Effects of Somatostatin on the Responses of Rostrally Projecting Spinal Dorsal Horn Neurons to Noxious Stimuli in Cats

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Somatostatin (SOM) is a widely distributed peptide in the central nervous system and exerts a variety of hormonal and neural actions. Although SOM is assumed to play an important role in spinal nociceptive processing, its exact function remains unclear. In fact, earlier pharmacological studies have provided results that support either a facilitatory or inhibitory role for SOM in nociception. In the current study, the effects of SOM were investigated using anesthetized cats. Specifically, the responses of rostrally projecting spinal dorsal horn neurons (RPSDH neurons) to different kinds of noxious stimuli (i.e., heat, mechanical and cold stimuli) and to the A δ -and C-fiber activation of the sciatic nerve were studied. Iontophoretically applied SOM suppressed the responses of RPSDH neurons to noxious heat and mechanical stimuli as well as to C-fiber activation. Conversely, it enhanced these responses to noxious cold stimulus and A δ -fiber activation. In addition, SOM suppressed glutamate-evoked activities of RPSDH neurons. The effects of SOM were blocked by the SOM receptor antagonist cyclo-SOM. These findings suggest that SOM has a dual effect on the activities of RPSDH neurons; that is, facilitation and inhibition, depending on the modality of pain signaled through them and its action site.

Key Words: Somatostain, Spinal cord, Dorsal horn, Nociception, Aδ-fiber, C-fiber, Pain

INTRODUCTION

Somatostatin (SOM), a cyclic tetradecapeptide, is widely distributed in the central nervous system and periphery. It acts as a neuromodulator that inhibits neuronal activity or modulates neurotransmitter release (Beitz et al, 1983; Patel, 1999). This peptide exists in organs processing nociceptive information, such as small dorsal root ganglion (DRG) cells (Rang et al, 1994; Helyes et al, 2000; Carlton et al, 2001), substantia gelatinosa neurons of the spinal dorsal horn (Hunt et al, 1981), intrinsic interneurones or relay neurons of the superficial dorsal horn (Lu and Ho, 1992; Mather and Ho, 1992), and midbrain periaqueductal gray that projects to the medullary nucleus raphe magnus (Beitz et al, 1983; Millhorn et al, 1987). However, the physiological function of SOM in the spinal nociceptive processing has not yet been fully elucidated. Pharmacological data in nociception are contradictory. When interpreted, SOM's modulatory role has been viewed as either facilitatory (pro-nociceptive) or inhibitory (anti-nociceptive) (Traub and Brozoski, 1996; Chapman and Dickenson, 1992; Song et al, 2002). As established in previous studies, two hypotheses have been proposed: 1) SOM might be involved in the transmission of nociceptive information, because of the following: First, SOM is released from small DRG neurons by noxious thermal stimulation (Kuraishi et al, 1985; Morton et al, 1989). Second, SOM is distributed in small primary afferent nerve fibers (Rang et al, 1994) and colocalized with substance P and CGRP (Garry et al, 1989; Hanesch et al, 1995). Finally, the spinal application of SOM enhanced pain behavior, such as facilitating the response to noxious thermal stimulation (Seybold et al, 1981; Wiesenfeld-Hallin, 1985, 1986; Morton et al, 1989; Kamei et al, 1993ab). 2) In contrast with pro-nociceptive action, SOM may also have anti-nociceptive effects. First, SOM exhibits depressant actions on the excitability of neurons, particularly in the spinal cord (Murase et al, 1982; Taddese et al, 1995; Kim et al, 2002; Jiang et al, 2003). Second, SOM superfusion or systemic SOM *in vivo* inhibits the thermal responses of nociceptive spinal neurons (Sandkühler et al, 1990; Helmchen et al, 1995). Third, intrathecally applied SOM inhibits motor reflexes in response to noxious stimuli and reduces c-Fos expression and mechanical hyperalgesia in neuropathic pain model (Mollenholt et al, 1988; Tsai et al, 2002). Finally, SOM has been shown to be analgesic when given systemically to patients with cluster headache, or when given intrathecally to patients with cancer pain or postoperative pain (Sicuteri et al, 1984; Chrubasik et al, 1985; Meynadier et al, 1985; Penn et al, 1992; Paice et al, 1996). Collectively, these findings suggest that SOM plays a significant role

