Restoration of Electrical Activity of Guinea Pig Atria during Hypothermia

EFFECTS OF NOREPINEPHRINE AND ELECTRICAL STIMULATION ON MEMBRANE POTENTIALS

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ABSTRACT

Guinea pig right atria were perfused in vitro at 30°C. When the temperature was lowered to about 20°C, atrial activity ceased and the resting potential of atrial fibers decreased significantly. When activity was restored during hypothermia by electrical stimulation, both the resting and the action potentials were similar to those recorded at 30°C. Blockade of receptors by atropine or propranolol reduced the effects of electrical stimulation on the membrane potentials, and the reduction was greatest when both drugs were present. In particular, propranolol reduced the amplitude of the action potential. Strophanthidin also reduced the increment in resting potential induced by electrical stimulation at low temperature. Norepinephrine restored atrial activity, but the action potential and its rate of rise were small and the resting potential remained low. We concluded that (1) electrical stimulation restored atrial activity by simultaneously depolarizing the membrane to threshold, liberating autonomic mediators, and stimulating the sodium-potassium pump and (2) norepinephrine removed the sinoatrial block induced by low temperature by increasing the slow calcium and sodium currents.

KEY WORDS

neuromediator release sodium-potassium pump slow calcium and sodium currents atrial conduction atropine propranolol strophanthidin sinoatrial block

Spontaneously active mammalian atria perfused in vitro cease to beat at about 20°C (1, 2). The cause of this atrial arrest is a block of conduction between the sinus node and the atrium and not a cessation of pacemaker activity of the sinus node (2). Atrial activity can be restored during hypothermia by several agents such as vagal stimulation (3), acetylcholine (2, 4), catecholamines (5), and electrical stimulation (6). The mechanisms by which these agents restore excitation are different, and they are not fully understood in each case. Acetylcholine restores atrial activity by increasing the resting potential of atrial fibers and, thus, by removing sinoatrial block (2, 4). However, little is known about the mode of action of catecholamines in restoring atrial activity during hypothermia. Uncertainties also exist about the mechanism of action of electrical stimulation. At first sight, it would seem that electrical stimulation restores activity because it is more effective than is the sinus node in exciting the atrium: in contrast to sinus node action potentials, the intensity of electrical stimulation can be set at the value needed to excite the atrial fibers. In actuality, two findings suggest that other factors may be operative as well: electrical stimulation liberates neuromediators which in turn should affect atrial excitability and conduction, and the resting potential does not fall significantly when atrial preparations are electrically stimulated while they are being cooled (6).
The aim of the present investigation was to study the restoration of activity in cooled atria by analyzing (1) the separate roles of electrical stimulation per se and of the neuromediators released by the stimulation and (2) the mechanism of action of norepinephrine. The results show that there are considerable differences in the mode of action of different agents in restoring atrial activity.

**Methods**

Guinea pigs were killed by a blow on the head, the thorax was opened, and the heart was removed. A small strip of the right atrium including the sinus node was perfused in a tissue bath with Tyrode’s solution flowing at the rate of 60–80 drops/min at 30°C. This temperature is referred to as the control temperature. The millimolar composition of Tyrode’s solution was NaCl 137, KCl 5.4, CaCl₂ 2.7, MgCl₂ 1.05, NaHCO₃ 11.9, NaH₂PO₄ 0.45, and glucose 5.55. The solution was bubbled with 98% O₂-2% CO₂, and the pH was 7.4. The tissue bath was surrounded by a thermostatically controlled water bath which maintained the temperature of Tyrode’s solution recording the atrial strip constant within 0.5°C. This temperature was continuously monitored by a thin probe placed less than 1 mm from the atrial strip and connected to a Yellow Spring YSI Tele-thermometer. Electrical stimuli were delivered through a pair of silver electrodes in close proximity to the fibers. The duration of the stimulus was 10 msec, the mean voltage was 0.92 ± 0.03 v at 30°C and 1.25 ± 0.3 v at the temperature of arrest, and the frequency was 30/min.

