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# Chronic guanethidine and adrenal medullary function in the rat

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The adrenal medulla has long been likened to a modified sympathetic ganglion. Recently it has become well documented that high doses of guanethidine chronically administered are markedly toxic to sympathetic ganglia (Angeletti & Levi-Montalcini, 1970; Heath, Hill & Burnstock, 1974) in both adult (Burnstock, Evans & others, 1971; Juul & McIsaac, 1973; Jensen-Holm & Juul, 1971) and newborn (Eranko & Eranko, 1971a, b; Angeletti, Levi-Montalcini & Caramia, 1972; Johnson, Cantor & Douglas, 1975) rats. Ganglionic cellular lysis and a decreased cholinesterase activity have been reported by Jensen-Holm & Juul (1968, 1970) and Juul & McIsaac (1973). Burnstock & others (1971), using histochemical fluorescence, found that less than 2% of the nerve cell bodies remained in the superior cervical ganglion after six weeks of guanethidine treatment (25 to 30 mg $kg^{-1}$ $day^{-1}$, i.p.). Thus, to ascertain whether guanethidine-induced neurotoxicity extends to the adrenal medulla, we have examined the effect of chronic guanethidine treatment upon the release of medullary catecholamines.

Male Sprague-Dawley rats (175–200 g), fed standard rat pellets and with free access to water, were randomly divided into four groups (2 control and 2 test). One test group was injected with guanethidine monosulphate 20 mg $kg^{-1}$ $day^{-1}$ (i.p.) for 14 days, and the other with 100 mg $kg^{-1}$ $day^{-1}$ (i.p.) for 14 days. Both control groups received an equal volume of 0·9% w/v sodium chloride $day^{-1}$ (i.p.) for 14 days. To more clearly control any chronically induced changes, one of the control groups received an acute dose of guanethidine (20 mg $kg^{-1}$, i.p.) 2 h before use.

On the day of study, animals were pretreated with atropine (1 mg $kg^{-1}$, i.p.), anaesthetized with sodium pentobarbitone (60 mg $kg^{-1}$, i.p.) and pithed to enable stimulation of the entire sympathetic outflow of the thoraco-lumbar region of the spinal cord according to the method of Gillespie & Muir (1967). Rats were surgically prepared for the recording of blood pressure and for the intravenous injection of drugs. Selective field stimulation of the whole left adrenal gland was made as described previously (Romanyshyn, Asaad & Clarke, 1974; Clarke & Romanyshyn, 1976). The method assesses adrenal medullary release by comparing the blood pressure rise following electrical stimulation with dose-effect curves to intravenous adrenaline.

Fig. 1 shows the frequency-response curves to adrenal field stimulation and the corresponding dose-effect curves to adrenaline. Adrenal release appears largely unimpaired regardless of whether guanethidine was administered acutely or chronically. For instance, compared with acute guanethidine, the frequency-response

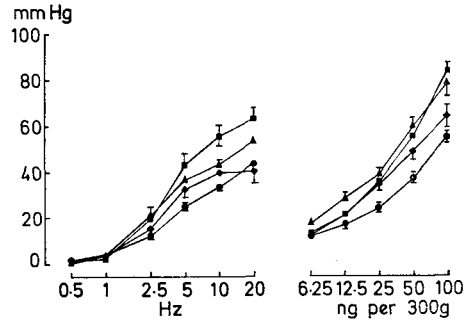


FIG. 1. Relation between blood pressure increase (mm Hg) and log frequency (Hz) of adrenal field stimulation (1 ms, 20V for 20 s) or dose of intravenously injected adrenaline (ng per 300 g body weight) in rats. ● control (n = 6). ■ guanethidine (20 mg $kg^{-1}$, i.p. 2 h previously, n = 7). ▲ guanethidine (20 mg $kg^{-1}$ $day^{-1}$, i.p. for 14 days, n = 7). ◆ guanethidine (100 mg $kg^{-1}$ $day^{-1}$, i.p for 14 days, n = 7).

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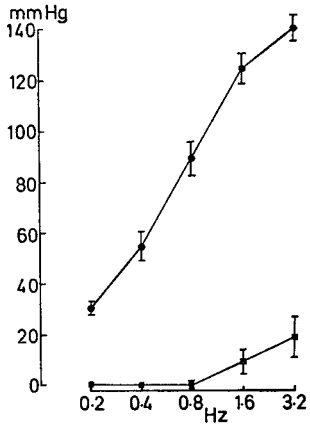


FIG. 2. Relation between blood pressure increase (mm Hg) and frequency (Hz) of spinal cord stimulation (1 ms, 60 v for 10 s) in rats. ● control (n = 6). ■ guanethidine (20 mg $kg^{-1}$ $day^{-1}$, i.p. for 14 days, n = 7).

curve following the 100 mg $kg^{-1}$ treatment is depressed but a similar shift accompanied the dose-effect curve to adrenaline. In general, changes in the frequency-response relations may be explained by changes in the cardiovascular responsiveness of the released amines. That guanethidine given acutely fails to alter adrenal medullary release has been shown previously in other species (Abercrombie & Davies, 1963; Boura & Green, 1963).

In some experiments, the entire sympathetic outflow was stimulated at the level of the spinal cord (Fig. 2). In all cases, animals treated with guanethidine (20 mg $kg^{-1}$ $day^{-1}$, i.p. for 14 days) exhibited marked depression of the evoked pressor responses. These observations confirmed that guanethidine remained active on neurons and helped to validify the lack of effect on the adrenal medulla. In fact, the remaining responses, at 1·6 and 3·2 Hz, may be attributed to adrenal medullary release.

The present findings prove that adrenal catecholamine release remains within functionally normal limits following doses of guanethidine which are known to profoundly damage sympathetic ganglia. These data are in agreement with biochemical determinations showing normal adrenal adrenaline concentrations following chronic guanethidine administration (Cass & Callingham, 1964; Johnson & others, 1975). Noradrenaline concentrations have been reported to increase after daily doses of guanethidine (10 mg $kg^{-1}$) but a higher dose (50 mg $kg^{-1}$) revealed no change (Cass & Callingham, 1964). Thus, it cannot be construed that guanethidine is completely without effect upon the adrenal medulla. However, the previous biochemical data and the present functional studies may be combined to conclude that adrenal medullary cells are distinctly unlike those of sympathetic neuronal cell bodies with regard to guanethidine-induced toxicity.

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