Biochemical Pharmacology, Vol. 38, No. 19, pp. 3145–3146, 1989.
Printed in Great Britain.

0006-2952/89 $3.00 + 0.00

RAPID COMMUNICATION

DISTURBANCES IN THE CARDIOVASCULAR SYSTEM CAUSED BY ENDOTHELIN AND SARAFOTOXIN

A. BDOLAH, Z. WOLLBERG, I. AMBAR,* Y. KLOOG,* M. SOKOLOVSKY* and E. KOCHVA
Departments of Zoology and *Biochemistry, George S. Wise Faculty of Life Sciences,
Tel Aviv University, Tel Aviv 69978, Israel

(*Accepted* 28 *April* 1989)

The highly lethal sarafotoxins (SRTXs) from snake venom and the endothelins from the mammalian vascular system are powerful vasoconstrictors [1, 2] which show a high degree of sequence homology; both have four cysteins and about 60% of their 21 amino acid residues are identical [3, 4]. In addition, sarafotoxins and endothelins strongly affect the cardiovascular system, both *in vivo* and *in vitro* [1, 2]. We show here that endothelin too can cause severe disturbances in the function of the heart at the level of the A-V conduction system and the coronary vessels, ultimately leading to cardiac arrest.

The effects of endothelin on the activity of the intact heart and its LD_{50} were assessed by i.v. injection of a freshly prepared solution of synthetic porcine endothelin (Peptides International, Louisville, KY), using ICR mice (males 20 g).

The LD_{50} obtained for endothelin was 15 μg/kg body weight, a dose which is equal to that of SRTX-b [1]. The changes induced by endothelin in the ECG of anesthetized ICR mice (Avertin, 2% 2,2,2 tribromoethanol, 10 ml/kg i.p.), were examined by using recording procedures described previously [1]. In order to determine the effects of endothelin on the heart, 25 μg per kg were injected into one of the caudal veins. The first changes in the ECG appeared within less than 10 sec (Fig. 1a). They included an increase in the amplitude of the R wave, a diminution of S wave and a marked but transient elevation of the S-T segment, reaching a maximum after about 10 sec and a complete recovery after another 5 sec. At this phase, the amplitude of the S wave was restored and often exceeded the control amplitude. At the same time, a severe A-V block developed, starting with a prolongation of the P-R interval and culminating, after about 2.5 min, in a complete electrical atrioventricular dissociation (3rd degree A-V block). These results, which indicate disturbances in the A-V conduction system and vasospasm of the coronary vessels are, most probably, independent events [1]. Intravenous administration of SRTX-b (25 μg/kg) under exactly the same conditions, resulted in essentially the same pattern of ECG distortions (Fig. 1b).

The sequence of events following intravenous administration of lethal doses of porcine endothelin or of SRTX-b, as depicted by the ECG deterioration, suggests that these two peptides affect the heart of mice by a similar mechanism(s), possibly through

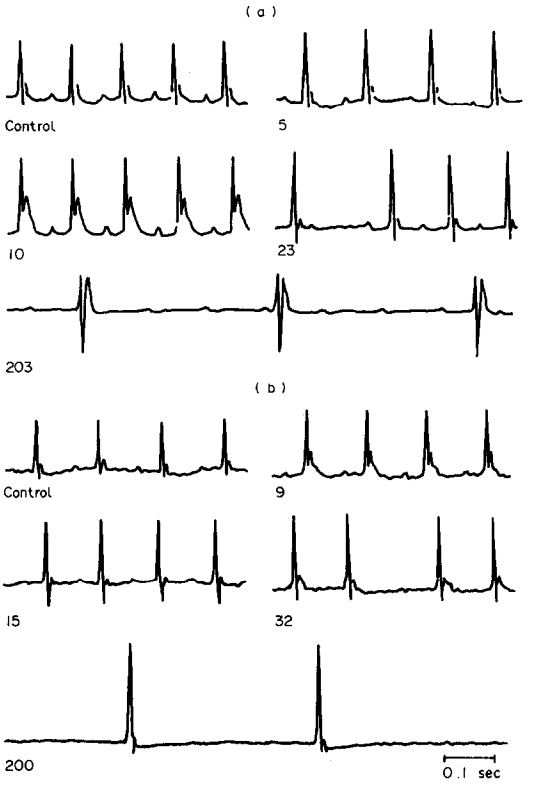

Fig. 1. The effects of lethal doses (25 μg/kg body weight) of endothelin and SRTX-b on the ECG of anesthetized mice. Selected samples from continuous paper recordings. (a) Porcine endothelin; (b) SRTX-b. Recording was carried out with bipolar limb leads, comparable to lead II. The number under each trace indicates time lapse in seconds from endothelin or SRTX-b administration. It should be stressed that the apparent differences in the QRS complexes between the 203 sec and the 200 sec traces, in (a) and (b) respectively, during the complete A-V block, are not drug specific. These differences represent individual variability, indicating erratic activation of ectopic pacemakers located at different sites in the ventricular musculature.

their binding to the ^{125}I-SRTX-b receptors of the heart, which activate phosphoinositide hydrolysis [3]. In order to determine whether endothelin and sarafotoxin bind to the same population of receptor sites in the heart, we performed competition binding

experiments, as described previously [3]. We found that endothelin competes with ^{125}I-SRTX-b for binding to rat atrial preparations with an IC_{50} value of 12 nM. The value for SRTX-b in this preparation was 19 nM. It should be pointed out that the mutually exclusive binding of endothelin and SRTX is not only characteristic for the rat atrium, but is also found in various regions of the rat brain [5].

The identical effects of endothelin and SRTX-b on the heart, their similar vasoconstriction potency [6], their mutually exclusive binding to heart and brain membranes and induction of phosphoinositide hydrolysis [5] indicate that porcine endothelin and SRTX-b interact with the same receptors and induce similar patophysiological changes in the cardiovascular system. Endothelins apparently operate as normal modulators of intracellular Ca^{2+} thereby regulating vasoconstriction of blood vessels in different organ systems. The high toxicity of endothelin and its influence on the heart raises the question of possible damage that might be caused by it under failure or malfunction of its regulatory mechanism.

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