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Effect of drugs influencing central 5-hydroxytryptaminergic mechanisms on molindone-induced catalepsy in the rat

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The cataleptic action of neuroleptics is reduced after lesions of the 5-hydroxytryptaminergic raphé system or depletion of 5-HT stores by *p*-chlorophenylalanine (Kostowski et al 1972; Gumulka et al 1973). However, Costall et al (1975) have reported that lesions of the 5-HT-ergic raphé system, though effective in reducing the cataleptic action of haloperidol, fluphenazine, oxiperomide and spiroxatrine, had no consistent effect on the cataleptic action of the dibenzazepine neuroleptics, loxapine and clothiapine, while the weak cataleptic action of clozapine was potentiated, suggesting thereby that the 5-HT-ergic raphé system exerts a variable influence on the cataleptic action of different neuroleptics.

Molindone, a dihydroindolone compound, unrelated chemically to the phenothiazines or butyrophenones, is a recently introduced neuroleptic for the treatment of schizophrenia (Abuzzahab 1973; Ayd 1974). It is reported to induce catalepsy (Rubin et al 1967) by blocking striatal dopamine receptors (Bunney et al 1975).

We have investigated on molindone-induced catalepsy in the rat, the effect of pretreatment with clomipramine, a selective blocker of neuronal reuptake of 5-HT (Ross & Renyi 1975), quipazine, a drug that stimulates 5-HT post-synaptic receptors (Rodriguez et al 1973) and also stimulates the release (Hamon et al 1976) and inhibits the reuptake of 5-HT (Medon et al 1973), L-tryptophan, a precursor of 5-HT (Aghajanian & Asher 1971) and methysergide, a 5-HT receptor antagonist.

Male albino rats, 120–180 g, with free access to a standard diet and tap water were used once only. During the experiments the animals were individually housed in wire netting cages at 27–30 °C in a noiseless room. All observations were made between 10 and 16 h.

Catalepsy was scored according to Costall & Naylor (1975). Animals were tested for the presence of catalepsy by placing both front limbs over a horizontal bar placed 8 cm above the bench surface. Those animals maintaining the cataleptic posture from 0 to 10 s scored 0, 10 to 30 s = 1, 30 s to 1 min = 2, 1 to 2 min = 3, 2 to 3 min = 4, 3 min to ∞ = 5. The animals were tested for catalepsy 0·5, 1·0, 2·0, 3·0, and 4·0 h after molindone treatment.

Molindone HCl (Endo Laboratories), clomipramine HCl (Ciba-Geigy), quipazine maleate (Miles Laboratories), methysergide hydrogen maleinate (Sandoz Products Ltd) were dissolved in distilled water while L-tryptophan (Sigma) was dissolved in a minimum quantity of HCl and made up to volume with distilled water. All agents were injected intraperitoneally, molindone, clomipramine and quipazine in a volume of 2 ml kg^{-1}, while methysergide and L-tryptophan were injected in a volume of 5 ml kg^{-1}. Except for L-tryptophan, doses refer to the salt. For each dose, 10 animals were used. Clomipramine and methysergide were injected 30 min and quipazine and L-tryptophan 60 min before molindone treatment. Control groups received the requisite volume of vehicle intraperitoneally before receiving molindone. Results were analysed by the Mann-Whitney U-test for non-parametric data.

Molindone (1·25 mg kg^{-1} i.p.) induced no catalepsy while higher doses (2·5–20 mg kg^{-1} i.p.) induced a state of sedation and dose-dependent degree of catalepsy, without loss of righting reflex or apparent change in muscle tone or motor coordination. The cataleptic effect was present at 30 min and reached maximum at 1 h (Fig. 1). Doses beyond 20 mg kg^{-1} tended to produce motor incoordination and ataxia.

Clomipramine (5, 10, 20 mg kg^{-1}) did not induce catalepsy. Higher doses were not tested as they tended to produce motor incoordination and ataxia. Clomipramine pretreatment potentiated the cataleptic effect of molindone (2·5, 5·0 mg kg^{-1}) dose-dependently (Fig. 2).

