and the identity of the substance in spot X with the *N*-glucuronide of CPP suggest an additional route of trazodone metabolism.

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The potentiating effects of prostaglandins on bradykinin-induced pain and the effects of various analgesic drugs on prostaglandin E_1-potentiated pain in rats

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Ferreira (1972) found prostaglandins (PGs) to potentiate bradykinin-induced pain in man while aspirin did not alter the pain potentiated by PGE_1. Ferreira et al (1973) and Moncada et al (1975) reported a similar observation using a method of assessing the pressor reflex as a measure of nociceptive activity in dogs. It has therefore been suggested that non-steroidal anti-inflammatory drugs (NSAIDs) which block the synthesis of PGs (Ferreira et al 1971; Takeguchi & Nih 1972; Flower 1974; Ku & Wasvary 1975; Ziel & Krupp 1975), may exert their analgesic effects by preventing the sensitizing effect of PGs on the pain receptors. We now describe the potentiating effect of PGs on bradykinin-induced pain in rats and the effects of various analgesics on this pain.

Bradykinin, with or without PGs, was injected into the right common carotid artery of unanaesthetized Wistar male rats, 200 to 300 g, following the procedure described by Abe et al (1971). The injections were made through a polyethylene catheter (5·5 mm long; i.d. 0·58 mm; Clay-Adams PE-50), inserted centripetally under light ether anaesthesia into the carotid artery and passed through the subcutaneous tissue to protrude from the back of the animals. On the next day, for each animal, the liminal dose of bradykinin required to provoke both pain responses, that is, dextrorotation of the head and flexion of the right forelimb, was measured. Doses, in 0·2 ml 0·9% NaCl (saline), were 0·125, 0·250, 0·500 and 0·750 μg/animal. The potentiating effects of PGs on the ability of bradykinin to provoke pain responses were tested by the concomitant use of subliminal doses of bradykinin and PGs. In assessing the effects of analgesics on PGE_1-potentiated pain, similar results were obtained whether the doses of bradykinin used with PGE_1 (1·5 μg/animal) were subliminal or not. The present results were mainly obtained from subliminal doses of bradykinin. Aspirin, phenylbutazone, indomethacin, ibuprofen and amido-

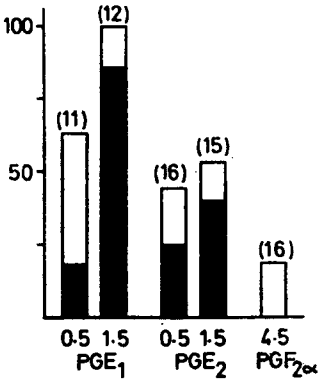

FIG. 1. The potentiating effects of PGs on the pain-provoking ability of the subliminal doses of bradykinin. Closed column: both pain responses, that is, dextrorotation of the head and flexion of the right forelimb were observed. Open column: either pain response was observed. Figures in parentheses indicate the number of animals tested. Abscissa: dose (μg/animal). Ordinate: % potentiation.

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pyrine were suspended or dissolved in 0·5% carboxymethyl cellulose containing 2% Tween 80, and administered intraperitoneally. Morphine hydrochloride was dissolved in saline and administered subcutaneously. All drugs were administered in volume of 10 ml kg^{-1} and the efficacy of drugs in inhibiting pain responses was tested at 30 min intervals for 2 h after the drug was given. When both pain responses were abolished, the drug was regarded as 'effective'. Five to 9 animals were used for each dose.

PGE_1 and PGE_2, but not $PGF_{2\alpha}$, potentiated the ability of bradykinin at a subliminal dose to provoke pain responses (Fig. 1). The potentiating effects of the PGs, which did not provoke pain responses by themselves in the doses used, were nearly dose-dependent. PGE_1 was more potent than PGE_2.

Aspirin (200 mg kg^{-1}), phenylbutazone (15 and 60 mg kg^{-1}), indomethacin (5 and 20 mg kg^{-1}) and ibuprofen (25 and 100 mg kg^{-1}) inhibited the bradykinin-induced pain responses, however, these NSAIDs, even when given at higher doses, did not cause significant inhibition of the pain responses induced by the concomitant use of bradykinin and PGE_1 (Fig. 2). On the other hand, morphine (8 mg kg^{-1}) inhibited the bradykinin-induced pain responses whether PGE_1 was present or not. Amidopyrine caused significant inhibition of the pain responses induced by bradykinin alone and in combination with PGE_1, but it was less potent against the combination.

PGE_1 and PGE_2, but not $PGF_{2\alpha}$, potentiated the effect of bradykinin to provoke pain when kinin and PG were injected together into the rat carotid artery. These results were consistent with earlier findings (Ferreira 1972; Ferreira et al 1973; Moncada et al 1975; Nakano & Taira 1977) on other preparations. Moreover, the present observations on the inhibitory effects of several analgesics on bradykinin-induced pain responses confirm the results of others (Deffenu et al 1966; Blane 1968; Abe et al 1971) on the same preparation. However, the effects of these analgesics on bradykinin-induced pain responses potentiated by PGs have not been reported for the rat carotid artery preparation.

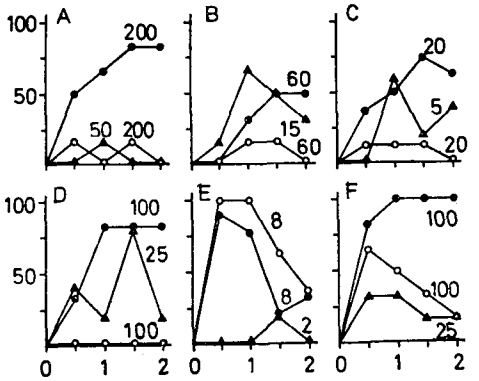

FIG. 2. Representative response curves obtained after the administration of analgesics to rats receiving bradykinin alone (▲●) or in combination with PGE_1 (○) intra-arterially at regular intervals. A, aspirin. B, phenylbutazone. C, indomethacin. D, ibuprofen. E, morphine hydrochloride. F, amidopyrine. Doses (mg kg^{-1}) of drugs administered are indicated. Drugs were all administered intraperitoneally except for morphine hydrochloride given subcutaneously at zero time. Five to 9 animals were used for each dose. Ordinate: % inhibition. Abscissa: time (h).

We have tested the effects of analgesics on the pain responses induced by the concomitant use of bradykinin and PGE_1. NSAIDs did not exert any significant inhibitory effects on the PGE_1-potentiated pain responses. Such a finding supports the suggestion of Ferreira (1972) that NSAIDs might produce their analgesic effects on the bradykinin-induced pain by preventing PG synthesis. On the other hand, morphine's inhibitory effect on the bradykinin-induced pain was not modified when bradykinin and PGE_1 were given together. Thus, it may be possible to distinguish between NSAIDs, with analgesic effects attributed to inhibition of PG synthesis, and other types of analgesic, such as morphine, by making an assessment of the effects of drugs on the pain responses induced by the concomitant use of bradykinin and PGs.

Amidopyrine showed a significant inhibition on the pain responses induced by bradykinin alone and in combination with PGE_1, but it seemed to be less potent towards the combination. Amidopyrine inhibits the bradykinin-induced increase in unit discharge of lamina V cells of the spinal dorsal horn in intact and spinal rabbits (Satoh et al 1976) and PG synthesis in bovine seminal vesicles (Flower 1974). These facts suggest that it may act, at least in part, on spinal and/or more peripheral sites to produce its inhibitoy effect on bradykinin-induced pain by preventing PG synthesis.

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