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Antinociceptive effects of neonatal capsaicin in rats with adjuvant arthritis

Akiyoshi Hara, Tsukasa Sakurada, Shinobu Sakurada, Hisao Matsumura, and Kensuke Kisara

Department of Pharmacology, Tohoku College of Pharmacy, 4-4-1 Komatsushima, Sendai 983, Japan

Summary. Rats were treated with capsaicin (50 mg/kg, SC) either on the second day or on the second and third days of life. A significant attenuation of the responses to noxious stimuli was obtained in the capsaicin treated animals as measured by the hot-plate or paw pressure tests but not by the tail-flick test. Furthermore, neonatal capsaicin produced a significant reduction of response in the formalin test. Capsaicin reduced the reaction latency in rats with adjuvant arthritis as measured by the hot-plate and paw pressure tests, though capsaicin did not alter the overall time course of the response to Freund's adjuvant. Capsaicin also attenuated the weight loss or the decreased ambulatory and rearing behaviours which occurred in the control animals with adjuvant arthritis. It is suggested that neonatal treatment with capsaicin may relieve the responsiveness to long-lasting nociceptive stimuli by adjuvant in rats.

Key words: Neonatal capsaicin – Antinociceptive effects – Adjuvant arthritis – Substance P – Rat

Introduction

We have already reported that synthetic pure capsaicin or dihydrocapsaicin produces a marked elevation of neuronal activity in areas of the thalamus which respond to noxious stimuli (Ando et al. 1980). It was also found by the same authors that tachyphylaxis was occurred by the repeated administration of capsaicin or dihydrocapsaicin as observed electrophysiologically. Recently, it has been shown that capsaicin depletes the undecapeptide substance P (SP) from skin and from primary afferent neurons in rats and guinea-pigs (Jessell et al. 1978; Gamse et al. 1980, 1981a, b; Hayes and Tyers 1980; Nagy et al. 1980; Buck et al. 1981; Cuello et al. 1981; Lembeck and Donnerer 1981). SP has been implicated as a neurotransmitter in primary sensory neurons in the dorsal horn of the spinal cord and specifically associated with nociception (Henry 1976; Randić and Miletić 1977). Capsaicin specifically acts on the primary sensory neurons without affecting the level of SP in the ventral horn of the spinal cord or in the brain except for medulla oblongata (Gamse et al. 1980, 1981b). The experimental results in 2 day old rats treated with capsaicin showed that up to 95% small diameter fibers are loss (Jancsó et al. 1980; Larsson and Nickels 1980) whilst similar treatment of neonates with capsaicin results in a permanent reduction in the spinal cord content of SP (Gamse et al. 1980; Nagy et al. 1980; Hayes et al. 1980; Helke et al. 1981). However, in adult rats, repeated doses of capsaicin cause a loss of SP from the dorsal horn of the spinal cord, but there is no nerve fiber degeneration (Jessell et al. 1978; Hayes and Tyers 1980). There are inconsistent results in published reports concerning the nociceptive response in rats neonatally pretreated with capsaicin (Holzer et al. 1979; Faulkner and Growcott 1980; Hayes et al. 1980, 1981; Hill et al. 1980; Nagy et al. 1980; Cervero and McRitchie 1981). In the present paper, we examined the effects on the response in the tail-flick, hot-plate, paw pressure and formalin tests, when capsaicin was administered to newborn rats. There are several behavioural reports that adjuvant arthritis may present an animal model of chronic pain in rats (Newbould 1963; Colpaert 1978, 1979; Costa et al. 1981). Therefore, the present investigation was also carried out to determine the effects of neonatally administered capsaicin on adjuvant-induced arthritis.

Offprint requests to T. Sakurada at the above address

Materials and methods

Capsaicin treatment. In all experiments, male Wistar rats were injected subcutaneously at the dorsum neck with either vehicle or capsaicin (Merck, Darmstadt, FRG). The rats were supplied with food and water *ad libitum* and kept on a 12-h light-dark cycle. Capsaicin was suspended in a vehicle consisting of 10% ethanol, 10% Tween 80 in saline. Control rats received only the vehicle. For behavioural observations, one group of two-day-old rats was given capsaicin once (50 mg/kg, SC) and the other group of neonate rats was given capsaicin twice (50 mg/kg, SC, 2 days) on the 2nd and 3rd days of life, i.e. one injection each on two subsequent days.

