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Cross tolerance between methylamphetamine and morphine in the mouse

Recent work has attempted to explain the mechanism of narcotic agonist action in terms of interference with chemical transmission in the central nervous system. Evidence for the involvement of both cholinergic and monoaminergic systems has been reported (Harris, 1970).

Amongst the evidence in support of these hypotheses is the fact that both sympathomimetics (Colville & Chaplin, 1964) and cholinomimetics (Gross, Holland & others, 1948; Chen, 1958) possess antinociceptive activity.

The characteristics of morphine and sympathomimetic antinociception have been compared by Major & Pleuvry (1971). They showed that drugs known to cause changes in the content of putative transmitters in the central nervous system had a qualitatively similar effect upon the antinociceptive activity of morphine and methylamphetamine. Antinociception was increased when 5-hydroxytryptamine content was raised relative to noradrenaline, dopamine or both. Subsequent work in this laboratory has shown that whilst physostigmine antinociception has similar characteristics to that of morphine and methylamphetamine, oxotremorine antinociception has not.

Tolerance development is a characteristic of both morphine-like agonists and the sympathomimetics. In a further attempt to examine similarities between these various antinociceptive agents, the characteristics of tolerance to them has been compared.

Antinociception was estimated by the hot plate reaction time test (Bousfield & Rees, 1969). Drugs were administered twice daily for five days. The drugs were morphine sulphate (10 mg/kg, i.p.), methylamphetamine hydrochloride (10 mg/kg, i.p.), physostigmine salicylate (0·1 mg/kg, s.c.), oxotremorine (0·05 mg/kg s.c.) and saline (0·1 ml i.p. or s.c.). Single injections of the above doses of antinociceptive agents were approximately equipotent in the hot plate reaction time test. Reaction times in groups of 12 mice were measured at 5 min intervals for the first 30 min after the first injection each day and then at 10 min intervals until the reaction times were not significantly different from those of saline pretreated control mice.

In the afternoon of the fifth day, mice pretreated with methylamphetamine, physostigmine or oxotremorine were injected with 10 mg/kg morphine sulphate and the concurrently tested morphine-treated mice injected with either methylamphetamine, physostigmine or oxotremorine. Saline-pretreated mice were injected with either morphine, methylamphetamine, physostigmine or oxotremorine. The reaction

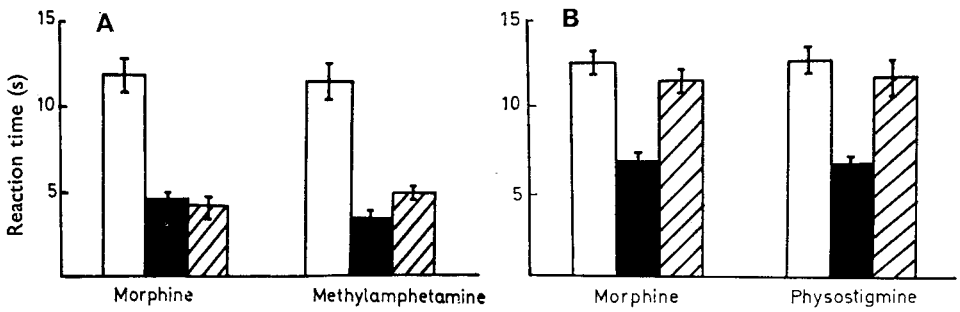

FIG. 1. A. Cross tolerance between the antinociceptive activity (ordinate) of morphine and methylamphetamine as morphine sulphate (10 mg/kg, i.p.) and methylamphetamine HCl (10 mg/kg, i.p.). The open columns show the effect on the first day of tolerance induction (see text), the closed columns show the effect on the fifth day of tolerance induction and the hatched columns show the effect in mice pretreated for five days with the alternate antinociceptive agent. The results are expressed as maximum mean reaction times ± s.e. of groups of 12 mice.

B. Absence of cross tolerance between the antinociceptive activity (ordinate) of morphine and physostigmine as morphine sulphate (10 mg/kg, i.p.) and physostigmine salicylate (0·1 mg/kg, s.c.).

times obtained with these agents in saline pretreated mice were not significantly different from those obtained with the same agent in non-pretreated control mice.

Tolerance developed to the antinociceptive activity of morphine, methylamphetamine and physostigmine during the pretreatment course. No tolerance developed to the effects of oxotremorine, there being no significant difference between the response on day 1 and day 5 ($P > 0{\cdot}30$).

The results obtained for morphine, methylamphetamine and physostigmine are shown in Fig. 1A and B.

Marked cross tolerance was detected between methylamphetamine and morphine (Fig. 1A). Mice pretreated with methylamphetamine, when challenged with morphine, responded in a quantitatively identical manner to those pretreated with morphine ($P > 0{\cdot}60$).

No cross tolerance existed between physostigmine and morphine, morphine having a similar effect in both physostigmine pretreated and non-pretreated control mice ($P > 0{\cdot}50$).

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