ON THE EXISTENCE OF METABOLIC α-ADRENERGIC RECEPTOR IN THE MYOCARDIUM

Shoichi IMAI, Takeshi OTORII, Keisuke TAKEDA, Yumi KATANO, Tokumasa TSUKADA and Yoshito NAKAGAWA

Department of Pharmacology, Niigata University School of Medicine, Niigata 951, Japan

Accepted May 14, 1976

Although it is the common opinion of all that catecholamines produce myocardial hypoxia through augmentation of the myocardial O₂ consumption, several researchers have recently reported on an improvement of the myocardial redox state by these compounds (1, 2). In view of the importance of having a precise knowledge of the metabolic action of these compounds for a better understanding of the pathophysiological basis of such an important disease as angina pectoris or ventricular arrhythmia following acute myocardial infarction, we have undertaken to study the effects of catecholamines on the myocardial redox state with the aid of an organ redoximeter. As representative catecholamines, adrenaline, noradrenaline and isoproterenol were used. It was found that noradrenaline and adrenaline could produce a definite improvement of the myocardial redox state and that the activation of the adrenergic α-receptor is involved in the improvement. Since there have been as yet no reports suggesting the existence of adrenergic α-receptor primarily concerned with metabolic action of catecholamines, we would like to report on our results briefly.

Experiments were performed in the canine heart-lung preparation supported by a donor, the details of which were described in our previous publication (3). In order to record the oxidation-reduction state of the pyridine nucleotides within the cell continuously, an organ redoximeter constructed on the basic principle developed by Chance et al. (4), but equipped with an analog computer which compensates for a "hemodynamic artifact" (5) (Tateishi OMRON Electronics Co. HEF-4) was used. The light source is a super pressure mercury lamp (OSRAM HBO-50 w/2) which illuminates one branch of the trifurcate end of a light guide composed of UV-transmitting optical fibres through primary filters which select the 366 nm mercury line and 720 nm light. In order to couple the light source with the heart, the other end of the light guide is put on a duralumin socket sewn onto the surface of the left ventricle. For transmission of the light one third of the total fibres of the light guide distributed randomly among the remaining fibres were used. The remaining optical fibres in the common end of the optical guide receive reflectance signals of 720 nm wave-length which serve as a measure of the tissue blood content and fluorescence signals of 460 nm emitted from the heart upon excitation at 366 nm ("uncorrected fluorescence"). These are conducted from the animal to two further branches of the trifurcate end of the light guide each coupled through a suitable secondary filter to a photomultiplier. The output voltages of two photomultiplier are fed to an analog computer which by subtraction of the reciprocal
of the reflection output from the logarithm of fluorescence output gives pyridine nucleotides fluorescence changes undistorted by an optical artifact derived from variations in tissue blood content ("hemodynamic artifact"). The practical validity of applying the fluorometric method for monitoring the intracellular redox state of pyridine nucleotides was supported by concurrently determining the nucleotides levels with biochemical methods (6, 7).

Catecholamines (1–10 μg/min of noradrenaline and adrenaline and 0.1–1 μg/min of isoproterenol) were infused continuously into the rubber tubing leading to the venous cannula of the preparation. Blockers were injected into the venous reservoir (1–10 mg of phentolamine and 10–20 mg of dibenamine and 0.3–3 mg of propranolol).

Fig. 1. illustrates a biphasic fluorescence change produced by 10 μg/min of noradrenaline. A definite decrease in the fluorescence was observed, followed by an increase, which developed keeping pace with a well-known positive inotropic and chronotropic effects and an increase in the coronary flow, indicating that the substance induced an improvement of the myocardial redox state followed by a debasement. Adrenaline could produce qualitatively the same type of response, while isoproterenol produced only an increase in the fluorescence.

Pretreatment of the preparation with α-adrenergic blockers, phentolamine or dibenamine, resulted in a dose-dependent inhibition of the initial improvement of the myocardial redox state produced by adrenaline or noradrenaline, while the debasement by isoproterenol remained unchanged. Fig. 2. depicts the effects of 10 μg/min of noradrenaline in the presence of 5 mg of phentolamine. Phentolamine itself produced practically no change in the redox state of the myocardium.

