Action of cytochrome C on transmembrane potentials of normal or hypoxic guinea-pig myocardial strips

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It has been previously reported that cytochrome C modified the cardiac membrane effects produced by hypoxia (Lechat, Auclair, Dechezleprêtre & Lemeignan, 1975). The mechanisms involved were investigated on isolated stimulated (1 Hz) right ventricle strips of guinea-pig heart. The strips were placed in Tyrode solution saturated with either 95% O_2 and 5% CO_2 (normal strips) or 95% N_2 and 5% CO_2 (hypoxic strips). Action potentials (A.P.) were recorded using microelectrodes and contractions using a transducer.

In normal strips cytochrome C (1 μg/ml) did not modify either the A.P. or the contraction [number of experiments (n) = 35]. In hypoxic strips cytochrome C did not modify the resting potentials. The plateau phase and the A.P. duration decreased under hypoxic conditions (n = 30). Addition of cytochrome C again increased them (n = 20), but the contraction which had also decreased under hypoxic conditions was not restored. After blocking the sodium-calcium channel by $MnCl_2$ (10 mM), the action of hypoxia became more rapid (n = 8), but cytochrome C failed to induce the previous effects (n = 8). In K^+ and Ca^{2+} rich Tyrode solution ($K^+ \times 10$; $Ca^{2+} \times 4$) with an equimolar reduction in Na^+, the rapid sodium channel was blocked and slow A.P. could be induced by stimulation, which disappeared under hypoxic conditions. Addition of cytochrome C delayed their disappearance (75 min instead of 35 min) but did not increase the amplitude and duration of the slow A.P. These results showed that cytochrome C did not modify the rapid sodium movements, but was acting by interfering with the calcium-sodium movements. However, a direct activation of the slow calcium-sodium current, isoprenaline-like, is probably not involved since cytochrome C did not modify the slow A.P. configuration. In order to see if, in cytochrome C effects, an eventual modification of K^+ movements was implied, the action of tetraethylammonium (TEA) was studied in similar conditions. As with cytochrome C, TEA again increased the A.P. duration which had decreased under hypoxia, as well as the plateau phase. Contrary to cytochrome C, TEA lengthened the A.P. repolarization of normal strips (n = 6), did not maintain the slow A.P. and restored the contraction which had decreased under hypoxic conditions (n = 6).

Cytochrome C could maintain, in hypoxia, the slow inward calcium-sodium movements of the guinea-pig myocardial membrane, being however unable to restore contraction. The mechanism of this action could be at least partly related to a change in K^+ movements, without excluding other pathways.

Reference

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Analysis of the effects of isoxsuprine on guinea-pig atria and trachea

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Isoxsuprine is a smooth muscle relaxant used in the treatment of cerebral and peripheral vascular disorders and in premature labour. Initial studies suggested that it possessed β-adrenoceptor stimulant effects, a direct papaverine-like action and α-adrenoceptor blocking activity on various smooth muscle preparations (Lish, Dungan & Peters, 1960). In the present study, the effects of isoxsuprine on the guinea-pig trachea (Coleman & Farmer, 1971) and spontaneously beating paired guinea-pig atria have been examined.

On the trachea, isoxsuprine (0.03–3.0 μg/ml) added cumulatively, caused a dose-dependent relaxation ($ED_{50} = 0.12 \pm 0.03$ μg/ml; n = 12). Isoxsuprine was 120 times less potent than isoprenaline and gave a similar maximal response. The response was inhibited by propranolol (10 ng/ml, dose ratio = 1136 ± 282: n = 8). This marked inhibition of isoxsuprine was greater than that observed with standard β-adrenoceptor stimulants. For example, the dose-ratio obtained with salbutamol was 12.3 ± 4.1 (n = 4). Cocaine (10 μg/ml) had no effect on responses to isoxsuprine. The response to a submaximal dose of isoxsuprine (1 μg/ml) was not subject to tachyphylaxis on repeated administration. The effects of larger doses of isoxsuprine, however, were not repeatable. For example isoxsuprine (10 μg/ml) given as a single dose.

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