Failure of substance P to produce analgesia in the mouse

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(Introduced by M.J. TURNBULL)

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Several authors have reported that Substance P (SP) induces analgesia when administered either intracerebroventricularly (Frederickson, Burgis, Harrell & Edwards, 1978), intracerebrally into the periaqueductal grey region (Stewart, Getto, Neldner, Reeve, Krivoy & Zimmermann, 1976; Malick & Goldstein, 1978) or intraperitoneally (Starr, James & Gaytten, 1978; Stewart *et al.*, 1976). Of particular interest were the findings that SP produced analgesia following intraperitoneal injection. Stewart and coworkers demonstrated significant analgesia following i.p. injection of SP (5 ng) per mouse, whilst Starr *et al.* (1978) found a smaller, although still statistically significant, effect following a dose of 5 μg per mouse. In this latter experiment, SP was found to be approximately 200 times more potent than morphine. Thus these two reports differ over the potency of SP by a factor of at least 1000. In an attempt to clarify this situation we have examined the analgesic activity in mice of SP from two sources (Beckman and Penninsula Laboratories) in comparison with the C-terminal hexapeptide of SP (synthesized by Mr. N.N. Petter, ICI) and morphine.

Groups of 10 female mice of the Alderley Park strain weighing 25–27 g were used. SP and the hexapeptide were dissolved in 0.01 N acetic acid and morphine was prepared in saline. All drugs were injected intraperitoneally in a volume of 0.1 ml per mouse. At 15, 30, 60 and 90 min after dosing the reaction times of the mice were determined on a hot plate at 55°C. All experiments were performed blind. The potencies of the two samples of SP and the hexapeptide to contract the guinea pig isolated ileum were also determined. The EC_{50} values (concentration producing 50% of maximal contraction) were $8.02 \pm 1.99 \times 10^{-9}$M for Beckman S.P., $7.27 \pm 2.24 \times 10^{-9}$M for Penninsula S.P. and $6.40 \pm 3.80 \times 10^{-9}$M for the hexapeptide. Thus all three peptides were of similar potency.

The results shown in Table 1 clearly demonstrate that morphine produces a dose-related analgesic effect at doses between 2.5 mg/kg and 10 mg/kg. However, we failed to demonstrate any significant analgesia with either of the samples of SP or the hexapeptide. Thus we were unable to confirm the findings of Stewart *et al.*, (1976) and Starr *et al.*, (1978). As the techniques employed in the present study and those reported in the literature were apparently identical, the reason for this discrepancy remains unclear.

References

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Table 1 Mean reaction of mice in the hote-plate test following i.p. injection of morphine, Substance P or the c-terminal hexapeptide of Substance P.

Drug	*Reaction Time (s) Time After Dosing (min)* 15	30	60	90
Saline	7.1 ± .53	6.6 ± .48	6.0 ± .65	7.3 ± .71
0.01N Acetic acid	7.9 ± .98	6.2 ± .37	7.5 ± .53	6.6 ± .77
Morphine 2.5 mg/kg	8.8 ± .77	8.7 ± .85[a]	6.0 ± .74	6.1 ± .71
Morphine 5 mg/kg	12.8 ± .87[c]	12.9 ± .86[c]	11.7 ± .63[c]	9.9 ± 1.1
Morphine 10 mg/kg	17.5 ± 1.51[c]	17.7 ± 1.49[c]	13.1 ± 1.83[b]	10.9 ± 1.35[a]
Substance P (Beckman) 40 μ g/kg	9.2 ± 1.37	7.25 ± .68	7.1 ± .89	7.7 ± .67
Substance P (Beckman) 200 μ g/kg	8.9 ± .75	7.3 ± .69	7.0 ± .47	6.3 ± .38
Substance P (Penninsula) 40 μ g/kg	8.0 ± .48	6.6 ± .53	6.2 ± .45	6.3 ± .42
Substance P (Penninsula) 200 μ g/kg	8.7 ± 1.2	8.3 ± 1.1	9.4 ± 1.3	7.8 ± 1.2
Hexapeptide 40 μ g/kg	9.6 ± 1.21	7.7 ± 1.0	7.9 ± .67	8.1 ± .95
Hexapeptide 200 μ g/kg	9.3 ± 1.0	7.1 ± .29	7.8 ± 1.2	8.4 ± .74

a significantly different from vehicle $P<0.05$
b significantly different from vehicle $P<0.01$
c significantly different from vehicle $P<0.001$