Effect of Histamine and of the Anaphylactic Reaction on Isolated Guinea Pig Atria

By MARIO PENNA, M.D., ALEJANDRO ILLANES, M.D., MARIO UBILLA, M. D., AND SERGIO MUJICA, M.D.

Addition of specific antigen to the isolated atria of sensitized guinea pigs and of histamine to those of nonsensitized animals resulted in an increase of both frequency and amplitude of contraction and in the appearance of rhythmic activity in the isolated left atrium. On a quantitative basis the anaphylactic response looks like the effects of histamine in concentrations between $10^{-3}$ and $10^{-2}$ mM/L. No qualitative differences between the effects of histamine and those of the anaphylactic reaction were observed. Since isolated atria thus are seen to participate in tissue sensitization, the heart should be considered as a potential shock organ in the anaphylactic reaction.

EXPERIMENTS performed during the second decade of this century showed that during induced anaphylaxis there were disorders of cardiac frequency and rhythm which were not prevented by vagotomy. Electrocardiographic studies disclosed increases in heart rate, alterations in atrioventricular conduction, and changes in the origin and propagation of the excitation wave. The conditions prevailing in these experiments did not permit a decision on whether these observed changes were due to a direct effect of the anaphylactic reaction upon the myocardium or were attributed to myocardial ischemia and other alterations in circulatory dynamics.

Wilcox and Andrus in 1939 studied this question on the isolated heart. During the anaphylactic reaction induced by the addition of specific antigen they observed sinus tachycardia, prolongation of P-R interval, A-V dissociation, nodal and ventricular tachycardias, and other disorders of rhythm. Since a decrease of coronary flow was also present, the authors suggested that these changes in rhythm might be the consequence of an impairment of myocardial oxygenation. Kellner, Penna and Schweid reported that the addition of minute quantities (0.02 to $2 \mu g.$) of the sensitizing antigen to the fluid perfusing isolated guinea pig hearts, previously sensitized to crystalline streptococcal proteinase, bovine $\gamma$-globulin, or crystalline egg albumin, resulted in a considerable increase in frequency, usually accompanied by a marked increase in amplitude of contraction and certain disorders of rhythm (premature contractions, A-V dissociation, even complete heart block). This reaction was highly specific for the agent used to sensitize the animal. Coronary flow was simultaneously measured and no consistent changes were observed. Experiments on isolated atria of sensitized guinea pigs, reported in the same paper, showed reactions similar to those observed in the whole isolated heart, when such preparations were exposed to the sensitizing agent in concentrations as low as 0.001 $\mu g.$/ml.

Wilcox and Andrus studied the effects of histamine and of the anaphylactic reaction on the isolated guinea pig heart and observed that both involved an increase in heart rate, arrhythmias, and a decrease of coronary flow. They also reported that atropine antagonized the histamine effect on coronary flow, but not the tachycardia or the arrhythmias, and that this drug did not alter the anaphylactic reaction in the isolated guinea pig heart.

In order to elucidate this phenomenon further by avoiding changes in coronary flow it seemed desirable to study the effect of histamine and of the anaphylactic reaction in isolated atria while registering simultan-
**TABLE 1.—Effect of Histamine and of Anaphylactic Reaction on Isolated Guinea Pig Atria**

<table>
<thead>
<tr>
<th>Effect of histamine</th>
<th>Number of experiments</th>
<th>Changes of frequency (per cent of initial)</th>
<th>Changes of amplitude (per cent of initial)</th>
<th>Appearance of rhythmic activity in isolated left atrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1 \times 10^{-6}$</td>
<td>24</td>
<td>$+2.3 \pm 1.5$</td>
<td>$+13.6 \pm 2.05$</td>
<td>0/11</td>
</tr>
<tr>
<td>$1 \times 10^{-5}$</td>
<td>23</td>
<td>$+14.2 \pm 1.7$</td>
<td>$+28.3 \pm 5.5$</td>
<td>3/11</td>
</tr>
<tr>
<td>$1 \times 10^{-4}$</td>
<td>25</td>
<td>$+41.5 \pm 6.0$</td>
<td>$+68.1 \pm 15.9$</td>
<td>10/11</td>
</tr>
<tr>
<td>$1 \times 10^{-3}$</td>
<td>26</td>
<td>$+43.0 \pm 12.0$</td>
<td>$+66.6 \pm 7.5$</td>
<td>10/11</td>
</tr>
</tbody>
</table>