Quipazine (1, 2, 4 mg kg^{-1}) did not induce a cataleptic state. Shortly after its injection animals exhibited a behavioural syndrome, comprising of increased locomotor activity, slight tremor, intensive sniffing and rubbing of the nose, which lasted for 30–40 min. After about 45 min the behaviour was almost normal. With higher doses (10, 20 mg kg^{-1}) there was an increase in the intensity of the behavioural syndrome and the animals also showed abduction and extension of hind limbs, motor incoordination and marked hypotonia, therefore these doses were not further tested. Pretreatment with quipazine (1, 2, 4 mg kg^{-1}) potentiated the cataleptic effect of molindone (2·5, 5 mg kg^{-1}) dose-dependently (Fig. 2). Similarly, pretreatment with L-tryptophan (100, 200 mg kg^{-1}) potentiated the cataleptic effect of molindone (2·5, 5 mg kg^{-1}) dose-dependently (Fig. 2).

Methysergide (5, 10 mg kg^{-1}) did not induce catalepsy in the rats. Pretreatment with methysergide (5, 10 mg kg^{-1}) decreased the cataleptic effect of molindone (10 mg kg^{-1}) dose-dependently (Fig. 2).

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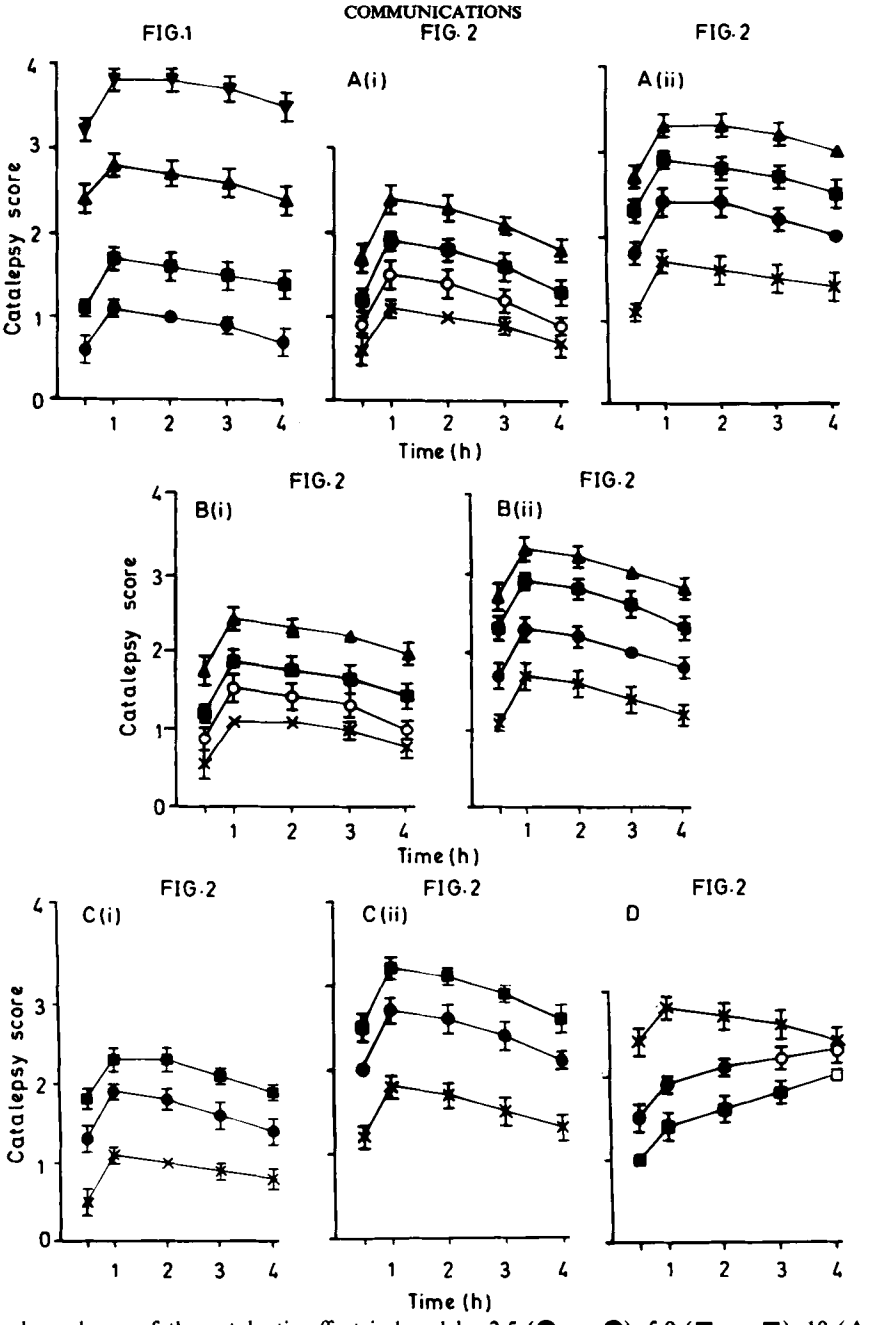

