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Comparison of Somatostatin and Morphine Action on the Responses of Wide Dynamic Range Cells in the Dorsal Horn to Peripheral Noxious Mechanical and Heat Stimulation in Cats

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The purpose of present study was to compare the effects of somatostatin (SOM) and morphine (Mor) on the responses of wide dynamic range (WDR) cells to peripheral noxious stimulation. Single neuronal activity was recorded with a carbon-filament electrode at the lumbosacral enlargement of cat spinal cord. After identifying WDR cells, their responses to peripheral noxious mechanical or thermal stimuli were characterized and the effects of SOM and Mor, applied either iontophoretically or intrathecally, were studied. In most cells SOM and Mor suppressed noxious stimulus-evoked WDR neuronal activity, though a few WDR neurons showed no change or were excited by SOM and Mor. Systemically applied naloxone, a non-specific opioid antagonist, always reversed the Mor induced suppression of neuronal activity evoked by noxious mechanical stimuli, but did not always reverse the suppression of neuronal activity elicited by SOM. The suppressive effect of Mor on thermal stimulus-evoked neuronal activity was partially reversed by naloxone, while that of SOM were not reversed at all. The above results suggest that both Mor and SOM exert an inhibitory effect on thermal and mechanical stimulus-evoked WDR neuronal activity in cat spinal dorsal horn, but the mechanisms are dependent upon the functional populations of dorsal horn nociceptive neurons.

Key Words: WDR cells, Somatostatin, Morphine, Naloxone, Mechanical and thermal noxious stimuli

INTRODUCTION

Pain is a kind of normal physiological process to warn the subject of the existence of actual or potential tissue damage, and does not seem to be evoked by a single mechanism. After an acute injury, for example, one can experience initial sharp pain, followed by delayed burning pain; the initial pain is thought to be mediated by Aδ-fiber and the delayed pain, by C-fiber (Lewis, 1942).

It has been accepted that there are at least two types of nociceptors, Aδ- mechanonociceptor and C-polymodal nociceptor. The former seems to mediate initial fast pain, and the latter, delayed slow pain (Willis, 1985). Cell bodies of peripheral nociceptors are located in the dorsal root ganglion (DRG). Aδ-fibers are axons of medium-sized DRG neurons and C-fibers are those of small dark DRG neurons (Harper & Lawson, 1985; Lee et al, 1986). C-cells are especially sensitive to capsaicin, which is known to activate C-polymodal nociceptors and thus evoke burning pain (Szolcsanyi, 1988; LaMotte et al, 1992).

DRG neurons contain various neurotransmitters and peptides, of which calcitonin gene-related peptide (CGRP) is found in 28~50% of cells ranging in size from relatively small to large; substance P occurs in 12~38% of small and medium sized cells and somatostatin (SOM) is found in 5~15% of cells whose size ranges from small to intermediate (Rang et al, 1994).

Aδ-fibers terminate in lamina I, the outer portion of lamina II and lamina V, and C-fibers terminate in

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the inner portion of lamina II (Cervero & Iggo, 1980; Sugiura et al, 1986).

All these facts imply that the nociceptive process involves multiple pathways and mechanisms, and that the same is true for the antinociceptive process. Morphine (Mor), for example, the best known analgesics, elicits its effect through the operation of both supraspinal and spinal mechanisms (Duggan & North, 1984), and in general, suppresses dorsal horn activity; it can, however, also activate a group of dorsal horn cells (Hylden & Wilcox, 1986; Wilcockson et al, 1986; Jones et al, 1990; Magnuson & Dickenson, 1991). It is known to effectively suppress C-fiber mediated delayed pain (Taddese et al, 1995) and to inhibit lamina I cold nociception mediated by Aδ -fiber (Mokha, 1993; Craig & Serrano, 1994). Other reports have stated that even cold sensitive neurons are either activated or suppressed by Mor (Craig & Hunsley, 1991).

SOM, which is found in 5~15% of DRG neurons (Hökfelt et al, 1976; Rang et al, 1994), seems to play an important role in the nociceptive process. Some reports have claimed that it mediates nociception and pain is thus evoked (Seybold et al, 1982; Wiesenfeld-Hallin, 1985; Kamei et al, 1993a; 1993b), but others state that it produces analgesic effects (Renaud et al, 1975; Randic & Miletic, 1978; Long, 1988; Sandkühler et al, 1990). Some of the effects of SOM are known to be associated with opioid action (Maurer et al, 1982; Pelton et al, 1986; Mulder et al, 1988; Betoin et al, 1994), and SOM is reported to suppress the heat-evoked nociception effectively (Morton et al, 1989; Sandkühler et al, 1990). According to another reports, SOM suppresses initial Aδ -pain (Taddese et al, 1995). All these findings imply heterogenous roles of SOM in the nociceptive process.

