Changes of physical morphine dependence in rats chronically treated with drugs acting on brain 5-hydroxytryptamine

R. SAMANIN*, L. CERVO, C. ROCHAT, *Istituto di Ricerche Farmacologiche "Mario Negri" Via Eritrea, 62-20157 Milan, Italy*

Way et al (1968) reported a reduction of morphine dependence in mice treated with *p*-chlorophenylalanine (PCPA), a 5-hydroxytryptamine (5-HT) synthesis inhibitor. However, other authors have failed to confirm these findings (Schwarz & Eidelberg 1970; Cheney et al 1971; Marshall & Grahame-Smith 1971). Although explanations for the discrepancies were offered and new evidence was added (Ho et al 1972), the question remains whether 5-HT plays an important role in the mechanism of development of morphine dependence. We have re-examined the problem by studying the physical dependence induced by chronic graded doses of morphine in rats which received concomitant treatment with (+)-fenfluramine, a 5-HT releaser and uptake inhibitor (Garattini et al 1975; Costa et al 1971) or methergoline, a potent central 5-HT antagonist (Mawson & Whittington 1970). A significant interaction has been previously reported (Duncan & Spencer 1973) between a sub-acute treatment with fenfluramine and the analgesic effect of morphine in mice.

Male CD-COBS rats, Charles River, Italy, about 200 g at the beginning of the experiments, received two intraperitoneal injections of 10 mg kg^{-1} of morphine sulphate the first day of treatment (at 10 a.m. and 6 p.m.). The dose of morphine was doubled every other day to reach a total daily dose of 160 mg kg^{-1} which occurred on 7th day. This regimen was continued for 3 days. On day 11 the animals received the last injection of morphine (at 10 a.m.). One hour before each morphine injection the animals received intraperitoneally (+)-fenfluramine hydrochloride (2·5 mg kg^{-1}), methergoline maleate (5 mg kg^{-1}) or an equal volume of vehicle. Pretreatment was discontinued 24 h before the last morphine injection. Physical dependence was assessed by precipitating an abstinence syndrome with naloxone hydrochloride (1 mg kg^{-1} i.p.). 4 h after the last injection of morphine. Withdrawal signs within 30 min were recorded by observers unaware of the animal's treatment, according to the procedure previously described (Samanin & Miranda 1976). The data are expressed as proportion of positive animals in the various experimental groups, and differences analysed statistically by the χ^2 test.

Table 1. Abstinence signs in animals treated with (+)-fenfluramine or methergoline.

Treatment	Proportion of positive animals	
	Jumping	Diarrhoea
Control	8/19	14/19
(+)-Fenfluramine	13/14*	7/14
Methergoline	1/19*	13/19

*P <0·01 compared with control (χ^2 test).

As shown in Table 1, repeated (+)-fenfluramine treatment significantly increased the number of jumpers after naloxone injection while methergoline markedly reduced them. Signs such as diarrhoea and others as previously described (Samanin & Miranda 1976) were not significantly affected. Therefore, differences between the withdrawal signs considered and the means used to induce dependence by previous investigative groups could have contributed to the discrepancies. Of the various withdrawal signs, the frequency of jumping has been found to correlate best with the degree of morphine dependence in rats (Bläsig et al 1973).

The present data, as suggested by Way et al (1968), support a role of brain 5-HT in physical morphine dependence. As for analgesia (Samanin et al 1970), brain 5-HT appears to act by favouring the development of physical dependence to morphine. 5-HT antagonists such as methergoline, when given at the initial stages of morphine addiction, might be useful in reducing the development of physical dependence.

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* Correspondence.

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