Nociceptive responses. Nociceptive responses were determined in the rats at 3–4 months old. We used four different tests; the tail-flick, hot-plate, paw pressure and formalin tests. In the tail-flick test, the latency of the tail-flick response produced by radiant heat from a projector bulb focused to a segment 2 cm from the tip of the tail was determined. In the hot-plate test, the reaction time of the response was determined with a steel plate (27 × 30 cm) maintained at a temperature of 54° C. "Front paw licking" and "hind paw licking or stamping" were taken as nociceptive response to noxious heat. Cut-off time of 15 s and 20 s was used in the tail-flick and hot-plate tests, respectively. In the paw pressure test, mechanical nociceptive thresholds were determined by applying the pressure to both hind paws and the level of pressure threshold evoking vocalization or a strong strug-

gling behaviour was noted using an "Analgesy-meter" (Ugo Basile, Milan). In the tail-flick, hot-plate and paw pressure tests, each rat was tested 3 times at 24 h intervals and the average of the 3 values was taken as nociceptive thresholds. In the formalin test, each animal was allowed to explore the observation cage (28 × 35 cm) for a period of 15 min, 5% of formalin (50 µl/animal) was injected subcutaneously into the main pad of the right hind paw and the chemical nociceptive rating score was assessed for 60 min according to the following 4-point scale (Dubuisson and Dennis 1977); a rating of 0 was given when an injected hind paw was in complete contact wiith the floor surface; a rating of 1 was given when an injected hind paw was only minimum contact with the floor or it was held very near to the floor; a rating of 2 was given when an injected hind paw was held off the floor and close the body; a rating of 3 was given when an injected hind paw was licked. Rats were observed in each 5-min interval over a period of 1 h; each rat was taken a mean score of 12 times for 60 min. The final rating score of each animal was expressed as the average of these 12 values. The number of licking of the injected site was also counted throughout the experiment. The values represent the total number of licking for 60 min.

Preparation and inoculation of Mycobacterium tuberculosis. After the nociceptive response was assessed by means of the hot-plate and paw pressure tests in rats neonatally pretreated with capsaicin, adjuvant arthritis was induced by a subplantar injection of 0.1 ml of a 0.5% suspension of *Mycobacterium tuberculosis* (MT) in paraffin oil into the main pad of the right hind paw. Another group which was not pretreated with capsaicin also received the suspension of MT. On days 1, 3, 7, 14, 21 and 28 after inoculation, nociceptive heat thresholds were measured using the hot-plate (54° C) test as described above, and mechanical paw pressure was applied to the right hind paw with arthritis induced by MT. The development of the adjuvant arthritis by MT was followed by measuring foot thickness of both hind feet with a micrometer across the sagittal section and changes in body weight of rats by MT were also recorded on the days when the nociceptive tests were performed. The ambulatory and rearing activities of rats put in the open-field apparatus (diameter 60 cm, height 50 cm) were quantified by counting the number of ambulations and rearings occurring within 3 min (Hall 1934). Data were analyzed statistically with the two tailed Student's *t*-test and *P* value of 0.05 or less was considered significant.

Results

Effect of neonatal administration of capsaicin on nociceptive responses produced by heat, mechanical and chemical stimuli

The results obtained in the tests using noxious heat after capsaicin treatment are shown in Figs. 1 and 2. There were no substantial changes in tail-flick latency in capsaicin-pretreated rats. In contrast, capsaicin treatment had significant effects on the latencies for licking of the hind paws but not of the fore paws in the hot-plate test (Fig. 2). In the paw pressure test, pretreatment of neonatal rats with capsaicin produced a marked increase of the threshold (Fig. 3). As shown in Figs. 2 and 3, the intensity of antinociceptive effects after one or two administration of capsaicin was

