# Morphine and apomorphine stimulate prostaglandin production by rabbit brain homogenate

H.O.J. COLLIER, WENDY J. McDONALD-GIBSON & S.A. SAEED*

*Miles Laboratories Limited, Stoke Poges, Slough SL2 4LY, Buckinghamshire*

Morphine and other opiates block the stimulation by prostaglandin E (PGE) of cyclic AMP formation by rat brain homogenate, without lessening the basal rate of cyclic AMP formation (Collier & Roy, 1974). This may be the basis of the inhibitory effects of opiates, such as analgesia and hypothermia. Morphine, too, has stimulant effects, such as hyperthermia, emesis and hyperglycaemia, that E prostaglandins also possess. In investigating such effects of morphine and apomorphine, we found that both drugs stimulated the biosynthesis of PG from arachidonic acid by bull seminal vesicle homogenate (Butt, Collier, Gardiner & Saeed, 1974). Because these actions of morphine and apomorphine are central, we have studied their effects on prostaglandin synthesis by rabbit brain homogenate without added co-factors.

The whole brain from male New Zealand White rabbits (4 kg) was homogenized at 4°C in 50 mM phosphate buffer at pH 7.4 containing 0.5 mM EDTA, and centrifuged once for 10 min at 200 *g*. To 1 ml of the supernatant, 20 $\mu$g sodium arachidonate was added, with or without morphine sulphate or apomorphine hydrochloride, to make 2 ml of incubate. After incubation, with aeration and shaking for 10 min at 37°C, the reaction was terminated with 2.5 ml 0.2 M citric acid. Prostaglandins were extracted with ethyl acetate. Total PG was assayed against $PGE_2$ on rat stomach strip; or prostaglandins were separated by thin layer chromatography on the A I system (Gréen & Samuelsson, 1964) and the E and F zones were extracted and assayed on rat stomach strip and colon.

In six experiments, morphine (0.075, 0.75 and 7.5 $\mu$g/ml) stimulated total PG production by, respectively, 1.6 times ($P < 0.05$), 2.0 times ($P < 0.025$) and 2.3 times ($P < 0.025$) the PG production (mean 81 ng) in the absence of drug. The slope of the concentration/response line was, however, not quite significant. In five experiments, apomorphine (26 $\mu$g/ml) stimulated PG production by 1.9 times ($P < 0.05$). In experiments in which $PGE_2$ and $PGF_{2\alpha}$ were separately estimated, morphine stimulated the production of both prostaglandins. Morphine does not inhibit bovine prostaglandin dehydrogenase (A.C. Roy, unpublished).

E prostaglandins elicit fever, vomiting and hyperglycaemia and $PGF_{2\alpha}$ elicits vomiting. This implies that the stimulation of PG synthetase observed in brain homogenate might explain such effects of morphine or apomorphine. All the data needed to test these possibilities are not available; but, in the rabbit, injection of morphine (25-500 $\mu$g) into a lateral cerebral ventricle elicits hyperthermia (Banerjee, Burks, Feldberg & Goodrich, 1968). Such doses might well produce a sufficient concentration of morphine in the anterior hypothalamus to stimulate PGE production. Thus the way is open to explain some stimulant effects of morphine and apomorphine *in vivo*.

## References

BANERJEE, U., BURKS, T.F., FELDBERG, W. & GOODRICH, C.A. (1968). Temperature effects and catalepsy produced by morphine injected into the cerebral ventricles of rabbits. *Br. J. Pharmac. chemother.*, **33**, 544-551.

BUTT, A.A., COLLIER, H.O.J., GARDINER, P.J. & SAEED, S.A. (1974). Effects on prostaglandin biosynthesis of drugs affecting gastrointestinal function. *Gut*, **15**, 344.

COLLIER, H.O.J. & ROY, A.C. (1974). Morphine-like drugs inhibit the stimulation by E prostaglandins of cyclic AMP formation by rat brain homogenate. *Nature, Lond.*, **248**, 24-27.

GRÉEN, K. & SAMUELSSON, B. (1964). Thin layer chromatography of the prostaglandins. *J. Lipid Res.*, **5**, 117-120.