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ABBREVIATIONS: SOM, somatostatin; DRG, dorsal root ganglion; RPSDH, rostrally projecting spinal dorsal horn; GLU, glutamate; cyclo-SOM, cyclo (7-aminoheptanoyl-Phe-D-Trp-Lys-Thr[Bzl]); RF, receptive field.

in the transmission of nociceptive information.

The inconsistency of the above mentioned experimental reports on the action of SOM in nociceptive processing and analgesic mechanisms might be due to diverse nociceptive processes and pain modality. Hence, the present study was taken to clarify this issue by examining the effects of SOM on the responses of RPSDH neurons to various noxious stimuli in cat.

METHODS

Animal preparation

The experiments were performed on 31 cats of either gender weighing 2.5 to 3.0 kg. After treatment with atropine sulfate (0.2 mg/kg, s.c.) and ketamine hydrochloride (30 mg/kg, i.m.), cats were anesthetized with α-chloralose (60 mg/kg, i.v.). Moreover, it was ventilated artificially with the end-tidal CO_2 level which was maintained between 3.5 and 4.5%. Rectal temperature was maintained at 37°C throughout the experiment, and arterial blood pressure was continuously monitored. A laminectomy on the spinal cord levels L2~S3 exposed the lumbosacral enlargement. Around the exposed spinal cord, a mineral oil pool was made. Afterwards, the pool temperature was maintained near body temperature. The left sciatic nerve was dissected free from the surrounding connective tissue and placed on the platinum tripolar stimulating electrodes.

Electrophysiology

Seven-barreled glass micropipette assemblies were used for simultaneous recording from RPSDH neurons and microiontophoretic application of drugs. The low impedance (< 2 MΩ measured at 1 kHz) carbon fiber in the center barrel of the array served as an electrode for recording extracellular single-unit activities. The signals amplified through an AC amplifier (DAM 80, WPI) were fed into a window discriminator which was connected to a laboratory interface (CED 1401) and a personal computer to provide basis for sampling and analysis of the spontaneous and evoked neuronal activity.

Noxious stimulation and electrical stimulation

Mechanical stimuli were generated by manually squeezing the receptive field (RF) for 10 s using serrated forceps. The heat stimuli (50°C for 20 s, given at intervals of >15 min) were applied to the glabrous foot pad by a radiant heat source. The cold stimuli of -15°C, 10 s in duration, were delivered to the RF through contact of a piece of dry ice with the RF. The sciatic nerve was electrically stimulated to activate Aδ-fibers (single square wave pulse of 1 mA of 0.1 ms width) and C-fibers (a single pulse or a train of three square wave pulses of 10 mA of 0.5 ms width, 50 Hz). The intensity to activate C-fibers was determined to be a couple of hundred times greater than that of the Aα-β-fiber threshold strength. Aδ-and C-fiber responses were identified through the latency of the responses. Since the length from the stimulating to the recording site was 15~20 cm, cellular activities appearing in less than 50 ms (conduction velocity, 3~30 m/s) were considered as Aδ-responses, while those after 150 ms (0.3~1.3 m/s) were viewed as C-responses. Evoked responses were expressed as total number of impulses. Also, twenty sweeps were compiled as a peristimulus time histogram (bin width; 2 ms).

Identification of RPSDH neurons

The antidromic stimulation technique was employed to confirm the RPSDH neurons. After a laminectomy at cervical vertebrae, a bipolar electrode was placed on the contralateral ventrolateral funiculus at the C2 spinal cord segment for antidromic activation. The criteria for an antidromic activation were: 1) constant latency of the evoked response (100 μA and 1 Hz); 2) neuron's ability to follow high-frequency stimulus trains (333 Hz, 3 pulses) with spikes; and 3) collision between the antidromic spike and the orthodromic action potentials evoked by natural stimulation to the RF.

