The Effect of Hypertonic Solution on the Wet Weight and Contractions of Rat Uterus and Vas Deferens*

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ABSTRACT The role of propagated activity in the responses to agonist drugs was studied for the rat uterus and vas deferens. Hypertonic solutions were used to inhibit propagation of activity by shrinking cells. Tissue weight was used to indicate cell volume. Hypertonic solutions after 10 min caused weight loss and reduced the size of contractions in response to submaximal doses of drugs, to KCl, and to external electrical stimulation. Contractions in response to KCl and drugs were diminished to a similar degree in the vas deferens, but in the uterus, drug contractions were depressed much more. Prolonged action of hypertonic solution also differed for the two tissues. In the uterus, weight changes correlated with changes in size of the drug-induced contractions. Uterine contractions reduced in hypertonic solution could be increased by using supra-maximal doses of drug. When stimulation was applied to one end of the uterus in a three compartment bath, propagation of spontaneous drug- and KCl-induced contraction occurred, but it was prevented by placing hypertonic solution in the center compartment. An increase of the KCl to 44 mM in the hypertonic solution restored propagation. These experiments yielded no evidence of propagated responses in the rat vas deferens. It was concluded that propagated activity plays a role in drug-induced contractions in the rat uterus but not in the rat vas deferens. Hyperpolarization of shrunken cells might be involved in inhibition of propagation by hypertonic solutions.

INTRODUCTION
When a drug causes the maximal contraction of a smooth muscle it may act in one of two ways, either on each individual muscle cell, or on a few sensitive

* Dr. P. M. Carroll died suddenly on 22 October 1968, after submission of this paper. The final revision which appears here was made by Dr. Mollie Holman, Department of Physiology, Monash University, Melbourne, Australia, and Dr. E. E. Daniel, Department of Pharmacology, University of Alberta, Edmonton, Canada. Requests for reprints should be sent to Dr. E. E. Daniel.
cells which may be considered to initiate cell-to-cell excitation (Daniel, 1964 b). Evidence as to which is the mode of action for any particular drug on any particular smooth muscle is frequently lacking. When potassium chloride causes the contraction of a smooth muscle, it is generally believed to act on each individual muscle cell because any cell investigated by microelectrodes has been found to be depolarized. The investigations reported here were designed to determine whether propagation is involved in the responses of the rat uterus and the rat vas deferens to drugs. Hypertonic solutions were used to inhibit propagation of activity since Barr et al. (1968) and Johansson and Ljung (1967) have shown that such solutions inhibit conduction in the guinea pig taenia coli and the rat portal vein.

Since it has been suggested that blockage of conduction by hypertonic solutions is due to shrinkage of smooth muscle cells and the rupture of intercellular connections (nexuses) (Barr et al. 1968), tissue wet weights were determined as an indication of cell volume. The spontaneous contractions of the uterus, its response to electrical stimulation and drug action were initially depressed by hypertonic solutions and the degree of depression was correlated with the decrease in tissue wet weight. Responses of the vas deferens to drug action, and responses of both smooth muscles to KCl were also depressed but to a much smaller extent. A triple compartment bath was used to demonstrate first that conduction of responses to drugs can occur in the uterus but not in the vas deferens, and second that hypertonic solutions block conduction in the uterus.

These results are in accordance with the hypothesis that drugs act directly on only a few sensitive cells in the uterus and the activity then propagates from cell-to-cell, whereas in the rat vas deferens drugs act directly on each individual muscle cell.

**METHODS**

**Solutions**

The physiological salt solution (PSS) contained NaCl (118 mM), KCl (4.5 mM), CaCl₂ (1.4 mM), MgCl₂ (1.16 mM), Na₂HPO₄ (1.16 mM), NaHCO₃ (25 mM), and glucose (11.1 mM).

