ANALYSIS OF SUPERSENSITIVITY IN THE ISOLATED SPLEEN OF THE CAT\(^1\)

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ABSTRACT

Green, Richard D., III and William W. Fleming: Analysis of supersensitivity in the isolated spleen of the cat. J. Pharmacol. Exp. Therap. 162: 254-262, 1968. In vitro experiments were performed in which dose-response curves to d-norepinephrine or L-norepinephrine, \(pA_2\) values for L-NE-phen tolamine and \(pD_2\) values for L-NE-phenox ybenzamine were determined in separate strips cut from each spleen. Denervation and cocaine (in reserpine-pre-treated preparations) produced supersensitivity to L-NE but not to d-NE. Reserpine (0.1 mg/kg for 14 days) did not produce supersensitivity to L-NE. Reserpine (1.0 mg/kg for 2 days) produced subsensitivity to d-NE. The \(pA_2\) and \(pD_2\) values in all groups were not significantly different from control. Tissue NE concentrations were approximately 10% of control 14 days after denervation and after chronic treatment with reserpine. Results are presented which indicate that the innervation of the spleen is not homogeneous and that the denervation procedure employed produced a complete denervation of the wide or medial end of the spleen but only a partial denervation of the thin or lateral end. It is concluded that the supersensitivity of the isolated spleen observed after denervation or cocaine is of presynaptic origin. Postsynaptic supersensitivity after chronic denervation or chronic reserpine treatment, although demonstrable in other tissues, could not be demonstrated in the spleen.

Burn and Rand (1959) have presented evidence that supersensitivity can be induced in the cat spleen by chronic denervation and by the administration of large doses of reserpine (3.0 mg/kg daily for 2 days). They determined the threshold dose of L-norepinephrine, given intravenously, to produce a volume change of the spleen in the spinal cat preparation. Trendelenburg (1963) has pointed out that the determination of threshold doses is not a reliable method for measuring sensitivity. Green and Robson (1965) have obtained data by plethysmographic techniques indicating the presence of supersensitivity after chronic denervation and after chronic adrenergic neuron blockade. Although they obtained dose-response curves their data are difficult to interpret because the shifts in their dose-response curves were not parallel and there appeared to be a pronounced change in the maximum response after denervation or adrenergic neuron blockade.

Trendelenburg (1965) has provided evidence for the view that the specific supersensitivity produced by cocaine results from the ability of cocaine to prevent the uptake of amines into tissue stores. Several investigators have suggested that other supersensitivity phenomena may be the result of postsynaptic changes (Carr er and Holland, 1965; Hudgins and Fleming, 1966; Varma, 1966). Green and Fleming (1967) found quantitative evidence in the nictitating membrane of the spinal cat that the supersensitivity after cocaine administration is entirely due to a presynaptic change, whereas the supersensitivity after chronic denervation, chronic decentralization or chronic treatment with reserpine is due, in part at least, to a postsynaptic mechanism of action.

Most of the information concerning the vari-

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ous types of supersensitivity in smooth muscle has been obtained in the nictitating membrane of the spinal cat. For this reason it would seem desirable to make a detailed study of supersensitivity in other preparations and thus test the general applicability of theories based on experiments in the nictitating membrane. The purpose of the present experiments was therefore 2-fold: 1) to determine whether supersensitivity could be demonstrated in vitro in the cat spleen and 2) after supersensitivity had been demonstrated to determine whether it was of presynaptic or postsynaptic origin.

Methods. Cats of 1.5 to 3.5 kg b.wt. and of either sex were used. The spleens were removed through a lateral abdominal incision from cats under ether anesthesia and washed in warm modified Krebs-Henseleit solution. The composition of this solution has been presented previously (Green et al., 1968). Strips measuring approximately 25 by 5 mm were cut and placed in organ baths containing 30 ml of Krebs-Henseleit solution which was bubbled with 95% oxygen and 5% carbon dioxide and maintained at 38°C (Innes, 1962). The contractions of the spleen were measured isometrically with a Grass force-displacement transducer and polygraph.