Drugs and solutions

In this study, the drug concentration and pH were as follows: L-monosodium-glutamate (GLU, Sigma), 0.2 M, pH 8.5; somatostatin (SOM, Sigma), 0.1 M, pH 7.0; somatostatin receptor antagonist cyclo (7-aminoheptanoyl-Phe-D-Trp-Lys-Thr[Bzl]) (cyclo-SOM; Sigma), 0.1 M, pH 7.0; and sodium chloride (NaCl, Sigma), 150 mM, pH 7.0. All these drugs were applied iontophoretically with cationic currents, except GLU which was expelled through an anionic current. The retaining currents were kept at 8 nA, while the current neutralization via 150 mM NaCl-filled balancing barrel was used during all drug applications.

Statistical analysis

The data were expressed as mean±standard error. Differences in the data were evaluated by means of Student's t-test. A p-value <0.05 was taken as a statistically significant difference.
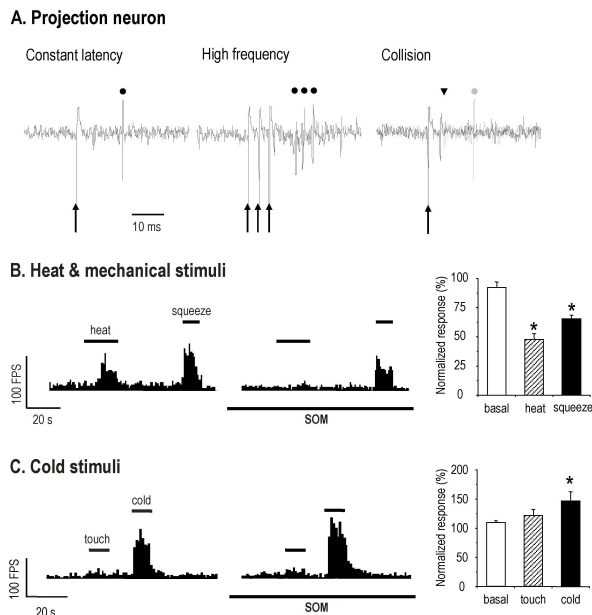
RESULTS

Identification of RPSDH neurons

The spinal dorsal horn neurons, located in the laminae II-VI of Rexed (200~3,000 μm), served as the basis for recording. These neurons had excitatory RFs at one or more toes of the ipsilateral hindpaw or footpad. The RPSDH neurons were identified by applying the antidromic stimulation to the cervical dorsal column (Fig. 1A).

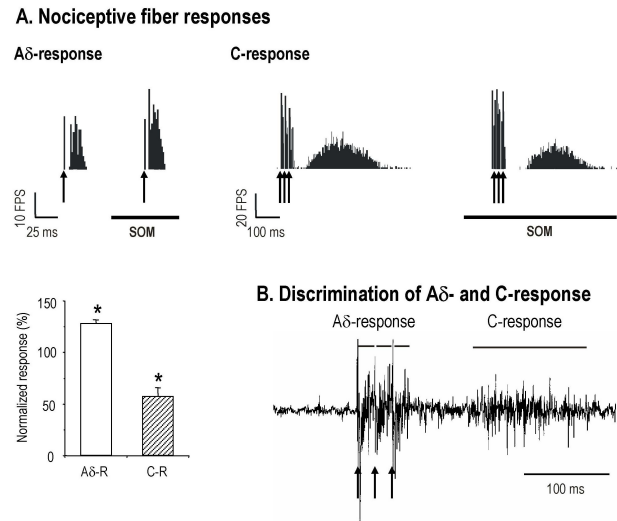### Effects of SOM on the responses of RPSDH neurons to noxious heat, mechanical, and cold stimuli

Iontophoretically applied SOM (100 nA) was revealed to have no significant effects on the basal and innocuous touch-induced activities (Fig. 1B and 1C). Nevertheless, it altered the responses of RPSDH neurons to noxious stimuli: it decreased the number of action potentials induced by noxious heat and mechanical stimuli (Fig. 1B) and enhanced the neuronal firing elicited by cold stimulation (Fig. 1C). On the average, SOM suppressed the heat-evoked response to 47.7±5.0% of the control (n=27, p<0.05) and the noxious mechanical stimulus-evoked response to 65.5±3.1% (n=33, p<0.05). In contrast, the cold-evoked response was increased to 146.8±15.9% of the control (n=8, p<0.05).

