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Migration of Dominant Pacemaker Region in Rat Sinoatrial Node

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The location of dominant pacemaker region in isolated rat sinoatrial node in the presence of different concentrations of norepinephrine is determined by intracellular recording of action potential. A linear relationship is revealed between the concentration of norepinephrine and the shift of pacemaker zone along the node axis within physiological concentrations of the transmitter. At high concentrations norepinephrine affects primarily the parameters of action potential in pacemaker cells.

Key Words: *sinoatrial node; dominant pacemaker region; norepinephrine*

Sinoatrial node (SAN) is a heterogenous population of cardiomyocytes consisting of two major functional groups: dominant and latent pacemakers [2-5,7]. However, various factors, in particular, neurotransmitters [5], electrical stimulation [6], potassium ions [4] induce migration of the dominant zone within the sinoatrial node. This phenomenon is difficult to study because of complex spatial configuration of SAN in standard experimental animals (dogs and rabbits). Rat SAN is more convenient for analysis, since the trajectory of dominant pacemaker region (DPR) in rats is directed along the long axis of the node situated around the sinus node artery [1-3] and can be approximated to a straight line.

The aim of the present study was to analyze the dose-effect relationship for DPR migration in rat SAN *in vitro* in the presence of different concentrations of norepinephrine (NE).

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats weighing 80-150 g. The heart was removed under Nembutal narcosis (40 mg/kg), placed into Hanks' buffer (pH 7.35, 15-20°C), and a fragment containing the anterior wall, *v. cava superior* and *inferior*, and auricula was excised, since SAN is located on the boundary between *v.cava superior* and auricula. The preparation was placed into a thermocontrolled flow cuvette with modified Krebs-Ringer solution (37-38°C) adjusted to pH 7.4 with 5% carbogen (1.7 ml/min flow rate). The location of DPR was determined with glass microelectrodes and mapped using a ruler build into the objective (1 graduation mark corresponded to 0.0235 mm). Dominant pacemakers were identified by the shape of the action potential curve (the presence of slow diastolic depolarization and its smooth transition to rapid rise of the membrane potential, as well as a low rate of initial rapid rise of the membrane potential [2-5,7]).

When DPR was found, ascending concentrations of NE bitartrate (0.6×10^{-4}, 0.6×10^{-4}, 0.6×10^{-4} mg/ml, Serva) were successively added to the cuvette with 15-min washout periods (series 1). The location of DPR was redetermined for each concentration. The basal repetition rate of action potentials and its changes induced by varied concentrations of NE were measured. Series II was carried out to avoid artifacts caused by repeated addition of NE to the

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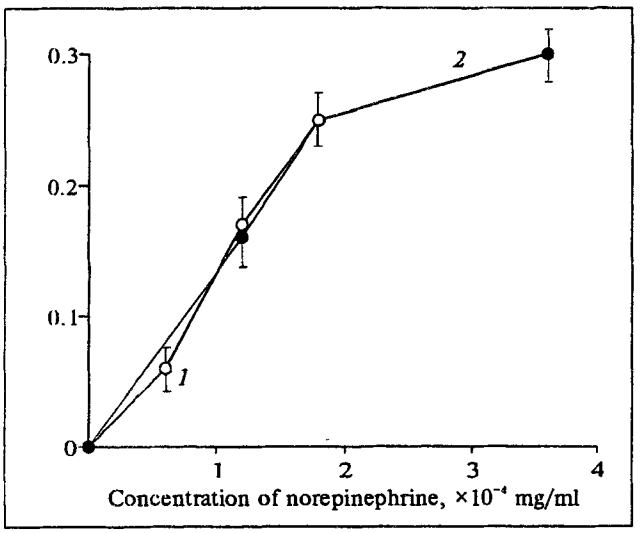

Fig. 1. Shifts of dominant pacemaker region (DPR) induced by successive (*1*) and single (*2*) addition of norepinephrine to the incubation medium. Ordinate: position of DPR relative to the initial location of dominant pacemaker, mm.

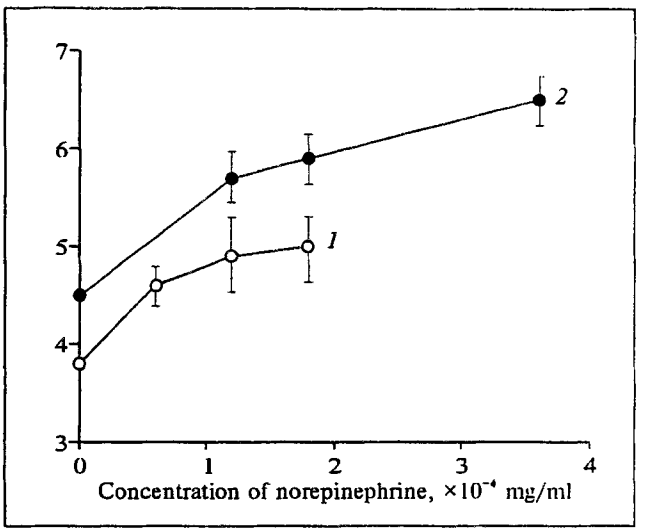

Fig. 2. Changes in repetition frequency of action potentials induced by successive (*1*) and single (*2*) addition of norepinephrine to the incubation medium. Ordinate: repetition frequency of action potentials, sec^{-1}.

cuvette. In this series only NE was singly added to the cuvette in concentrations of 1.2×10^{-4}, 1.8×10^{-4}, and 3.6×10^{-4} mg/ml.

RESULTS

Addition of NE induced an approximately linear shift of DPR and an increase in repetition frequency of action potentials (Figs. 1, *1* and 2, *1*). Large deviations of experimental values in Fig. 2 are due to considerable variations of the basal repetition rate of action potentials in cultured preparations. The data of experimental series II are presented in Figs. 1, *2* and 2, *2*. Curves *1* and *2* in Figs 1 and 2 are identical within the low concentration range, while at high concentrations these curves become nonlinear and reach a plateau.

Our experimental findings can be interpreted as follows. Within the low NE concentration range the repetition rate of action potentials increases due to:

— an increase in the slope of action potential during slow diastolic depolarization and a decrease in the threshold potential [1,5];

— transition of the dominant pacemaker zone to cells which are more susceptible to a given concentration of NE [5].

At higher NE concentrations, DPR reaches the point functionally corresponding to the lower boundary of the central zone of SAN. Further increase in the repetition frequency of action potentials is not accompanied by DPR shifts and is effected through increasing the slope of slow diastolic depolarization curve and a decrease in the threshold potential

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