An initial tension of 2 to 3 g was applied to the spleen strip. Readjustments were made as necessary until the strip stabilized at a tension of 1.0 to 1.5 g. The spleen strip returned spontaneously to this tension between responses. The responses were recorded as increases in tension above this base-line value. After an equilibration period of 1 hr drugs were added to the bath from a 1-ml graduated syringe. Washout of drugs was accomplished by draining and refilling the bath a minimum of three times after each response. All responses were calculated as percentages of the maximal response. Only one dose-response curve was determined on each spleen strip. Pretreatment with reserpine and long-term denervation (30-65 days) did not affect the mean maximal response obtained in any of the groups studied. The maximal response to l-norepinephrine appeared to be lower in the groups denervated for shorter periods of time. As the supersensitivity present 14 days after denervation (group with lower maximal response) was indistinguishable from that present 30 to 65 days after denervation (group with normal maximal response), this variation in maximal response had no effect on the present experiments or their interpretation.

Denervation was accomplished by severing the splenic nerve (postganglionic fibers) within 1 to 2 cm of the spleen. Anesthesia for this procedure was produced with pentobarbital sodium given i.p. in a dose of 35 mg/kg. Reserpine was administered i.p. in two dosage schedules: 1) 0.1 mg/kg daily for 12 to 14 days and 2) 1.0 mg/kg daily for 2 days. Cocaine was dissolved in the Krebs-Henseleit solution to give a concentration of 10 µg/ml. Only spleens from cats pretreated with reserpine (1.0 mg/kg for 2 days) were used in the cocaine experiments; spleens from control animals partially contracted in the presence of cocaine.

pA2 or pD2* values for phentolamine (equilibrium competitive antagonist) and phenoxybenzamine (nonequilibrium competitive antagonist) were determined to quantify adrenergic blocking activity. The pA2 values were determined by the method described by Schild (1947). Two spleen strips were exposed to a concentration of agonist which produced a submaximal response at 15-min intervals until the responses were uniform. Phentolamine, in two different concentrations, was then added, allowed to remain in contact with the strip for 5 min and, without washing, a double dose of agonist was added and the response was recorded. The response to the double dose of the agonist was then recorded as a percentage of the response to the single dose. The pA2 values were then determined by linear interpolation on a log scale as described by Schild (1947). In a few experiments the pA2 values were determined by close linear extrapolation, the lower dose of phentolamine being slightly greater than the pA2 concentration. The pA2 values for l-norepinephrine-phentolamine were not statistically different when phentolamine was allowed to be in contact with the tissue for 5 or 20 min (pA2 for 5 min = 6.29 ± 0.08; pA2 for 20 min = 6.26 ± 0.10). Thus the 5-min values are good estimates of the true pA2 value, i.e., the affinity constant of phentolamine for the receptor population. A dose-response curve to the same agonist was simultaneously determined on a third spleen strip. After the maximum response was obtained and shown to be repeatable, phenoxybenzamine was added for a 5-min period and, after several washes, the maximum response to the agonist was again determined. The pD2* values

pA2 is defined as the negative logarithm of the molar concentration of an equilibrium competitive antagonist which reduces the effect of a double concentration of agonist to that of a single one (Schild, 1947). The pD2* value is the negative logarithm of the molar concentration of noncompetitive or nonequilibrium competitive antagonist which reduces the maximal effect of an agonist to one-half its initial value (Ariëns and van Rossum, 1967; Bickerton, 1963).
were then calculated from the following equation (Bickerton, 1963):

\[ pD'_1 = pD'_0 + \log \left[ \frac{E_{A1m}}{E_{A2m}} - 1 \right] \]

where \( pD'_0 \) is the negative logarithm of the molar concentration of phenoxybenzamine employed and \( E_A \) and \( E_{AB} \) are the maximal response in the absence and in the presence of phenoxybenzamine, respectively. The \( pD'_0 \) values obtained with a 5-min period of exposure to phenoxybenzamine are not necessarily the values that would be obtained with an infinite exposure period. In some cases a fourth sample of spleen was analyzed for catecholamines by the automated trihydroxyindole method of Robinson and Watts (1965).