A. Projection neuron

Constant latency   High frequency   Collision

B. Heat & mechanical stimuli

C. Cold stimuli

Fig. 1. Effects of iontophoretically applied SOM on the RPSDH neuron response to peripheral noxious stimuli. Single cell activity was recorded in the lumbosacral area using an extracellular electrode. (A) RPSDH neurons exhibit several characteristics; namely, 1) constant latency, 2) the responses to high frequency (333 Hz) stimulation, and 3) collision. Arrow ($\uparrow$) represents the electrical stimuli to sciatic nerve. The activity of RPSDH neuron ($\bullet$) by electrical stimuli was observed after a constant latency. Gray circle ($\bullet$) means the activity of RPSDH neuron, which vanished after collision ($\blacktriangledown$) by cervical dorsal column stimulation. In this experiment, RPSDH neurons were used. (B) Iontophoretic application of SOM (100 nA) resulted in the inhibition of nociceptive response to noxious heat (50°C) stimuli subjected for a 20 sec duration and to mechanical stimuli (squeeze) for 10 sec. After an iontophoretic application of SOM (100 nA), the heat-evoked and the noxious mechanically evoked responses were suppressed. (C) The effects of SOM on the response of RPSDH neuron to peripheral noxious cold stimulation are presented. SOM (100 nA) increased the cold-evoked response of the RPSDH neuron. Each bar graph represents mean value±standard error for SOM effect on noxious stimuli such as heat, squeeze, and cold. The asterisk shows significant difference in SOM effect (non paired t-test, $p < 0.05$).

Effects of SOM on the responses of RPSDH neurons to the activation of Aδ-and C-fibers in the sciatic nerve

These SOM effects could be associated with nerve fiber types which transmit nociceptive information or their functional properties. Taking this into account, the effects of SOM on the Aδ-and C-fiber-elicited responses of RPSDH neurons were investigated. Fig. 2 shows that SOM increased the Aδ-fiber-elicited response to 128.4±3.4% of the control in 8 of 13 cells tested ($p < 0.05$). However, it did not exhibit any effect on the remaining five cells. On the other hand, SOM reduced the C-fiber-elicited response in all cells (n=9) tested to 57.7±8.3% ($p < 0.05$) of the control. It was noted that SOM facilitated the responses of RPSDH neurons to cold stimuli in all of the 4 neurons, enhancing the Aδ-fiber-elicited responses.

A. Nociceptive fiber responses

Aδ-response   C-response

B. Discrimination of Aδ- and C-response

Aδ-response   C-response

Fig. 2. Effects of iontophoretically applied SOM on the RPSDH neuron response to noxious electrical stimuli of the peripheral nerve. (A) The single ($\uparrow$) or triple ($\uparrow \uparrow \uparrow$) electrical stimulation at 500 ms was applied to the sciatic nerve with Aδ-strength (1 mA with 0.1 ms width) or with C-strength (10 mA with 0.5 ms width). SOM increased Aδ-fiber response of this cell, whereas the C-fiber response of the same cell was markedly suppressed. The summary bar graph was derived from the normalized SOM effect on Aδ- (Aδ-R) and C-responses (C-R). (B) Electrical stimuli were applied to the sciatic nerve for the activation of Aδ-or C-fibers (a single or a train of three square wave pulses). In doing so, the responses were discriminated using window discriminator. The Aδ-response was the sum of activities appearing in less than 50 ms, while the C-response are those after 150 ms. Evoked responses were expressed as the total number of impulses. Also, twenty sweeps were compiled as a peristimulus time histogram (bin width; 2 ms, 20 sweeps). The bar graph represents mean value±standard error for SOM effect on noxious electrical stimuli. The significant difference in SOM effect (non paired t-test, $p < 0.05$) is represented by the asterisk.