**Effect of antigen**

<table>
<thead>
<tr>
<th>Sensitized guinea pigs</th>
<th>12</th>
<th>$+19.4 \pm 4$</th>
<th>$+40 \pm 17.1$</th>
<th>5/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsensitized guinea pigs</td>
<td>8</td>
<td>$+0.5 \pm 0.6$</td>
<td>$-8 \pm 3.2$</td>
<td></td>
</tr>
</tbody>
</table>

*Positive cases of total isolated left atrium.*

The addition of different amounts of histamine to the bath was followed by an increase in rate which progressed with the concentration of the drug between $1 \times 10^{-4}$ mM/L and $1 \times 10^{-2}$ mM/L, beyond which higher concentrations elicited no further acceleration.

As a rule, lower concentrations of histamine ($10^{-4}$ and $10^{-5}$ mM/L) did not disturb the rhythm, but higher concentrations ($10^{-2}$ and $10^{-1}$) frequently produced irregularities in the electrocardiogram unaccompanied by changes in the shape of the complexes.

**Methods**

The experiments were performed on isolated atria of adult guinea pigs of both sexes. The animals were previously sensitized with horse serum.

**Isolated Atria.** The isolated atria were suspended in 50 ml of oxygenated tyrode solution at 29° C. The left atrium was attached lower than the right and was tied with a silk thread to a glass hook. The upper part of the right atrium then was joined to an isotonic lever which recorded on the smoked paper of a kymograph.

In some experiments the right and left atria were carefully isolated, placed in separate baths, and attached to writing levers. The electrocardiogram was recorded with a model III D Grass electroencephalograph. A unipolar lead was obtained by means of a U-shaped silver electrode in contact with the central part of the left atrium, with an indifferent electrode lying free in the bath. This lead is similar to the one used by Garb and Chenevard for recording the unipolar electrocardiogram on the isolated cat papillary muscle.

The anaphylactic reaction was elicited by the addition of the specific antigen to the bath. In other preparations obtained from normal guinea pigs, the effect of various doses of histamine was studied.

**Results**

**Effects of Histamine**

The effects of different doses of histamine on the isolated atria are summarized in table 1. Changes in the rate and amplitude of contraction of the preparation containing both atria and of the isolated right atrium are considered together, since in both cases the spontaneous rhythm originated in the sinus node. In view of individual variations, the changes in amplitude are expressed in per cent of the initial value.

**Frequency and Rhythm.** The addition of different amounts of histamine to the bath was followed by an increase in rate which progressed with the concentration of the drug between $1 \times 10^{-4}$ mM/L and $1 \times 10^{-2}$ mM/L, beyond which higher concentrations elicited no further acceleration.

As a rule, lower concentrations of histamine ($10^{-4}$ and $10^{-5}$ mM/L) did not disturb the rhythm, but higher concentrations ($10^{-2}$ and $10^{-1}$) frequently produced irregularities in the electrocardiogram unaccompanied by changes in the shape of the complexes.

**Amplitude of Contraction.** The addition of histamine induced an increase in the amplitude of contraction that appeared shortly after the increase in frequency. The effect on amplitude was also correlated with the concentration up to $1 \times 10^{-2}$ mM/L.

The increase in amplitude observed at the latter concentration was $68.1 \pm 15.9$ per cent of the control value. This increase was not exceeded with higher histamine concentrations (table 1). An example of the effect of various histamine concentrations appears in figure 1.