We assume that all the above findings concerning the nociceptive processes and analgesic mechanisms are based on the belief that the nociceptive process itself is really heterogenous and depends upon the type of injury, type of nociceptors, analgesic drugs and routes of administration. The present study thus aimed to clarify the different responses of spinal dorsal horn neurons to peripheral noxious mechanical and heat stimuli, and the effect of intraspinal Mor and SOM on these responses.

METHODS

Preparation of animal

A total of 25 cats of either sex (body weight, 1.8~2.5 kg) were used. After pretreatment with atropine sulfate (0.2 mg/kg, s.c.) and ketamine hydrochloride (Ketalar, Yu-han, 30 mg/kg, i.m.), an animal was anesthetized with α-chloralose (60 mg/kg, i.v.) and the trachea and femoral artery and vein were cannulated. To relax the musculature, pancuronium bromide (Mioblock, Organon; initial dose 0.4 mg, maintenance dose 0.4 mg/hr) was administered and the animal was ventilated artificially; end-expiratory CO_2 concentration was maintained in the range of 3.5~4.5% (Normocap CO_2 & O_2 monitor, Datex, Finland). Rectal temperature was monitored and maintained at $37.5 \pm 1^{\circ}C$ by using an electric blanket (Hoemothermic Blanket Control Unit, Harvard Apparatus). Arterial blood pressure was monitored and Hartmann solution was infused continuously.

Lumbosacral enlargement was exposed by a laminectomy done on of the L2-S3 vertebrae. After identifying the entry of the L7 and S1 dorsal roots, several small pia holes were made for the insertion of the recording electrode. To expose the upper thoracic spinal cord for antidromic stimulation, a further laminectomy was performed at T1-T6 vertebrae. After completing the operation, the animal was transferred to a stereotaxic animal fixation apparatus. A warm mineral oil pool was made by using skin flaps and maintained warm by a heating coil in which warm water was circulated. The animal was allowed to recover for one hour or longer before the actual recording.

Stimulation and recording

A carbon-filament was inserted into the center barrel of a seven barrel capillary tube and the capillary was pulled down to make a carbon-filament recording electrode leaving six barrels for iontophoretic drug application. Tip resistance of the recording electrode was 1~3 MΩ and the iontophoretic electrodes were filled with the following drugs: 0.2 M L-monosodium glutamate (pH 8.5), 10 mg/ml (13 mM) morphine sulfate, 0.4 mg/ml (1 mM) naloxone hydrochloride, 100 μg/ml (66 μM) octreotide (as acetate) and 0.15 M sodium chloride for current neutralization; maintenance currents were 8 nA.

Signals picked up by the recording electrode were amplified by an AC amplifier (DAM 80, WPI) and fed into window discriminator through a laboratory interface (CED 1401, Cambridge Electronic Design, U.K.). The signals were stored and analyzed by personal computer.

To determine whether the recorded cells send axons further than the thoracic spinal cord, a bipolar electrode was placed at the contralateral dorsolateral funiculus and inserted to a depth of 3~4 mm. For antidromic activation, square pulses of 1 mA intensity and 0.1 ms width were applied continuously through the electrode. The criteria for this activation of ascending fibers were: 1) constant latency, 2) following of high frequency stimuli and 3) collision with orthodromic action potentials.

Noxious mechanical stimulation involved the manual application of squeeze using serrated forceps and noxious heat stimuli (55°C) were applied by a radiant heat source with a thermal electrode of which thermistor monitored the surface temperature of the receptive field.