Concentrations of \( l \)-norepinephrine bitartrate and \( d \)-norepinephrine bitartrate refer to the free bases and were dissolved in saline to which 100 mg/liter of ascorbic acid were added. Reserpine was prepared according to the formulation of Martindale (1968). Phenoxybenzamine \( HCl \) was dissolved in acidified ethanol (Benfey and Grillo, 1969) and diluted in saline. All other drugs were dissolved in distilled water. The concentrations of phenolamine methanesulfonate, phenoxybenzamine \( HCl \) and potassium chloride refer to the active base or ion; the doses of reserpine and concentration of cocaine \( HCl \) refer to the salts.

The results are presented as dose-response curves as well as the geometric means of EC50 (effective concentration, 50%) values. Statistical evaluations of differences in sensitivity were determined by analysis of variance and Duncan's multiple range tests (Steel and Torrie, 1960) of the EC50 values. The determinations of mean EC50's and the statistical analyses were made by the West Virginia University Computer Center.

**RESULTS.** Although more than one parameter was studied simultaneously the results are best reported separately. Dose-response curves for \( l \)-norepinephrine before (control) and after various periods of denervation are presented in figure 1 and the geometric means of the EC50 values are presented in table 1. There was approximately a 3-fold increase in the sensitivity 7 days after denervation (P < .05). Although the shift in the dose-response curve 14 days after denervation was somewhat greater, the increase in sensitivity from 7 to 14 days was not significant. The sensitivity after prolonged denervation (30-65 days) was indistinguishable from that after 14 days.

Figure 2 and table 1 show the effect of two dosage schedules of reserpine and of cocaine on the dose-response curve and mean EC50 of \( l \)-norepinephrine. Chronic reserpine treatment (0.1 mg/kg daily for 12-14 days) did not pro-

![Figure 1](image.png)

**Fig. 1.** The effect of various periods of denervation on the dose-response curve for \( l \)-norepinephrine in isolated spleen strips. Each curve represents the mean results from 5 to 7 experiments. Vertical bars indicate standard errors.
TABLE 1

Geometric means with 95% confidence intervals of EC50 values obtained with \(l\)-norepinephrine and \(d\)-norepinephrine in spleen strips

<table>
<thead>
<tr>
<th>Strip Samples</th>
<th>Group No.</th>
<th>Treatment*</th>
<th>Mean EC50(\mu)l</th>
<th>Confidence Interval</th>
<th>Groups Compared Statistically(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-NE Random</td>
<td>1</td>
<td>Control</td>
<td>1.60</td>
<td>0.88-2.92</td>
<td>1 2 5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Den. 7</td>
<td>0.60</td>
<td>0.28-1.29</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Den. 14</td>
<td>0.40</td>
<td>0.21-0.76</td>
<td>.01 NS</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Den. &gt;14</td>
<td>0.28</td>
<td>0.16-0.52</td>
<td>.01 NS</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Res. 2</td>
<td>0.77</td>
<td>0.35-1.63</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Res. 2 + Coc.</td>
<td>0.10</td>
<td>0.05-0.22</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Res. 12-14</td>
<td>2.09</td>
<td>1.10-3.92</td>
<td>NS</td>
</tr>
<tr>
<td>d-NE Random</td>
<td>8</td>
<td>Control</td>
<td>3.20</td>
<td>1.86-5.50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Res. 2</td>
<td>8.06</td>
<td>4.69-12.85</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Res. 2 + Coc.</td>
<td>6.47</td>
<td>3.77-11.12</td>
<td>.05 NS</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Den. 14</td>
<td>2.78</td>
<td>1.61-4.75</td>
<td>NS</td>
</tr>
<tr>
<td>l-NE Medial</td>
<td>12</td>
<td>Control</td>
<td>1.03</td>
<td>0.65-1.65</td>
<td>12 14 15 16</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>Den. &gt;14</td>
<td>0.12</td>
<td>0.06-0.18</td>
<td>.01 NS</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Den. &gt;14 + Coc.</td>
<td>0.06</td>
<td>0.04-0.10</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Control</td>
<td>2.30</td>
<td>1.44-3.62</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>Den. &gt;14</td>
<td>0.89</td>
<td>0.38-0.90</td>
<td>NS .01</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>Den. &gt;14 + Coc.</td>
<td>0.08</td>
<td>0.05-0.12</td>
<td>.01</td>
</tr>
</tbody>
</table>

* Treatments were as follows: Den. 7 = denervation, 7 days; Den. 14 = denervation, 14 days; Den. >14 = denervation, greater than 14 days; Res. 2 = reserpine, 1.0 mg/kg/day, 2 days; Res. 12-14 = reserpine, 0.1 mg/kg/day, 12 to 14 days; Coc. = cocaine, 10 \(\mu\)g/ml.