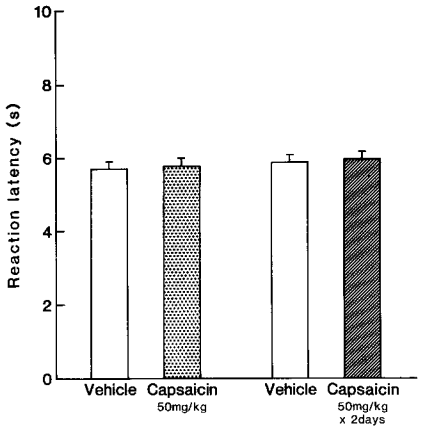

Fig. 1. Effects of neonatal administration of capsaicin on nociceptive heat thresholds (tail-flick test) in rats. Animals were tested from 3–4 months after neonatal capsaicin administration. Each value is the mean ± SEM, $N = 8-13$

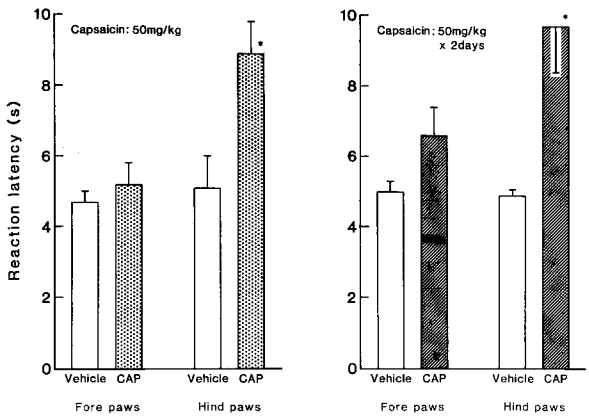

Fig. 2. Effects of neonatal administration of capsaicin on nociceptive heat thresholds (hot-plate test) in rats. Animals were tested from 3–4 months after neonatal capsaicin administration. Each value is the mean ± SEM, $N = 8-14$. $^{*}P<0.01$ compared to vehicle control

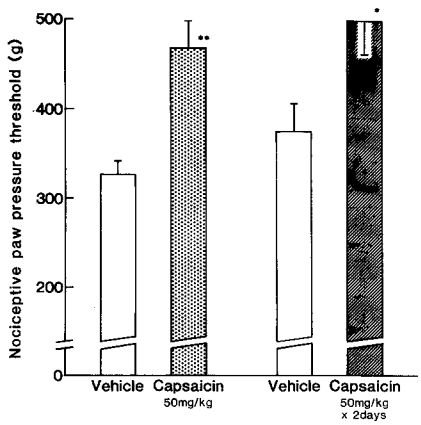

Fig. 3. Effects of neonatal administration of capsaicin on nociceptive mechanical thresholds in rats. Animals were tested from 3–4 months after neonatal capsaicin administration. Each value is the mean ± SEM, $N = 8-15$. $^{*}P<0.05$, $^{**}P<0.001$ compared to vehicle control

almost the same. Furthermore, the number of licking and the average rating score in the formalin test were less in the rats treated with a single dose of capsaicin than in the vehicle control (Fig. 4). This difference is statistically significant at $P<0.001$ considering both criteria.

Effect of neonatal administration of capsaicin on the adjuvant-induced arthritis

The development of the adjuvant arthritis in capsaicin pretreated and vehicle control rats was followed by measuring the changes in foot thickness. There was no statistical difference in the thickness between the two groups. Fourteen days after inoculation, inflamed lesion was detected on the left hind paw, which began to increase in thickness. Before adjuvant injection, there was no significant difference on spontaneous ambulatory and rearing activities in capsaicin pretreated and vehicle control rats (Fig. 5). However, the spontaneous activities were much higher in capsaicin treated rats than vehicle treated controls on the 7th and 21st days after inoculation, for example, the number of ambulation and rearing on the 7th day was: 12.9 ± 1.7 and 3.6 ± 0.8 for capsaicin treated rats, and 6.7 ± 1.1 and 0.6 ± 0.2 for vehicle treated controls, respectively. After inoculation, the thresholds as measured by the two nociceptive tests (hot-plate and paw pressure tests) were significantly higher in capsaicin treated rats than in vehicle treated controls (Fig. 6). In particular, even if the value was expressed as percent of reaction latency compared with the value before adjuvant injection, it was significantly higher latencies for licking of the hind paws in capsaicin treated rats than vehicle controls on the 7th and 14th days after inoculation in the hot-plate test. Similarly, a significant difference was obtained in the paw pressure test on the 1st day after inoculation. The body weight loss induced by adjuvant was not significantly different in two groups during the first 7 days. However, on the 14th, 21st and 28th days, the body weight loss was much smaller in capsaicin pretreated rats as compared with vehicle treated controls.

