Korean J. of Pharmacology
Vol. 29, No. 1, pp. 33-41, 1993

Capsaicin Induces Acute Spinal Analgesia and Changes in the Spinal Norepinephrine Level**

Hyoungsup Park[1]* and Kyung-Pyo Park[2]

[1]*Department of Pharmacology, University of Ulsan College of Medicine* [2]*Laboratory of Pharmacology and Toxicology, Asan Institute for Life Sciences 388-1 Pungnap-dong Songpa-gu, Seoul 138-040, Korea*

ABSTRACT

Central analgesic effect of capsaicin was assessed by the tail flick reflex (TFR) test, using male Sprague-Dawley rats under anesthesia with pentobarbital sodium (induction with 40 mg/kg and maintenance with 4~8 mg/kg/hr). Level of norepinephrine in the spinal cord was also measured. Capsaicin, 35~150 μg, was injected intrathecally, and the TFR latency was measured before, 10, 30, and 60 minutes after the drug administration. TFR latency was increased 100% or more immediately by intrathecal capsaicin, from 2.9 seconds to the maximum of 7.0 seconds at 10 minute after the drug; $P < 0.01$. The increase in TFR latency was maintained during the course of experiment of 2 hours. Concomitant reduction of NE content in the spinal cord was observed; from 16 ng/mg protein to 7 ng/mg protein. On the other hand, subcutaneous injection of capsaicin of 50 mg/kg did not change the TFR latency although the NE content reduced similarly to the case of intrathecal injection. Pretreatment of the animal with 0.5 mg/kg of MK-801 reversed the increase of TFR latency and NE reduction induced by intrathecal capsaicin. These results suggest that capsaicin causes analgesia at the spinal cord level by activating the excitatory amino acid-NE-dorsal horn interneurons axis of the descending inhibitory pain modulation pathway.

Key Words: Capsaicin, Analgesia, Spinal cord, Norepinephrine

INTRODUCTION

Capsaicin (8-methyl-N-vanilly-6-nonenamide), a major pungent ingredient of red pepper (genus *Capsicum*), is well known to have a biphasic effect on the peripheral sensory nerves: the initial stimulation or irritation followed by the inhibition or depression of the nerve activity. These effects on peripheral sensory nerves are attributed to the acute release and subsequent depletion of peptide neurotransmitters, especially substance P from nerves such as C- and A-∂ fibers (Jancso *et al.*, 1977; Virus and Gebhart, 1979). Nonpeptide transmitters such as acetylcholine and other monoamines appeared to be resistant to the capsaicin-induced depletion (Jancso *et al.*, 1977; Gamse *et al.*, 1981).

Mechanism of central analgesic effects of capsaicin is still not clear. Capsaicin also causes depletion of substance P from the central nervous system as well as the induction of the central analgesia, when administered systemically (Buck *et al.*, 1981; Hayes and Tyers, 1980; Hayes *et al.*,

*To whom correspondence should be addressed

**This study was supported by KOSEF Grant 913-0412-010-2 and a grant from Asan Institute for Life Sciences, and also in part supported by Korea Research Institute of Chemical Technology

1981). This has drawn interests from many investigators in view of developing non-narcotic central analgesics. Although other neuropeptides such as cholecystockinin, somatostatin, vasoactive intestinal polypeptide and β-endorphin were also reported to be affected by capsaicin (Pristley *et al.*, 1982; Buck *et al.*, 1983; Nagy *et al.*, 1983; Panerai *et al.*, 1983), the central analgesic effect of capsaicin is generally considered to be due to the depletion of substance P (Hayes and Tyers, 1980; Buck *et al.*, 1981), for substance P neurons are the major component of the primary ascending pain pathway which runs from the dorsal root of spinal cord to the brain stem. But, the depletion of substance P and analgesia do not correlate exactly. First, a temporal discrepancy; the systemic capsaicin of proper dose induces the central as well as peripheral analgesia immediately while the depletion of substance P from the spinal cord or from the dorsal root ganglia is apparent only after a couple of days (Miller *et al.*, 1982). The second discrepancy is the dose: Hayes *et al.* (1981) observed a short-lived ($<$ 3 hrs) analgesia with a single dose of subcutaneous capsaicin as low as 1 mg/kg which was too low a dose to deplete substance P significantly.

