The role of norfenfluramine in fenfluramine-induced mydriasis

Mydriasis has been described in patients after fenfluramine overdosage (White, Beckett & Brookes, 1967) and can also be detected after single oral doses of 40 or 80 mg. Local administration of fenfluramine 1% as eye drops did not produce pupillary dilatation in human volunteers (Turner, 1970). Norfenfluramine hydrochloride, the principal metabolite of fenfluramine, has been instilled into the conjunctival sac of one eye in 4 normal subjects in concentrations in water of 0·1 and 1% (pH 6·7 and 6·4 respectively), and pupil responses measured photographically by the method of Sneddon & Turner (1969). Dose-related mydriases occurred which were maximal at 1 or 2 h after administration (Fig. 1). Further studies in the same subjects showed that pretreatment of one eye for 2 days with guanethidine 5% in methylcellulose twice daily did not prevent the mydriasis produced by norfenfluramine 1%. In one of these subjects, 5 days pretreatment with guanethidine in one eye was followed by a norfenfluramine-induced mydriasis (12%), identical to that in the untreated eye. Pretreatment with thymoxamine 0·5% eye drops in one eye, 30 min before norfenfluramine 1% was instilled in both eyes of the same 4 subjects, reduced but did not completely prevent the mydriasis. Treatment with thymoxamine 0·5% eye drops in one eye 2 h after instillation of norfenfluramine 1% in both eyes completely abolished the mydriasis within 1 h in all subjects.

The interactions of norfenfluramine with guanethidine and thymoxamine differ from those seen with the indirectly-acting sympathomimetic amines amphetamine, hydroxyamphetamine, phenmetrazine and tyramine (Turner & Sneddon, 1968; Sneddon & Turner, 1969), in which the mydriases were prevented by pretreatment with guanethidine eye drops for 48 to 72 h and with thymoxamine eyedrops for 30 min. Sneddon & Turner (1969) also found that the mydriasis produced by the directly-acting amine phenylephrine was increased by pretreatment with guanethidine eye drops and suggested that this represented denervation supersensitivity produced by guanethidine. It may be, however, that increased conjunctival permeability due to an irritant action of guanethidine, might account for this phenomenon, and the mydriasis produced by norfenfluramine in the guanethidine-treated eye, similar to that in the control eye, may indicate that there is a direct sympathomimetic component of its

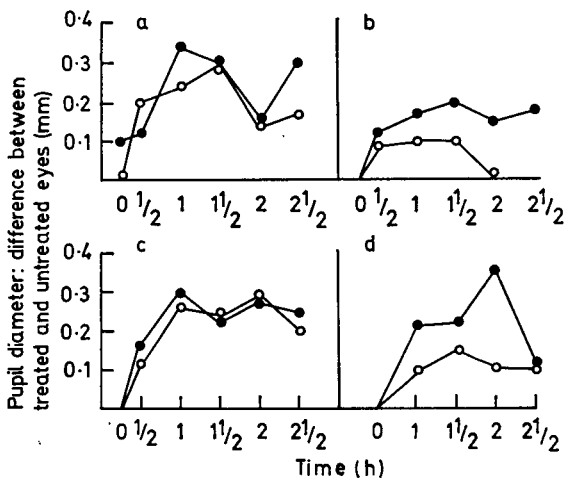

FIG. 1. Mydriatic action of norfenfluramine 0·1 (○) and 1·0% (●) in 4 subjects (a–d) expressed as the difference in pupil diameter (mm) between the treated and untreated eye.

action. It is unlikely that the mydriasis is produced by an anti-acetylcholine action because thymoxamine readily reversed it and also because norfenfluramine does not reduce acetylcholine-induced contractions of human gastric smooth muscle in concentrations of 1–100 ng ml^{-1} (Francis, personal communication).

The time course of mydriasis after oral fenfluramine 40 mg is more closely related to plasma levels of norfenfluramine than fenfluramine (Campbell & Kramer, personal communication), and it is probable, therefore, that fenfluramine-induced mydriasis is produced by norfenfluramine.

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MAO-inhibitory properties of anorectic drugs

Some anorectic drugs, like aminorex, chlorphentermine and phenmetrazine are known to induce pulmonary hypertension both in man and in animals (Loogen, 1972; Lüllmann, Parwaresch & others, 1972).

In examining the hypertensive mechanism involved in this drug-induced disease (Mielke, Seiler & others, 1972; 1973) we found a correlation between the increase of 5-hydroxytryptamine (5-HT) concentration in the lungs and the degree of pulmonary hypertension. Besides affecting the liberation and accumulation of 5-HT, some of the anorectic drugs seemed to influence the metabolic breakdown of this biogenic amine. Therefore the activity of monoamine oxidase was determined *in vitro* in the presence of several drugs of interest: aminorex, chlorphentermine, phentermine, phenmetrazine, methysergide (as 5-HT antagonist), and as reference compound the MAO-inhibitor iproniazid. Rat liver mitochondria were used as enzyme source.

Rat liver mitochondria were isolated according to Hawkins (1952) and to Davison (1957), the freeze-dried mitochondria were stored at −20°. The activity of the enzyme preparation was determined according to Mutschler, Springer & Wassermann (1970). The substrate was 5-HT (5×10^{-3}M). The compounds are shown in Fig. 1.

The slopes of the dose-response curve of the compounds are shown in Fig. 2. The I50-values (molar inhibitory concentrations, which depress the enzyme activity to 50%) of the compounds are: iproniazid 5×10^{-4}M, aminorex 5×10^{-4}M, chlorphentermine 4×10^{-3}M, phentermine 1×10^{-2}M; phenmetrazine and methysergide did not display any inhibitory activity.

Aminorex—a compound with a cyclized phenethylamine structure, and which gives rise to severe pulmonary hypertension in man (Gurtner, Gertsch & others, 1968; Loogen, 1972)—inhibited MAO to the same extent as iproniazid. This is of special interest with respect to its ability to liberate 5-HT *in vivo*. After a single injection of aminorex (10 mg kg^{-1}, rat) the 5-HT concentration of the lungs was three times as high as that of control animals. Furthermore, during chronic treatment with this compound the