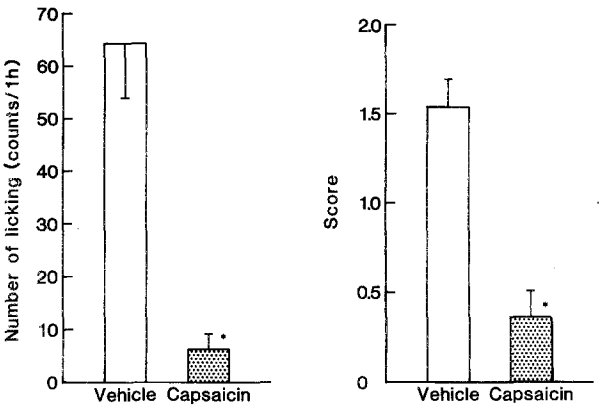

Fig. 4. Effects of neonatal administration of capsaicin (50 mg/kg, SC on day 2 of life) on nociceptive chemical thresholds in rats. Animals were tested from 3–4 months after neonatal administration. Each value is the mean ± SEM, $N = 6$. $^*P<0.001$ compared to vehicle control

Discussion

The present study shows that pretreatment of newborn rats with capsaicin produced a marked decrease of nociceptive response in the formalin and paw pressure tests, and a prolongation of the reaction time in the hot-plate test. It has shown firstly that rats treated neonatally with capsaicin showed an elevation of the threshold to noxious heat (Holzer et al. 1979; Hill et al. 1980; Nagy et al. 1980), while other groups have not been able to establish a significant change of reaction latency using the tail-flick test (Buck et al. 1982a), or the tail-immersion test (Hayes et al. 1980, 1981). Here, in the tail-flick test, we have also observed no indication of increased reaction latency even in rats pretreated neonatally with a large dose of capsaicin. On the other hand, capsaicin treatment produced a significant prolongation of the reaction time in the hot-plate test when taken as hind paw licking or stamping. This is in agreement with studies of Nagy et al. (1981) that the intrathecal capsaicin treatment had marked effects on the latencies for licking of the hind paws but not of the fore paws in the hot-plate test, though the injection route and the rat age were different. A methodological question should be taken into consideration when comparing