Electrophysiological observations suggest that capsaicin opens non-specific cation channels on the membrane of sensitive neurons resulting in the depolarization. This increases intracellular calcium concentration by opening of voltage-gated calcium channel, which finally evokes the release of substance P from the sensitive neurons (Wood *et al.*, 1988; Bevan and Szolcsanyi, 1990). However it has been shown that the high potassium-induced depolarization brings about further release of substance P after the maximum release of the peptide by treating the spinal cord slice with the ceiling concentration of capsaicin (Gamse *et al.*, 1979b). Thus, the single dose of capsaicin does not deplete completely the releasable pool of the peptide in acute phase. Capsaicin might increase the rate of inactivation of voltage-gated calcium channels and thus inhibit activities of sensitive neuron in peripheral sensory fibers, in dorsal root ganglia, and in the spinal cord (Bevan and Szolcsanyi, 1990).

Above studies on substance P release and electrophysiological evidences support that the peptide depletion is not the mechanism of acute central analgesia which is observed within minutes to hours after the capsaicin administration. There must be a separate mechanism of capsaicin-induced acute analgesia, although the depletion of substance P might be the underlying mechanism of the chronic or late phase analgesia.

In addition, possibilities of direct interactions with substance P receptors as well as opioid receptors have already been ruled out (Gamse *et al.*, 1979a; Mayer *et al.*, 1980). Thus, it is very possible that capsaicin induces the acute central analgesia via other component (s) in the mechanism of pain perception and modulation than the substance P system.

According to Basbaum and Fields (1984), the modulation of pain perception occurring in the dorsal horn of spinal cord, especially in the substantia gelationsa of layer II, is under the influence of a certain group of cells in the rostral ventromedial medulla (RVM). These cells constitute the descending inhibitory pathway of pain modulation. In this pain modulation, various neurotransmitters are involved: 5-hydroxytryptamine (5-HT), enkephalin, γ-aminobutyric acid (GABA), norepinephrine (NE), neurotensin and excitatory amino acids (EAA) (Aimone *et al.*, 1987; Aimone and Gebhart, 1986; Basbaum and Fields, 1984; Marchand and Hagino, 1983; Beitz, 1982). RVM again receives inputs from periaqueductal gray (PAG) and nucleus cuneiformis (Aimone and Gebhart, 1986). The modes of transmission of pain from the primary pain fibers to the upper hierarchy in the CNS, and its modulation at each level of spinal cord, brain stem and in the cerebral hemisphere are very complicated. Although the whole scheme is yet far from complete, a couple of simplified pictures can be drawn based on pieces of informations accumulated so far (Fields *et al.*, 1991; Hamon *et al.*, 1988). First, the major path of pain perception after the excitation of the peripheral pain fibers is the primary afferent pathway along the spinal cord, of which substance P is the major neurotransmitter. Second, activities of the primary afferent neurons are modulated by local interneurons in the dorsal horn. These interneurons are under control of RVM via on-cells and off-cells, increasing and decreasing pain perception respectively. The neurotransmitter (s) of on-cells are not clearly defined yet, but 5-HT and NE are suggested as major transmitters used

by off-cells. Third, the major transmitter of the input to RVM from PAG is suggested as EAA, for the iontophoresis of glutamate, or N-methyl-D-aspartate (NMDA) into RVM produces analgesia equivalent to the analgesia induced by electrical stimulation of PAG.

We have examined in the preliminary study the changes of 5-HT and NE levels after capsaicin treatment. Although 5-HT has been identified as the neurotransmitter of a group of off-cells at the level of the medulla and spinal cord (Aimone *et al.*, 1987; Skagerberg and Bjorklund, 1985) we could not show any significant change in the 5-HT level at the spinal cord by capsaicin treatment, suggesting that 5-HT might not contribute significantly to the capsaicin-induced analgesia. Instead, we oberved the reduction of NE content in the spinal cord by systemic capsaicin treatment (unpublished data). It is quite possible that NE system is involved in the capsaicin induced acute analgesia, for NE also was reported to be involved in the spinal analgesia (Sagen and Proudifit, 1985). The current study is to further investigate the acute analgesia induced by capsaicin at the spinal cord level, to relate this analgesia with the changes of NE system, and to study the mode of capsaicin action on the spinal NE system. To localize the effect on the spinal cord, capsaicin was introduced through the intrathecal cannula and the effect was compared with the effect of systemic administration.

MATERIALS AND METHODS

Chemicals and instruments

Capsaicin, MK-801, norepinephrine hydrochloride, dihydroxybenzylamine hydrobromide were purchased from Research Biochemical Incorporated, Natic, MA, U.S.A. Aluminum oxide (Alumina), dimethylsulfoxide and perchloric acid were purchases from Sigma. Sodium octylsulphate, EDTA, and other general chemicals were of the highest analytic grade commercially available.