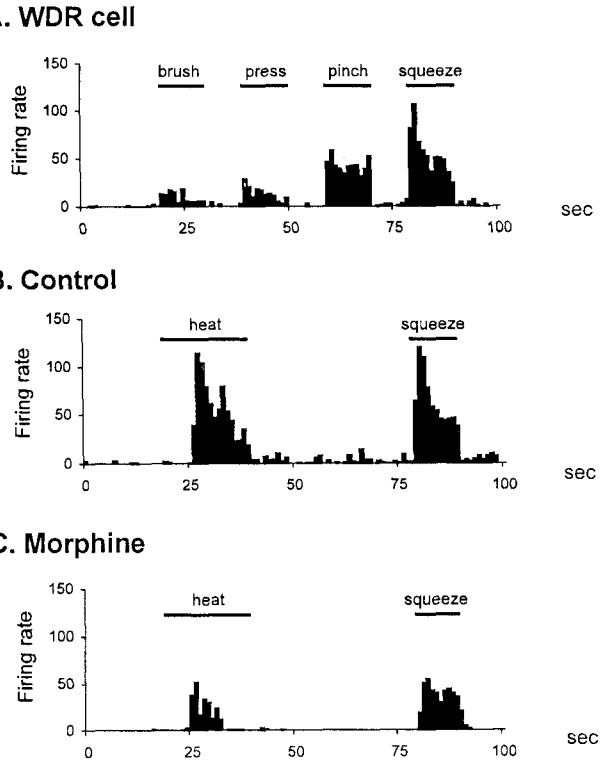
Experimental procedure

After the cell was classified according to responses to graded mechanical stimuli applied to the receptive field, its response to noxious mechanical and thermal stimuli was characterized. The usual depths of recorded neurons were 300~1,200 and 1,500~3,000 μm. Noxious mechanical and heat stimuli were applied before and after the iontophoretic, intrathecal or systemic application of Mor and SOM. In the case of intrathecal application, Mor (13 mM, 0.01 cc; 0.02 mg) and SOM (66 μM, 0.01 cc; 1 μg) were dropped on the filter paper (5×5 mm^2), which contacted with the dorsal surface of spinal cord and the changes in the single cell activities was observed after 20 min (The maximal decremental responses were at 20 min). To reverse the effects of the drug, naloxone (0.1 mg/kg) was then administered intravenously or iontophoretically. The results were compared by compiling single pass time histograms (SPTH).

At the end of the experiment, the animal was euthanized by an overdose of anesthetics. The lumbosacral as well as thoracic spinal cord were removed and fixed with 4% formalin for over one week. By means of conventional histologic examination, the recording sites and sites of antidromic stimulation were identified. All data were expressed as mean± s.e.m and the statistical significance was determined from Students' t-test as a p-value of 0.05 or less.

RESULTS

Fig. 1 shows the results of an experiment in which the effects of Mor on the responses of a dorsal horn WDR neuron to peripheral noxious stimuli were tested. The cell was recorded 800 μm below the dorsal surface and was identified as a typical WDR



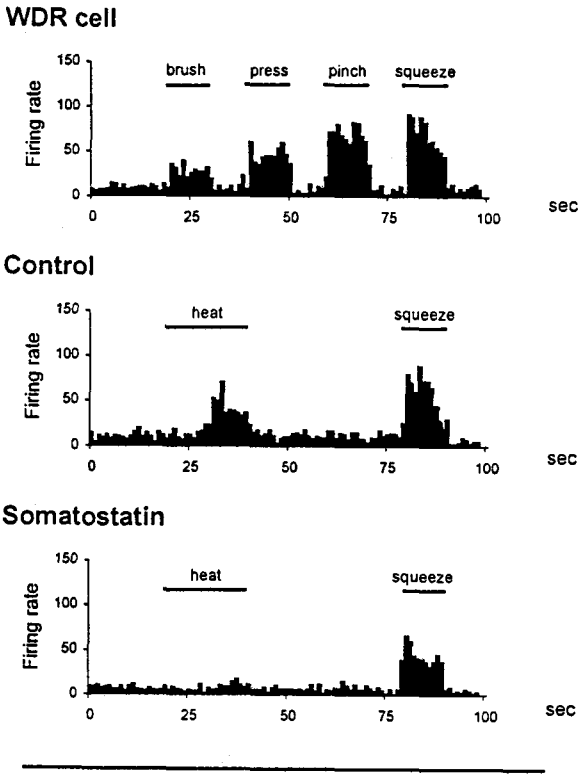
		Type of Stimulus	
		Heat	Mechanical
Morphine	Inhibition	15	21
	No response	3	1
	Excitation	2	1

Fig. 1. Effects of morphine on the response of dorsal horn neuron to peripheral noxious stimuli. Single cell activity was recorded in the lumbosacral area (depth: 800 μm) using an extracellular electrode. (A) The cell was identified as a WDR cell. (B, C) Direct spinal application of morphine (0.02 mg) reduced the neuronal response to noxious heat and squeeze.