Transmembrane potentials of atrial muscle fibers were recorded with two glass microelectrodes of the Ling Gerard type, filled with 3M KCl. The tip of one microelectrode was immersed in the perfusion fluid, and the other microelectrode was inserted intracellularly. Transmembrane potentials of 10–20 different fibers at different distances from the sinoatrial (SA) node or the stimulating electrodes were usually measured. The recording apparatus consisted of a push-pull cathode follower stage, a direct-coupled Tektronix type 3A3 dual-trace differential amplifier, and a Tektronix model 565 dual-beam oscilloscope. The traces were photographed with a Kymograph camera (Grass Instruments Company).

The preparations were allowed to equilibrate in Tyrode’s solution for 60–90 minutes, and then the membrane potentials were measured. To obtain a gradual cooling of the preparation over 45–60 minutes, the bottle containing Tyrode’s solution was placed in a thermost flask containing ice. At the same time, the temperature of the water bath was gradually reduced by readjusting the setting of the thermostat (71 Thermistemp temperature controller). In this manner, cool Tyrode’s solution was warmed to progressively lower temperatures. The tubing leading from the reservoir containing Tyrode’s solution to the bath was thermally insulated by a thick layer of Neoprene rubber. Once the atrial strips became quiescent in cold Tyrode’s solution, the temperature of the solution was allowed to fall about another 0.5°C and was maintained at that level. The resting potential was recorded, and then the preparations were either electrically stimulated or exposed to norepinephrine (3.95 × 10⁻⁶M). Membrane potentials were recorded 30 minutes later. This period was sufficient to attain a new steady state, since values recorded from different fibers during the subsequent 15 minutes did not differ significantly. Once the recordings were completed, the preparations were slowly rewarmed to 30°C in Tyrode’s solution. The recovery membrane potentials were recorded 30 minutes later. The values reported in the figures and tables are steady-state values.

The following drugs were also employed: atropine sulfate (1.44 × 10⁻⁵M), propranolol (1.93 × 10⁻⁷M), and strophanthin (0.62–1.24 × 10⁻⁷M). After completing the control procedures, the selected drug was added to Tyrode’s solution perfusing the preparation and recordings were repeated about 60 minutes later. Then the preparation was cooled, and the procedure described above was carried out. Once the recordings at low temperature were completed, the perfusion of the drug was discontinued, the preparation was rewarmed, and recovery membrane potentials were recorded as usual.

The mean values and the standard errors (SE) were calculated for the membrane potentials recorded at each temperature in each experiment and also for the potentials recorded in each series of experiments. Statistical treatment of the data was carried out using Student’s t-test (7).

**Results**

**ELECTRICAL STIMULATION**

The effect of low temperature on the membrane potentials of atrial fibers is shown in Figure 1. As the temperature was lowered, the atrial fibers became quiescent, and their resting potentials decreased relative to control values. With electrical stimulation at low temperature, the amplitudes of the resting and the action potentials were similar to those during the control period. In other words,
FIGURE 1

Effect of low temperature and electrical stimulation on membrane potentials. Membrane potentials obtained in a single experiment (top) and average values (bottom) collected during control period (C), quiescence at low temperature (Q), electrical stimulation at low temperature (S), and recovery (R). Voltage (0–50 mV) and time calibrations (200 msec at 30°C, 500 msec at low temperature) are the vertical and horizontal lines, respectively, at the top. Note that during stimulation, the end of repolarization is distorted by mechanical artifact. The graph shows the average values ± SE of the amplitude of the action potential (AP), the overshoot (OS), and the resting potential (RP).

Quiescent fibers stimulated in cold Tyrode's solution showed a gradual increase in resting potential with respect to the value before stimulation. After the temperature of Tyrode's solution returned to the control value, resting potential increased and spontaneous atrial activity resumed: the temperature-induced changes were reversible. The average values of resting potential, overshoot, and action potential amplitude for six experiments are given in Table 1. When spontaneous activity ceased at low temperature (20.7 ± 1.0°C), the resting potential was significantly (P < 0.001) below the control value. As electrical stimulation was started, both resting and action potentials increased to values which were not significantly different (P > 0.01 and P > 0.1, respectively) from control values. Overshoot during stimulation was also not significantly different (P > 0.1) from its control value.