![Fig. 1. Effects of 10 μg/min of noradrenaline in the canine heart-lung preparation supported by a donor.](image)

Tracings are from top to bottom: Pyridine nucleotides (NADP, NADPH, NAD and NADH, designated collectively as NADH and NAD) fluorescence recorded by an organ redoximeter, oxygen saturation (%o) (VO2) of the coronary venous blood, heart rate (HR), right atrial pressure (RAP) and coronary sinus outflow (Cor. flow). Dog, 11 kg, male. Heart weight: 110 g. Total blood volume at the beginning of the experiment: 1100 ml.
After pretreatment of preparation with an adrenergic β-blocker, propranolol, which completely abolished the positive inotropic and chronotropic effects of three catecholamines, noradrenaline and adrenaline produced a dose-dependent decrease in the pyridine nucleotides fluorescence together with a decrease in the coronary blood flow, which lasted as long as the continuous infusion was maintained. Administration of isoproterenol under this condition resulted in no change in the myocardial redox state.

These findings suggest that there exists an adrenergic α-receptor in the myocardium, the direct activation of which by adrenaline and noradrenaline results in an improvement of the myocardial energy metabolism. In view of the finding that the improvement of the myocardial redox state was more definite and sustained after adrenergic β-blocker, which completely abolished the positive inotropic and chronotropic effect of these catecholamines, the improvement of the myocardial redox state could not have been resulted from an accumulation of ADP attributable to an increased work of the heart and the consequent acceleration of the oxidative metabolism. Presumably, these substances exerted some ameliorating effect upon the oxidative metabolism itself.

The debasement of the redox state was observed keeping pace with development of the positive inotropic and chronotropic effects and an increase in the coronary flow. As mentioned in the introduction section, this debasement is usually taken to represent a hypoxia of the myocardium due to an increased oxygen demand only partially compensated by a simultaneous increase of the coronary blood flow. It is true that adrenaline and noradrenaline produce a hypoxia of the myocardium as a result of a constriction of the coronary vasculature. However, as far as isoproterenol is concerned, there was no such constriction and the increased oxygen demand is fully compensated by corresponding increase in oxygen supply (3). It is, therefore, unlikely that a hypoxia of the tissue is a factor contributing to the ob-
served fluorescence increase produced by this compound. An augmentation of the glycolysis and consequent accumulation of lactate within the cytoplasm could be the cause of the debasement.

Thus, it is now clear that catecholamines produce both an improvement and a debasement of the myocardial redox state by directly affecting the myocardial energy metabolism. We are now studying the intracellular localization of the increased fluorescence and the biochemical events which underlie both the improvement and the debasement of the myocardial redox state.

REFERENCES

NONSPECIFIC INHIBITORY ACTION OF CHINOFORM ON GASTROINTESTINE

Issici TAKAYANAGI, Kazuichi HAYAKAWA*, Yasufumi TERAWAKI,
Zenzo TAMURA* and Keijiro TAKAGI
Department of Chemical Pharmacology and *Department of Analytical Chemistry, Faculty of Pharmaceutical Sciences, University of Tokyo, Bunkyo-ku, Tokyo 113, Japan
Accepted May 17, 1976

The effectiveness of chinoform (5-chloro-7-iodo-8-quinolinol) in the treatment of amoebic dysentery has been established (1, 2), however, recently it was concluded that SMON (Subacute Myelo-Optico-Neurophathy) is concerned with untoward side effects of chinoform (3). As gastrointestinal pharmacology of chinoform remains obscure, the present study was an attempt to determine the mode of action of chinoform on the gastrointestinal.

Male guinea pigs (350 to 450 g in body wt.) were sacrificed by a blow on the neck and the ileum was isolated. A piece (3 to 4 cm) of the ileum was suspended in a 30 ml organ bath filled with Locke Ringer solution, kept at 32°C and bubbled with air. Responses of the ileum to drugs were recorded through an isotonic lever. In most experiments, chinoform was applied to the serosal surface by addition to the bath fluid. In some experiments chinoform was applied to the mucosal surface, that is, into the lumen of the intestinal segment, by passing a vinyl tube, the tip of which was within the intestinal sac (4). In other experiments the longitudinal muscle with Auerbach's plexus was carefully removed from a segment of the guinea pig ileum and was slipped onto a rectangular Lucite holder. The holder was