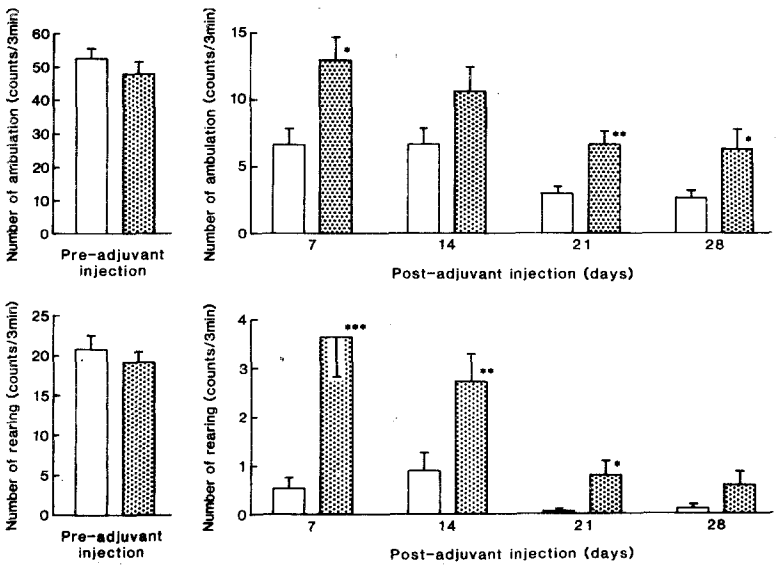

Fig. 5
Effects of neonatal administration of capsaicin (50 mg/kg, SC on day 2 of life) on ambulation and rearing in adjuvant-induced arthritic rats. Animals were tested from 3–4 months after neonatal capsaicin administration prior to adjuvant treatment. The dotted columns represent capsaicin-treated rats and the open columns vehicle-treated rats. Each value is the mean ± SEM, $N = 17$. $^*P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ compared to vehicle control

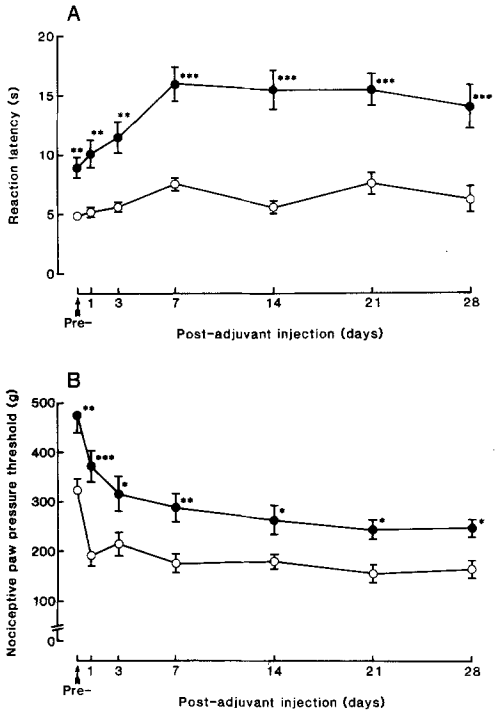

Fig. 6. Effects of neonatal administration of capsaicin (50 mg/kg, SC on day 2 of life) on nociceptive heat (**A**: hot-plate test) and mechanical pressure (**B**: paw pressure test) thresholds in adjuvant-induced arthritic rats. Animals were tested from 3–4 months after neonatal capsaicin administration prior to adjuvant treatment. The closed circles represent capsaicin-treated rats and the open circles vehicle-treated rats. Each value is the mean ± SEM, $N = 8-15$. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared to vehicle control

nociceptive responses from the hot-plate test; some studies demonstrated a higher threshold for capsaicin treated rats by measuring the latency for licking of the hind paws (Gamse 1982; Nagy and Kooy 1983), whereas the other group took the latency for licking of the fore paws as the measure of nociceptive threshold and reported no change in threshold (Cervero and McRitchie 1981; Hayes et al. 1981). On the other hand, Holzer et al. (1979) found significantly higher threshold in rats neonatally treated with capsaicin by determining the latency for the fore paw licking and jumping reaction. The temperature in the hot-plate test also seems important; when using the higher 55° C, small elevation of the threshold could be obscure by a faster heat transfer process and account for the inconsistent evidence. Therefore, the source of these inconsistencies may be due to methodological differences in nociceptive threshold testing. The different results as measured by the two tests of nociceptive heat stimuli may be interpreted in terms of the assumption that the tail-flick test is mainly a spinally mediated reflex, whereas the hot-plate test involves more complex motor responses, for instance, the licking of the fore paw, the hind paw or stamping.

The results confirm that capsaicin treatment of neonatal rats caused a significant increased threshold of nociceptive paw pressure and formalin induced stimuli. Particularly, chemical nociception produced by formalin was greatly reduced. The present result obtained shows that treatment with capsaicin was much more effective in the formalin test than in acetylcholine-induced mouse writhing reaction test (approximately 50% inhibition from our calculation) reported by Hayes et al. (1981). These results agree with the report of Jancsó et al. (1977) that neonatal capsaicin treatment results in a completely irreversible impairment of the function of chemosensitive primary sensory neurones.