In the experiments just illustrated, the rate of stimulation at low temperature was far slower than the sinus node rate at control temperature. Since the driving rate may influence the action potential amplitude (8, 9), the question arose whether the changes observed were due to the different driving rates, the electrical stimulation per se, or both. It was impossible to stimulate the preparations during hypothermia at the sinus node rate at 30°C, because the fibers would not follow such a frequency. Therefore, two sets of strips were cut from the same atrium and perfused at 30°C. One strip contained the sinus node and was spontaneously active; the other did not discharge spontaneously. The spontaneously active strips were driven by the sinus node at an average rate of 122 ± 1.3/min; the inactive strips were stimulated at 30/min, which was the frequency...
TABLE 1

Membrane Potentials of Guinea Pig Atrial Fibers at 30°C and with and without Electrical Stimulation during Hypothermia

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Quiescent</th>
<th>Stimulated</th>
<th>Recovery</th>
</tr>
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<tbody>
<tr>
<td>RP (mv)</td>
<td>78.6 ± 0.47</td>
<td>69.9 ± 0.56*</td>
<td>76.7 ± 0.78†</td>
<td>79.9 ± 0.53</td>
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<tr>
<td>OS (mv)</td>
<td>23.4 ± 0.59</td>
<td>23.6 ± 0.71‡</td>
<td>22.0 ± 0.40</td>
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<tr>
<td>AP (mv)</td>
<td>102.0 ± 0.79</td>
<td>100.3 ± 1.11‡</td>
<td>101.9 ± 0.73</td>
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</table>

Control results were obtained at 30°C. Low-temperature results were obtained at 20.7 ± 1.0°C, the temperature at which the spontaneous activity of atrial fibers ceased. Recovery results were obtained in the same preparations on rewarming to 30°C. Each value is an average (± SE) for a minimum of 55 to a maximum of 74 impalements in six atrial preparations. RP = resting potential, OS = overshoot amplitude, and AP = action potential amplitude.

*Significantly different from control, P < 0.001.
†Significantly different from quiescent, P < 0.001, but not significantly different from control, P > 0.01.
‡Not significantly different from control, P > 0.1.

used for cooled preparations. As shown in Figure 2, atrial fibers stimulated electrically at 30/min (right) exhibited action potentials which were larger than those obtained from the same atrium driven by the sinus node (left). Similar results were obtained in a total of six experiments. The mean amplitude of the spontaneous action potentials was 101.9 ± 0.79 mv and that of those elicited electrically was 107.8 ± 1.17 mv (P < 0.001); this increase was due to an enhancement of the overshoot from 24.4 ± 0.50 mv to 30.4 ± 0.76 mv (P < 0.001). The resting potentials were not significantly different (77.2 ± 0.73 mv and 77.6 ± 0.57 mv, respectively). To test whether the enhancement of the action potential was due to the electrical stimulation per se or to the slower rate of discharge, spontaneously beating preparations were electrically stimulated at a rate slightly faster than that of the sinus node. In three preparations, the resting potential was the same whether the fibers were discharged by the sinus node or by electrical stimulation (79.0 ± 0.63 mv and 78.3 ± 0.84 mv, respectively). In two of these experiments, the overshoot increased significantly when the preparations were electrically stimulated. The averages of the overshoot values in the three experiments were 25.0 ± 0.31 mv when the fibers were driven by the sinus node and 27.7 ± 0.68 mv when the fibers were electrically stimulated (P < 0.005).

These experiments suggested that the increase in the amplitude of the overshoot was due to the electrical stimulation itself rather than to the slow rate. The findings in three preparations in which action potentials were recorded just before the cold-induced cessation of atrial activity supported this conclusion. At low temperature, the sinus node was firing at a rate of 29.0 ± 2.38/min, and in each preparation both the resting and the action potentials were lower (72.9 ± 0.76 mv and 95.2 ± 0.93 mv, respectively) than they were at the control temperature (79.2 ± 0.66 mv and 105.2 ± 1.01 mv, respectively). As soon as atrial activity ceased, the fibers were stimulated electrically at 30/min, and the resting and the action potentials approached control values.

