Effect of morphine on brain apomorphine concentrations in the rat

ASTON L. SYMES†, SAMARTHJI LAL, THEODORE L. SOURKES*, *Departments of Psychiatry, Montreal General Hospital and *McGill University Montreal, P.Q., Canada*

Morphine is reported both to antagonize apomorphine-induced stereotyped behaviour (ASB) in the rat (Janssen, Niemegeers & Jageneau, 1960; Kuschinsky & Hornykiewicz, 1972; Puri, Reddy & Lal, 1973) and to potentiate it (Vedernikov, 1970; McKenzie & Sadof, 1974; Cowan, Dettmar & Walter, 1975). Kuschinsky (1975) found that acute morphine inhibited ASB slightly and that chronic morphine treatment was ineffective in increasing the response of rats to apomorphine. The reasons for these discrepancies might well be that the widely different dosage schedules of both drugs and varying intervals of morphine pretreatment employed could influence the extent of morphine antagonism of central dopamine receptors and/or the concentration of apomorphine in brain at the times the observations were made. We have determined the effect of morphine on brain apomorphine concentrations.

Male Sprague-Dawley rats, ∿150 g, were injected with morphine sulphate (Sterilab, Downsview, Ontario and Laboratoire Demer Limitée, Québec, P.Q.) (45 mg kg^{-1}) 5 min before apomorphine (Merck Frosst, Kirkland, P.Q.) (10 mg kg^{-1}) and groups of animals decapitated at 5, 10, 20, 50 or 90 min after injection. Apomorphine was measured in whole brain by the fluorimetric assay of Symes, Lal & Sourkes (1975). Morphine did not affect the fluorescence of apomorphine. During the experiments the onset and termination of ASB was recorded by direct observation (Lal & Sourkes, 1973). Five experimental and five control animals were used at each time interval except at 90 min when 6 animals per group were used. In an additional experiment, behavioural observations were made on rats (n = 6 rats per group) receiving 1 mg kg^{-1} apomorphine 5 min after morphine sulphate (45 mg kg^{-1}) or saline. Further controls were observed after morphine alone and saline alone. All drugs were administered intraperitoneally. Doses are expressed as the base.

Following apomorphine (10 mg kg^{-1}) alone, ASB developed in all animals within 2 min of injection and had terminated within 60 min. The brain concentration of apomorphine reached a peak by 5 min and thereafter followed a logarithmic decline (Fig. 1). The biological half-life of apomorphine in brain is 13 min.

In rats pretreated with morphine the onset of ASB also occurred within 2 min of injection of apomorphine (10 mg kg^{-1}). The termination time of ASB, however, was prolonged beyond that of rats receiving apomorphine alone (65–75 min). Prior treatment with morphine prolonged the half-life from 13 to 17 min. A statistically significant difference exists between the slopes of the two regression lines ($P < 0.05$). After morphine pretreatment the concentration of apomorphine in brain was significantly higher at both 5 min ($P < 0.05$) and 90 min ($P < 0.001$) but not at any of the other time intervals.

In rats receiving 1 mg kg^{-1} apomorphine alone the onset of ASB occurred within 2 min and ceased in all animals by 20 min. In contrast, the onset of ASB was delayed for 15 min in rats pretreated with morphine and the termination time extended beyond 20 min (35–40 min).

The present results show that morphine in high doses both antagonizes and potentiates apomorphine effects. ASB is mediated by direct stimulation by apomorphine of dopamine receptors (Sourkes & Lal, 1975). The site of action of morphine in relation to dopaminergic neurons has not been fully clarified. Puri & others (1973) and Lal, Gianutsos & Puri (1975) have provided evidence that the action is at the postsynaptic receptor, although the latter authors recognize the possibility of indirect blockade through reduction of input into dopaminergic systems. Blockade by acute morphine administration at the postsynaptic receptor would be consistent with our present results of antagonism towards ASB.