FIG. 1. Dose-dependency of the cataleptic effect induced by 2·5 (●——●), 5·0 (■——■), 10 (▲——▲) and 20 (▼——▼) mg kg^{-1} i.p. molindone in the rat. Each value represents the mean score of 10 rats. Vertical bars represent s.e. Times given are counted from the injection of molindone.

FIG. 2. (A) Effect of clomipramine pretreatment at the doses of 5·0 (●——●), 10·0 (■——■) or 20·0 (▲——▲) mg kg^{-1} on molindone (×——×)-induced catalepsy in rats. (B) Effect of quipazine pretreatment at the doses of 1·0 (●——●), 2·0 (■——■) or 4·0 (▲——▲) mg kg^{-1} on molindone (×——×)-induced catalepsy in rats. (C) Effect of L-tryptophan pretreatment at the doses of 100 (●——●) or 200 (■——■) mg kg^{-1} on molindone (×——×)-induced catalepsy in rats. (D) Effect of methysergide pretreatment at the doses of 5·0 (●——●) or 10·0 (■——■) mg kg^{-1} on molindone (×——×)-induced catalepsy in rats. Clomipramine was injected 30 min, and quizapine and L-tryptophan were injected 60 min before molindone (i): 2·5 mg kg^{-1}, i.p. (ii): 5·0 mg kg^{-1} i.p. Methysergide was injected 30 min before molindone 10 mg kg^{-1}, i.p. Each value represents the mean score of 10 rats. Vertical bars represent s.e. Solid symbols indicate statistical significance ($P < 0.05$ or less). Times given are counted from the injection of molindone.

Thus, drugs that influence the central 5-HT-ergic mechanisms affect the cataleptogenic effect of molindone. Pretreatment with clomipramine, quipazine and L-tryptophan, potentiated the cataleptic effect of molindone while pretreatment with methysergide decreased the cataleptic effect. These results indicate an important role for 5-HT in the regulation of the cataleptic effect of molindone and suggest that the activation of the central 5-HT-ergic system has a facilitatory effect on the catalepsy induced by molindone while inhibition of the central 5-HT-ergic system decreases the cataleptic effect of molindone. Further, our results also indicate that the central 5-HT-ergic system influences molindone-induced catalepsy in the same manner as it influences haloperidol or chlorpromazine-induced catalepsy (Kostowski et al 1972; Gumulka et al 1973; Carter & Pycock 1977; Balsara et al 1979) or catalepsy induced by brain-amine depleting neuroleptics (Fuenmayor & Vogt 1979) and suggest that the central 5-HT-ergic system may be exerting an inhibitory influence on the central dopaminergic system and that the cataleptic effect of neuroleptics apparently depends on the balance between the two systems. These findings also concur with clinical reports. Thus, clinical improvement of chronic schizophrenic patients, in whom hyperfunctioning of the c.n.s. dopaminergic system has been hypothesized (Matthysse 1973; Snyder et al 1974) was achieved by medication with precursors of 5-HT, L-tryptophan (Pollin et al 1961) or 5-hydroxytryptophan (Wyatt et al 1972). In contrast, the symptoms of parkinsonism, a clinical condition in which there is a deficiency of dopamine (Franz 1975), were exacerbated after treatment with L-tryptophan or 5-hydroxytryptophan (Chase & Murphy 1973). The mutual interdependence of the two systems has also been demonstrated morphologically. 5-HT-ergic fibres arising from the raphé nuclei have been shown to make synaptic contacts with dopaminergic cells in the substantia nigra (Parizek et al 1971; Aghajanian & Bunney 1975). Further, the neostriatum and limbic striatum brain areas which receive dopaminergic input have also been shown to receive 5-HT-ergic input from the raphé nuclei (Fuxe & Jonsson 1974) and recently Carter & Pycock (1978) have shown that a localized depletion of 5-HT in the substantia nigra or nucleus accumbens reduces the catalepsy induced by the neuroleptic fluphenazine.