RELEASE OF NEUROMEDIATORS

The results reported so far show that electrical stimulation increases the amplitude of the action potential at the control temperature and the resting potential and the amplitude of the action potential at low temperature. Electrical stimulation may cause these changes by releasing neuromediators. In one series of experiments, the possible effect of acetylcholine release was tested by employing atropine sulfate. The results are shown in
Figure 3. Recording the membrane potential in the absence and in the presence of atropine at the control temperature showed that atropine did not induce significant changes \((P > 0.01)\). When the preparation was cooled in the presence of atropine, it became quiescent and the resting potential fell as usual. On electrical stimulation, the resting potential increased but not to the control value \((P < 0.001)\). The action potential also was smaller than the control potential. These effects were reversible: action potential amplitude and resting potential returned to control values at 30°C about 60 minutes after atropine was removed from Tyrode’s solution perfusing the preparation.

The average temperature (six experiments) at which the preparations became quiescent in the presence of atropine \((19.3 ± 0.4°C)\) was not significantly different from that in the absence of atropine \((20.7 ± 1.0°C, P > 0.10)\). The resting potential at that temperature in the presence of the drug was significantly below control value \((66.3 ± 0.64 mv\) compared with \(78.7 ± 0.45 mv, P < 0.001\) (Table 2). When the preparations were electrically stimulated at low temperature, the resting potential increased significantly to \(73.8 ± 0.46 mv (P < 0.001)\); however, it remained significantly \((P < 0.001)\) below control value in all but one experiment. Also, the amplitudes of the action potential and the overshoot were lower than at 30°C in the presence of atropine \((P < 0.001)\). The results with atropine suggest that acetylcholine released by electrical stimulation contributed to the hyperpolarization observed on stimulation since the increase in resting potential was less than it was in the absence of atropine. However, acetylcholine was not entirely responsible for the hyperpolarization, since a significant increase in resting potential still occurred in the presence of atropine.

The possible effects of norepinephrine release by electrical stimulation were tested by employing propranolol. The results are illustrated in Figure 4. The action potentials were recorded at 30°C in the absence and the presence of propranolol; the drug at the concentration used did not modify the membrane potentials to a significant extent \((P > 0.01)\) or in any consistent way. The preparation was cooled while it was perfused with Tyrode’s solution containing propranolol, and the resting potential fell as usual. On electrical stimulation, the resting potential increased but not to the control value. Quite obviously in this experiment (as well as in the others), the action potential and its rate of rise were below control value. These effects were reversible.

The temperature at which the preparations (six experiments) became quiescent in the presence of propranolol \((18.7 ± 0.6°C)\) was not statistically different from either the temperature in Tyrode’s solution or in the...
presence of atropine ($P > 0.10$). The resting potential of the quiescent fibers at low
temperature with propranolol decreased in all
preparations ($64.9 \pm 0.76$ mV compared with
$76.7 \pm 0.42$ mV, $P < 0.001$) (Table 2). In the
presence of propranolol in five of six prepara-
tions, the voltage of the stimulus had to be
increased two to three times to elicit excita-
tion; the other preparation was inexcitable.
The resting potential increased significantly
($P < 0.001$) only in three of five strips which
were excitable. In contrast to the results of the
previous series of experiments with atropine,
there were areas of transient conduction block in
the cooled propranolol-treated atria. This
finding may be related to the fact that the
action potential and the rate of rise were
always smaller and the overshoot sometimes
absent.

In another series of experiments (four
preparations), atropine and propranolol were
administered together to find out whether a
simultaneous blockade of the actions of
sympathetic and vagal mediators would result
in a smaller hyperpolarization on electrical
stimulation. This expectation is borne out by
the results shown in Figure 5. At 30°C the
membrane potentials were essentially the
same in the absence and the presence of
atropine and propranolol together. At low
temperature, electrical stimulation caused a
small increase in resting potential (from
$63.6 \pm 0.59$ to $66.0 \pm 0.57$, $P > 0.01$) (Table
2); the action potentials were also small with
a slow upstroke. The potentials recorded at
low temperature, but in the absence of
atropine and propranolol, clearly show an
enhancement of the resting potential, the
action potential amplitude, and the rate of rise
of the upstroke. If both atropine and propran-
olol similarly reduced the increase in resting
potential on electrical stimulation at low
temperature, the amplitude of the action
potential was strikingly smaller when propran-
olol was present.