The potassium-rich solution for inducing contractures (122.5 mM KCl) was prepared by replacing the sodium chloride of the PSS by equimolar potassium chloride. For some experiments weaker potassium solutions (44 and 24 mM) were obtained by mixing appropriate volumes of the 122.5 mM KCl salt solution and PSS. Solutions were made hypertonic by the inclusion of sucrose, choline chloride, or mannitol, without altering the concentrations of the other constituents. 10% sucrose, 5% mannitol, and 2% choline chloride are approximately osmotically equivalent to PSS. Carbogen® (95% O₂ + 5% CO₂) was bubbled through all solutions.
Tissues

Wistar rats were killed by a blow on the head. The vasa deferentia were freed of adhering tissue and washed through to remove epididymal secretions. Uterine horns from 180 g rats, pretreated for 6 days with 50 μg diethylstilbestrol per day, were cut open longitudinally. After setting up a tissue, at least 1 hr was allowed for recovery before commencing tests.

Drugs

Unless otherwise stated, submaximal doses of drugs were used which gave two-thirds to three-quarters of the maximal response. The dose was determined for each tissue because of variation from animal to animal but was usually 200 μg/ml of acetylcholine chloride for the vas deferens and 0.1 μg/ml of acetylcholine chloride, 4 ng/ml of serotonin creatinine sulfate, and 0.12 ng/ml of angiotensin for the uterus.

Single Compartment Baths

Baths had a capacity of 50 ml and recordings were made isotonically, using smoked drums and lightly loaded levers (× 10).

Triple Compartment Baths

Baths were constructed, so that approximately 1 cm of the central portion of the tissue was in the center compartment, and the two ends were in the large end compartments, capacity 40 ml. Thin rubber diaphragms separated the compartments, with small holes to accommodate the tissues without strangling them. Leakage between the compartments was prevented by applying a little silicone grease at the diaphragms, and at the end of each experiment, absence of leakage was checked by adding methylene blue to the center compartment. In some experiments, tissues were fixed at the middle of the center compartment by pinning with a fixed needle, to prevent contraction of one end of the tissue mechanically moving the other end, and the two halves of the tissue were put at right angles to each other to completely eliminate the possibility of mechanical influence. The two ends of the tissue were connected to Grass FT03 strain gauges and isometric contractions were recorded on a Grass Model 5 polygraph. In experiments in which potassium chloride was placed in the center compartment, some uteri were fixed twice by pinning with two needles, close to the diaphragms but in the outer compartments. Both ends of the tissue were then placed at right angles to the center portion so that any contractions in the center compartment could not mechanically affect the strain gauges.

Hypertonic sucrose-PSS was placed only in the center compartment; drug and KCl depolarizing solution used to contract the muscles, were placed only in one or the other of the end compartments.

Temperature

Experiments in single baths were all at 20–21°C, because the uterus has rhythmic spontaneous contractions at 37°C. Experiments in triple baths were at 37°C for the vas deferens and at 37°C for the uterus when spontaneous rhythmic contractions
Electrical Stimulation

Platinum electrodes (each of tuning fork shape) were placed 4 mm apart at one end of the tissue, or 2.5 cm apart at opposite ends of the tissue. The stimulus was 15 v for 15 sec at a frequency of 60 cps AC.

Weight Changes in Hypertonic Solutions

All tissues were first incubated in physiological salt solution for 1–2 hr, initially at room temperature and then cooled to 20°C. Then the tissues were gently blotted between sheets of filter paper, weighed rapidly, and incubated either in hypertonic solution or in physiological salt solution as a control. One horn of each uterus or one vas deferens of each pair was used for the control. At intervals tissues were removed, blotted, weighed, and returned to the incubating baths, which process took 60 sec.

Variations in Hypertonicity, Single Baths

Each contraction in hypertonic PSS (drug, potassium chloride, or electrical stimulation) alternated with a similar test in normal PSS. The average of the contractions in PSS (before and after that in hypertonic PSS) was designated 100, and the smaller contraction in the hypertonic PSS was calculated as a percentage of that value. Exactly 10 min elapsed between the addition of the hypertonic PSS and the test with the drug, potassium chloride, or the first of two electrical stimulations. The potassium chloride solution was introduced into the bath by upward displacement and had the same tonicity as the solution used for the preceding 10 min incubation. Electrical stimulation occurred 10 and 15 min after the addition of the hypertonic solution, and the heights of the two contractions were averaged. After removal of the hypertonic solutions, the baths were refilled twice with normal PSS. Ample time was allowed for the tissue to relax before the next test.

