Species difference in the lowering of brain 5-hydroxytryptamine by *m*-chloroamphetamine

Pletscher, Bartholini & others (1964) reported that *p*-chloromethamphetamine and related compounds caused a lowering of brain 5-hydroxytryptamine (5-HT) in rats and in guinea-pigs. These observations had previously been extended in rats by (Fuller, Hines & Mills, 1965) who found that *p*-chloroamphetamine was the most active among the series of compounds studied in lowering brain 5-HT and that *m*-chloroamphetamine did not lower 5-HT. Rats metabolize amphetamine by *p*-hydroxylation (Dring, Smith & Williams, 1970). The failure of *m*-chloroamphetamine to lower 5-HT in rats may be attributed to the fact that it is rapidly metabolized by *p*-hydroxylation, whereas *p*-chloroamphetamine cannot be so metabolized. I therefore have compared the effects of the compounds in the guinea-pig, which metabolizes amphetamine exclusively by deamination and not by *p*-hydroxylation (Dring & others, 1970).

Male guinea-pigs, averaging 280 g, or male albino rats, averaging 140 g, were used in groups of 5. Drugs were injected intraperitoneally at 0·1 mmol/kg. Six h after injection of the drugs, or of saline, the animals were decapitated, and the brains were removed and frozen on dry ice. The 5-HT content was measured spectrofluorometrically by the *o*-phthalaldehyde condensation method of Maickel & Miller (1966).

In rats, there was a slight but statistically significant ($P < 0{\cdot}005$) reduction in brain 5-HT 6 h after *m*-chloroamphetamine. I found earlier that when brain 5-HT was measured 16 h after *m*-chloroamphetamine it was not different from control values at that time. The effect of *p*-chloroamphetamine was significantly greater ($P < 0{\cdot}001$) than that of *m*-chloroamphetamine in rats, in agreement with our earlier results. On the contrary, there was no difference in guinea-pigs ($0{\cdot}05 < P$) between the effects of *m*-chloroamphetamine and of *p*-chloroamphetamine. The *p*-chloro compound lowered 5-HT in guinea-pigs to an identical extent as in rats (to 29% of the control value), whereas the *m*-chloro compound lowered 5-HT significantly more in guinea-pigs (to 35% of the control value) than in rats (84% of the control value). Control values were for rats 0·63 μg/g and for guinea-pigs 0·45 μg/g.

These results demonstrate that *m*-chloroamphetamine has the potential of lowering brain 5-HT in the same manner as does *p*-chloroamphetamine; that potential is realized in the guinea-pig, a species that does not inactivate the *m*-chloro compound by *p*-hydroxylation. The mechanism by which *p*-chloroamphetamine lowers brain 5-HT (whether by impairment of 5-HT binding or by inhibition of its synthesis) has yet to be established, and the potential of *m*-chloroamphetamine to act in the same manner may be useful information in elucidating the mechanism of action.

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REFERENCES

DRING, L. G., SMITH, R. & WILLIAMS, R. T. (1970). *Biochem. J.*, **116**, 425–435.

FULLER, R. W., HINES, C. W. & MILLS, J. (1965). *Biochem. Pharmac.*, **14**, 483–488.

MAICKEL, R. P. & MILLER, F. P. (1966). *Analyt. Chem.*, **38**, 1937–1938.

PLETSCHER, A., BARTHOLINI, G., BRUDERER, H., BURKARD, W. P. & GEY, K. F. (1964). *J. Pharmac. exp. Ther.*, **145**, 344–350.