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TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>Control (30°C)</th>
<th>Drug (30°C)</th>
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<th>Stimulated</th>
<th>Recovery (30°C)</th>
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<td>Quiescent</td>
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<td>66.3 ± 0.64†</td>
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<td>RP (mv)</td>
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<td>OS (mv)</td>
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<tr>
<td>AP (mv)</td>
<td>102.8 ± 0.68</td>
<td>103.0 ± 0.70*</td>
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<td>Propranolol</td>
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<td>64.9 ± 0.76†</td>
<td>71.0 ± 1.20</td>
<td>79.6 ± 0.44</td>
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<tr>
<td>RP (mv)</td>
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<td>OS (mv)</td>
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<td>AP (mv)</td>
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<td>100.4 ± 0.62*</td>
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<td>Atropine + Propranolol</td>
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<td>63.6 ± 0.39‡</td>
<td>66.0 ± 0.57</td>
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<td>RP (mv)</td>
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<td>OS (mv)</td>
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<tr>
<td>AP (mv)</td>
<td>101.4 ± 0.60</td>
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<td>Strophanthidin</td>
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<td>66.8 ± 0.51†</td>
<td>69.5 ± 0.50</td>
<td>78.0 ± 0.32</td>
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<td>RP (mv)</td>
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<td>OS (mv)</td>
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<td>27.7 ± 0.53*</td>
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<tr>
<td>AP (mv)</td>
<td>102.5 ± 0.57</td>
<td>104.5 ± 0.64*</td>
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Each value is the average ± se of 22-74 impalements from four to six preparations.

*Not significantly different from control, P > 0.01, and significantly different from stimulated, P < 0.001.
†Significantly different from control, P < 0.001, significantly different from drug at 30°C, P < 0.001, and significantly different from stimulated at low temperature, P < 0.001.
‡Significantly different from control, P < 0.001, significantly different from drug at 30°C, P < 0.001, but not significantly different from stimulated at low temperature, P > 0.01.
¶Significantly different from control, P < 0.001.

EFFECT OF STROPHANTHIDIN

The effects noted might have involved change not only in passive but also in active transport of ions across the membrane (10). To test this point, strophanthidin was administered in six experiments since glycosides are known to block the sodium pump (11). Figure 6 shows that strophanthidin had little effect on membrane potentials at 30°C (P > 0.01); possibly this lack of effect was related to the duration of exposure and the dose of strophanthidin. At low temperature, strophanthidin had been perfused for more than 90 minutes, and on stimulation the resting potential increased but little (Table 2). In contrast, the action potential was almost as large as in the control. The poisoning of the pump by strophanthidin is reversible (12), and this accounts for the recovery.

EFFECT OF ADMINISTERED NOREPINEPHRINE

The results obtained with the administration of norepinephrine are illustrated in Figure 7. When a preparation arrested at low temperature was exposed to norepinephrine, atrial activity was restored within 1 minute. However, the activity was always irregular, and areas of transient conduction block were apparent. The restoration of activity by norepinephrine did not involve an increase in the resting potential: it remained unchanged (Table 3). The atrial fibers were activated in all instances at an average rate of 54.4 ± 2.51/min (range 42 to 78/min). The action potential was consistently smaller than it was at the control temperature (78.5 ± 2.40 mv compared with 102.0 ± 0.69 mv, P < 0.001), and the rate of rise of the upstroke was reduced.