The tail-flick tester was purchased from Ugo Basile of ltaly. High performance liquid chromatogrpahy was from Pharmacia-LKB of Sweden, and the Nova-Pak C_{18} column from Waters was used.

Tail flick reflex (TFR) Test; (modified from Sinclair *et al.*, 1988)

Male Sprague-Dawley rate of 250~300 g were used. The animal was anesthetized with pentobarbital sodium, 40 mg/kg i.p., and the femoral vein cannula was established. An intrathecal catheter was inserted via cisterna to reach the lumbar enlargement of the spinal cord (10 cm from the cisternal orifice). And the animal was kept under the anesthesia of the level to show the corneal reflex by infusing pentobarbital sodium at the rate of 8 to 10 mg/hr through the femoral cannula throughout the course of tail flick test. Thermal stimulation was given as the infra-red ray of the energy equivalent to the temperature of 60℃. The arbitrary cut-off time to prevent the tissue damage was 7 seconds. For one series of TFR test at the designated time, four tests were performed at intervals of two minutes with the stimulation site on the tail moving provimally 1 cm each time starting from the distal one third point. The result of the TFR test was presented as seconds of latency, averaging the four measurements. Test drugs were administered when the TFR latency was stabilized at 2.5~3 seconds. In cases of the intrathecal administration, 35 to 150 μg of capsaicin in 10 μl of the vehicle composed of dimethylsulfoxide (DMSO), ethanol and artificial cerebrospinal fluid (10:40:50) was injected in 10 minutes period through the cannula. For the systemic administration of capsaicin, the dose of 50 mg/kg was injected s.c. in the vehicle of 10% Tween 80 and 10% ethanol in saline (1 ml). 10 minutes before the capsaicin s.c. injection, 1 mg of atropine sulfate was injected through the femoral cannula to prevent the bronchospasm. In some experiments the EAA receptor, MK-801, in saline (0.5 mg/kg) was injected through the femoral cannula, 20 minutes before capsaicin. For the control animal of each group, the corresponding volume of vehicle was injected. TFR latency was measured before, and at 10, 30, 60 minutes and sometimes at 120 minutes after the injection.

Measurement of NE contents in the spinal cord

The NE content in the spinal cord was measured on the high performance liquid chromatog-

raphy (HPLC) as follows (Sunol *et al.*, 1988; Marsden and Joseph, 1986). The spinal cord was rapidly removed from the animal at 10, 30 and 60 minute points, and homogenized in ice-cold 0.1 M perchloric acid (10 ml per g of wet tissue) containing 0.4 mM sodium metabisulfite. The homogenate was centrifuged at 3,000 × g for 10 minutes. The supernatant was collected and the activated alumina (200 mg/ml) was added to adsorb catecholamines. At this point, 3,4-dihydroxybenzylamine (DHBA) at the concentration of 100~500 ng/ml was added to the supernatant as the internal standard of HPLC. After the alumina was washed twice with distilled water, catecholamines were extracted with 0.5 M perchloric acid containing 0.4 mM sodium metabisulfite (100 μl per 100 mg of alumina). Then, the extract was analyzed with the HPLC. For the HPLC, a C-18 reverse phase column (Nova-Pak) of 4 μm bid size and 0.5 × 12 cm dimension was used. The composition of the mobile phase was; 0.1 M NaH_2PO_4, 0.1 mM EDTA, 1.0 mM sodium octylsulphate, 9% methanol, and pH 3.6. The flow rate was 0.5 ml/minute. The electrochemical detector was used for the detection. Quantitation of NE was done by calculating the peak area and multiplying it by the conversion factor obtained from the standard curves of NE and DHBA. The quantity of NE was expressed as ng per mg protein, and the protein was measured by Bradford method (Stoscheck, 1990; Bradford, 1976).

Statistics

Unpaired t-test of the data was done using StatView IV program on Macintosh LC personal computer.

RESULTS

Intrathecal capsaicin (Fig. 1)

The TFR latency was increased from 2.9 seconds to the maximum value of 7 seconds within 10 minutes after the intrathecal administration of capsaicin. Meanwhile, NE content of the spinal cord was decreased by more than 50%, from 14 ng to 6.5 ng per mg protein at the time of 30 minute and this decrease lasted more than an hour (even up to 2 hours). Both of the changes in TFR latency and NE content were statistically significant against the control values before the injection of capsaicin ($p < 0.01$). These effects were observed consistantly in the range of capsaicin dose from 35 to 150 μg. The analgesia was inconsistant below the range, and the writhing or even outright convulsion happened with the dose above the range. Fig. 1 shows the result at the dose of 35 μg which was the lowest dose having the consistancy in the analgesic effect. Injection of the vehicle only did not change the TFR latency or NE contents (data not shown).

