording technique and reported that SOM had an analgesic effect on the heat nociception (Sandkühler et al, 1990). But, Taddese et al (1995) suggested that MOR inhibits C-fiber response, while SOM inhibits the early pain via A δ-fiber. In present study the effects of SOM on WDR cell were observed with direct recording cellular activity and this correspond the previous report that SOM has the inhibitory effect on dorsal horn cells (Randic & Miletic, 1978; Sandkühler et al, 1990).

Although our findings in heat and mechanically evoked responses were consistent with the previous results, results in A δ-fiber response and cold-evoked response were contradict. Assumed that the heat and mechanical nociceptions are composed of acute pain via Ad-fiber and delayed pain via C-fiber (Fruhstorfer et al, 1974; Konietzny et al, 1975), SOM might suppress heat and mechanically evoked responses via a great deal of C-fiber. It is well known that cutaneous A δ-nociceptors contribute to the sensation of cold pain (Fruhstorfer et al, 1974; Hallin et al, 1981). Present study shows that SOM facilitated the cold evoked nociception and A δ-response. Assumed that the majority of cold nociception transmitted via A δ-fibers, our result suggested that the response to cold stimuli is associated with the increment of A δ-response by SOM. This fact suggested that the effects of SOM might vary with types of noxious stimuli as the types of nociceptive information vary with either kinds of noxious stimuli or that of fibers, which transmit the nociceptive information.

The analgesic effect of SOM is known to be associated, at least partially, with opioid action (Rezeket al, 1978; Pelton et al, 1986; Betoin et al, 1994). From the facts that pain of cancer patients with MOR tolerance was suppressed by intrathecal SOM (Chrubasik et al, 1985; Pascual et al, 1991), however, it was suggested that SOM have the analgesic mechanism unlike MOR. Our results show that SOM has an opposite action in comparison to MOR in the same cells (Fig. 6). Thus, SOM in spinal cord is not associated with opioid pathway. Furthermore, the A δ-response and the cold-evoked response were decreased by MOR, but not by SOM.

Based on the above results, it is suggested that the pathway of SOM action on nociceptive neurons may diverse. The suppressive effect of SOM in cellular level was supported by many reports. They described that SOM enhanced K^+ currents in rat sympathetic ganglion cell and frequency of action potential was decreased by hyperpolarization of membrane potential after SOM application (Lewis et al, 1986; Ikeda et al, 1989; Kleuss et al, 1991; Shaprio et al, 1993). In a view of the enhancement of nociception, SOM may inhibit inhibitory interneuron or presynaptic inhibition in inhibitory synapse, considered as acting inhibitory by blocking calcium inward current in neuron (Ikeda et al, 1989; Kleuss et al, 1991). In the present study, cold nociception or A δ-response, which were enhanced by SOM, may come under this case. Likewise, it is considered that analgesic effect of SOM is raised by inhibition of projection neuron or by inhibition of excitatory interneuron.

In conclusion, systemic SOM suppresses the transmission of nociceptive heat and mechanical stimuli, especially via C-fiber, while it facilitates those of cold stimuli via A δ-fiber. It suggested that SOM might have dual action in nociceptive processing of the spinal cord.

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REFERENCES

Banks WA, Schally AV, Barrera M, Fasold MB, Durham DA, Csernus VJ, Groot K, Kastin AJ. Permeability of the murine blood-brain barrier to some octapeptide analogue of somatostatin. *Proc Natl Acad Sci USA* 87: 6762−6766, 1990

Basbaum AI, Fields HL. Endogenous pain controls mechanism-review and hypothesis. *Ann Neurol* 4: 451−462, 1978.

Beitz AJ, Shepard RD, Wells WE. The periaqueductal gray-raphe magnus projection contains somatostatin, neurotensin and serotonin but not cholecystokinin. *Brain Res* 261: 132−137, 1983.

Betoin F, Ardid D, Herbet A, Aumaitre O, Kemeny JL, Duchene-Marullaz P, Lavarenne J, Eschalier A. Evidence of a central long-lasting antinociceptive effect of vapreonide, an analog of somatostatin, involving an opioidergic mechanism. *J Pharmacol Exp Therapeutics* 296: 7−14, 1994.

Chrubasik J, Meynadier J, Scherpereel P, Wunsch E. The effect of epidural somatostatin on postoperative pain. *Anesth Analg* 64: 1085−1088, 1985.

Delfs J, Robbins R, Connolly JL, Dichter M, Reichlin S. Somatostatin production by rat cerebral neurones in dissociated cell culture. *Nature* 283: 676−677, 1980.

Eschalier A, Aumaitre O, Ardid D, Fialip J, Duchene-Marullaz P. Long-lasting antinociceptive effect of RC-160, asomatostatin analog, in mice and rats. *Euro J Pharmacol* 199: 119−121, 1991.

Fruhstorfer H, Zenz M, Notle H, Hensel H. Dissociated loss of cold and warm sensibility during regional anesthesia. *Pflugers Arch* 349: 73-82, 1974.

Hallin RG, Torebjork NF, Wiesenfield Z. Nociceptors and warm receptors innervated by C-fibers in human skin. *J Neurol-Neurosurg-Psychiat* 44: 313−319, 1981.

Helmchen C, FuQ-C, Sandkühler J. Inhibition of spinal nociceptive neurons by microinjections of somatostatin into the nucleus raphe magnus and midbrain periaqueductal gray of the anesthetized cat. *Neurocsi Lett* 187: 137−141, 1995.