Discussion

The cessation of atrial activity at low temperature (1-4, 13) is due to development of sinoatrial block rather than to sinus arrest (2).
The mechanism of this block probably involves a decrease in the amplitude of the action potentials of the SA node (2, 8) and, perhaps more importantly, a fall in the resting potential of atrial fibers (2, 8, 14). The combination of these two variables would decrease the spread of activation to such a degree that conduction would fail. There are several ways in which such a sinoatrial block can be removed. One, clearly, would be an increase in the resting potential of atrial fibers. The action of acetylcholine (2, 4) and vagal stimulation (3, 15) in restoring the activity of quiescent atrial preparations at low temperature is explained on this basis. An increase in the resting potential (brought about by an increase in potassium conductance [16]) increases the sodium-carrier availability (17) and, therefore, the excitability of the blocked fibers, thus removing the conduction block. Since acetylcholine does not increase the amplitude of the action potential of the SA node (at least at normal temperature [18]), it is unlikely that such a factor would play a role in the restoration of atrial activity.

There are, however, other possible mechanisms by which a conduction block could be removed without an increase in fast inward sodium current. In this connection, two phases (fast and slow) can be distinguished in the upstroke of the action potential of certain cardiac tissues (19, 20). These two phases have different characteristics and are due to different ionic currents. The fast phase depends on the level of the resting potential (19) and is inhibited by tetrodotoxin (20), suggesting that it is due to the opening of conventional fast sodium channels. But the slow phase is independent of resting potentials more negative than —40 mv, is not influenced by high potassium concentrations (19) and is depressed by manganese ions (20). This slow phase is due to calcium and sodium currents flowing through a slowly activated channel (21, 22).

In relation to the mechanism of action of
Atrial activity in hypothermia

Figure 5

Atrial membrane potentials during control (C), in the presence of atropine and propranolol (ATROP + PROP), and during recovery (R) at 30°C. Membrane potentials at temperature of arrest during quiescence (Q) and during electrical stimulation (S) in the presence (LOW TEMP + ATROP + PROP) and in the absence of the drugs (LOW TEMP). Descending phase of action potential has been retouched in the first, second, and last panels. Average results plotted in the bottom of the figure are for four experiments. Voltage and time calibrations and other abbreviations are the same as in Figure 1.

catecholamines in relieving the cold-induced sinoatrial block, the following observations are of particular interest. It is generally agreed that catecholamines do not increase the resting potential (19, 23, 24) but do increase the amplitude of the action potential at normal temperature (24). In high external potassium, catecholamines restore excitability without affecting the diminished resting potential (25). As shown by the present experiments, at low temperature norepinephrine restores action potentials without affecting the resting potential. However, the rate of rise and the amplitude of the action potentials are lower than they are in the control, suggesting that norepinephrine does not affect the fast sodium channels, in agreement with data obtained at normal temperature (23, 28, 27). Instead, the findings suggest that norepinephrine increases the slow membrane currents. In fact, it has been shown that epinephrine increases the slow calcium and sodium currents, which in turn increase the slow phase of the upstroke and the duration of the action potential, respectively (23). Rather significantly, epinephrine shifts the threshold for the slow inward currents to more negative values (23). In other words, under conditions (decrease in resting potential) when little or no fast response is possible, epinephrine allows slow currents to be activated by a smaller depolarization from the resting potential. Thus, the mechanism by which norepinephrine abolishes the sinoatrial block strikingly resembles the restoration of excitation and conduction in muscle fibers perfused in high external potassium. In both instances, the resting potential is decreased and the catecholamines act by substituting slow inward calcium and sodium currents for the fast sodium component abolished by the low resting potential. In the case of hypothermia,
Atrial membrane potentials during control (C), in the presence of strophanthidin (STROPH), and during recovery (R) at 30°C. LOW TEMP + STROPH: membrane potentials at temperature of arrest in the presence of the drug during quiescence (Q) and during electrical stimulation (S). For further explanation, see Figure 1.

A catecholamine-induced increase in the amplitude of sinoatrial action potentials (24) may be a contributing factor in the restoration of conduction.

