Inhibition of amine uptake in tubero-infundibular dopamine neurones and in catecholamine cell bodies of the area postrema

SIR,—Previous studies using the histochemical fluorescence method (*cf.* Hillarp, Fuxe & Dahlström, 1966) have demonstrated the existence of tubero-infundibular dopamine neurones, the terminals of which converge on the primary capillary plexus of the hypophysial portal system (Fuxe, 1963; 1964; Fuxe & Hökfelt, 1966; Lichtensteiger & Langemann, 1966). Since these dopamine nerve terminals and their non-terminal axons lie outside the blood-brain barrier as do the catecholamine cell bodies of the area postrema (Fuxe & Hillarp, 1964) it has proved possible to examine the uptake of catecholamines in these neurones. It was found that these neurones, like the peripheral adrenergic neurones (Hamberger, Malmfors, Norberg & Sachs, 1964; Malmfors, 1965), have an amine uptake-concentration mechanism which is unaffected by reserpine treatment (Fuxe & Hillarp, 1964). *In vitro* experiments by Hamberger & Masuoka (1965) on the uptake of amines in brain slices showed that most of the central dopamine and noradrenaline neurones appear to have this mechanism. Experiments with the peripheral and central noradrenergic neurones (Malmfors, 1965; Carlsson, Fuxe, Hamberger & Lindqvist, 1966) showed that this uptake-concentration mechanism (the "membrane pump"), which in all probability is localised at the level of the nerve cell membrane, can be blocked by desipramine and (+)-amphetamine but not by reserpine. The present investigation aimed at examining the effects of these drugs on the uptake mechanism of the tubero-infundibular dopamine neurones and that of the catecholamine cell bodies of the area postrema and of the superior cervical ganglia in reserpine-treated animals.

α-Methylnoradrenaline (0·2–1 mg/kg) and dopamine (1–5 mg/kg) were given slowly in the sublingual vein of male Sprague-Dawley (200–250 g) rats, reserpine-pretreated (10 mg/kg, i.p., 4–12 hr before killing) to block the uptake in the amine granules and deplete the endogenous monoamines (Carlsson, 1965). In the experiments with dopamine, nialamide (100 mg/kg, i.p.) was given 3 hr before death. The rats were killed 15 min after the amine injection by decapitation under light ether anaesthesia. To certain groups of rats, desipramine (25 mg/kg, i.p.) and (+)-amphetamine (10–25 mg/kg i.p.) respectively were administered 30 min before the amine injection. The animals were killed and the medulla oblongata, diencephalon and the superior cervical ganglia were dissected, freeze-dried and treated with formaldehyde gas for 1 hr (Dahlström & Fuxe, 1964; Hamberger, Malmfors & Sachs, 1965). From all animals iris stretch preparations were made (Malmfors, 1965). The catecholamine cell bodies of the area postrema and of the superior cervical ganglia were studied only after α-methylnoradrenaline injection.

In the rats treated with reserpine or reserpine-nialamide alone, no fluorescent dopamine nerve terminals could be seen in the external layer of the median eminence, nor could any catecholamine cell bodies be distinguished in the area postrema. After α-methylnoradrenaline or dopamine injection, green fluorescent nerve terminals and non-terminal axons appeared in the median eminence, in the rat iris and around the basal arteries with low to strong intensity depending on the dose used. The catecholamine nerve cell-bodies of the area postrema and the superior cervical ganglia appeared with a green fluorescence of medium to strong intensity. If desipramine was given before the amine injection, no fluorescence appeared in the area postrema catecholamine cells, whereas the appearance of fluorescence in the dopamine nerve terminals and non-terminal axons of the median eminence could not be prevented. However, in the same

animal the uptake of amine into the noradrenaline nerve terminals of the iris and of the basal arteries was completely blocked. This was true also for the noradrenaline cell bodies of the superior cervical ganglion. If, on the other hand, (+)-amphetamine was given, the amine uptake was completely blocked both in the dopamine nerve terminals and non-terminal axons of the median eminence and in the catecholamine cell bodies of the area postrema. The uptake of amine was blocked also in peripheral noradrenaline cell bodies and terminals.

The present paper gives further evidence for the view that the "membrane-pump" is distributed along the entire catecholamine neurone (cell body, axon, terminal) since the uptake is blocked in all parts of the neurone. The findings strongly suggest that desipramine is active only on noradrenaline neurones, and not on dopamine neurones, whereas amphetamine is able to block the uptake of dopamine or α-methylnoradrenaline in both noradrenaline and dopamine neurones. Thus, fundamental differences probably exist between the dopamine and noradrenaline neurones. Experiments with brain slices and on the dopa-induced amine accumulation in the brain have given similar results (*cf.* Carlsson & others, 1966).

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