only caused 69.1 ± 6.2% relaxation ($n=6$). A further relaxation could not be obtained by increasing the dose of isoxsuprine into the range 20–80 μg/ml, but instead a contraction was obtained. Doses of isoxsuprine greater than 80 μg/ml, however, did relax the preparation. In the presence of isoxsuprine (10 μg/ml) the sensitivity of the trachea to isoprenaline was reduced.

On spontaneously beating atria (bathed in McEwens solution at 37°C) isoxsuprine (0.1–10 μg/ml) increased both the rate and force of contraction. The peak change in rate was only 45.7 ± 6.8% ($n=4$) of that achieved with isoprenaline. Responses to isoxsuprine (10 μg/ml) were completely abolished by propranolol (10 ng/ml, $n=4$), but were not affected by cocaine (3 μg/ml, $n=4$). The sensitivity of the atria to isoprenaline was reduced after the application of isoxsuprine. Decreases in the rate and force of contraction were often obtained with large doses of isoxsuprine (> 10 μg/ml), particularly when administered in the presence of propranolol.

It is concluded that responses of the guinea-pig atria and trachea to low concentrations of isoxsuprine (up to 10 μg/ml) are mediated by β-adrenoceptors. The results suggested that isoxsuprine had partial agonist properties on both preparations. Despite structural similarities to tyramine and other indirectly-acting sympathomimetics, the effects of isoxsuprine did not include an indirect sympathomimetic component. There was evidence that at high concentrations isoxsuprine possessed non-specific depressant activity. The pharmacological profile of isoxsuprine on these tissues is very similar to that described for the structural analogue, oxyfedrine (Sakai, Shiraki & Hashimoto, 1973).

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Altered reactivity of stomach fundus smooth muscle in Okamoto spontaneous hypertension

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Okamoto & Aoki (1963) obtained a strain of spontaneously hypertensive rats (SHR) which develop a disease that resembles human essential hypertension. Shibata & Kurahashi (1972), Bohr (1974) and Janis & Triggle (1973) have observed that the response of SHR carotid and aortic muscle to Sr^{2+}, La^{3+}, Mn^{2+}, Ba^{2+}, Ca^{2+} and diazoxide is changed in SHR, suggesting an alteration in excitation-contraction coupling mechanisms in SHR arterial smooth muscle. In order to know if the changes in reactivity are related to the primary cause of hypertension in SHR or are just an adaptation induced by the high arterial blood pressure (Folkow, Hallbäck, Lundgren, Sivertsson & Weiss, 1972) we have proceeded to test the contractile response of a visceral smooth muscle. A longitudinal strip of the rat fundus of 20 weeks old male and female SHR and Wistar normotensive (NW) rats was prepared according to the method of Vane (1957). All the following experiments were performed in a normal physiological Tris buffered solution at 37°C and gassed with 100% O_2. After equilibration during 2 h the contractile response to $SrCl_2$, $MnCl_2$, $LaCl_3$ and $BaCl_2$ was examined. The response to Ba^{2+} in male SHR strips was lower (ED_{50} $1.4 \times 10^{-3} \pm 0.3$ M, $n=10$) than in the male NW strips ($3.0 \times 10^{-4} \pm 0.2$ M, $n=10$; $P<0.01$). Maximal responses were identical. Male SHR fundus strips contracted much more with Sr^{2+} (SHR: 42 ± 3% of Mx response to Ba^{2+}, $n+10$; NW: 19 ± 4, $n=10$, $P<0.01$) than NW strips. This confirms Bohr's (1974) results but on the other hand there was no difference in the response to both $BaCl_2$ and $SrCl_2$ between female SHR and NW fundus strips, and $MnCl_2$ and $LaCl_3$ were relaxant in all cases. The dose-response curves to Ca^{2+} of depolarized SHR and NW fundus strips and the study of the antagonism of diazoxide on Ca^{2+} contractions was performed using Janis & Triggle (1973) method. The contractile action of Ca^{2+} in depolarized preparation was enhanced in both male and female SHR strips. The effect of diazoxide was more marked in SHR strips than in NW fundus strips. In conclusion, SHR fundus smooth muscle presents the same modification of reactivity to Ba^{2+}, Sr^{2+}, Ca^{2+} and diazoxide that was previously described in arterial smooth muscle. This indicates that the cellular modification responsible for the increase of vascular tonus in SHR is not an adaptable reaction to high blood pressure. The differences between female SHR and male SHR responses are not unexpected

considering the natural evolution of hypertension in Okamoto rats which is milder in female SHR.

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Molecular mechanism of post-nephrectomy uterine supersensitivity to angiotensin

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Bilateral nephrectomy has been shown to induce a specific supersensitivity of the response of isolated rat uteri to angiotensin II which is expressed by a shift to the left of the dose-response curve. This phenomenon could not be explained by a simple freeing of receptor sites secondary to the disappearance of endogenous angiotensin. The pA_2 values of two competitive antagonists of angiotensin II were not modified by nephrectomy suggesting that supersensitivity was related neither to a change in the affinity of receptors nor to a variation of a possible equilibrium existing between active and inactive receptor conformations (Meyer, Papadimitriou & Worcel, 1974). If angiotensin receptor affinity is unchanged after nephrectomy, two hypotheses may explain the supersensitivity to angiotensin, both based on the obligatory assumption that a limiting factor of the angiotensin effect after nephrectomy exists beyond the receptor site (i) *increase in the number of receptors.* If the limiting factor is distal to the receptor site, an increase in the number of receptors would be responsible for the supersensitivity, and maximal contraction would be obtained at an angiotensin concentration lower than in control experiments, (ii) *no variation in the number of receptors but an increase in the 'efficiency' of the limiting factor distal to receptors.* In this case, an increased response would result from the same number of hormone-receptor interactions.

In order to test these hypotheses, we have studied the specific binding of a [^{3}H]-angiotensin II with high specific activity and intact biological activity to membranes of uteri isolated from normal and nephrectomized rats. In normal rats, the specific binding of [^{3}H]-angiotensin II to uterine membranes was half saturated and saturated at angiotensin concentrations of 2×10^{-8} M and 10^{-7} M respectively. The similarity of these values to the ED_{50} value and to the angiotensin concentration inducing maximal contraction suggests that in normal rats a linear relation exists between angiotensin receptor occupancy and contraction.

Bilateral nephrectomy produces, after 18–20 h, a 70% increase in the total number of binding sites (control 0.7 pmol mg^{-1}; nephrectomized 1.2 pmol mg^{-1} protein) which cannot be accounted for by variations in the occupancy of receptor sites, and no significant variation in the apparent dissociation constant (Chevillotte, Rouzaire-Dubois, Devynck & Meyer, 1974). It has also been demonstrated that the variations in angiotensin receptor number was directly related to plasma angiotensin levels.

These pharmacological and biochemical results allow the following conclusions which will be analysed in this communication: (i) Supersensitivity of uterine muscle to angiotensin observed after nephrectomy is secondary to a true increase in angiotensin receptors without significant variation in their affinity for the