BACKGROUND:
It has been demonstrated that the sigma-1 receptor is distinct from any other known neurotransmitter receptors. Recent reports have revealed that the formalin-induced pain behavior is reduced in knock-out (KO) mice for sigma-1 receptor in comparison to wild type animals. However, the most active site and related neurophysiological mechanism of sigma-1 receptor in nociception is still remained to be determined.

PURPOSE:
This study was designed to evaluate following subjects.
1. There is no direct evidence to address the role of spinal sigma-1 receptor in nociception, yet. Therefore, possible effect of spinal sigma-1 receptor blockade was determined in the mouse formalin test.
2. It was determined that the time- and dose-dependent effect of intrathecally injected sigma-1 receptor agonist on protein kinase C (PKC)-dependent phosphorylation of N-methyl-D-aspartate (NMDA) receptor subunit 1 (pNR1), which plays an important role in central sensitization. In addition, it was investigated whether sigma-1 receptor agonist-induced increase of pNR1 played a major role in nociception using two behavioral tests such as intrathecal (i.t.) NMDA-induced pain test as well as the tail flick assay.
3. The possible role of spinal sigma-1 receptor was investigated in induction and/or maintenance of mechanical allodynia using chronic constriction injury-induced neuropathic pain in rats.

MATERIALS AND METHODS:
1. Formalin (1%, 20ul) was injected subcutaneously into the plantar surface of the right hind paw and formalin-elicited pain behavior was recorded and analyzed for 30 min in ICR mice. Then two selective sigma-1 receptor antagonists (BD-1047 and BMY-14802) were intrathecally administered to examine the role of spinal sigma-1 receptor in formalin-induced pain and pNR1.
2. After i.t. treatment of sigma-1 receptor agonist, time- and dose-dependent change of pNR1 was examined using western blotting and immunohistochemistry. In order to investigate the possible effect of sigma-1 ligand-induced pNR1 on nociception, both of i.t. NMDA-induced pain model and tail flick assay was performed. NMDA pain test was induced by i.t. injection of NMDA (60 ng) and pain-related behavior was recorded and analyzed for 15 min. Tail flick test was performed by applying the radiant heat source to the tail area and latency (sec) was measured until tail of mouse was flicked.
3. Chronic constriction injury (CCI) was created by 4 loose ligation of common sciatic nerve at mid-thigh level of right hind leg. After the surgery, nerve injury-induced mechanical allodynia was examined by von Frey filament (2 g). The possible effect of sigma-1 receptor blockade on mechanical allodynia was determined at the different time points of developmental and maintenance periods.

RESULTS:
1. The i.t. injection of sigma-1 receptor antagonists, BMY-14802 and BD-1047 significantly suppressed the formalin-induced pain-related behavior of the second phase. In addition, these antagonists also reduced the formalin-induced Fos and pNR1 (ser 896 and ser 897) expression of
the spinal dorsal horn, suggesting that the spinal sigma-1 receptor plays an important role in the formalin-elicited pain.

2. The i.t. treatment of sigma-1 receptor agonist, carbetapentane time- and dose-dependently upregulated the PKC-dependent pNR1 (ser 896) in the spinal dorsal horn, which is important area for sensory function. The peaked level of pNR1 was detected at 60 min post injection of 10 nmol of carbetapentane. In addition, pan-PKC and isoforms in each class such as alpha, epsilon and zeta was significantly translocated from cytosolic to membrane fraction. In the two behavioral pain tests, carbetapentane remarkably potentiated the pain sensation as compared with that of saline-injected control. The sigma-1 ligand-induced enhancement of pain sensation was mediated by the phospholipase C, PKC and Ca2+ATPase pathway.

3. Sigma-1 receptor immunoblot of spinal dorsal horn in the ipsilateral right side was significantly increased and maintained for 3 days after injury as compared with that of contralateral left side. The repeated i.t. treatment of sigma-1 receptor antagonist, BMY-14802 (200 nmol) at initial period of chronic constriction injury (CCI, from one day before to 5 days after nerve injury, twice a day) prevented the development of nerve injury-induced mechanical allodynia. However, single or multiple (3 days, twice a day) treatment of BMY-14802 at 200 nmol did not suppress the mechanical allodynia after the neuropathic pain was already established (at day 9 post injury).

CONCLUSIONS:
1. The result of present study clearly demonstrated that the spinal sigma-1 receptor played a critical role in formalin-induced pain behavior, spinal Fos and pNR1 (ser 896 and ser 897) expression.

2. The i.t. injection of carbetapentane apparently upregulated the pNR1 expression in the spinal cord. This sigma-1 ligand-induced pNR1 was mediated by the activation/translocation of PKC pathway. In behavioral tests, it was demonstrated that this upregulated pNR1 was a critical factor to enhance the pain sensitivity. These results strongly suggested that pain sensation is mediated by the direct inter-neural interaction between sigma-1 receptor and NMDA receptor in spinal dorsal horn.

3. In CCI-induced rats, increase of sigma-1 receptor was observed in the induction stage, suggesting that the sigma-1 receptor might act as a main factor in the development of neuropathic pain rather than the maintenance. Spinal sigma-1 receptor blockade was more effective in the initial phase of neuropathic pain rather than in the maintenance period. These results also indicated that the spinal sigma-1 receptor played as a critical factor to produce antinociceptive effect on acute and chronic pain sensation.

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