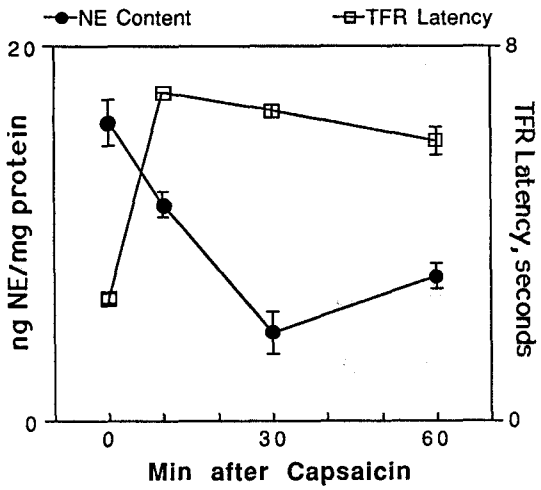

Fig. 1. Intrathecal capsaicin on TRF and spinal cord NE level. Capsaicin, 35 μg in 10 μl vehicle, was injected through the intrathecal cannula as described in Method. TFR latency was measured before capsaicin (0 time), 10 min, 30 min, and 1 hr after capsaicin injection (open squares). The spinal cord NE level was measured at each time point as described in Method (closed circle). the value at each point represents mean ± S.E. from 5 animals or more.

Subcutaneous injection of capsaicin (Fig. 2)

Subcutaneous injection of capsaicin, 50 mg/kg, did not affect the TFR latency, but decreased NE contents in the same fashion as the intrathecal injection. The dose was the maximum single dose which was reported to decrease substance P levels in the CNS without bronchospasm or shock.

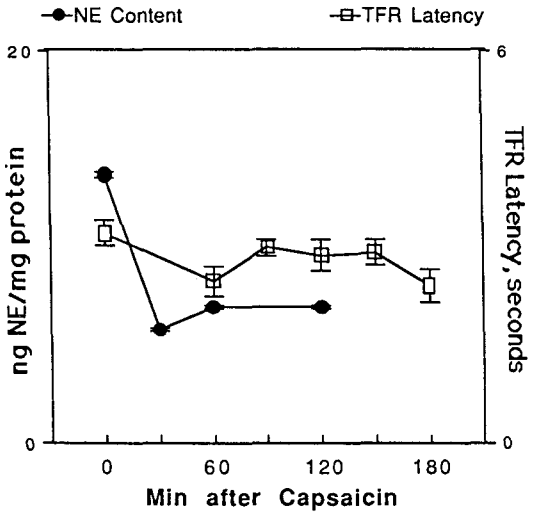

Fig. 2. Subcutaneous capsaicin on TFR and spinal cord NE level. Capsaicin of 50 mg/kg was injected subcutaneously. At the designated time point, TFR latency (open square) and spinal cord NE level (closed circle) were measured as described for Fig. 1. The value at each point represents mean ± S.E. from 5 animals or more.

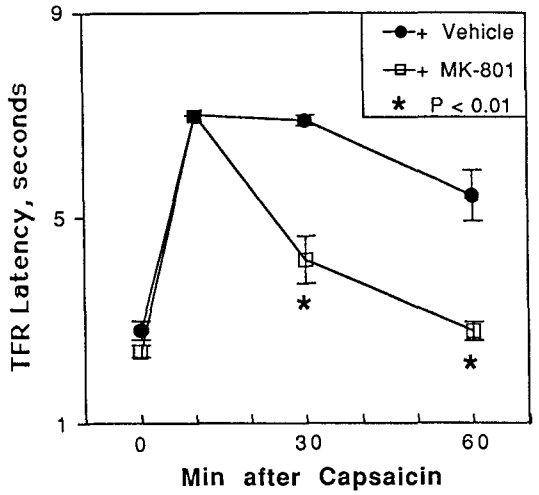

Fig. 3. MK-801 on intrathecal capsaicin-induced analgesia. MK-801 of 0.5 mg/kg or vehicle only were injected 20 minutes before the intrathecal injection of capsaicin (50 μg in 10 μl of vehicle). The TFR latency was measured as described in Method at each time point. Open squares are for animals pretreated with MK-801; closed circles, vehicle only. The value at each point represents mean ± S.E. from 5 animals or more. Asterisks: P < 0.01 between MK-801 and vehicle only groups.