**Automaticity of Isolated Left Atrium.** The isolated left atrium bathed in tyrode...
solution at 29 C. usually does not exhibit rhythmic activity, either mechanical or electrical. An occasional spontaneous contraction may be observed occurring at intervals ranging from 0.5 to 3 min. Histamine induced a regular automaticity in both electrogram and kymogram. Data summarized in table 1 shows that the proportion of cases in which histamine induced this effect increased with the concentration. In low concentrations (1 × 10⁻⁴ mM/L.) histamine did not induce any automaticity while higher concentrations succeeded in almost all cases. Figure 2 shows an example of the automaticity induced by histamine. This effect generally appeared 2 to 3 min. after the addition of the drug.

Dose-Response Relationship. The results indicate that, with respect to effects on rate, amplitude of contraction of both atria and automaticity of the left atrium, a concentration of 10⁻⁴ mM/L. of histamine can be considered the threshold level and 10⁻² mM/L. the maximum. Concentrations ten times higher than the latter had no greater effect.

**Effect of the Anaphylactic Reaction**

The results obtained in experiments with specific antigens are summarized in table 1.

**Frequency and Rhythm.** The addition of 1 ml. of the antigen solution to the 50 ml. bath containing the atria of a sensitized guinea pig induced an increase in frequency. The average increase observed in 12 preparations was 19 ± 4 per cent of the initial rate. No disorders of rhythm were observed.

In similar experiments on 8 isolated atria from normal nonsensitized guinea pigs, the addition of the same amount of antigen had no effect on frequency of contraction.

**Amplitude of Contraction.** The addition of the antigen caused the isolated atria of sensitized animals to show a constant increase in amplitude of contraction. The average of 12 experiments was 40 ± 17.1 per cent of control values. In 8 isolated atria from normal, nonsensitized animals the addition of the antigen induced an insignificant decrease in amplitude. Figure 3 shows the result of one experiment in which the antigen was added to the isolated atria of a normal and a sensitized animal.

**Automaticity of Isolated Left Atrium.** This was studied in 8 isolated atria from sensitized animals. The addition of 1 ml. of the antigen
solution to the 50 ml. bath induced automaticity in 5 cases (fig. 4).

Delay of Anaphylactic Reaction. The data summarized in table 2 show that the effect of antigen on the rate and amplitude of contractions of the right atrium, or both atria appeared after a latent period ranging from 1 to 2 min. Automaticity of the left isolated atrium appeared after a slightly greater delay (fig. 4).

Relationship Between Effects of Antigen and Histamine

The effects induced by the anaphylactic reaction on the rate and amplitude of contraction are similar to those induced by histamine in concentrations between $1 \times 10^{-3}$ and $1 \times 10^{-2}$ mM/L. The proportion of cases in which automaticity was induced by the anaphylactic reaction in the isolated left atrium was similar to that observed with histamine at these concentrations. The anaphylactic reaction did not induce changes in rhythm and these were seen after histamine only in concentrations $1 \times 10^{-2}$ mM/L or higher.

Discussion

The effects of histamine observed on the preparation of both isolated atria of guinea pigs are in agreement with those reported by Riegler and Tiemann in the same preparation of the rabbit and by Burn in that of the guinea pig. These experiments do not reveal whether the effects on rate and amplitude of contraction are separable, or whether the latter is merely secondary to the former, as it has been shown to be in other isolated heart preparations when stimulated electrically (Szent-Györgyi, Bowditch, Kruta, Gold and Catell).

These experiments performed on the isolated left guinea pig atrium confirm in this animal the automaticity-inducing effect of histamine in the isolated left rabbit atrium reported by Riegler and Tiemann. The histamine concentrations used by these authors were lower (about $1 \times 10^{-3}$ mM/L), however, than in this experiment and the frequency of the automatic rhythm induced by histamine was also lower.