In conclusion, we would like to state that our results suggest an involvement of the 5-hydroxytryptaminergic raphé system with central dopaminergic systems in the mediation of behavioural states like catalepsy.

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REFERENCES

Abuzzahab, F. S. Sr. (1973) J. Clin. Pharmacol. 13: 226–233

Aghajanian, G. K., Asher, I. M. (1971) Science 172: 1159–1161

Aghajanian, G. K., Bunney, B. S. (1975) in: Boissier, J. R., Hippius, H., Pichot, P. (eds) Neuropsychopharmacology. Excerpta Medica, Amsterdam, pp 444–452

Ayd, F. J. Jr. (1974) Dis. Nerv. Syst. 35: 447–452

Balsara, J. J., Jadhav, J. H., Chandorkar, A. G. (1979) Psychopharmacology 62: 67–69

Bunney, B. S., Roth, R. H., Aghajanian, G. K. (1975) Psychopharm. Commun. 1: 349–358

Carter, C. J., Pycock, C. J. (1977) Br. J. Pharmacol. 60: 267–268

Carter, C. J., Pycock, C. J. (1978) Naunyn-Schmiedeberg's Arch. Pharmacol. 304: 135–139

Chase, T. N., Murphy, D. L. (1973) in: Elliot, H. W., Okun, R., George, R. (eds) Annual Review of Pharmacology. Vol. 13 Annual Reviews Inc., Palo Alto, pp 181–197

Costall, B., Fortune, D. H., Naylor, R. J., Marsden, C. D., Pycock, C. J. (1975) Neuropharmacology 14: 859–868

Costall, B., Naylor, R. J. (1975) J. Pharm. Pharmacol. 27: 67–69

Franz, D. N. (1975) in: Goodman, L. S., Gilman, A. (eds) The Pharmacological Basis of Therapeutics. 5th edn Macmillan, New York, pp 227–244

Fuenmayor, L. D., Vogt, M. (1979) Br. J. Pharmacol. 67: 309–318

Fuxe, K., Jonsson, G. (1974) in: Costa, E., Gessa, G. L., Sandler, M. (eds) Serotonin: New Vistas; Advances in Biochemical Psychopharmacology. Vol. 10 Raven Press, New York, pp 1–12

Gumulka, W., Kostowski, W., Czlonkowski, A. (1973) Pharmacology 10: 363–372

Hamon, M., Bourgoin, S., Enjalbert, A., Bockaert, J., Hery, F., Ternaux, J. P., Glowinski, J. (1976) Naunyn-Schmiedeberg's Arch. Pharmacol. 294: 99–108

Kostowski, W., Gumulka, W., Czlonkowski, A. (1972) Brain Res. 48: 443–446

Matthysse, S. (1973) Fed. Proc. 32: 200–205

Medon, P. J., Leeling, J. L., Phillips, B. M. (1973) Life Sci. 13: 685–691

Parizek, J., Hassler, R., Bak, I. J. (1971) Z. Zellforsch. 115: 137–148

Pollin, W., Cardon, P. V., Kety, S. (1961) Science 133: 104–105

Rodriguez, R., Rojas-Ramirez, J. A., Drucker-Colin, R. R. (1973) Eur. J. Pharmacol. 24: 164–171

Ross, S. B., Renyi, A. L. (1975) Acta Pharmacol. Toxicol. 36: 382–394

Rubin, A. A., Yen, H. C., Pfeffer, M. (1967) Nature (London) 216: 578–579

Snyder, S. H., Banerjee, S. P., Yamamura, H. I., Greenberg, D. (1974) Science 184: 1243–1253

Wyatt, R. J., Vaughan, T., Galanter, M., Green, R., Kaplan, J. (1972) Ibid. 177: 1124–1126