These results show that angiotensin increases responses to endogenously released noradrenaline in the absence of both an intact central nervous system and adrenal glands. The mechanism of the effect is probably different from that of noradrenaline, tyramine or DMI.

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**Uptake and metabolism of $^3$H-noradrenaline by normal and by denervated vasa deferentia of guinea-pigs and rats**

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Surgical denervation of the organs innervated by the superior cervical ganglion reduces but does not abolish the uptake of catecholamines by these tissues (Hertting, Axelrod, Kopin & Whitby, 1961 ; Strömblad & Nickerson, 1961 ; Fischer, Kopin & Axelrod, 1965). Uptake of noradrenaline by the heart is also reduced after sympathetic ganglionectomy (Hertting & Schiefthaler, 1964 ; Hertting, 1965). We have now compared noradrenaline uptake by normally innervated and by denervated vasa deferentia.

Guinea-pigs and rats were killed 8 days after surgical denervation of one vas deferens by separating it from its mesenteric attachments (Birmingham, 1967, 1968). The uptake and metabolism of $^3$H-noradrenaline by the freshly chopped tissue of normal and denervated vasa was measured by the method previously described for hearts (Iversen, 1963). After incubation for 10 min in 10 ml. Krebs–Henseleit solution containing (±)-$^3$H-noradrenaline 137 nc/ml. the tissue was homogenized with 0.4N perchloric acid. Aliquots of the supernatant perchloric acid were used for the assay of total radioactivity and of $^3$H-noradrenaline and $^3$H-normetanephrine fractions obtained by ion exchange chromatography. Total endogenous noradrenaline content was assayed on the same samples by a spectrophotofluorimetric method (Euler & Lishajko, 1961) ; for denervated vasa it was reduced by more than 95% when compared with control values.

Normal vasa from both species showed a considerable accumulation of radioactivity after incubation with $^3$H-noradrenaline (Table 1), giving a tissue : medium ratio of almost 10 : 1. Denervated vasa from the same animals also accumulated radioactivity, but only to levels between 30 and 40% of normal vasa. There was a significantly higher proportion of labelled noradrenaline metabolites in the denervated vasa than in the controls (Table 1).

TABLE 1. *Radioactivity (nc/g; mean±S.E.M., six experiments) of perchloric acid extracts of normal and denervated vasa deferentia after 10 min incubation with $^3$H-noradrenaline (137 nc/ml.; $7 \times 10^{-7}$M)*

| | Rats | | Guinea-pigs | |
|---|---|---|---|---|
| | Normal | Denervated | Normal | Denervated |
| Total radioactivity | 1110±80 | 472±44† | 1287±59 | 585±37† |
| $^3$H-noradrenaline fraction | 1020±63 | 349±31† | 1242±53 | 491±29† |
| $^3$H-normetanephrine fraction | 12·8±1·5 | 25·0±4·1* | 10·1±1·5 | 15·4±1·6* |
| $^3$H-deaminated metabolites | 77 | 98 | 35 | 79 |
| Noradrenaline concentration (μg/g) | 9·56±0·52 | 0·30±0·19 | 9·57±0·75 | 0·38±0·10 |

The figure for deaminated metabolites was obtained by subtracting the figures for noradrenaline and normetanephrine from the total radioactivity.
The extracellular space is 40% of wet weight; total radioactivity and noradrenaline values include a correction to allow for this.

* $P<0.05$. † $P<0.001$ normal compared with denervated.

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The residual capacity of surgically denervated vasa to take up noradrenaline may be considered to be a consequence of incomplete denervation or to represent an uptake mechanism independent of adrenergic nerves. If the lack of response of stripped vasa deferentia to electrical stimulation and to tyramine, the increased sensitivity to noradrenaline, the virtual disappearance of endogenous noradrenaline and the disappearance of fluorescent varicose nerve terminals (Birmingham, 1967, 1968) are accepted as evidence of complete denervation, then the residual uptake mechanism is not in adrenergic nerve terminals. Evidence has already been presented for the presence of residual, presumably extraneuronal, monoamine oxidase in denervated vasa (Iversen, Jarrott & Langer, 1968); perhaps the residual uptake mechanism has a similar location.

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**Comparative β-adrenoceptive stimulant properties of salbutamol (AH 3365), orciprenaline and soterenol (MJ 1992)**

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The activities of the β-adrenoceptive receptor stimulants salbutamol, soterenol and orciprenaline have been examined on *in vitro* and *in vivo* preparations of the guinea-pig for potency, duration and selectivity of action. Salbutamol and orciprenaline have been the subject of previous reports (Brittain, Farmer, Jack, Martin & Simpson, 1968; Engelhardt, Hoefke & Wick, 1961).

Salbutamol (0.02–0.5 μg/ml.), soterenol (0.02–0.5 μg/ml), and orciprenaline, (0.25–10 μg/ml.) inhibited responses of the isolated guinea-pig trachea to transmural electrical stimulation. Increases in the force of contraction of guinea-pig left atria which were isolated and electrically driven were obtained with salbutamol, (1–50 μg/ml.), soterenol (5–100 μg/ml.) and orciprenaline (0.25–10 μg/ml.). The cumulative dose-response curves for salbutamol and soterenol on isolated trachea and isolated atria were less steep and had lower maxima than those obtained with isoprenaline. The dose-response curves for orciprenaline were similar in shape and height to those for isoprenaline on both these tissues.

In anaesthetized guinea-pigs intravenous doses producing a 60% inhibition of the bronchoconstrictor response to acetylcholine were: salbutamol, 18 μg/kg, soterenol, 32 μg/kg and orciprenaline, 447 μg/kg. At equipotent doses all three drugs were longer-acting than isoprenaline.

In conscious guinea-pigs both salbutamol and soterenol (5 mg/kg orally) prolonged by a factor of 4 the time taken to onset of dyspnoea caused by an acetylcholine aerosol. The effect lasted more than 6 hr with salbutamol and 2–4 hr with soterenol. At the same dose level soterenol caused a greater increase in heart rate than salbutamol. Orciprenaline at 20, 50 and 100 mg/kg gave inconsistent results but in no instance was there a pronounced increase in the time to dyspnoea. When given by aerosol (0.1 mg/ml. for 1 min) both salbutamol and soterenol caused a 4-fold increase in the time to onset of dyspnoea. The effects of both drugs lasted for about 1 hr. Orciprenaline, in aerosol form, was less potent; 1 mg/ml. solution sprayed for 1 min caused a 2-fold increase in the time to onset of dyspnoea and this effect lasted 7 min. At 10 mg/ml. there was a 3–4-fold increase which lasted for 30 min. In aerosol form all compounds were without effect on heart rate at the concentration used.

The *in vitro* results show that both salbutamol and soterenol possess a selectivity for β-receptors in bronchial smooth muscle relative to those in cardiac muscle. This