Prevention of DOCA saline hypertension by central 6-hydroxydopamine; role of saline intake

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Destruction of central noradrenergic neurones by intracisternal (i.c.) injection of 6-hydroxydopamine (6-OHD) prevents the onset of renal hypertension in rabbits, (Chalmers, Dollery, Lewis & Reid, 1974) DOCA saline and spontaneous hypertension in rats (Haeusler, Finch & Thoenen, 1972). Central noradrenergic neurones may initiate the rise in arterial pressure in experimental hypertension. However, since food and water appetite is diminished in animals treated with central 6-OHD, an alternative explanation might be that these animals are salt depleted and show less rise in arterial pressure for this reason. Breese, Cooper & Smith (1973) noted DOCA saline rats treated with i.c. 6-OHD consume less saline than intact DOCA saline rats.

We have investigated the role of saline consumption in the effect of i.c. 6-OHD on this type of hypertension by restricting saline intake in a group of rats implanted with DOCA (30 mg pellet). Rats in this group D (n = 10) were given saline equivalent to the average consumption of rats in group C (n = 10) which had been pretreated with intraperitoneal pargyline (40 mg kg) and i.c. 6-OHD (200 μg x 2) and implanted with DOCA. Two control groups were used, a normotensive group A (n = 8) without DOCA implant and an hypertensive group B (n = 7) with DOCA implant. All rats were uninephrectomized and given only 0.9% saline to drink.

At 5 weeks after implantation of DOCA the systolic arterial pressures in the groups were: A 140.4 ± 3.5, B 200.4 ± 6.9, C 150.1 ± 3.3, D 190.9 ± 5.4 (mmHg ± SEM). Saline consumption in Group C was significantly diminished throughout, and during the 5th week the consumption in Group C was 29.3 ± 5.0 ml/100 g/24 hrs compared with 44.1 ± 6.1 ml/1000 g/24 hrs in Group B. However, restriction of Group D to this intake did not prevent the hypertension.

Hence although saline intake is diminished in rats centrally depleted of noradrenaline, this is not the explanation for the failure to develop hypertension. Central noradrenergic neurones play a more direct role in maintaining arterial pressure.

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Loss of noradrenergic and dopaminergic terminals in the chronically isolated cerebral cortex of the cat.

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The increased epileptogenicity of chronically isolated cortex is most probably a consequence of denervation. One possibility is that denervation suppresses inputs of extracortical origin that normally exert a tonic inhibitory control on cortical excitability. Amongst the transmitter candidates for such an inhibitory control other than GABA, the authors have studied catecholamines (CA) in the cat cerebral cortex.

The synthesis of ^{3}H-noradrenaline (NA) and ^{3}H-dopamine (DA) from ^{3}H-tyrosine estimated in slices of the suprasylvian gyrus and of the cerebellar cortex revealed that the ^{3}H-DA/^{3}H-NA ratio was higher in the cerebral cortex than in the cerebellum. The uptake of ^{3}H-DA estimated in homogenates of the suprasylvian cortex was not only partially blocked by desipramine but also by benztropine (blocker of CA uptake in dopaminergic terminals). These data suggest that catecholaminergic innervation in the cerebral cortex of the cat can be attributed to dopaminergic as well as noradrenergic terminals and are in agreement with recent biochemical and

histochemical results which clearly indicated the existence of DA terminals in the rat cerebral cortex.

In further experiments: 1-^{3}H-dopamine uptake was estimated in homogenates of the chronically isolated suprasylvian gyrus and compared to that of the contralateral side. ^{3}H-dopamine uptake was markedly reduced 27 days after the operation and the residual ^{3}H-amine uptake was not sensitive to benztropine or desipramine. 2-^{3}H-CA synthesis from ^{3}H-tyrosine was no more detectable in slices of the chronically isolated suprasylvian gyrus (27 days). Thus these two techniques lead to similar results: both types of catecholaminergic terminals degenerate in the chronically isolated area and dopaminergic as well as noradrenergic terminals, are exclusively of extracortical origin. This latter fact suggests the absence of dopaminergic interneurons in the cat neocortex.

The authors discuss the possibility that this dramatic decrease in the CA available, secondary to deafferentation, could be in part responsible for the augmented duration of the epileptiform after discharge in the chronically isolated cortex.

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The effect of dopamine receptor stimulants on locomotor activity and cyclic AMP levels in the rat striatum

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Stimulation of central dopamine receptors leads to enhanced locomotor activity (Van Rossum & Hurkmans, 1964) and dopamine stimulates striatal adenyl cyclase preparations (Kebabian, Petzold & Greengard, 1972; Miller, Horn, Iversen & Pinder, 1974). This work examines the interrelationship between the actions of three potential dopamine receptor stimulants upon both locomotion and cyclic AMP levels in the caudate nucleus of rats.

Drugs dissolved in 5μl of 0.9% NaCl were injected into the lateral ventricles of male Wistar rats using the method of Noble, Wurtman & Axelrod (1967). Twenty minutes later individual animals were placed in an Animex type DSE activity meter and large movements recorded on sensitivity 10 for 24 hours. Cyclic AMP was measured in the striatum and cortex by the *in vitro* system of Munday, Poat & Woodruff (1974). The cyclic AMP was extracted and estimated using a bovine muscle protein (Gilman, 1970). Injections of 2-amino-6, 7-dihydroxy-1,2,3,4-tetrahydronapthalene (ADTN) caused a stimulation of motor activity. There was a lag of 1-2 h before the onset of the effect and once initiated the stimulation continued for up to 18 hours.

The activity characteristically consisted of forward walking, rearing and running movements. Activity was increased to 260% of controls after a 50μg injection and a maximum stimulation of 648% occurred at 200 μg (6 rats in each group). The dimethylether of ADTN injected over a similar dose range was without effect. Ergometrine, 50 or 100 μg, also stimulated locomotor activity, although rearing movements were absent. The time course of the effect was also different, the lag period being short (10-20 min) and the duration 5 hours. The locomotor stimulation induced by either ADTN or ergometrine was abolished by pimozide (0.1 mg/kg i.p.) or haloperidol (0.5 mg/kg i.p.) injected 30 min before intraventricular injection.

Dopamine and ADTN (30 μM) caused striatal cyclic AMP levels to rise to 339 ± 97.3% (4) and 269 ± 33.8% (4) of control levels. Basal levels were in the range 13-18 pmoles cAMP/mg protein. Ergometrine (30 μM) caused a smaller but highly significant stimulation (160 ± 14.3% (6)). The dimethylether of ADTN was ineffective even at 100 μM. Dopamine and ADTN were equipotent at 10, 30 and 100 μM which agrees with iontophoretic studies (Woodruff, Elkhawad, Crossman & Walker, 1974). At 30 μM all three compounds were without effect upon cortical cyclic AMP, but at 100 μM dopamine and ergometrine caused an approximate doubling of the levels.