cell, as shown in panel A. In panel B, the cell showed marked nociceptive responses to 20 sec of noxious heat (55°C) stimulus and 10 sec of mechanical squeeze. After Mor (0.02 mg) was applied intrathecally, the nociceptive response to heat stimulus decreased by 68% (the number of action potentials decreased from 714 in B to 228 in C) and the response to mechanical stimulus decreased by 39% (from 664 in B to 402 in C). As summarized in the table below panel C, Mor applied intrathecally suppressed the response in 91% of cells (21 of 23 cells) exposed to noxious mechanical stimuli and in 75% of cells (15 of 20 cells) exposed to heat stimulus. In a small group of cells, Mor elicited no effect (±10% or less of control value) or even increased the responses to peripheral noxious stimuli.

An example of SOM experiment is shown in Fig. 2. The cell was at a depth of 150 μm and was a typical WDR cell, as shown in panel A. Before applying SOM intrathecally, the cell responded to noxious heat and mechanical stimuli with 564 and 591 action potentials; 20 min after the application of SOM (1 μg) to the dorsal surface of the lumbosacral spinal cord, the response to heat stimulus had disappeared completely but more than 70% of the response to noxious mechanical stimulus remained. As shown in the table below panel C, SOM suppressed in 81% of cells (26/32) subjected to noxious heat stimulus and in 77% of cells (23/30) subjected to noxious mechanical stimulus. In a small group of cells SOM elicited increased nociceptive responses.

Mor and SOM sometimes exerted an additive effect on dorsal horn neurons; an example of such an



		Type of Stimulus	
		Heat	Mechanical
Somatostatin	Inhibition	26	23
	No response	4	4
	Excitation	2	3

Fig. 2. Effects of somatostatin on the response of dorsal horn neuron to peripheral noxious stimuli. Direct spinal application of somatostatin (1 μg) resulted in complete inhibition of nociceptive response to heat and partial inhibition of response to squeeze.

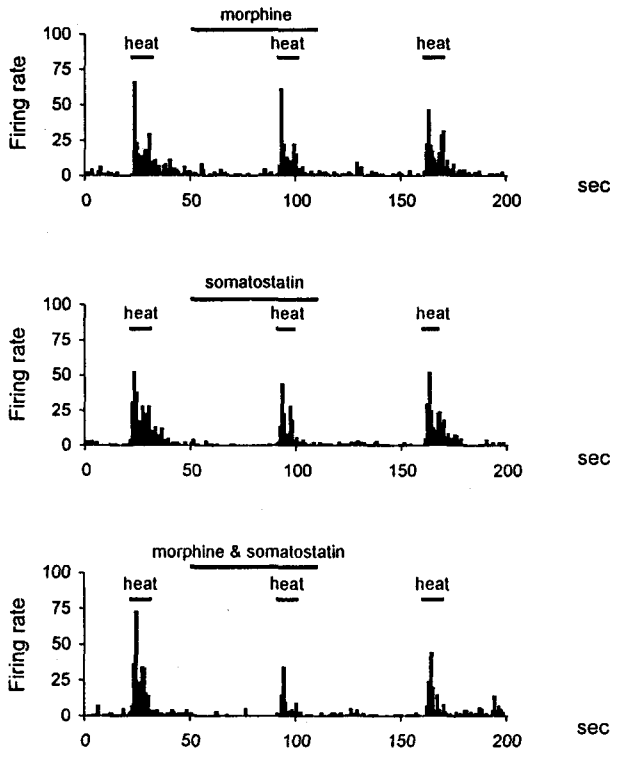


Fig. 3. An example of the additive action of iontophoretically applied morphine and somatostatin. The separate administration of morphine (100 nA) or somatostatin (100 nA) resulted in slight inhibition of the neuronal response to heat, while combined administration resulted in marked inhibition.

