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

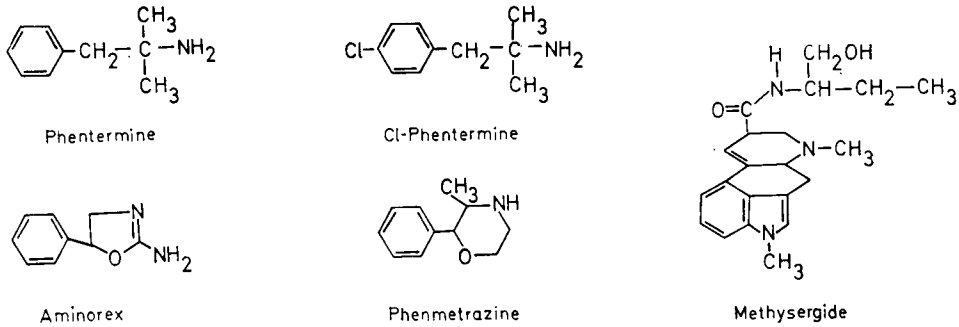

FIG. 1. Structure of some anorectic drugs and methysergide (5-HT antagonist).

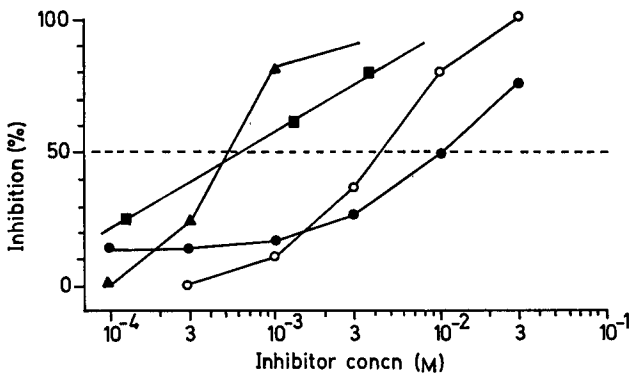

FIG. 2. Dose-response curves of some anorectic drugs and iproniazid using rat liver mitochondria as source for MAO and 5-HT (5×10^{-3} M) as substrate. The points are means of at least 10 single experiments, the standard error is in all cases <5%. ▲ iproniazid, ■ aminorex, ● phentermine, ○ chlorphentermine.

5-HT content of the rat lung remained elevated, even 24 h after the last injection (Mielke & others, 1972; 1973). This persistent high 5-HT concentration is probably caused by a synergism between liberation and inhibition of metabolic breakdown of 5-HT by aminorex.

Amphetamine-derivatives are known to have weak MAO inhibitory properties; the extent of inhibition however, depends on the substituents of the original molecule (Beregi, Hugon & others, 1970). We found chlorphentermine to be a less potent MAO inhibitor than aminorex, but more active than phentermine. The effectiveness of chlorphentermine *in vivo* is supposed to be greater than expected from *in vitro* experiments because chlorphentermine, in contrast to phentermine, is accumulated in several tissues, especially in the lungs during chronic treatment of rats (Rossen, Seiler & Wassermann, 1972; Lüllmann, Rossen & Seiler, 1973).

Methysergide increases the 5-HT concentrations particularly in the lungs (Mielke & others, 1972; 1973) and in tissues like gastrointestinal tract where 5-HT is extensively biosynthesized (Thompson & Campbell, 1967). Since our experiments did not reveal an inhibition by methysergide of MAO, other mechanisms must be responsible for raising 5-HT levels, like stimulation of 5-HT-biosynthesis (Thompson & Campbell, 1967).

A similar mechanism may be attributed to phenmetrazine. In our experiments this drug did not inhibit the MAO of rat liver mitochondria. It does, however, increase the excretion of 5-hydroxyindole-3-acetic acid, the main metabolite of 5-HT, in man, which is discussed as a stimulation of 5-HT biosynthesis by Degkwitz & Sieroslawski (1963).

According to our results the MAO inhibitory properties of aminorex and chlorphentermine may essentially be involved in the pathogenesis of pulmonary hypertension induced by these drugs, while the role of phenmetrazine in this disease is to effect high 5-HT levels originating from a stimulated biosynthesis.

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Depression of ganglionic transmission by normetadrenaline

It is generally accepted that the synaptic action of noradrenaline is terminated by neuronal reuptake and extraneuronal uptake, as well as by enzymatic 3-*O*-methylation (COMT). Free noradrenaline released from the noradrenergic neuron by some drugs (Kopin, 1966; Leitz & Stefano, 1971), released spontaneously (Langer, 1970) or during electrical stimulation (Hertting & Axelrod, 1961; Langer, 1970) is metabolized in the first step mainly to normetadrenaline (NMA), although in some tissues deamination prevails (Tarlov & Langer, 1971). Free noradrenaline in the brain is also converted to NMA (Glowinski & Baldessarini, 1966; Jonason, 1969; Schildkraut, Draskoczy & Sun Lo, 1972).

Many experimental data prove the role of noradrenaline and dopamine as potential inhibitory transmitters in ganglionic transmission (for ref. see Kadzielawa, 1972). In sympathetic ganglia, COMT is located extraneuronally (Giacobini & Kerpel-Fronius, 1969), and thus is probably involved in the enzymatic inactivation of noradrenaline and dopamine in ganglionic synapses. The question arises whether NMA, as a metabolite of synaptically active noradrenaline, can modify synaptic transmission. This study reports the results of our experiments on the ganglionic effects of NMA.

Cats were anaesthetized intraperitoneally with a mixture of chloralose (40 mg kg^{-1}) and urethane (600 mg kg^{-1}), as described by Kadzielawa, Gawecka & Kadielzawa (1968) and Kadzielawa & Widy-Tyszkiewicz (1969) and the preganglionic sympathetic trunk isolated from vagus nerve was stimulated with rectangular pulses. Evoked postganglionic activity was recorded from the external carotid nerve by bipolar