The results reported here indicate that the heart is a potential "shock organ" during the anaphylactic reaction. The latent period of about 1 min. observed in the anaphylactic reaction in the atria is in agreement with
ANAPHYLACTIC REACTION

the observation of Schultz-Dale phenomenon on the isolated uterus. The effects of the anaphylactic reaction are similar to those induced by histamine and are quantitatively equivalent to the effects of histamine in concentrations between $1 \times 10^{-5}$ and $1 \times 10^{-2}$ mM/L. This relationship of concentrations is similar to that observed by Varela in the Schultz-Dale phenomenon on the isolated guinea pig uterus.

These findings support the concept that the cardiac effects of histamine and of the anaphylactic reaction are exerted directly on the myocardium and are not dependent on changes in coronary flow, since in the isolated atria preparation the coronary circulation is not involved and the antigen or drug reaches the cell by diffusion from outside.

The fact that both histamine and the anaphylactic reaction induce automaticity in the isolated left atrium increases the evidence supporting the similarity of histamine to the substances liberated during the anaphylactic reaction.

**Summary**

The comparative effects of histamine and of the anaphylactic reaction on the isolated guinea pig atrium were studied. The dose: response relationship for histamine showed that, with regard to the increase of frequency and amplitude of contraction as well as the appearance of rhythmic activity in the left isolated atrium, $1 \times 10^{-4}$ mM/L was a threshold concentration and $1 \times 10^{-2}$ mM/L was maximal. In the isolated atria from sensitized guinea pigs, the addition of the specific antigen induced effects to those of histamine in concentrations between $1 \times 10^{-5}$ and $1 \times 10^{-2}$ mM/L, but only after a latent period of about 1 min. Histamine and the anaphylactic reaction led to the appearance of rhythmic activity in the isolated left atrium. In both cases the automatic activity began after a latent period of from 1 to 6 mins. No qualitative differences between the effects of histamine and the anaphylactic reaction were observed. Since the latter effects are due to sensitization of cardiac tissue itself, the heart should be considered as a potential shock organ during the anaphylactic reaction.

*Table 2.—Latent Period of Effect of Histamine and Anaphylactic Reaction on Isolated Guinea Pig Atria*

<table>
<thead>
<tr>
<th>Histamine concentration (mM/L)</th>
<th>Both Atria and right atrium</th>
<th>Isolated left atrium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of experiments</td>
<td>Time range (min.)</td>
</tr>
<tr>
<td>Effect of histamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$1 \times 10^{-4}$</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>$1 \times 10^{-3}$</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>$1 \times 10^{-2}$</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>$1 \times 10^{-1}$</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Effect of antigen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitized guinea pigs</td>
<td>12</td>
<td>1 - 2</td>
</tr>
</tbody>
</table>

*Only cases exhibiting an effect considered.*

**SUMMARIO IN INTERLINGUA**

Esseva studiate le effectos comparative de histamina e del reaction anaphylaetic super le isolate auricula de porcos de India. Le relation inter dosage e responsa pro histamina mostrava que, con respecto al augmento del frequentia e del amplitude de contraction e etiam con respecto al apparition de activitate rhythmic in le isolate auricula sinistre, le concentration limine esseva $1 \times 10^{-4}$ mM/L e le concentration de efficacia maximal $1 \times 10^{-2}$ mM/L. In auriculas isolate ab sensibili-sate porcos de India, le addition del antigeno specific induceva effectos simile a illos de histamina in concentrationes inter $1 \times 10^{-5}$ e $1 \times 10^{-2}$ mM/L, sed solmente post un periodo latente de circa un minuta. Histamina si ben como le reaction anaphylaetic resultava in le apparition de un activitate rhythmic in le isolate auricula sinistre. In ambe casos le activitate automatic commenciava post un periodo latente de inter un e sex minutas, Nulle differentias qualitative inter le effectos de histamina e le reaction anaphylaetic es-seva observe. Viste que le effectos hie dis-cultite es causate per sensibilisation del histos cardiac mesme, le corde debe esser considerate como potentialmente un organo de choc durante le reaction anaphylaetic.
REFERENCES


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Circ Res. 1959;7:521-526
doi: 10.1161/01.RES.7.4.521

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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