The centrally induced fall in blood pressure after the infusion of amphetamine and related drugs into the vertebral artery of the cat

According to Schmitt, Schmitt & Fenard (1971) the central hypotensive action of clonidine is due to the stimulation of central α-adrenoceptors belonging to an inhibitory neuron, located in the region of the nucleus tractus solitarii. The stimulation of such receptors would lead to a *decrease* in sympathetic tone in the periphery, thus bringing about a reduction in blood pressure similar to that induced by short-lasting stimulation of the carotid sinus. According to this view, the antihypertensive drug clonidine should be considered as a *sympathomimetic* agent with predominating central action, although weak peripheral sympathomimetic properties have also been demonstrated (Hoefke & Kobinger, 1966). If this hypothesis is correct, all sympathomimetic agents with central action should decrease peripheral sympathetic tone when applied to the region where the postulated α-receptors are located. For this purpose we studied the influence of amphetamine and some related compounds on blood pressure after infusion into the left vertebral artery. Upon infusion into the cat left vertebral artery the test drug will initially reach the rhombencephalon where the receptors are believed to be located. The technique has been described (van Zwieten, Bernheimer & Hornykiewicz, 1966; Sattler & van Zwieten, 1967; Henning & van Zwieten, 1968). The experiments were made in cats of either sex (2–4 kg) anaesthetized with 60 mg chloralose/kg, given intraperitoneally. The drugs (in saline) were infused into the left vertebral artery at a rate of 0·1 ml kg^{-1} min^{-1}. Arterial blood pressure was taken from a femoral artery and recorded continuously on a smoked drum. Amphetamine (50 μg/kg) caused an acute and pronounced fall in blood pressure (~20 mm Hg), although the intravenous injection of the same dose increased pressure by about 30% of its control value. A higher dose (150 μg/kg) of amphetamine decreased blood pressure by approximately 35% of its control value after infusion into the vertebral artery. The effects were confirmed in at least 6 cats for each dose. Intravenously injected piperoxan (0·6 mg/kg) caused a transient fall in blood pressure by about 10 mm Hg. After normalization of pressure the infusion of amphetamine (150 μg/kg) into the vertebral artery did not influence blood pressure any more (n = 4). Similar results were obtained with yohimbine (n = 3). Consequently, both α-sympatholytic agents abolish the central hypotensive action of amphetamine (present studies) but also that of clonidine (Schmitt & others, 1971). Similarly, pretreatment of the animals with 1 mg haloperidol/kg, given intravenously 30 min before amphetamine (150 μg/kg, vertebral artery) abolished the central hypotensive action of the latter drug. Haloperidol has been reported to block central adrenoceptors (Andén, Corrodi & others, 1970). In reserpine-pretreated cats (1 mg/kg, 24 h before the actual experiment), the blood pressure was about 20 mm lower than in normal cats. In reserpinized cats the infusion of amphetamine 150 μg/kg into the left vertebral artery did not reduce blood pressure, but induced a small hypertensive effect probably due to the transition of amphetamine into the peripheral circulation. The present studies suggest that, like clonidine, amphetamine is also capable of stimulating the hypothetical α-adrenoceptors in the rhombencephalon, resulting in a decrease in peripheral sympathetic tone. The stimulation of the α-receptors in the cns after infusion of amphetamine into the vertebral artery probably occurs by noradrenaline, mobilized by amphetamine rather than by the drug itself, since the central hypotensive action did not occur in reserpinized rats. The injection of noradrenaline into the cisterna or into the lateral ventricle (to avoid the blood brain barrier) have been reported to decrease peripheral sympathetic tone

(Kaneko, 1960; McCubbin, 1960). Clonidine, which does not mobilize noradrenaline in the brain, probably stimulates the α-receptors itself (direct central sympathomimetic action).

Ephedrine (50 μg/kg), phentermine (300 μg/kg), and chlorphentermine (300 μg/kg) also reduced blood pressure after infusion into the left vertebral artery. The effect of ephedrine developed rather slowly and persisted for about 1 h. Chlorphentermine was more active than phentermine. Intravenously injected ephedrine (50 μg/kg) or phentermine (300 μg/kg) showed hypertensive effects, but chlorphentermine slowly reduced blood pressure after intravenous injection (300 μg/kg). Probably, the central effect of this drug is quantitatively more important than its peripheral sympathomimetic properties. The high lipid solubility of chlorphentermine may contribute to this phenomenon.

The decrease in peripheral sympathetic tone, initiated by the stimulation of central α-adrenoceptors seems to be a general principle which would apply to all drugs with central sympathomimetic properties when applied via a central route of administration. Until now, clonidine is the most potent drug in this context. The central hypotensive properties of α-methyldopa (Henning & van Zwieten, 1968), L-dopa (Rubenson, 1971) and *m*-tyrosine (Rubenson, 1971) might also be explained by such a mechanism, since in the brain these amino-acids are known to be converted into sympathomimetic agents that may stimulate the central α-adrenoceptors.

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