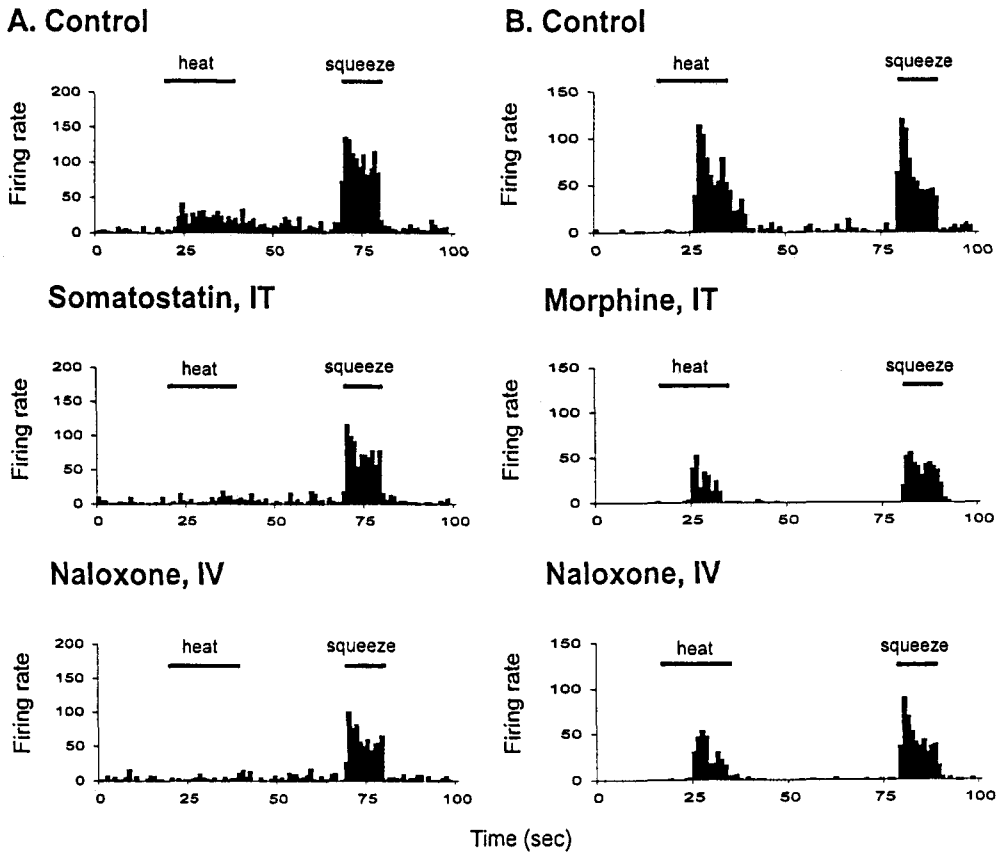


Fig. 4. Effects of naloxone on the analgesic action of somatostatin and morphine on peripheral noxious stimuli. Naloxone (0.1 mg/kg, IV) did not reverse the analgesic effect of somatostatin on the cell subjected to heat or mechanical stimuli, while it partially reversed the effect of morphine.

experiment, in which Mor and SOM were applied iontophoretically is shown in Fig. 3. The cell was at a depth of 1060 μm. Mor and SOM applied at 100 nA for 60 sec decreased the nociceptive response to heat by 12% and 48% respectively and simultaneous application resulted in a decrease of 65%. In some cells the additive effect was so strong that the response to noxious heat showed no recovery.

An additive effect implies the existence of certain common mechanisms, and we investigated whether the action of SOM is μ-opioid receptor mediated. To determine whether it can reverse the effects of Mor and/or SOM, naloxone (0.1 mg/kg) was intravenously administered; examples of such an experiment are shown in Fig. 4. SOM completely suppressed the nociceptive heat response of the cell shown in the left panel, while the nociceptive mechanical response was partially suppressed; these effects were not reversed by naloxone, though the effect of Mor on the nociceptive process was reversed by naloxone in the left panel. As shown in Fig. 5, naloxone applied iontophoretically decreased heat response by 20% (from 349 to 279) and mechanical response by 13% (from 867 to 751). Pretreatment with naloxone did not prevent the suppressive effect of SOM. Statistical data relating to the effects of Mor and SOM are shown in Fig. 6. Mor decreased the mechanical nociceptive response of dorsal horn WDR cells to $56.2 \pm 3.8\%$ (n=27) and the heat nociceptive response to $64.9 \pm 4.6\%$ (n=15), while SOM decreased the mechanical response to $63.9 \pm 3.2\%$ and the heat response to $50.7 \pm 4.9\%$.

The effects of naloxone on Mor and SOM action are summarized in Table 1. The inhibitory effect of Mor on mechanical response was blocked completely, and the effect on heat response was reduced by 60%; at the same time, naloxone did not alter the effect of SOM on heat response, but reduced its effect on mechanical response by 40%.