\(a\) EC50, concentration of drug producing 50% of the maximum response to that drug in a single strip.

* Statistical analyses were performed using Duncan's multiple range test. Levels of significance are given between appropriate groups. NS, not significant.

duce supersensitivity. Short-term reserpine treatment (1.0 mg/kg daily for 2 days) produced a small shift to the left of the dose-response curve, but the difference was not significant at the EC50. The presence of cocaine caused a marked shift of the curve to the left (reserpine plus cocaine > reserpine alone at the .01 level of probability).

Figure 3 and table 1 show the effects of short-term treatment with reserpine, short-term treatment with reserpine plus cocaine and chronic denervation on the dose-response curve and mean EC50 for \(d\)-norepinephrine. Short-term treatment with reserpine (2 days) produced a significant decrease in the sensitivity of the spleen strips to \(d\)-norepinephrine (P < .05). The presence of cocaine did not significantly increase the sensitivity to \(d\)-norepinephrine. Similarly, denervation had no effect on the sensitivity to \(d\)-norepinephrine. It is interesting to note that \(l\) and \(d\)-norepinephrine used in these experiments differed very little in potency in control spleens. The mean EC50 of \(d\)-norepinephrine was only twice the mean EC50 of \(l\)-norepinephrine (table 1). There is no explanation for this fact at present, although the possibility exists that the \(d\)-norepinephrine was contaminated with a small amount of \(l\)-norepi-
The effect of reserpine pretreatment and the presence of cocaine on the dose-response curve for l-norepinephrine in isolated spleen strips. Each curve represents the mean results from 5 to 7 experiments. Vertical bars indicate standard errors.

Table 2 summarizes the results of the pA₂ and pD₂' determinations. The mean pD₂' for l-norepinephrine–phenoxybenzamine did not differ significantly from control in any group studied nor did the mean pA₂ for l-norepinephrine–phenolamine.
nephrine-phenolamine differ from control in any of the groups studied.

Table 3 summarizes the results of the catecholamine determinations. The maximum depression of tissue norepinephrine occurred between 7 and 14 days after denervation. Chronic treatment with reserpine (0.1 mg/kg/day for 14 days) produced the same degree of depletion of norepinephrine as that produced by chronic denervation. Neither denervation nor chronic treatment with reserpine had any detectable effect on the concentration of epi-
nephrine in the spleen. However, the very low epinephrine levels approach the limits of detection of the method.

After completion of the work thus far presented it was learned that the cat spleen can be partially denervated (U. Trendelenburg, personal communication). Additional experiments were then performed to determine the homogeneity of the sensitivity to l-norepinephrine of control and denervated spleens. Four strips from each of several control spleens were studied, two strips each from the medial (wide) and lateral (thin) ends. The sensitivity across the width of the spleen did not vary. The responses of adjacent pairs of strips were therefore averaged to compare the sensitivities of the opposite ends of the spleen. The medial end of the spleen was significantly more sensitive to l-norepinephrine than the lateral end (P < .05). The results of these experiments are shown in figure 4 and table 1. Chronically denervated spleens (14 days or more) were then studied. Four strips from each denervated spleen were prepared and the following groups were studied: 1) medial end, 2) medial end in the presence of cocaine (10 µg/ml), 3) lateral end and 4) lateral end in the presence of