Prolonged Exposure to Hypertonic Solution

The drug- or KCl-induced contraction was first recorded in solution of normal tonicity and designated as 100 %. The bath was refilled with hypertonic PSS and the tissue tested at intervals with drug or KCl solution (made hypertonic to the same degree). The drug or KCl was washed out and the bath replenished with hypertonic PSS each time.

RESULTS

Weight Changes in Hypertonic Solutions

Figs. 1 A and 1 B show the effect of solutions made hypertonic with 5 % and 10 % sucrose, 5 % mannitol, and 2 % choline chloride on the wet weight of the uterus and Fig. 2 shows the effect of solutions made hypertonic with 10 % sucrose and 5 % mannitol on the wet weight of the vas deferens. In all experi-
ments, the control tissue incubated in PSS lost a little weight, but in hypertonc PSS the loss was always greater. The uterus lost approximately 16% wet weight in 10% sucrose-PSS and 5% mannitol-PSS, and 11% wet weight in 5% sucrose-PSS but it gradually regained weight after 25 to 30 min.

![Graph](image)

**Figure 1A.** The change in wet weight of uterine horns in hypertonic 5% sucrose-PSS (●) and hypertonic 10% sucrose-PSS (▲) compared with control horns in PSS (x). There were four horns in each group.

![Graph](image)

**Figure 1B.** The change in wet weight of uterine horns in hypertonic 5% mannitol-PSS (●) compared with control horns in PSS (○); also in hypertonic 2% choline chloride-PSS (▲) compared with control horns in PSS (△). There were four horns in each group.

The vas deferens did not regain weight, even after 2 hr, by which time the loss was approximately 24% in 10% sucrose-PSS or 5% mannitol-PSS.

**Contractions in Hypertonic Solutions, Single Baths**

Fig. 3 shows that for the uterus, exposure to hypertonic sucrose-PSS for 10 min reduced the size of the contraction induced by submaximal doses of drug
irrespective of the drug used. Thus the sucrose was not interfering with any particular drug receptor. The effect on the contractions in response to the drug was clearly greater than that on the contractions in response to the potassium. That the effect of sucrose was due to its osmotic action and not to chemical action, was shown by experiments in which mannitol at concentrations osmotically equivalent to those of sucrose had a very similar effect on the uterine contractions in response to drugs.

In the vas deferens (Fig. 4) 10 min exposure to hypertonic sucrose-PSS had an identical effect on the drug-induced contractions (submaximal doses) and on the contractions in response to KCl in contrast with the results from the uterus. In Table I the actions of 7.5% sucrose-PSS on the uterus and vas deferens are compared. For the uterus there was a significant difference between the effect on drug- and KCl-induced contractions, whereas there was no significant difference in the vas deferens.

Figs. 3 and 5 show that electrically stimulated and drug-induced uterine contractions were diminished by hypertonic sucrose-PSS to a similar degree. The results with the electrodes 4 mm apart at one end of the tissue were the same as with the electrodes 25 mm apart at opposite ends. Thus propagation

![Graph showing change in wet weight of vas deferens](image-url)
FIGURE 3. The effect of hypertonic sucrose-PSS on the drug-induced contractions of rat uterus compared with its effect on the KCl-induced contractures. 4 experiments were performed with each drug (total of 12 horns) and 8 experiments were performed with KCl.

FIGURE 4. The effect of hypertonic sucrose-PSS on the drug-induced contractions of rat vas deferens compared with its effect on the KCl-induced contractures. Five experiments were performed with KCl and five with acetylcholine.
of excitation was prevented by hypertonic solutions irrespective of the distribution of stimulation.