### Effects of SOM receptor antagonist on nociceptive responses

We next examined whether SOM receptor antagonist blocked SOM action on RPSDH neurons. As shown in Fig. 3, cyclo-SOM (200 nA), a SOM receptor antagonist, blocked both the facilitatory and inhibitory effects of SOM on the responses of RPSDH neurons to noxious stimuli. However, the cyclo-SOM itself did not affect the basal activity (92.4±11.8%, n=5; data not shown). In addition, the effects of SOM on the Aδ-& C-fiber-elicited responses were blocked by cyclo-SOM. This result indicated that SOM effect was mediated by the activation of SOM receptor.

Mode of SOM action

In order to investigate whether SOM acted directly on the postsynaptic RPSDH neurons, the effects of SOM on glutamate (GLU)-evoked responses of RPSDH neurons were examined (Fig. 4). The application of GLU (100 nA) to RPSDH neurons induced excitatory responses, and these responses declined in magnitude during the application of SOM (Fig. 4A; 100 nA and 200 nA, to 39.8±4.1% and 10.1±7.3% of the control, respectively, n=10, $p < 0.05$). Furthermore, this SOM
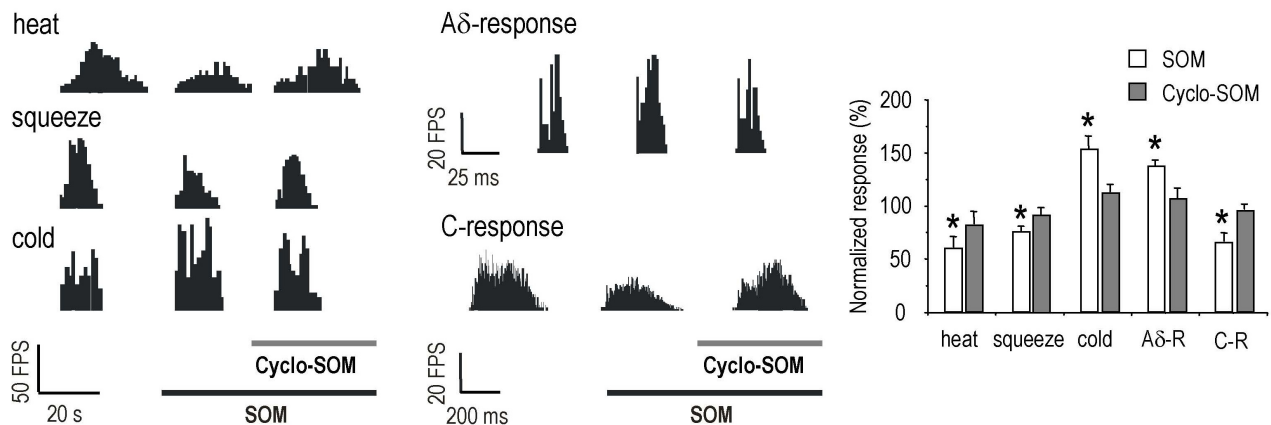
Fig. 3. Blockade of SOM effect by SOM receptor antagonist, cyclo-SOM. The cyclo-SOM (100 nA) blocked the inhibitory effects of SOM (100 nA) on heat (59.2±9.8→80.8±11.5%, n=5) and squeeze (74.6±4.6→90.3±6.9%, n=6) as well as the facilitatory effect on cold stimulation (151.5±11.5→110.8±6.6%, n=4). In the case of activities by electrical stimuli such as Aδ - and C-response, SOM effect was also inhibited by cyclo-SOM (Aδ-response, 135.4±6.2→105.4±9.2%, n=5; C-response, 64.6±7.7→93.8±5.2%, n=5). Each bar graph represents mean value±standard error for SOM-and cyclo-SOM effect on noxious stimuli. The asterisk shows significant difference in SOM effect (paired t-test, p<0.05).
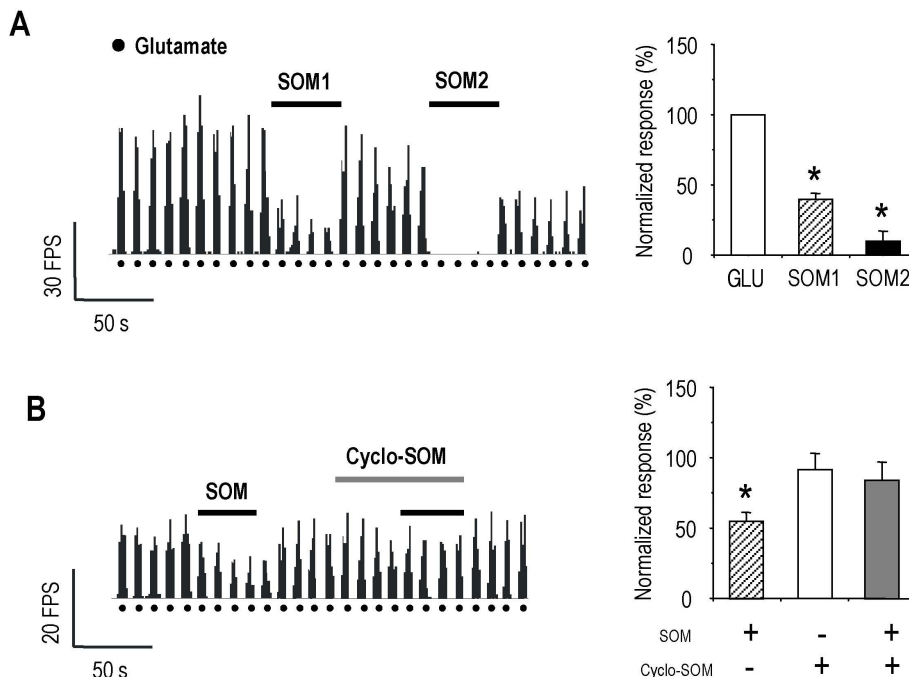
Fig. 4. Effects of SOM on glutamate-evoked activity of RPSDH neuron. Iontophoretical application of GLU (100 nA every 5 seconds) induced the activity of RPSDH neuron. SOM has inhibitory action on the GLU-evoked activity of RPSDH neuron in a dose dependent manner (SOM1, 100 nA; SOM2, 200 nA). This inhibitory effect of SOM was blocked by cyclo-SOM (100 nA). Each bar graph represents mean value±standard error for SOM-and cyclo-SOM effect on glutamate-evoked activity of RPSDH neuron. Similarly, the asterisk shows significant difference in SOM effect (paired t-test, p<0.05).