The antinociceptive effects of capsaicin may partially be explained by degeneration of unmyelinated primary afferent fibers and a permanent reduction of the putative peptide neurotransmitter SP in the dorsal horn of the spinal cord (Jancsó et al. 1977; Holzer et al. 1979; Nagy et al. 1980; Helke et al. 1981). Recently, some investigators explained that other peptides were present in primary sensory neurons, such as somatostatin (SOM) (Hökfelt et al. 1976), cholecystokinin (CCK) (Lundberg et al. 1978; Larsson and Rehfeld 1979) and vasoactive intestinal polypeptide (VIP) (Lundberg et al. 1978). Jancsó et al. (1981) indicated that capsaicin decreased not only SP but also SOM, CCK and VIP like peptides present in the central branches of primary sensory neurons in the spinal cord. They suggested that the effects of capsaicin are not confined to SP immunoreactive primary sensory neurons. However, Buck et al. (1982b) reported that SP level in primary afferent neurons is markedly reduced while levels of other sensory neurons neuropeptides (SOM, CCK, VIP) do not appear to be affected. Therefore, the mechanism of action of capsaicin seems not to be apparent yet. It should be taken into consideration that the degeneration of unmyelinated afferents was not in a complete loss but a loss of 60–70% (Jancsó et al. 1977; Scadding 1980), though there is disagreement concerning the capsaicin effects on the number of unmyelinated fiber (Jancsó et al. 1980; Lasson and Nickels 1980). Judging from the present results, it is likely that there may not be in absolute loss of unmyelinated afferent fibers even when a large dose of capsaicin was treated neonatally. Because there is no significant difference of antinociceptive effects between a single and repeated capsaicin treatment.

Recent biochemical and behavioural studies demonstrated that arthritis by complete Freund's adjuvant in rats is associated with a state of chronic pain and the rats with arthritis are hypersensitive to the effect of morphine (Oliveras et al. 1979; Weil-Fugazza et al. 1979). It has been shown that the latency of the tail withdrawal from a hot water bath was greatly increased in arthritis rats (Colpaert 1979). In the present experiment, however, the response latency was elevated slightly in vehicle control rats with arthritis in the hot-plate test. It may be due to some differences of experimental procedure, e.g. nociceptive assay or inoculation method. The present data demonstrated that pretreatment of capsaicin in neonatal rats is effective on adjuvant-induced noxious stimuli. Firstly, neonatal capsaicin reduced the body weight loss in rats with adjuvant arthritis. Since the magnitude of inflamed swelling produced by adjuvant was not altered between capsaicin and vehicle control, capsaicin seems evident to be different from the effect of anti-inflammatory agents which could inhibit the swelling of the adjuvant-injected hind paw. A recent report indicated that acute treatment of capsaicin decreased loss of body weight or impairment of growth in adult rats with adjuvant arthritis (Colpaert et al. 1983). Pircio et al. (1975) reported that narcotics including morphine which possess analgesic activity were able to block arthritis rat vocalization without decreasing spontaneous motor activity. Moreover, the present results showed that the spontaneous ambulatory and rearing activities were much higher in capsaicin pre-

treated rats than vehicle controls after adjuvant. Therefore, these results suggest that condition of noxious stimuli which caused body weight loss or decreased spontaneous motor activity after adjuvant may be relieved by neonatal treatment of capsaicin.

Secondly, the hot-plate and paw pressure tests revealed that a significant elevation of the nociceptive threshold was observed in capsaicin pretreated rats with arthritis in comparison with control arthritic rats. Similar results have been reported in rats with yeast-induced inflammation by using the paw pressure test for the assessment of the threshold of nociceptive response (Faulkner and Growcott 1980).

As regards the biochemical changes in the spinal cord of arthritic rats, it is to be mentioned that adjuvant treatment resulted in increased 5-hydroxytryptamine turnover (Weil-Fugazza et al. 1979) and in elevated level of Met-enkephalin (Cesselin et al. 1980) compared to normal rats. Recently, the marked increase of SP in the sciatic nerve of rats with arthritis, but not in the dorsal spinal cord or dorsal root ganglia was shown by Lembeck et al. (1981). Capsaicin also attenuated this phenomenon (Colpaert et al. 1983).

