Indian J Physiol Pharmacol 2002; 46 (2) : 249–251

NIFEDIPINE POTENTIATES GABAPENTIN ANTINOCICEPTION IN RATS

R. K. DIXIT AND V. K. BHARGAVA*

Department of Pharmacology,
Postgraduate Institute of Medical Education & Research,
Chandigarh – 160 012

(Received on January 13, 2001)

Abstract : To evaluate the involvement of Ca^{++} channels in Gabapentin antinociception. In healthy male albino rats formalin (50 µl, 5%) was injected at the planter surface of the paw. Pain score was calculated. Antinociceptive effect of (10, 30 mg/kg) gabapentin and (3, 10 mg/kg) nifedipine alone and on co-administration of sub analgesic doses was studied 30 minutes after formalin injection and reduction in pain scores was calculated. Gabapentin (30 mg/kg) and nifedipine (10 mg/kg) reduced the pain score in formalin injected rats. Gabapentin (10 mg/kg) and nifedipine (3 mg/kg) given alone did not modify pain score, however, on co-administration they significantly reduced the pain score. Study provides evidence of involvement of Ca^{++} channels in gabapentin antinociception.

Key words : nifedipine gabapentin antinociception

INTRODUCTION

Gabapentin (GBP) a newer antiepileptic drug is known to possess antinociceptive effect in various experimental models of pain (1). In recent years clinical trials have suggested that gabapentin is effective in different neuropathic pain syndromes including painful diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia (2). Gabapentin is structurally related to the neurotransmitter γ-aminobutyric acid (GABA), but does not interact with either $GABA_A$ or $GABA_B$ receptors. Although a number of possible mechanisms have been hypothesized, the mechanisms involved in gabapentin antinociception are not well understood (3). However, evidence are accumulating which suggest that Ca^{++} channel interactions might by involved in GBP-induced activity because gabapentin has been shown to bind with alpha 2 delta subunits of calcium channels (4). Calcium ions play an important role in neurotransmission and calcium channels are targets for a variety of neurotransmitters. Calcium seems to play an important role in the endogenous regulation of pain sensitivity (5).

Nifedipine (NIF) one of the members of dihydropyridine calcium channel blockers is used for the treatment of hypertension and peripheral vascular diseases. Nifedipine on its own has shown to possess antinociceptive effect as well as it potentiates the antinociceptive actions of opioids (6, 7). However, it has been proposed that GBP

*Corresponding Author

does not involve the opioidergic pathway for its antinociceptive activity (3). Present study was therefore planned to evaluate the interaction of nifedipine and gabapentin in antinociception in rats using formalin test (8), which resembles more closely to the clinically experienced pain (9).

METHODS

The study was done in healthy male albino wistar rats weighing 200–250 gm. Animals were obtained from central animal house facility PGIMER Chandigarh and were kept under standard laboratory conditions with diet and water ad libitum. All experiments were performed between 8.00 and 12.00 hours in a noise free room at temperature ranging between 25–30°C. Rats were divided into 8 groups of 8 animals each and received drugs as follows: group 1, saline 2 ml/kg, s.c.; group 2, dimethylsulfoxide (DMSO) 2 ml/kg, ip; group 3, morphine 3 mg/kg, s.c.; group 4, gabapentin 10 mg/kg, s.c.; group 5, gabapentin 30 mg/kg, s.c.; group 6, nifedipine 3 mg/kg, ip; group 7, nifedipine 10 mg/kg, ip; and group 8, gabapentin 10 mg/kg, s.c. and nifedipine 3 mg/kg, ip simultaneously.

Following drugs were used: formalin, morphine hydrochloride (E Merck, Darmstadt, Germany); gabapentin (Parke-Davis Research Laboratories Ann Arbor MI); nifedipine, dimethyosulfoxide (Sigma Chemical Co. St Louis Mo). Drugs were dissolved in normal saline except nifedipine, which was dissolved in dimethylsulfoxide (DMSO).

Twenty minutes after the drug administration formalin (50 µl of 5% solution) was injected at planter surface of left hind paw of rat and animals were placed gently in Plexiglass chamber. Time spent by animal in different behavioral categories (8) was noted down for 30 min starting 20 min after the formalin injection, by an observer unaware of the groupings. Nociceptive scores were calculated by the following formula (12).

$$\text{Pain score} = \frac{(0 \times t_0 + 1 \times t_1 + 2 \times t_2 + 3 \times t_3)}{(t_0 + t_1 + t_2 + t_3)}$$

Where t_0–t_3 are the numbers of seconds spent in each of the behavioral categories. Individual behavioral ctegory is as follows: category 0 = injected paw is not favored, category 1 = injected paw rests lightly on the floor, category 2 = the injected paw is completely elevated from surface, category 3 = the injected paw is licked.

