The use of bradykinin-induced effects in rats as an assay for analgesic drugs

SIR,—Guzman, Braun, Lim, Potter & Rogers (1964) and Lim, Guzman, Rogers, Goto, Braun, Dickerson & Engle (1964) used the responses of dogs to intra-arterial injection of badykinin as a means of assessing analgesics. We have adapted this method to rats.

Bradykinin was injected into the right common carotid artery of unanaesthetised Wistar male rats, weighing from 280 to 320 g. The injections were made through a polyethylene catheter (internal diameter, 0·5 mm), inserted centripetally under light ether anaesthesia into the carotid artery. The catheter passed through the subcutaneous tissues to protrude from the back of the animal. After recovery from anaesthesia, the rats behaved normally. Bradykinin, tested 1 hr after recovery, produced dextro-rotation of the head, flexion of the right forelimb and occasionally squeaking. For each rat, we measured the minimum dose of bradykinin required to provoke these effects. This ranged from 0·125 to 0·500 μg/rat and was always dissolved in normal saline, 0·2 ml. Of 162 animals, the threshold of bradykinin was found to be higher than 0·500 μg in two rats only and these were discarded.

If the injection was made into the left carotid artery, the same symptoms occurred at the corresponding side. However, doses of bradykinin up to 1·5 μg were less active than those described above. We have tested codeine phosphate, phenacetin, acetylsalicylic acid, aminopyrine, phenylbutazone sodium and methadone bitartrate against the bradykinin effects. The compounds, suspended in 5% gum acacia solution or dissolved in normal saline, were injected (0·250 ml/100 g) intraperitoneally or subcutaneously. The threshold dose of bradykinin was injected 15 min after and subsequently at 5 min intervals, until the bradykinin effect reappeared. The criterion chosen for evaluating protection was the disappearance of the bradykinin effect after at least two consecutive doses of the polypeptide. Rats which did not recover the normal sensitivity were discarded. Each rat received one drug at one dose level. The ED50 values are given in Table 1.

TABLE 1. ED50 VALUES OF SIX ANALGESICS IN RATS INJECTED WITH BRADYKININ

Drug	ED50 mg/kg	Route	Number of rats
Methadone bitartrate ..	1·45 (0·97–2·18)	s.c.	23
Phenylbutazone sodium ..	16·8 (9·3–30·4)	i.p.	25
Aminopyrine	17·8 (8·1–39·2)	i.p.	26
Codeine phosphate	32·0 (10·7–96·0)	s.c.	28
Acetylsalicylic acid	88·0 (66·7–100·9)	i.p.	20
Phenacetin	108·0 (96·4–121·0)	i.p.	20

The ED50 and its 19/20 confidence limits (in parentheses) were estimated by the method of Litchfield & Wilcoxon (1949).

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