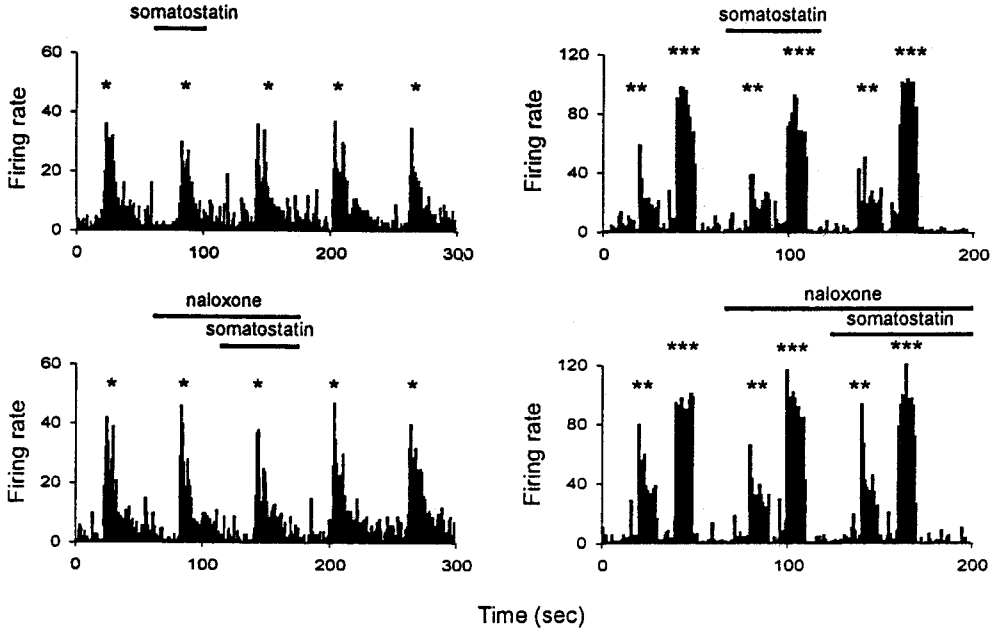
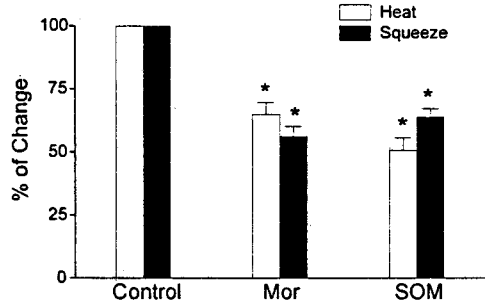


Fig. 5. Effects of naloxone pretreatment on the analgesic action of somatostatin on cells subjected to peripheral noxious stimuli. Intravenously administered naloxone did not block the effects of somatostatin on either heat- or mechanically-induced nociceptive responses. Naloxone (100 nA) and somatostatin (100 nA) were applied iontophoretically. (*heat; **press; ***squeeze)



	Type of Stimulus	
	Mechanical	Thermal
Morphine	56.19 +/- 3.85 (n=27)	64.87 +/- 4.55 (n=15)
Somatostatin	63.88 +/- 3.21 (n=25)	50.71 +/- 4.89 (n=21)

Fig. 6. Response of WDR cells in the dorsal horn of cat spinal cord to morphine or somatostatin following noxious thermal and mechanical stimulation. Asterisks indicate statistical significance (*,$p<0.05$) in paired t-test; values represent mean±s.e.m. relative to corresponding control values.

Table 1. Summarized results of the antagonistic effects of naloxone on the analgesic action of morphine and somatostatin

Drug	Type of stimulus	WDR Cell response		
		Antagonistic	No response	Total
Morphine	Thermal	3	2	5
	Mechanical	7	0	7
Somatostatin	Thermal	0	5	5
	Mechanical	2	3	5

Data were pooled from the experiments shown in Fig. 4. and 5.

DISCUSSION

The analgesic effect of Mor has been known for a long time, but the mechanism of its action was demonstrated only during the last two decades; its action plays a key role in the functioning of the endogenous analgesic system (Basbaum & Fields, 1978; 1984). The main axis of endogenous analgesia is periaqueductal gray (PAG)-nucleus raphe magnus