Statistical Analysis

The pain scores of individual groups were presented as mean ± SEM. ANOVA followed Wilcoxon ranksign test applied for statistical analysis and $P<0.05$ was considered as significant.

RESULTS

Formalin injection produced a mean pain score of 2.41 ± 0.46 and 2.36 ± 0.39 in saline treated and DMSO treated groups respectively. Morphine (3 mg/kg, s.c.) taken as positive control reduced pain score significantly as compared to control (pain score 1.67 ± 0.36, $P<0.05$). Gabapentin 10 and 30 mg/kg, s.c. doses reduced the pain scores to 2.1 ± 0.49 and 1.68 ± 0.29 ($P<0.05$) respectively as compared to control. The

effect with 10 mg/kg, s.c. dose was not statistically significant. Nifedipine also produced antinociception, the pain score being 2.08 ± 0.41 ($P>0.05$) and 1.63 ± 0.31 ($P<0.05$) with 3 and 10 mg/kg, i.p. doses respectively. Coadministration of sub antinociceptive doses of gabapentin (10 mg/kg, s.c.) and nifedipine (3 mg/kg, i.p.) significantly reduced the pain score as compared to controls (1.5 ± 0.39, $P<0.05$).

DISCUSSION

Gabapentin has been shown to produce antinociception in experimental and clinical studies (2). Its mechanism is not well understood. However, gabapentin has been shown to bind to α_2 δ subunit of calcium channels (4). This subunit is common to all voltage dependent calcium channels and seems to play an important role in the neuronal excitability. It is known that Ca^{++} influx is critical for the release of neurotransmitters implicated in nociception (10). Nifedipine is shown to impair the synaptic transmission at spinal level by blocking L-type channel to produce antinociception (11). In our study both nifedipine and gabapentin reduced the pain score in formalin induced pain in rats. Sub antinociceptive doses of gabapentin (10 mg/kg s.c.) and nifedipine (3 mg/lg, i.p.) alone failed to produce antinociception, however, on coadministration they reduced the pain score significantly suggesting that Ca^{++} channels may be involved in the antinociceptive action of gabapentin. Gabapentin and nifedipine coadministration may be potential drugs for the treatment of resistant neuropathic pain.

REFERENCES

1. Dixit R, Bhargava VK, Kaur N. Antinociceptive effect of gabapentin in the formalin test. *Methods Find Exp Clin Pharmacol* 1999; 21(7): 481–482.
2. Laird MA, Gidal BE. Use of gabapentin in the treatment of neuropathy pain. *The Ann Pharmacother* 2000; 34: 802–807.
3. Taylor CP, Gee NS, Su TZ, Kocsis JD, Welty DF, Brown JP, Dooley DJ, Boden P, Singh LA. A summary of mechanistic hypotheses of gabapentin pharmacology. *Epilepsy Res* 1998; 29: 233–249.
4. Gee NS, Brown JP, Dissanayake VU, Offord J, Thurlow R, Woodruff GN. The novel anticonvulsant drug gabapentin (Neurontin) binds to the alpha 2 delta subunit of a calcium channel. *J Bio Chem* 1996; 271: 5768–5776.
5. Miranda HF, Bustamante D, Kramer V, Pelissier T, Saavedre H, Paeile C, Fernandez E and Pinardi G. Antinociceptive effects of Ca^{++} channel blockers. *Eur J Pharmacol* 1992; 217: 137–141.
6. Wong CH, Wu WH, Yarmush J, Zbuzek VK. An antinociceptive effect of the intraperitoneal injection of nifedipine in rats measure by tail flick test. *Life Scie* 1993; 53: 249–253.
7. Omote K, Sonoda H, Kawamata M. Potentiation of antinociceptive effects of morphine by calcium channel blockers at the level of the spinal cond. *Anesthesiology* 1993; 79: 746–752.
8. Dubuisson D, Dennis SG. The formalin test a quantitative study of the analgesic effects of morphine meperidine and brainstem stimulation in rats and cats. *Pain* 1977; 4: 161–174.
9. Alreja M, Mutalik P. Nayar U, Manchanda SK. The formalin test: A tonic pain model in primate. *Pain* 1984; 20: 97–105.
10. Nechashen DA. Regulation of cytosolic calcium concentration in presynaptic nerve endings isolated from rat brain. *J Physisol* 1985; 363: 87–101.
11. Hara K, Saito Y, Kirihara Y, Sakura S and Koska Y. Antinociceptive effects of intrathecal L-type calcium channel blockers on visceral and somatic stimuli in the rats. *Anesth Analg* 1998; 87: 382–387.
12. Abbott FV. Peripheral and central antinociceptive actions of ethylketocyclazocine in formalin test. *Eur J Pharmacol* 1988; 152: 93–100.