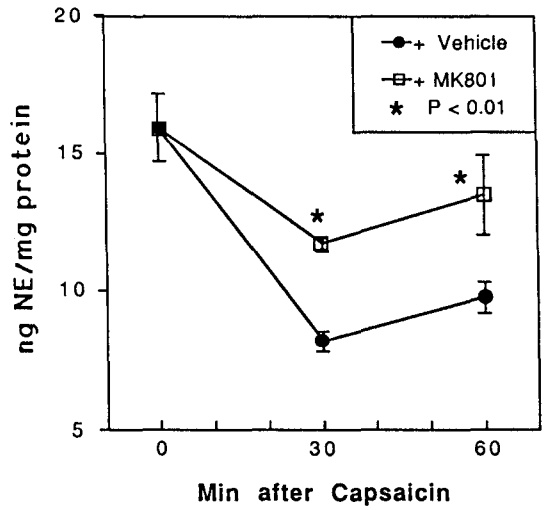

Fig. 4. MK-801 on intrathecal capsaicin-induced NE changes. Spinal cord NE levels were measured from rats conditioned as described from Fig. 3. The value at each point represents mean ± S.E. from 5 animals or more. Asterisks: P < 0.01 between MK-801 and vehicle only groups.

MK-801 and intrathecal capsaicin (Fig. 3, 4)

Pretreatment of MK-801, a non-competitive antagonist of NMDA receptor, reversed the capsaicin effects. The increase in TFR latency by intrathecal capsaicin of (dose = 50 μg) was reversed by the pretreatment of MK-801, 0.5 mg/kg, which was complete by the 60 min point (30 minute and 60 minute points after capsaicin, $p < 0.01$; Fig. 3). Changes in NE contents by capsaicin also were reversed by MK-801 (Fig. 4). MK-801, by itself, did not affect the TFR or NE content significantly (data not shown).

MK-801 and subcutaneous capsaicin (Fig. 5)

Pretreatment with MK-801, 2.5 mg/kg, partially reversed the depletion of NE induced by subcutanous capsaicin of 50 mg/kg (from 6.91 ng/

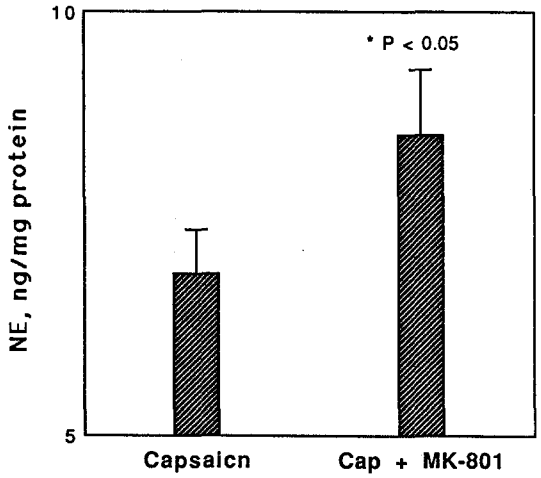

Fig. 5. MK-801 on subcutaneous capsaicin-induced NE changes. MK-801 (2.5 mg/kg) or vehicle were injected i.v. 20 minutes before the subcutaneous injection of capsaicin (50 mg/kg). At the 1 hr point after capsaicin, the spinal cord level of NE was measured. Each value represents mean ± S.E. from 5 animals for capsaicin only and 4 animals for capsaicin plus MK-801.

mg protein ± 0.51 to 8.54 ± 0.77 at 60 minutes after capsaicin injection, $P < 0.05$).

DISCUSSION

The current data showing the increaes of TFR latency and corresponding decrease of NE content induced by intrathecal capsaicin suggest that capsaicin causes central analgesia by activating the NE system in the spinal cord. The effects of capsaicin on non-peptide neurotransmitters such as NE, dopamine, acetylcholine, γ-amino butyric acid, and etc. have been reported to be equivocal at best (for review, Holzer, 1991). But, those studies were chronic or subacute ones equivalent to those for the peptide depletion studies. This is the first report so far of the acute effect of capsaicin on the spinal norepinephrine level. It is plausible that the intrathecally administered capsaicin induces spinal analgesia by activating the noradrenergic system, because there have been accumulated anatomical, electrophysiological and pharmacological evidences that NE is involved in the modulation of pain occurring in the dorsal horn of the spinal cord, especially in layers II and III (Sagen and Proudfit, 1985; and for a review, Proudfit, 1988). A number of cells in this area respond to peripheral noxious stimuli. Nerve terminals and varicosities containing NE were observed in layers II and III, and inotophoresis of NE into this region blocks neuronal activations by noxious stimuli along with the analgesia. Adrenoceptor involved in the pain modulation is thought to be of α_2-subtype because yohimbine, an α_2-blocker, reduces NE-induced analgesia (Sagen and Proudfit, 1985). Although the main source of the spinal NE is considered to be from terminals of NE cells whose cell bodies are at the brain stem and the medulla, the possibility of other sources of NE such as interneurons in the dorsal horn is not ruled out (Proudfit, 1988). Neither, the mode of modulation of NE neurons is clear yet.