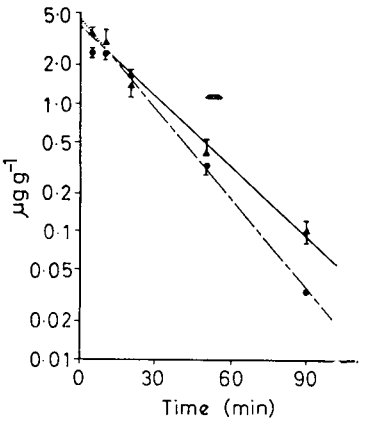

FIG. 1. Effect of morphine on brain apomorphine concentration (μg g^{-1}). Groups of rats injected with morphine, 45 mg kg^{-1}, (▲——▲) or saline (●——●) intraperitoneally 5 min before apomorphine (10 mg kg^{-1}) were killed at various times and the concentration of apomorphine was measured in brain. The points represent means of 6 determinations at each time interval and the vertical bars, standard errors of means. The regression lines were drawn by the method of least squares for the time intervals 10–90 min for the saline-pretreated rats and 5–90 min for the morphine-pretreated rats. The equations for the lines are log y = 0·6574 — 0·0235 X (r = 0·99) (●—●) and log y = 0·5866 — 0·0182 X (r = 0·99) (▲—▲). The slopes differ from each other significantly ($P < 0.05$).

† Correspondence.

Both morphine (Way & Adler, 1960; Boerner & others, 1975) and apomorphine (Kaul, Brochmann-Hanssen & Way, 1961) are metabolized mainly by glucuronidation so that competition for glucuronidating enzymes could account for the increase in half-life of apomorphine in brain.

The duration of ASB parallels brain concentrations of apomorphine (Symes & others, 1975). Thus the behavioural manifestations following morphine-apomorphine interactions at any one time presumably will depend on the degree of morphine blockade of dopamine receptors, the degree of morphine inhibition of apomorphine metabolism and the net concentration of apomorphine in brain. This would explain the findings of antagonism and potentiation of apomorphine effects reported in the literature following morphine pretreatment.

This work was supported by grants from the Medical Research Council of Canada and the George W. Stairs Memorial Fund. Additional support was received from Merck Frosst Laboratories, Kirkland, P.Q., Canada.

September 27, 1976

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Effect of ergotamine and dihydroergotamine on dopamine-stimulated adenylate cyclase in rat caudate nucleus

S. GOVONI, E. IULIANO, P. F. SPANO, M. TRABUCCHI*, *Department of Pharmacology and Pharmacognosy, University of Milan, Via Vanvitelli 32, 20129 Milan, Italy*

The mode, or, better, the modes of action of ergot alkaloids are not yet completely understood. They are probably different according to the specific ergot derivative, the pharmacological effect considered and the tissue studied.

Recently, some representatives of this class of drugs were found to activate central dopamine receptors *in vivo* and have been proposed as antiparkinsonian drugs (Calne, Leigh & others, 1974; Teychenne, Leigh & others, 1975).

Some ergot alkaloids like ergocornine, CB 154 (2-bromo-α-ergocryptine), ergotamine and dihydroergotamine are able to induce circling behaviour in rats unilaterally injected in the nigrostriatal bundle with 6-hydroxydopamine (Corrodi, Fuxe & others, 1973; Fuxe, Agnati & others, 1975). Also LSD, which is a synthetic ergot derivative, has been proved to be active in this experimental model (Pieri & Pieri, 1974). Spano, Kumakura & others (1975) recently demonstrated that in homogenates of rat striatum LSD may stimulate the activity of dopamine-sensitive adenylate cyclase, the enzyme related with the dopamine receptor. The same authors observed that LSD, in addition to being an agonist, may reduce the stimulation of the enzyme activity elicited by dopamine, thus behaving as a mixed dopamine agonist-antagonist. Trabucchi, Spano & others (1976) demonstrated that bromocriptine is a non-competitive inhibitor of dopamine-stimulated adenylate cyclase in rat striatal homogenates. In contrast, bromocriptine stimulates *in vivo* the

* Correspondence.