The mechanism of action of electrical stimulation is also complex and includes several different factors. Due to the fall in resting potential of atrial fibers (2), the SA node action potentials no longer can depolarize the neighboring atrial cells to the threshold potential. In contrast, electrical pulses of suitable intensity and duration depolarize the membrane of atrial cells to threshold. However, this depolarization is not the only change induced by electrical stimulation which is of importance for the resumption of atrial activity. Electrical stimulation of the atrium releases acetylcholine and norepinephrine (28-30), and the effects of autonomic blockers in the experiments in the present paper confirm this fact. Acetylcholine released by stimulation might be expected to enhance the amplitude of the action potential through an increase in the resting potential. Catecholamines released by stimulation might have other effects in addition to those on the slow currents, as discussed above. Thus, released catecholamines apparently increase the resting potential, since the hyperpolarization is less in the presence of propranolol. This observation suggests that an additional mechanism is brought into play by electrical stimulation, namely, a stimulation of active transport. There are several lines of evidence to indicate that active transport is enhanced by both electrical stimulation and norepinephrine. On electrical stimulation, the sodium influx per unit time increases, and this increase must stimulate the activity of the sodium pump (31). In fibers stimulated at a constant rate, catecholamines also increase active ion transport (32-34). An increase in active transport by electrical stimulation and norepinephrine would not alter the membrane potential if sodium and potassium are exchanged on a one to one basis. However, there are situations in
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Explains why hyperpolarization caused by the stimulation is less when the action of released norepinephrine is blocked by propranolol. It must be realized, however, that the smaller hyperpolarization during electrical stimulation in the presence of propranolol could have resulted from a nonspecific action of this blocker.

A contradiction to the concept that norepinephrine stimulates a larger sodium outward current seems to be the finding that norepinephrine (when given in the absence of electrical stimulation) restores atrial activity but does not cause hyperpolarization. However, the contradiction may be only apparent. When an atrial preparation arrested in hypothermia is exposed to norepinephrine, two changes occur. The first is an acceleration of the sinus pacemaker presumably due to the mechanism described by Hauswirth et al. (38) for Purkinje fibers. The second change involves the electrical current responsible for excitation. Norepinephrine does not increase sodium-carrier availability at the low resting potential of the arrested atrial fibers. However, as discussed above, norepinephrine does shift the threshold potential for slow currents to more negative potentials and increase these currents. This shift allows the SA node action potentials to activate the atrial fibers. If the slow current is carried predominantly by calcium, the onset of atrial activity would not necessarily cause an electrogenic extrusion of positive charges. Therefore, the resting potential of the atrial fibers would not increase. Supporting evidence for an electrogenic sodium extrusion during electrical stimulation of

TABLE 3

Effects of Norepinephrine on Membrane Potentials of Guinea Pig Atrial Fibers at 30°C and in Hypothermia

<table>
<thead>
<tr>
<th></th>
<th>Control (30°C)</th>
<th>Low temperature (20.2 ± 0.6°C)</th>
<th>Quiescent</th>
<th>Norepinephrine</th>
<th>Recovery (30°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP (mV)</td>
<td>77.3 ± 0.36</td>
<td>66.7 ± 0.65*</td>
<td>66.4 ± 0.70†</td>
<td>78.1 ± 0.50</td>
<td></td>
</tr>
<tr>
<td>OS (mV)</td>
<td>24.8 ± 0.57</td>
<td>13.5 ± 1.67*</td>
<td>24.4 ± 0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP (mV)</td>
<td>102.0 ± 0.69</td>
<td>78.5 ± 2.40*</td>
<td>102.5 ± 0.76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± se for 31–44 impalements from four atria.

*Significantly different from control, P < 0.001.
†Significantly different from control, P < 0.001, but not significantly from quiescent, P > 0.4.
cooled atrial fibers is provided by the experiments with strophanthidin. With the pump poisoned by the glycoside, the resting potential on electrical stimulation does not increase significantly.

In conclusion, there are two major mechanisms by which sinoatrial block can be removed during hypothermia. One is the increase in resting potential (acetylcholine, electrogenic extrusion of sodium) which in turn increases the availability of sodium carrier and permits the opening of fast sodium channels on depolarization. The other mechanism is a change in magnitude and threshold of slow current (catecholamines) which does not require a change in resting potential.

References


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ATRIAL ACTIVITY IN HYPOTHERMIA


Restoration of Electrical Activity of Guinea Pig Atria during Hypothermia: EFFECTS OF NOREPINEPHRINE AND ELECTRICAL STIMULATION ON MEMBRANE POTENTIALS
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