(NRM)-dorsal horn; Mor acts both at the supraspinal and spinal site of the axis (Duggan & North, 1984). It is known that WDR cells in the dorsal horn are generally suppressed by Mor, but a small group of these cells can be excited by Mor (Hylden & Wilcox, 1986; Wilcockson et al, 1986; Jones et al, 1990; Magnuson et al, 1991); this might be explained by either the suppression of pain transmission cells or the excitation of inhibitory interneurons in the pain transmission pathway. Hence, it is important to determine whether the recorded cell is a projection neuron or an interneuron (Craig & Serrano, 1994). Another possible explanation is that the analgesic effect of Mor may depend on the type of noxious stimulus. In this context, it is well known that Mor inhibits C-fiber mediated mechanical or heat nociception (Jurna & Grossman, 1976; Besson & Le Bars, 1979; Cooper et al, 1986; Taddese et al, 1995), and lamina I spinothalamic tract neurons, which carry Aδ -cold nociception, could be inhibited by Mor (Craig & Serrano, 1994). Another report, which failed to determine whether the recorded cells were interneurons or projection neurons, revealed that Mor either inhibited or excited spinal dorsal horn neurons mediating cold nociception (Mokha, 1993). All these facts imply that the mechanism of Mor action on spinal dorsal horn depends on the type of noxious stimulus, the peripheral nerve carrying the nociceptive information, and the type of cells in the dorsal horn.

The analgesic effect of SOM is blocked by naloxone, and has thus been associated, at least partially, with opioid action (Rezek et al, 1978; Maurer et al, 1982; Pelton et al, 1986; Mulder et al, 1988; Betoin et al, 1994). All these reports describe agonist binding studies or behavioral studies such as tail flick or the hot plate test. Other investigators have not drawn the same conclusions, however (Chrubasik et al, 1985; Sandkühler et al, 1990; Pascual et al, 1991); their reports describe the results of either extracellular single cell recording study or clinical studies.

Our results demonstrated that both SOM and Mor inhibited the responses of spinal dorsal horn neurons to noxious mechanical (75~90%) or heat stimuli (75~80%). Only 5~10% of recorded neurons were excited by either Mor or SOM. Although we could not record from many projection neurons, it seems that the action of Mor and SOM is mainly inhibitory. It can be stated with absolute certainty that the effect of SOM on thermal response is not blocked by naloxone and this implies, at least, that the analgesic effect of SOM on dorsal horn WDR cells subjected to noxious heat stimulus is not mediated through μ -opioid receptors. This result is inconsistent with other agonist binding studies or behavioral studies (Rezek et al, 1978; Maurer et al, 1982; Pelton et al, 1986; Mulder et al, 1988; Betoin et al, 1994) but consistent with the findings of Sankühler et al. (1990), who investigated that inhibition of heat-evoked response by SOM was not mediated via spinal μ-opioid receptors using an extracellular single cell recording technique.

Naloxone completely blocked the antinociceptive action of Mor on mechanical nociception thus implying that opioid μ-receptor is involved in the process. In general, an opioid most effectively suppresses C-fiber mediated nociception, and this explains the fact that both C-fiber mediated mechanical and chemical nociception are blocked by Mor. SOM suppresses heat mechanonociception. In view of this and assuming that a sizable portion of heat nociception is mediated through C-fiber and that this nociception is sensitive to Mor, it may be inferred that naloxone exerts some blocking effects on SOM action. Our results indicated that SOM suppressed the nociceptive response to both heat and mechanical stimuli but naloxone did not block the action of SOM. One possible explanation is that SOM may more effectively block the initial pain mediated by Aδ-fiber more efficiently than the delayed pain mediated by C-fiber (Taddese et al, 1995). Another possibility is that the C-fiber-mediated mechanical and heat nociceptive processes might be different. Further investigation is required.

In conclusion both Mor and SOM exert inhibitory effect on thermal and mechanical stimulus-evoked WDR neuronal activity in cat spinal dorsal horn; mechanical nociception is mediated through μ-opioid receptor but the action of SOM is not associated with this receptor. The mechanisms are, however, dependent upon the functional populations of the dorsal horn nociceptive neurons.

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REFERENCES

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

Basbaum AI, Fields HL. Endogenous pain control systems-brainstem spinal pathways and endorphin circuitry. *Ann Rev Neurosci* 7: 309−338, 1984

Besson JM, Le Bars D. Effects of intravenous administration of morphine and related compounds on the activity of dorsal horn neurons in the spinal cords. In Advances in Pain Research and Therapy (eds Bonica JJ, Liebeskind JC and Albbe-Fessard DG), Vol. 3, pp. 441−448. Raven Press, New York, 1979

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 Therapeut* 296: 7−14, 1994

Cervero F, Iggo A. The substantia gelatinosa of the spinal cord. A critical review. *Brain* 103: 717−772, 1980

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

Cooper BY, Vierck Jr CJ, Yeomans DC. Selective reduction of second pain sensations by systemic morphine in humans. *Pain* 24: 93−116, 1986

Craig AD, Hunsley SJ. Morphine enhances the activity of thermoreceptive cold-specific lamina I spinothalamic neurons in the cat. *Brain Res* 558: 93−97, 1991

Craig AD, Serrano LP. Effects of systemic morphine on lamina I spinothalamic tract neurons in the cat. *Brain res* 636: 233−244, 1994

Duggan AW, North RA. Electrophysiology of opioids. *Pharmacol Rev* 35: 219−281, 1984.