In Fig. 6 the average amplitude of spontaneous contractions measured during a 15 min period in normal solution was taken as 100%. A similar average was obtained for a 15 min period in hypertonic solution and expressed as a percentage of the control. Hypertonic solution had an effect on the spontaneous contractions similar to its effect on the drug-induced and electrically induced contractions.

**TABLE I**

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Contraction as per cent of normal contraction in PSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCl</td>
<td>75 ± 2.5 (7)</td>
</tr>
<tr>
<td>Drug</td>
<td>11 ± 5 (12)</td>
</tr>
</tbody>
</table>

Results expressed as mean ±se with the number of experiments in parentheses.

**Figure 5.** The effect of hypertonic sucrose-PSS on the electrically induced contractions of rat uterus. There were nine experiments with electrodes 4 mm apart at one end of the tissue (○) and four experiments with electrodes 25 mm apart at opposite ends of the tissue (△).

Prolonged Action of Hypertonic Solution on Contractions

Fig. 7 A shows that the contractions of the uterus in response to potassium remained unchanged during 2 hr exposure to hypertonic solution; contrac-
tions in response to drugs were markedly reduced but then gradually increased in size, increasing more rapidly in hypertonic choline chloride–PSS than in hypertonic sucrose-PSS. Additional experiments showed that 10 min exposure to hypertonic choline chloride–PSS caused reductions of serotonin- and acetylcholine-induced contractions which were similar to those reductions caused by hypertonic sucrose-PSS (Fig. 3) and by hypertonic mannitol-PSS. Thus it is reasonable to assume that the action of choline chloride was due to its osmotic activity and not to chemical activity. Hence it is possible that the

more rapid increase in size of the contractions in hypertonic choline chloride–PSS compared with those in hypertonic sucrose-PSS (Fig. 7 A) was due to faster intracellular penetration of choline chloride compared with sucrose.

Fig. 7 B shows that the contractions of the vas deferens caused by potassium and drugs were very similar during the first 80 min and thus again there is a marked difference between the uterus and the vas deferens.

Contractions in Response to Supramaximal Dose of Drug

Table II shows that while 7.5 % sucrose-PSS considerably reduced the contraction of the uterus in response to a dose of serotonin, which caused a maximal contraction in normal PSS, the contraction in hypertonic solution could be increased by increasing the drug concentration to supramaximal levels. The response to submaximal doses of angiotensin was more affected by hypertonic sucrose-PSS than was the response to maximal doses, but because the contractions in response to low levels of drug plus high levels of sucrose were
Hypertonic Solution Effect on Rat Uterus and Vas Deferens

Figure 7 A. The prolonged action of hypertonic 5% sucrose-PSS on the KCl-induced contractures (x) (two horns) and on the contractions induced by acetylcholine (●) (two horns) of rat uterus. Also the prolonged action of hypertonic 2% choline chloride-PSS on the KCl-induced contractures (x) (two horns) and on the contractions induced by serotonin (▲) (two horns) of rat uterus.

Figure 7 B. The prolonged action of hypertonic 5% sucrose-PSS on the KCl-induced contractures (x) and on the acetylcholine-induced contractions (●) of rat vas deferens. Two experiments are shown for both acetylcholine and KCl.

so tiny, further experiments were not performed. Additional data suggest that the results with angiotensin were not complicated by tachyphylaxis.

Contractions in Triple Baths

1. UTERUS

Fig. 8 A shows the spontaneous contractions of the uterus at 37°C with the two ends of the horn in complete synchrony. When hypertonic 10% or 15% sucrose-PSS was placed in the center bath, in some experiments the contrac-
tions of the two ends became desynchronized, the cervical end contracting at a slower rate than the ovarian end (Fig. 8 B), and in some experiments the cervical end ceased contracting during the 10 min that the hypertonic PSS was in the center bath. The replacement of PSS in the center bath restored the synchrony of the two ends (Fig. 8).

