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

platinum electrodes. Ganglion potentials were amplified and displayed on an oscilloscope. NMA hydrochloride (0·5–2·0 mg) and noradrenaline bitartrate (10–30 μg), dissolved in normal saline, were injected into the common carotid artery in a volume of 0·2 ml. Desipramine (6 mg kg^{-1}) was infused intravenously.

NMA (0·5–2·0 mg) injected into the common carotid artery transiently depressed ganglionic transmission. It was however about 50 times less potent than noradrenaline. This may be related to the synaptic barrier, as it is likely to be the case with dopamine. The sympathomimetic effects of metadrenaline and NMA are also about 40–100 or even 1000 times weaker than that of corresponding amines (Bacq & Renson, 1961; Allen, Calvert & Lum, 1969). NMA had no effect on the amplitude of the nerve-action potential in concentrations up to 10^{-3} g ml^{-1} (isolated sciatic nerve of frog).

Metadrenaline and NMA are potent inhibitors of the extraneuronal uptake of noradrenaline (Burgen & Iversen, 1965; Iversen, 1967; Gillespie, 1968) and this factor is probably responsible for the augmentation of the pressor and other responses to catecholamines by metadrenaline and NMA (Bacq & Renson, 1961; Allen & others, 1969), however in other studies only additive or inhibitory effects were noted. We were unable to demonstrate the potentiating influence of NMA (1–2 mg) on the inhibitory action of noradrenaline (20–30 μg) on ganglionic transmission. This is in accordance with the findings of Burgen & Iversen (1965) and Iversen (1967), who demonstrated that NMA does not inhibit neuronal uptake. Nevertheless, it would be interesting to know whether the neuronal pre- and postsynaptic uptake systems are identical.

We have previously demonstrated the potentiation of the ganglionic inhibitory effects of noradrenaline and adrenaline by desipramine (Kadzielawa & Widy-Tyszkiewicz, 1969). Desipramine (6 mg kg^{-1}, i.v.), however, does not change the ganglionic inhibitory action of NMA (1·5 mg). This fact may be taken into account in considering the possible influence of tricyclic antidepressants on the function of NMA in the brain.

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