Pretreatment with MK-801 obliterated the analgesic effect and reversed the concomitant reduction in the spinal NE level induced by the intrathecal capsaicin administration. This result provides another evidence supporting that the NE system is a part of the descending pain modulating pathway which is in turn under the influence of EAA (Aimone and Gebhart, 1986). So far, the major location of the modulation of the adrenergic activity of the pain modulation axis by EAA has been suggested to be medulla, especially rostral ventromedial area of the medulla (Aimone *et al.*, 1987). But, in our experiment, the capsaicin was introduced directly onto the lumbar section of the spinal cord through a intrathecal catheter inserted 10 cm from the cisterna, in a small volume of the vehicle (10 μl). It is not conceivable that capsaicin might reach the medulla considering its high solubility in lipid. Thus, the site of interaction of MK-801 with capsaicin should be at the spinal cord, although MK-801 was systemically administered.

The systemic administration of capsaicin via subcutaneous route, up to the maximum single dose of 50 mg/kg, did not produce acute analgesia. This observation confirms the previous observations reporting no analgesia or even frequent hyperalgesia in acute phases after the systemic administration of capsaicin (Baumann *et al.*, 1991).

Only previous repeated administrations of capsaicin enough to deplete the central and peripheral substance P elevate the pain threshold in the acute phase after a single dose (Buck and Burks, 1986). Because capsaicin is highly lipid soluble and has the molecular weight of about 300, the differences in the effects on the TFR due to different routes of administrations can not be explained by the restriction in the distribution across the blood-brain barrier. Actually, a pharmacokinetic study reported the higher concentrations in the brains and the spinal cord than in the blood or in the liver after i.v. administration of capsaicin (Saria *et al.*, 1981). In the same study, s.c. administration of capsaicin achieved the CNS concentration as much as the blood level. In our current study, the subcutaneous capsaicin in the bolus dose of 50 mg/kg reduced the spinal cord NE level in the same fashion as in the case of the intrathecal administration. This depletion of NE was reversed by the pretreatment with MK-801, although in less extent. This again evidences that subcutaneously administered capsaicin reaches the spinal cord and affects the adrenergic interneurons as in the case of intrathecal administration. The lack of analgesia with the subcutaneous administration in spite of the equivalent effect on the spinal NE to that with the intrathecal route might be explained as the following: first, the subcutaneous administration of capsaicin irritates the peripheral pain fibers facilitating the primary pain pathway; this facilitation activates the excitatory interneurons or on-cells in the dorsal horn of the spinal cord. The activation of excitatory interneurons in the dorsal horn would offset the analgesia mediated by the activation of off-cells or inhibitory interneurons. If this is true, the comparison of analgesic effects between systemic and intrathecal routes of administration can be employed for assessing the analgesic potency over the side effect of irritation in the course of developing the non-opioid analgesics from various capsaicin derivatives.

Two major explanations of the capsaicin-induced analgesia so far can be summarized as follows: first, the depletion of substance P which is relevant only in the chronic phase but not in the acute phase; second, the depolarized inhibition of the neuronal activity due to the prolonged opening of the cation channels on the neuronal membrane (Bevan and Szolcsanyi, 1990) which could explain acute analgesia but not the chronic because the depolarization does not last for a day or two with the single dose. Our current study adds the third aspect in understanding the analgesic mechanism of capsaicin; the activation of the descending pain modulation. The study also provides another evidence that the EAA-NE axis plays a crucial role in the pain modulation at the spinal cord level and above (Proudfit, 1988).

ACKNOWLEDGMENT

Authors appreciate excellent technical helps of M.A.Namgung, D.S. Choi and Y.J. Lee at the Pharmacology and Toxicology Lab of Asan Institute for Life Sciences, in the biochemical analysis and in the animal operation respectively. Authors also thank Dr. Y. J. C hang for the critical review of the manuscript and valuable comments.