When spontaneous contractions were eliminated by cooling (20 or 25°C), addition of serotonin to an end bath caused contraction of that end of the tissue and also a contraction at the end distant from the drug (Fig. 9). It was immaterial to which end the drug was added, excitation could travel in either direction. When hypertonic 10% or 15% sucrose-PSS was placed in the center bath and 10 min elapsed before stimulating one end of the horn with serotonin, then the far end of the tissue did not contract. After replacing PSS in the center bath and allowing 10 min to elapse, restimulation of one end of the horn with the drug again caused a contraction of the far end (Fig. 9).

Likewise addition of KCl depolarizing solution to an end bath caused a contraction of that end of the tissue and also a contracture at the end distant from the stimulus. This spread of excitation could be prevented by placing hypertonic sucrose-PSS in the center bath and could be restored by replacing PSS in the center bath (Fig. 10).

2. VAS DEFERENS

The vas deferens differed from the uterus. Addition of acetylcholine, adrenalin or KCl depolarizing solution to one end compartment while causing a contraction of that end of the tissue, failed to cause a contraction of the far end

TABLE II
THE EFFECT OF SUPRA- AND SUBMAXIMAL DOSES OF DRUGS ON THE SIZE OF CONTRACTION IN HYPERTONIC SUCROSE-PSS

<table>
<thead>
<tr>
<th>Serotonin Supramaximal dose</th>
<th>Contraction in sucrose-PSS*</th>
<th>Angiotensin Submaximal doses</th>
<th>Contraction in sucrose†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 X max. (4)</td>
<td>3</td>
<td>1 X max. (5)</td>
<td>43</td>
</tr>
<tr>
<td>4 X max. (4)</td>
<td>17</td>
<td>1/4 X max. (4)</td>
<td>34</td>
</tr>
<tr>
<td>25 X max. (4)</td>
<td>37</td>
<td>1/16 X max. (1)</td>
<td>9</td>
</tr>
<tr>
<td>50 X max. (4)</td>
<td>37</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>100 X max. (4)</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 X max. (4)</td>
<td>54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The numbers in parentheses refer to the number of experiments.
* 100 was assigned to the contraction in response to the maximum dose of serotonin in the absence of sucrose. The maximum dose for some tissues was 0.05 µg/50 ml.
† 100 was assigned to the contraction elicited by the test dose of angiotensin in the absence of sucrose. The maximum dose for most tissues was 0.025 µg/50 ml.
FIGURE 8. Spontaneous contractions of the ovarian end (o) and the cervical end (c) of the rat uterine horn in a three compartment bath. The top record of each pair has the base line at the top with contraction downwards; the bottom record of each pair has the base line at the bottom with contraction upwards. The central portion of the horn was in normal PSS in records A and C; the central portion was in hypertonic 10% sucrose-PSS in record B. Maximum contractions in these records were approximately 2 g.

FIGURE 9. Serotonin-induced contractions of rat uterine horn in a three compartment bath. The top tracing has the base line at the top; the bottom tracing has the base line at the bottom. The drug was applied to either end of the horn, as indicated, and contractions recorded from both ends. The composition of the solution in the central compartment is indicated for each test.
Tests of nine vasa deferentia gave the same result; thus I have been unable to demonstrate the spread of excitation across a gap of 1 cm in the rat vas deferens but cannot exclude the possibility that in all experiments damage to the tissue had occurred. However, the vas deferens was handled in the same way as the uterus in which propagation of activity could be demonstrated.

3. THE EFFECT OF POTASSIUM CHLORIDE IN THE CENTER COMPARTMENT ON THE ACTION OF HYPERTONIC PSS

When hypertonic solutions (with 10 or 15 % sucrose) were placed in the center bath, the activity of uteri showing spontaneous synchronous contractions was
disrupted. Asynchrony of contractions at each end or cessation of the contractions at the cervical end occurred. After 10 min, replacement by hypertonic sucrose-44 mM KCl-salt solution in the center bath caused immediate restoration of synchronous contractions (Fig. 12). When uteri were contracting spontaneously and synchronously in PSS, the placement of hypertonic sucrose (10 or 15%)–44 mM KCl–salt solution in the center bath did not disrupt the synchronous contractions. 44 mM KCl either restored or prevented the disruption of synchronous contractions by hypertonic sucrose-salt solution in all eight tests on five tissues.

