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

LECHAT, P., AUCLAIR, M.C., DECHEZLEPRÊTRE, S. & LEMEIGNAN, M. (1975). Effects of cytochrome C on functional consequences of different types of experimental hypoxia. *6th Int. Congress Pharmacology, Abstracts*, **545**, p. 236.

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.