INTRACISTERNAL 6-HYDROXYDOPAMINE (6-OHDA) AND 5,6 DIHYDROXYTRYPTAMINE (5,6-DHT) IN EXPERIMENTAL HYPERTENSION

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THE experiments reported here were designed to examine the role of central noradrenergic and serotonergic nerves in the pathogenesis of experimental renal hypertension and experimental neurogenic hypertension.

Small doses of 6-OHDA (600 μg/kg) or of 5,6-DHT (300 μg/kg) were injected intracisternally (i.c.) into New Zealand white rabbits to produce selective ablation of either catecholaminergic (THOENEN and TRANZER, 1968; URETSKY and IVERSEN, 1970; CHALMERS and REID, 1972) or serotonergic (BAUMGARTEN and LACHENMAYER, 1972; BAUMGARTEN *et al.*, 1971) nerves in the brain and spinal cord. Small doses of these drugs given in this way do not have any permanent effects on peripheral autonomic nerves (CHALMERS and REID, 1972).

Neurogenic hypertension was produced by section of the carotid sinus and aortic nerves causing an immediate increase in mean arterial pressure which persisted throughout a two-week observation period in control animals (Fig. 1A). In animals pretreated with 6-OHDA, sinoaortic denervation only produced a transient increase in arterial pressure lasting two days and thereafter pressure returned to pre-denervation control levels, (Fig. 1A). When 6-OHDA was given to rabbits with sustained neurogenic hypertension produced by sinoaortic denervation, it caused an immediate and persistent return of pressure to pre-denervation levels (Fig. 1B). Central norepinephrine concentrations were reduced in all brain and cord areas in the 6-OHDA treated animals, especially in the spinal cord where the levels fell to $<10\%$ of the values seen in control rabbits (CHALMERS and REID, 1972).

Intracisternal 6-OHDA was then used in rabbits with experimental renal hypertension produced by bilateral wrapping of the kidneys with cellophane. Pretreatment with 6-OHDA markedly reduced the rise in arterial pressure following renal wrapping (Fig. 1C). In rabbits with sustained hypertension following renal wrapping, intracisternal 6-OHDA caused the pressure to return towards control levels whether given six weeks (Fig. 1D, black circles) or 18 weeks (Fig. 1D, black squares) after the operation.

5,6-DHT given intracisternally caused a reduction in endogenous serotonin concentration, most marked in the spinal cord, where the levels fell to approximately 25 per cent of control. There were no significant changes in endogenous catecholamine concentrations. Pretreatment with 5,6-DHT caused a small reduction in mean arterial pressure in normal animals and completely prevented the hypertension that usually follows sinoaortic denervation (Fig. 1E). When given to animals with sustained neurogenic hypertension produced by section of the buffer nerves, 5,6-DHT caused a significant ($P < 0{\cdot}05$) fall in arterial pressure, though the pressure remained above initial normotensive control levels (Fig. 1F).

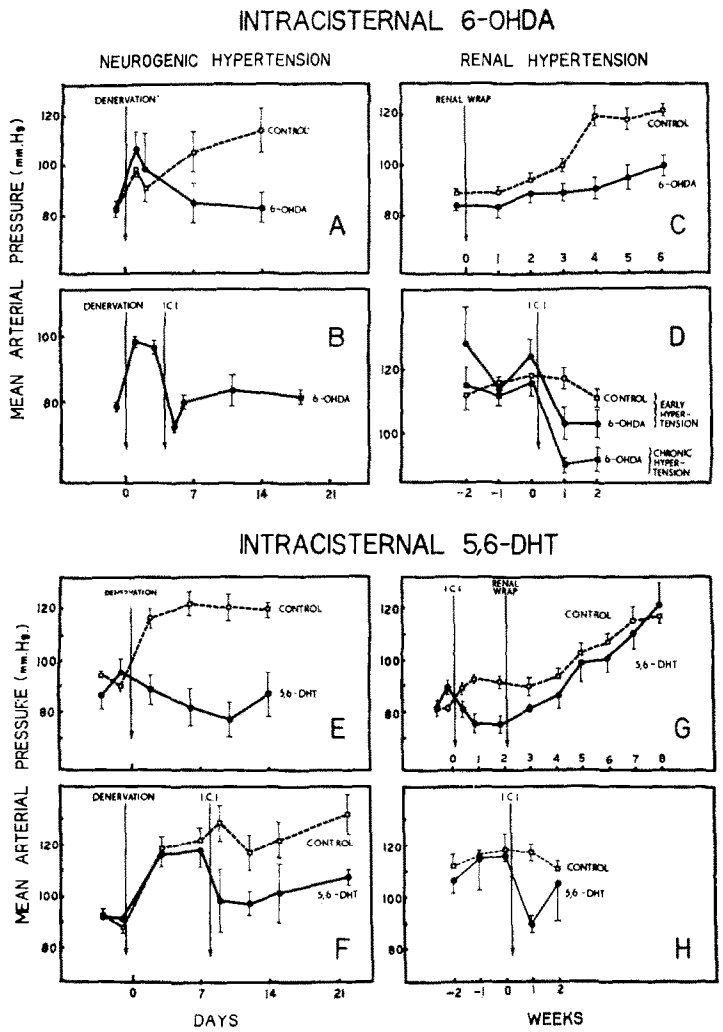

FIG. 1.—Mean arterial pressure changes in animals subjected to sinoaortic denervation (4 left panels) or bilateral renal wrapping (4 right panels). "ICI" indicates intracisternal injection of vehicle solution in control animals and of 6-OHDA or 5,6-DHT in test animals as labelled. Values represent means ± S.E. of the mean.

5,6-DHT given intracisternally did not in any way modify the development of renal hypertension produced by bilateral wrapping of the kidneys with cellophane; in animals pretreated with 5,6-DHT, renal wrapping caused the pressure to rise at the same rate and to the same extent as it did in the control rabbits (Fig. 1G). When the 5,6-DHT was given intracisternally six weeks after the development of renal hypertension, it caused only a transient and minor lowering of arterial pressure (Fig. 1H).

These experiments suggest that central noradrenergic and serotonergic nerves both participate in the regulation of systemic arterial pressure, though in different ways. Both types of neurones appear to play a role in neurogenic hypertension but only the noradrenergic nerves seem to be important in renal hypertension.

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