Hökfelt T, Elde R, Johansson O, Luft R, Nilsson G, Arimura A. Immuno-histochemical evidence for separate populations of somatostatin-containing and substance P-containing primary afferent neurons in the rat. *Neurosci* 1: 131−136, 1976.

Hunt SP, Kelly JS, Emson PC, Kimmel JR, Miller RJ, Wu JY. An immunohitochemical study of neuronal populations containing neuropeptides or GABA within the superficial layers of the rat dorsal horn. *Neurosci* 6: 1883−1898, 1981.

Ikeda S, Schofield G. SRIF block a Ca2+ current in rat sympathetic ganglion neurons. *J Physiol* 409: 221−240, 1989.

Kamei J, Hitosugi H, Kasuya Y. Nociceptive response to intrathecally administered substance P and somatostatin in diabetic mice. *Life Sci* 52: PL31−36, 1993a.

Kamei J, Ohhashi Y, Aoki T, Kasuya Y. Streptozotocin-induced diabetes in mice reduces the nociceptive threshold, as recognized after application of noxious mechanical stimuli but not of thermal stimuli. *Pharmacol Biochem Behav* Jun, 39 (2): 541−544, 1991.

Katz MD, Erstad BL. Octreotide, a new somatostatin analogue. *Clin Pharm* Apr, 8 (4): 255−273, 1989.

Kleuss C, Hescheler J, Ewel C, Rosenthal W, Schultz G, Wittig R. Assignment of G-protein subtypes to specific receptors inducing inhibition of calcium currents. *Nature* 353: 43−48, 1991.

Konietzy F, Hensel H. Warm fiber activity in human skin nerves. *Pflugers Arch* 359: 265−267, 1975.

Kuraishi Y, Hirota N, Sato Y, Hanashima N, Takagi H, Satoh M. Stimulus specificity of peopherally evoked substance P release from the rabbit dorsal horn in situ. *Neurosci* 30: 241−250, 1989.

Kuraishi Y, Hirota N, Sato Y, Hino Y, Satoh M, Takagi H. Evidence that substance P and somatostatin transmit separate information related to pain in the dorsal horn. *Brain Res* 325: 294−298, 1985.

Mollenholt P, Rawal N, Gordh T Jr., Olsson Y. Intrathecal and epidural somatostatin for patients which cancer. Analgesic effects and post mortem neuropathologic investigations of spinal cord and nerve roots. *Anesthesiology* Sep, 81 (3): 534−542, 1994.

Morton H, Kuraishi Y, Hendry IA, Duggan AW. Somatostatin: Evidence for a role in thermal nociception. *Brain Res* 488: 89−96, 1989.

Mulder AH., Wardeh G, Kazmierski W, Hurby VJ. Antagonist activity of the cyclic somatostatin analogue CTP at mu-but not delta-and kappa-opioid receptors involved involved in presynaptic inhibition of neurotransmitter release. *Eur J Pharmacol* 157: 109−114, 1988.

Pascual J, Freijanes J, Bercian J, Pesquera C. Analgesic effect of octreotide in headache associated with acromegaly is not mediated by opioid mechanism-Case report. *Pain* 47: 341−344, 1991.

Pelton JT, Kazmierski W, Gulya K, Yamamura HI, Hurby VJ. Design and synthesis of conformationally constrained somatostatin analogues with high potency and specificity for opioid receptors. *J Med Chem* 29: 2370−2375, 1986.

Penn RD, Paice JA, Kroin JS. Octreotide: a potent new-non-opiate analgesic for intrathecal infusion. *Pain* 49

(1): 13—19, 1992.

Randic M, Miletic V. Depressant action of methionine-enkephalin and somatostatin in cat dorsal horn neurons activated by noxious stimuli. *Brain Res* 152: 196—202, 1978.

Rezek M, Havlick V, Leybin L, Labella FS, Friesen H. Opiate-like naloxone-reversible actions of somatostatin given intracerebrally. *Can J Physiol Pharmacol* 56: 227—231, 1978.

Ruan HZ, Li XC, Cai WQ. Somatostatin inhibited pain modulation action of substance P in spinal cord. *Sheng Li Hsueh Pao* 49 (1): 13—17, 1997.

Sandkühler J, Fu QG, Helmchen C. Spinal somatostatin superfusion in vivo affects activity of cat nociceptive dorsal horn neurones: Comparison of spinal morphine. *Neurosci* 34: 565—576, 1990.

Seybold VS, Hylden JLK, Wilcox GL. Intrathecal substance P and somatostatin in rats: behaviors indicative of sensation. *Peptides* 3: 49—54, 1982.

Sicuteri F, Gppeti P, Marabini S, Lembeck F. Pain relief by somatostatin in attacks of cluster headache. *Pain* 18: 359—365, 1984.

Taddese A, Nah SY, McClesky EW. Selective opioid inhibition of small nociceptive neurons. *Science* 270: 1366—1369, 1995.

Terenius L. Somatostatin and ACTH are peptides with partial antagonist-like selectivity for opiate receptors. *Eur J Pharmacol* 38: 211—213, 1976.

Tessler A, Himes BT, Gruber-Bollinger J, Reichlin S. Characterization of forms of immunoreactive somatostatin in sensory neuron and normal and deafferented spinal cord. *Brain Res* 370 (2): 232—240, 1986.

Trevino DL, Coulter JD, Willis WD. Location of cells of origin of the spinothalamic tract in the lumbar enlargement of cat. *J Neurophysiol* 36: 750—761, 1973.

Wiesenfeld-Hallin Z. Intrathecal somatostatin modulates spinal sensory and reflex mechanisms; behavioral and electrophysiological studies in the rat. *Neurosci Lett* 62: 69—74, 1985.