effect was blocked by cyclo-SOM (55.9±5.9→84.7±12.9%, n=5, p<0.05) (Fig. 4B).

DISCUSSION

SOM is present in small to medium size cells in the dorsal root ganglion and is colocalized with other neuropeptides, such as substance P (Tuchscherer and Seybold, 1985). In addition, the SOM-immunoreactive cell bodies and neurites are found in the lamina II of the spinal dorsal horn (Stine et al, 1982). Therefore, it is generally thought that SOM may participate in pain signal processing. However, there is contradictory evidence with regards to the role of SOM in modulating the nociceptive transmission in the spinal cord. SOM elicits antinociceptive effects against acute noxious thermal and mechanical stimuli (Sandkühler et al, 1990) and attenuates the hyperalgesia in the formalin and carrageenin-induced inflammation model (Chapman and Dickenson, 1992; Pinter et al, 2002). On the other hand, the intrathecal administration of SOM facilitates the flexion reflex to C-fiber input and noxious

thermal stimulation (Seybold et al, 1981; Wisenfield-Hallin, 1985, 1986; Morton et al, 1989; Kamei et al, 1993ab). Also, the intrathecal administration of anti-SOM antisera attenuates hyperalgesia in experiments involving rats. Another effect is that it inhibits the response to thermal stimuli in normal and adjuvant inflamed rats (Ohno et al, 1988; Traub and Brozoski, 1996).