Harper AA, Lawson SN. Electrical properties of rat dorsal root ganglion neurones with different peripheral nerve conduction velocities. *J Physiol* 359: 47−63, 1985

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

Hylden JL, Wilcox GL. Antinociceptive effect of morphine on rat spinothalamic tract and other dorsal horn neurons. *Neuroscience* 19(2): 393−401, 1986

Jones SL, Sedivec MJ, Light AR. Effects of iontophoresed opioids on physiologically characterized lamina I and II dorsal horn neurons in the cat spinal cord. *Brain Res* 532: 160−174, 1990

Jurna I, Grossman W. The effect of morphine on the activity evoked in ventrolateral tract axons of the cat spinal cord. *Exp Brain Res* 24: 473−484, 1976

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, Hitosugi H, Misawa M, Nagase H, Kasuya Y. Cold water swim stress inhibits the nociceptive response to intrathecally administered somatostatin, but not substance P. *Life Sci* 52: PL169−174, 1993b

LaMotte RH, Lundberg LER, Torebjök HE. Pain, hyperalgesia and activity in nociceptive C units in humans after intradermal injection of capsaicin. *J Physiol* 448: 749−764, 1992

Lee KH, Chung K, Chung JM, Coggeshall RE. Correlation of cell body size, axon size and signal conduction velocity for individually labelled dorsal root ganglion cells in the rat. *J Comp Neurol* 243: 335−346, 1986

Lewis T. Pain. McMillan, New York, 1942.

Long JB. Spinal subarachnoid injection of somatostatin causes neurological deficits and neuronal injury in rats. Eur. J *Pharmac* 149: 287−296, 1988

Magnuson DSK, Dickenson AH. Lamina-specific effects of morphine and naloxone in dorsal horn of rat spinal cord *in vitro*. *J Neurophysiol* 66: 1941−1950, 1991

Maurer R, Gähwiler BH, Büscher HH, Hill RC, Römer D. Opiate antagonistic properties of an octapeptide somatostatin analog. *Proc Acad Sci USA* 79: 4815−4817, 1982

Mokha SS. Morphine alters the firing of cold-receptive neurons in the superficial dorsal horn of the medulla in the rat. *Brain Res* 602: 205−214, 1993

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- not delta- and kappa-opioid receptors involved in presynaptic inhibition of neurotransmitter release. *Eur J Pharmacol* 157: 109−114, 1988

Pascual J, Freijanes J, Berciano J, Pesquera C. Analgesic effect of octreotide in headahce associated with acromegaly is not mediated by opioid mechanisms-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 μ opioid receptors. *J Med Chem* 29: 2370−2375, 1986

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

Rang HP, Bevan S, Dray A. *Nociceptive peripheral neurons: cellular properties.* In: Textbook of Pain, Wall PD & Melzack R, 3rd ed., Churchill Livingstone,

chap 3, p57－78, 1994.

Renaud LP, Martin JB, Brazeau P. Depressant action of TRH, LH-RH and somatostatin on activity of central neurones. *Nature* 225: 233－235, 1975

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

Sandkühler J, Fu QG, Helmchen C. Spinal somatostatin superfusion *in vivo* affects activity of cat nociceptive dorsal horn neurons: comparison with 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

Sugiura Y, Lee CL, Perl ER. Central projections of identified, unmyelinated(C) afferent fibers innervating mammalian skin. *Science* 234: 358－361, 1986

Szolcsanyi J. Antidromic vasodilation and neurogenic inflammation. *Agents Actions* 23: 4－11, 1988

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

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

Wilcockson WS, Kim J, Shin HK, Chung JM, Wills WD. Actions of opioids on primate spinothalamic tract neurons. *J Neurosci* 6: 2509－2520, 1986

Willis WD. *The Pain System-the neural basis of nociceptive transmission in the mammalian nervous system.* Karger, p78－212, 1985