REFERENCES

Aimone LD and Gebhart GF: *Stimulation-produced spinal inhibition from the midbrain in the rat is mediated by an excitatory amino acid neurotransmitter in the medial medulla. J Neurosci 6: 1803-1813, 1986*

Aimone LD, Jones SL and Gebhart GF: *Stimulation-produced descending inhibition from the periaqueductal gray and nucleus raphe magnus in the rat: Mediation by spinal monoamines but not opioids. Pain 31: 123-136, 1987*

Basbaum AL and Fields HL: *Endogenous pain control systems; Brainstem pain pathways and endorphin circuitry. Ann Rev Neurosic 7: 309-338, 1984*

Baumann TK, Simone DA, Shain CN and LaMotte RH: *Neurogenic hyperalgesia: the seach for the primary cutaneous afferent fibers that contribute to capsaicin-induced pain and hyperalgesia. J Neurophysiol 66 (1): 212-227, 1991*

Beitz AJ: *The sites of origin of brain stem neurotensin and serotonin projections to the rodent nucleus raphe magnus. J Neurosci 2: 829-842, 1982*

Bevan S and Szolcsanyi J: *Sensory neuron-specific actions of capsaicin: mechanisms and applications. Trends in Pharmacol Sci 11 (8): 330-333, 1990*

Bradford MM: *A rapid and sensitive method for the*

quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 72: 248-254, 1976

Buck SH and Burks TF: *The neuropharmacology of capsaicin, review of some recent observations, Pharmacological Reviews 38 (3): 179-226, 1986*

Buck SH, Desknukh PP, Yammamura HI and Burks TF: *Thermal analgesia and substance P depletion induced by capsaicin guinea pigs. Neuorscience 6: 2217-2222, 1981*

Buck SH, Walsh JH, Davis TP, Brown RMR, Yamamura HI and Burks TF: *Characterization of the peptide and sensory neurotoxic effects of capsaicin in the guinea pig. J Neurosci 3: 2064-2074, 1983*

Fields HL, Heinricher MM and Mason P: *Neurotransmitters in nociceptive modulatory circuits. Ann Rev Neurosci 14: 219-245, 1991*

Gamse R, Holzer P and Lembeck F: *Indirect evidence for presynaptic location of opiate receptors on chemosensitive primary sensory neurons. Naunyn-Schmiedebergs Arch Pharmakol 308: 281-285, 1979a*

Gamse R, Leeman SE, Holzer P and Lembeck F: *Differential effects of capsaicin on the content of somatostatin, substance P, and neurotensin in the nervous system of the rat. Nauny-Schmiedebergs Arch Pharmakol 317: 140-148, 1981*

Gamse R, Molnar A and Lembeck F: *Substance P release from spinal cord slices by capsaicin. Life Sci 25: 629-636, 1979b*

Hamon M, Bourgoin S, le Bars D and Cesselin F: *In vivo and in vitro release of central neurotransmitters in relation to pain and analgesia. Prog Brain Res 77: 431-444, 1988*

Hayes AG, Skingle J and Tyers MB: *Effects of single doses of capsaicin on nociceptive thresholds in the rodents. Neuropharmacol 20: 505-511, 1981*

Hayes AG and Tyers MB: *Effects of capsaicin on nociceptive heat, pressure and chemical thresholds and substance P levels in the rat. Brain Res 189: 561-564, 1980*

Holzer P: *Capsaicin: Cellular targets, mechanisms of action, and selectivity for thin sensory neurons. Pharmacol Rev 43 (2): 143-201, 1991*

Jancso G, Kiraly E and Jancso-Gabor A: *Pharmacologically induced selective degeneration of chemosensitive primary sensory neurons. Nature (Lond.) 270: 741-742, 1977*

Marchand JE and Hagino N: *Afferents to the periaqueductal gray in the rat. A horseradish peroxidase study. Neuroscience 9: 95-106, 1983*

Marsden CA and Joseph MH: *Biogenic amines. HPLC of small molecules (ed. CK Lim) IRL Press: 29-47, 1986*

Mayer N, Gamse R and Lembeck F: *Effect of capsaicin pretreatment on substance P binding to synaptic vesicles. J Neurochem 35: 1238-1241, 1980*

Miller MS, Buck SH, Sipes G and Burks TF: *Capsaicinoid-induced local and systemic antinociception without substance P depletion. Brain Res 244: 193-197, 1982*