The present results demonstrate that iontophoretic application of SOM selectively suppressed the responses of RPSDH neurons to the noxious heat and mechanical stimuli and to C-fiber stimulation. The result in part contradicts with other reports that SOM is involved in mechanical or heat nociception (Kuraishi et al, 1985; Morton et al, 1989; Song et al, 2002). Nevertheless, it is in concordance with the previous reports that SOM has an inhibitory effect on dorsal horn neurons (Sandkühler et al, 1990; Helmchen et al, 1995; Taddese et al, 1995).

An interesting feature of the present results is the facilitation of cold-evoked and $A\delta$-fiber-elicited responses by SOM. Sandkühler *et al.* reported that the responses to electrical stimulation of primary afferent $A\beta$-and $A\delta$-fibers, were at least not decreased by SOM superfusion, although C-fiber-elicited responses were blocked (Sandkühler et al, 1990). This discrepancy between Sandkühler's and our present results might be due to the difference in drug administration route (iontophoretic application *in vivo* vs. bath-application *in vitro*) or the difference of pain modality such as cold- and $A\delta$-response. Assuming that the cutaneous $A\delta$-nociceptors contribute to the sensation of cold pain (Fruhstorfer et al, 1974; Willis WD, Coggeshall, 1991; Simone and Kajander, 1997), the results imply that the response to the cold stimuli is associated with the increment of $A\delta$-fiber response by SOM.

The exact mechanism underlying the dual effect of SOM-inhibitory and excitatory-on the nociceptive transmission remains unknown. However, two possibilities can be suggested. The analgesic effect of SOM may be explained as follows. At the cellular level, it has been reported that an iontophoretic and bath application of SOM result in hyperpolarization and in reduction of the spontaneous firing of dorsal horn neurons in both neonatal (Murase et al., 1982) and adult rats (Yajiri et al., 1997). Also, SOM-14 could hyperpolarize cortical neurons of the CNS. This is made possible by increasing K^+ current (Wang et al., 1989) and inhibiting a voltage-dependent Ca^{2+} current via a GTP-binding protein (Dichter et al, 1990; Kleuss et al, 1991). It was found that SOM inhibited the GLU-evoked response, indicating its inhibitory action on the excitability of postsynaptic neuron. Thus, SOM may directly act on the postsynaptic membrane and suppress the excitability of RPSDH neuron. This hypothesis is consistent with two recent studies (Kim et al, 2002; Jiang et al, 2003): They reported that SOM induced postsynaptic hyperpolarization via the activation of outward K^+ current in superficial dorsal horn neurons.

However, the facilitatory effect of SOM on nociception cannot be explained by the hyperpolarizing action at postsynaptic sites. SOM, which inhibits voltage-dependent K^+ currents in neurons in CNS (Dichter et al, 1990) and colonic crypts (Sandle et al, 1999), may directly excite presynaptic neuron, resulting in the enhancement of glutamate release from primary afferent. It is also possible that SOM inhibits GABAergic interneurons involved in the descending inhibition of spinal nociceptive transmission, because GABA and SOM have been shown to be co-localized in numerous neurons throughout the CNS, and many of the SOM pos-

itive neurons in the superficial dorsal horn are likely to represent inhibitory interneurones. In turn, they inhibit the release of GABA and the interaction with the GABAA receptor to modulate responses to this inhibitory transmitter (Robbins, 1985; Dichter et al, 1990).

The present results suggest that SOM may suppress the responses of dorsal horn neurons to noxious heat and mechanical stimuli by blocking the C-fiber input via postsynaptic inhibition. On the other hand, it may facilitate the responses of dorsal horn neurons to noxious cold stimuli by enhancing the $A\delta$-fiber input via presynaptic excitation. Thus, SOM has a dual effect on the activities of RPSDH neurons; facilitation and inhibition. Such an effect is dependent on the modality of the pain signals transmitted. Furthermore, this dual effect of SOM might also be determined by the action site of SOM -pre-or postsynaptic SOM receptors.

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