References

Andoh R, Shima K, Miyagawa T, Sakurada S, Kisara K, Osawa K, Takahashi M (1980) Excitatory effects of dihydrocapsaicin on nociceptive neurons in the medial thalamus. Jpn J Pharmacol 30:599–605

Buck SH, Deshmukh PP, Yamamura HI, Burks TF (1981) Thermal analgesia and substance P depletion induced by capsaicin in guinea-pigs. Neuroscience 6:2217–2222

Buck SH, Miller MS, Burks TF (1982a) Depletion of primary afferent substance P by capsaicin and dihydrocapsaicin without altered thermal sensitivity in rats. Brain Res 233:216–220

Buck SH, Walsh JH, Yamamura HI, Burks TF (1982b) Neuropeptides in sensory neurons. Life Sci 30:1857–1866

Cervero F, McRitchie HA (1981) Neonatal capsaicin and thermal nociception: a paradox. Brain Res 215:414–418

Cesselin F, Montastruc JL, Gros C, Bourgoin S, Hamon M (1980) Met-enkephalin levels and opiate receptors in the spinal cord of chronic suffering rats. Brain Res 191:289–293

Colpaert FC (1978) Long-term suppression of pain by narcotic drugs in the absence of tolerance development. Arch Int Pharmacodyn Ther 236:293–295

Colpaert FC (1979) Can chronic pain be suppressed despite purported tolerance to narcotic analgesia? Life Sci 24: 1201–1210

Colpaert FC, Donnerer J, Lembeck F (1983) Effects of capsaicin on inflammation and on the substance P content of nerve tissues in rats with adjuvant arthritis. Life Sci 32:1827–1834

Costa MDC, Sutter PD, Gybels J, Hees JV (1981) Adjuvant-induced arthritis in rats: a possible animal model of chronic pain. Pain 10:173–185

Cuello AC, Gamse R, Holzer P, Lembeck F (1981) Substance P immunoreactive neurons following neonatal administration of capsaicin. Naunyn-Schmiedeberg's Arch Pharmacol 315: 185–194

Dubuisson D, Dennis SG (1977) The formalin test: a quantitative study of the analgesic effects of morphine, meperidine, and brain system stimulation in rats and cats. Pain 4:161–174

Faulkner DC, Growcott JW (1980) Effects of neonatal capsaicin administration on the nociceptive response of the rat to mechanical and chemical stimuli. J Pharm Pharmacol 32: 656–657

Gamse R, Holzer P, Lembeck F (1980) Decrease of substance P in primary afferent neurons and impairment of neurogenic plasma extravasation by capsaicin. Br J Pharmacol 68:207–213

Gamse R, Lackner D, Gamse G, Leeman SE (1981a) Effect of capsaicin pretreatment on capsaicin-evoked release of immunoreactive somatostatin and substance P from primary sensory neurons. Naunyn-Schmiedeberg's Arch Pharmacol 316:38–41

Gamse R, Leeman SE, Holzer P, Lembeck F (1981b) Differential effects of capsaicin on the content of somatostatin, substance P and neurotensin in the nervous system of the rat. Naunyn-Schmiedeberg's Arch Pharmacol 317:140–148

Hall CS (1934) Defecation and urination as measures of individual differences in emotionality. J Comp Psychol 18:385–403

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

Hayes AG, Scadding JW, Skingle M, Tyers MB (1980) Effects of neonatally administered capsaicin on nociceptive thresholds and dorsal horn substance P levels in conscious rats and mice. J Physiol 305:99p

Hayes AG, Scadding JW, Skingle M, Tyers MB (1981) Effects of neonatal administration of capsaicin on nociceptive thresholds in the mouse and rat. J Pharm Pharmacol 33:183–185

Helke CJ, DiMicco JA, Jacobowitz DM, Kopin IJ (1981) Effect of capsaicin administration to neonatal rats on the substance P content of discrete CNS regions. Brain Res 222:428–431

Henry JL (1976) Effects of substance P on functionally identified units in cat spinal cord. Brain Res 114:439–451