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Norepinephrine</th>
<th>Epinephrine</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.99 ± 0.25</td>
<td>0.08 ± 0.05</td>
<td>5</td>
</tr>
<tr>
<td>Denervated (7 days)</td>
<td>0.68 ± 0.34</td>
<td>0.16 ± 0.18</td>
<td>4</td>
</tr>
<tr>
<td>Denervated (14 days)</td>
<td>0.14 ± 0.08</td>
<td>0.04 ± 0.02</td>
<td>4</td>
</tr>
<tr>
<td>Denervated (&gt;14 days)</td>
<td>0.25 ± 0.05</td>
<td>0.04 ± 0.01</td>
<td>5</td>
</tr>
<tr>
<td>Reserpine (0.1 mg/kg/day, 14 days)</td>
<td>0.21 ± 0.04</td>
<td>0.09 ± 0.01</td>
<td>5</td>
</tr>
</tbody>
</table>

* N, number of cats.
† Significant decrease, P < .01.

![Figure 4](image-url)
cocaine. The results of these experiments are also shown in figure 4. The sensitivities of both ends of the denervated spleen were greater than their respective controls (P < .01). After denervation the sensitivity of the medial end was significantly greater than that of the lateral end (P < .01). The presence of cocaine had little or no effect on the sensitivity of the denervated medial end to l-norepinephrine but significantly increased the sensitivity of the denervated lateral end (P < .01). The sensitivities of the two ends of denervated spleens were similar in the presence of cocaine.

Discussion. Trendelenburg (1965) has studied the changes in sensitivity to d-norepinephrine and l-norepinephrine resulting from cocaine administration, denervation and decentralization of the nictitating membrane of the spinal cat. He has shown that supersensitivity of presynaptic origin (cocaine and one component of denervation supersensitivity) is specific in the sense that it is much greater for l-norepinephrine than for d-norepinephrine. He further showed that decentralization supersensitivity, which is now believed to be of postsynaptic origin, produced a moderate supersensitivity to both isomers. It seems reasonable, therefore, that a procedure or treatment which initiates the development of supersensitivity is producing postsynaptic changes if the supersensitivity exists equally to both d- and l-norepinephrine but is acting presynaptically if the supersensitivity is much greater for the L-isomer. The present experiments demonstrate that in the isolated cat spleen cocaine produces supersensitivity to l-norepinephrine but not to d-norepinephrine. Chronic denervation also produced supersensitivity to l-norepinephrine but failed to produce a change in the sensitivity to d-norepinephrine. These results suggest that the supersensitivity occurring in the spleen after denervation is entirely of presynaptic origin.

Chronic treatment with reserpine (0.1 mg/kg daily for 14 days) did not produce any change in the sensitivity of the spleen strips to l-norepinephrine. The supersensitivity produced by chronic treatment with reserpine in the nictitating membrane is of postsynaptic origin (Green and Fleming, 1967). Since a postsynaptic type of supersensitivity could not be produced in this preparation by denervation, it is not surprising that chronic reserpine treatment failed to produce supersensitivity.

The short-term treatment with reserpine (1.0 mg/kg daily for 2 days) produced subsensitivity to d-norepinephrine. The subsensitivity to d-norepinephrine could either be the result of a depressant action of the large dose of reserpine or the result of a small amount of indirect (catecholamine-releasing) action contributing to the overall activity of d-norepinephrine seen under control conditions. For this reason the conclusion that denervation produced no supersensitivity to d-norepinephrine is open to question. It is possible that the loss of an indirect component of action masked a small amount of supersensitivity.

Green and Fleming (1967) have determined "pAᵢ" and "pDᵢ" values in the nictitating membrane of the spinal cat. Chronic denervation, chronic decentralization, chronic reserpine treatment and acute cocaine administration, all procedures previously shown to produce supersensitivity in that preparation, did not alter "pAᵢ" values for l-norepinephrine-phenolamine. Denervation, decentralization and chronic treatment with reserpine all significantly lowered the "pDᵢ" for l-norepinephrine-phenoxbenzamine. Cocaine had no effect on this value. This was interpreted as evidence that supersensitivity from cocaine is entirely of presynaptic origin whereas a postsynaptic component contributes, in part at least, to the supersensitivity resulting from denervation, decentralization and treatment with reserpine. The postsynaptic alteration was concluded to be either a change in the number of available receptors or a change in the relationship between receptor occupation and response, i.e., a change in the physiology of the responding cells. The latter possibility was favored in view of the non-specificity of the supersensitivity.