Nagy JI, Iversen LL, Goedert M, Chapman D and Hunt SP: *Dose dependent effects of capsaicin on primary sensory neurons in the neonatal rat. J Neurosci 3: 399-406, 1983*

Panerai AE, Martini A, Locatelli V and Mantegazza P: *Capsaicin decreases beta-endorphin hypothalamic concentrations in the rat. Pharmacological Res Com 15: 825-832, 1983*

Pristley JV, Bramwell S, Bucher LL and Cuello AC: *Effect of capsaicin on neuropeptides in areas of terminals of primary sensory neurons. Neurochemistry Intern 4: 57-65, 1982*

Proudifit HK: *Pharmacologic evidence for the modulation of nociception by noradrenergic neurons. Prog Brain Res 77: 357-370, 1988*

Sagen J and Proudfit HK: *Effect of intrathecally administered noradrenergic antagonist on nociception in the rat. Brain Res 310: 295-301, 1985*

Saria A, Skofitsch G, Lembeck F: *Distribution of capsaicin in rat tissues after systemic administration. J Pharm Pharmacol 24: 273-275, 1981*

Sinclair JG, Main CD and Lo GF: *Spinal vs. supraspinal actions of morphine on the rat tail-flick reflex. Pain 33: 357-362, 1988*

Skagerberg G and Bjorklund A: *Topographic principles in the spinal projections of serotonergic and non-serotonergic brainstem neurons in the rat. Neuroscience 15: 445-480, 1985*

Stoscheck CM: *Quantitation of Protein. Methods in Enzymology 182: 50-68, 1990*

Sunol C, Tusell JM, Gelpf E and Rodriguez-Farre E: *Regional concentrations of GABA, serotonin and noradrenaline in brain at onset of seizures induced by lindane. Neuropharmacology 27 (7): 677-681, 1988*

Yirus RM and Gebhart GF: *Minireview-pharmacological actions of capsaicin. Apparent involvement of substance P and serotonin. Life Science 25: 1273-1284, 1979*

Wood JN, Winter J, James IF, Rang HP, Yeats J and Bevan S: *Capsaici-induced ion fluxes in Dorsal Root Ganglion Cells in Culture. J Neurosci 8 (9): 3208-3220, 1988*

=국문초록=

Capsaicin에 의한 척수 수준에서의 급성 진통효과와 Norepinephrine의 변화

울산대학교 의과대학 약리학교실, *아산생명과학연구소 약리독물학 연구실

박 형 섭 · *박 경 표

Capsaicin의 중추신경계에 대한 진통효과를 척수 수준에서 규명하고, 이에 대한 norepinephrine (NE)계의 역할을 규명하기 위하여 tail flick reflex (TFR) latency time의 증가와 척수 내 NE 양의 변화를 측정하였다. 웅성의 Sprague-Dawley 백서를 pentobarbital sodium으로 마취를 하여 femoral vein cannulation과 intrathecal catheterization을 하였고, 이를 통하여 시험약제를 투여하였다. TFR은 capsaicin 또는 용매 투여전, 투여후 10분, 30분, 60분, 때로는 2시간에 측정하였다. MK-801은 capsaicin 투여전 20분에 femoral vein을 통하여 주입하였다. 35～150 μg의 capsaicin을 intrathecal로 주었을 때, TFR latency가 최고치인 7초를 넘어 정상인 2.9초에 비해 100% 이상의 증가를 보였고, 척수 내 NE은 16 ng/mg protein에서 7 ng/mg protein으로 50% 이상 감소하였다. 이와 같은 TFR latency의 증가와 NE의 감소는 전 실험기간 (capsaicin 투여후 2시간)에 걸쳐 관찰되었다. 반면, 50 mg/kg의 capsaicin을 피하로 전신투여 하였을 경우에 척수 NE은 같은 변화를 보였으나 TFR latency의 차이는 없었다. 또한, 0.5 mg/kg의 MK-801를 i.v.로 전처치 하였을 때, intrathecal capsaicin에 의한 TFR latency의 증가와 척수 내 NE의 감소가 모두 억제되었다. 이상의 결과는 capsain이 excitatory aminoacid (EAA)계 - NE계 - 척수 dorsal horn으로 이루어진 동통전달의 하행성 억제계 축의 활성을 항진시켜 진통효과를 가져옴을 보여준다. 또한, capsaicin의 피하 주사시에 진통효과를 볼 수 없음을 말초 동통전달신경의 흥분에 의한 중추 동통전달계 활성의 촉진이 진통효과를 상쇄함을 암시한다.