Hill RG, Hoddinott ML, Keen PM (1980) Action of substance P on trigeminal nucleus caudalis neurones in capsaicin-treated rats. In: Marsan CA, Traczyk WZ (eds) Neuropeptides and neural transmission, vol 7. Raven Press, New York, pp 31–41

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

Holzer P, Jurna I, Gamse R, Lembeck F (1979) Nociceptive threshold after neonatal capsaicin treatment. Eur J Pharmacol 58:511–514

Jancsó G, Kiraly E, Lancsó-Gabor A (1977) Pharmacologically induced selective degeneration of chemosensitive primary sensory neurons. Nature 270:741–743

Jancsó G, Kiraly E, Jancsó-Gabor A (1980) Chemosensitive pain fibers and inflammation. Int J Tiss React 2:57–66

Jancsó G, Hökfelt T, Lundberg JM, Kiraly E, Halász N, Nilsson G, Terenius L, Rehfelt J, Steinbusch H, Verhofstad A, Elde R, Said S, Brown M (1981) Immunohistochemical studies on the effect of capsaicin on spinal and medullary peptide and monoamine neurons using antisera to substance P, gastrin/CCK, somatostatin, VIP, enkephalin, neurotensin and 5-hydroxytryptamine. J Neurocytol 10:963–980

Jessell TM, Iversen LL, Cuello AC (1978) Capsaicin-induced depletion of substance P from primary sensory neurons. Brain Res 151:183–188

Larsson LI, Rehfeld JF (1979) Localization and molecular heterogeneity of cholecystokinin in the central and peripheral nervous system. Brain Res 165:201–218

Lawson SN, Nickels SM (1980) The use of morphometric techniques to analyse the effect of neonatal capsaicin treatment on the rat dorsal root ganglia and dorsal roots. J Physiol 303:12p

Lembeck F, Donnerer J (1981) Time course of capsaicin-induced functional impairments in comparison with changes in neuronal substance P content. Naunyn-Schmiedeberg's Arch Pharmacol 316:240–243

Lembeck F, Donnerer J, Colpaert FC (1981) Increase of substance P in primary afferent nerves during chronic pain. Neuropeptides 1:175–180

Lundberg JM, Hökfelt T, Nilsson G, Terenius L, Rehfelt J, Elde R, Said S (1978) Peptide neurons in the vagus, splanchnic and sciatic nerves. Acta Physiol Scand 104:499–501

Nagy JI, Vincent SR, Staines WA, Fibiger HC, Reisine TD, Yamamura HI (1980) Neurotoxic action of capsaicin on spinal substance P neurons. Brain Res 186:435–444

Nagy JI, Emson PC, Iversson LL (1981) A re-evaluation of the neurochemical and antinociceptive effects of intrathecal capsaicin in the rat. Brain Res 211:497–502

Nagy JI, Kooy D (1983) Effects of neonatal capsaicin treatment on nociceptive thresholds in the rat. J Neurosci 3:1145–1150

Newbould BB (1963) Chemotherapy of arthritis induced in rats by mycobacterial adjuvant. Br J Pharmacol 21:127–136

Oliveras JL, Bruxelle J, Clot AM, Besson JM (1979) Effects of morphine and naloxone on painful reaction in normal and chronic suffering rats. Neurosci Lett suppl 3:S263

Pircio AW, Fedele CT, Bierwagen ME (1975) A new method for the evaluation of analgesic activity using adjuvant-induced arthritis in the rat. Eur J Pharmacol 31:207–215

Randić M, Miletić V (1977) Effect of substance P in cat dorsal horn neurons activated by noxious stimuli. Brain Res 128:164–169

Scadding JW (1980) The permanent anatomical effects of neonatal capsaicin on somatosensory nerves. J Anat 131:473–484

Theriault E, Otsuka M, Jessell T (1979) Capsaicin-evoked release of substance P from primary sensory neurons. Brain Res 170:209–213

Weil-Fugazza J, Godefroy F, Besson JM (1979) Changes in brain and spinal tryptophan and 5-hydroxyindole acetic acid levels following acute morphine administration in normal and arthritic rats. Brain Res 175:291–301

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