The pDᵢ values determined for l-norepinephrine-phenoxbenzamine in the present experiments did not differ significantly from control in any of the groups studied. This determination alone supports the hypothesis that the supersensitivity in the spleen after denervation or cocaine is entirely of presynaptic origin. It would not seem possible that a change in a pAᵢ value could occur in the absence of a simultaneous change in a pDᵢ value. In the present studies the pAᵢ values for l-norepineph-
Super sensitivity of nervation to selected nerved and supersensitivity reduce both probably shown lenburg tissue opposite curves isolated chronic rine. Supersensitivity the medial since nictitating denervation the data values of is catecholamine and supersensitivity in the cat spleen. The tissue catecholamine values indicate that the denervation and chronic treatment with reserpine both produced good depletion of norepinephrine. The failure of either procedure to produce postsynaptic supersensitivity was therefore not due to inadequate depletion. The supersensitivity seen in most tissues after chronic treatment with reserpine is generally considered to be due to prolonged loss of contact with the neuro-mediator. This type of supersensitivity is not demonstrable in the isolated spleen.

It is clear that the sensitivities of the two ends of the spleen are different in both control and denervated spleens. The dose-response curves employing unselected control and denervated (14-day) spleen strips fit nicely between the two extremes represented by the opposite ends of the spleen (fig. 4). This indicates that the unselected spleen strips represent a good random sampling of the spleen and that the data and conclusions based on these experiments are valid. The tissue catecholamine values presented were determined on large unselected samples which were composed of multiple pieces of tissue and are therefore regarded as being representative of the effects of denervation and reserpine treatment on the tissue concentrations of these amines. Trendelenburg and Dráskóczy (1967) have recently shown the inferior muscle of the isolated nictitating membrane to be twice as sensitive to l-norepinephrine as the medial muscle. Since the inferior muscle had only 65% of the endogenous l-norepinephrine content of the medial muscle they suggested that the difference in sensitivity to l-norepinephrine is a function of the densities of the innervations to the two muscles. As the sensitivities of the two ends of the spleen after denervation plus cocaine were equal it is likely that the same explanation is applicable to the present results. Since the addition of cocaine had little or no effect on the sensitivity of the medial end of denervated spleens this end must be nearly or completely denervated by the procedure employed. However, cocaine did significantly increase the sensitivity to l-norepinephrine of the lateral end of denervated spleens, and it must be concluded that this end was not completely denervated in the present experiments.

Postsynaptic supersensitivity in cat spleen strips was produced by chronic denervation and by cocaine. Postsynaptic supersensitivity could not be demonstrated. This form characteristically takes a period of time to develop and is believed to be due to the removal of tonic impulses traveling from the CNS to the effector tissue (Emmelin, 1961; Trendelenburg, 1963). It is possible that a postsynaptic supersensitivity does not develop because the number of tonic impulses traveling to the spleen under normal conditions is low and thus the removal of these impulses produces little change. This hypothesis has previously been invoked to explain a somewhat similar situation in the submaxillary gland of the cat (Emmelin and Engström, 1960). Another possibility exists, however. Tsai et al. (1967), in a very thorough study, have been unable to detect the nonspecific type of supersensitivity in the isolated nictitating membrane. Since this type of supersensitivity has been demonstrated in other isolated tissues (aorta, Hodgins and Fleming, 1966; ileum, Fleming, 1968), one cannot conclude that it is merely an in vivo phenomenon. It is possible that the “stress” to which tissues are subjected in the isolation procedures or in being bathed in salt solution rather than normal body fluids results in changes in membrane activity, distribution of ions, etc. which negate related changes which are responsible for supersensitivity. Since the magnitude of such changes would vary depending on the tissue and the isolation procedure, the consequence would be a failure of supersensitivity to appear in some isolated organs but not others. Recent studies (Westfall and Fleming, 1968) have provided evidence for a correlation between the isolation procedure...
and the demonstration of nonspecific (i.e., postsynaptic) supersensitivity within a single tissue, the pacemaker of the guinea-pig heart.

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REFERENCES