Similarly 24 mM KCl was used in the hypertonic sucrose-salt solution for four tests on two tissues; on three occasions it did not restore synchrony or prevent disruption of synchrony but on one occasion it did restore synchrony.

Thus 44 mM KCl can overcome the effect of the hypertonic solution but 24 mM KCl is hardly able to do so.

*Weight Changes in the Response to 44 mM KCl*

A high level of potassium chloride did not alter the pattern of uterine wet weight loss due to hypertonic sucrose-salt solution when it was added 10 min
after the onset of hypertonicity (Table III) and thus the ability of potassium chloride to restore synchronous spontaneous contractions is apparently not due to it causing a change of cell volume.

<table>
<thead>
<tr>
<th>TABLE III</th>
</tr>
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<tbody>
<tr>
<td>LACK OF ACTION OF 44 mM KCl ON WEIGHT LOSS OF UTERI IN HYPERTONIC SOLUTION</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time in hypertonic solution</th>
<th>10% sucrose-PSS</th>
<th>10% sucrose-PSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7.4</td>
<td>7.2</td>
</tr>
<tr>
<td>10</td>
<td>10.7</td>
<td>10.6</td>
</tr>
<tr>
<td>15</td>
<td>12.5</td>
<td>13.3</td>
</tr>
<tr>
<td>20</td>
<td>13.6</td>
<td>13.8</td>
</tr>
</tbody>
</table>

Results are the average of two experiments in which there were four horns in each group.

![Dose-Response Curves for Potassium Chloride](image)

**Figure 13.** The dose-response curve of the uterus (○) (six horns) and vas deferens (△) (four tubes) to an increasing concentration of KCl, obtained by mixing 122.5 mM KCl salt solution and PSS as indicated.

**Dose-Response Curves for Potassium Chloride**

Fig. 13 shows that the uterus contracts in response to a lower concentration of potassium than does the vas deferens, and the curve for the uterus is steeper than that for the vas deferens.
DISCUSSION

One of the aims of this work was to evaluate the contribution of conduction of excitation to the action of stimulant drugs on the rat uterus and vas deferens. It is often assumed that responses of smooth muscle to drugs are determined exclusively and directly by the interaction between drug and receptors, and no account is taken of conduction. On the other hand, Daniel (1960, 1964 a) found evidence for conducted electrical activity during drug-induced and spontaneous activity in the rat uterus.

In the experiments reported here, a triple compartment bath similar to that described by Johansson and Ljung (1967) was used to demonstrate that conduction can occur in the uterus whether activity was initiated spontaneously or in response to stimulant drugs or KCl. Similar experiments on the vas deferens gave no indication of conduction, at least over a distance of 1 cm.

Barr et al. (1968) have shown that hypertonic solutions block conduction in guinea pig taenia coli, and Johansson and Ljung (1967) came to the same conclusion as the result of their experiments on the rat portal vein. It was therefore decided to study the action of hypertonic solutions on the rat uterus and the vas deferens. Barr et al. (1968) reported that hypertonic solutions caused shrinkage of smooth muscle cells and the disruption of intercellular connections (nexuses). Such connections have been observed in the uterus (Laguens and Lagrutta, 1964; Silva, 1967; Bergman, 1968). In the experiments reported here, tissue wet weight was taken as a qualitative measure of cell volume. It was found that the wet weight of both the uterus and vas deferens decreased during the first 20–30 min immersion in hypertonic solution. After reaching a minimum value (16 % reduction for solutions of approximately twice normal tonicity) the wet weight of the uterus began to increase. The wet weight of the vas deferens, however, continued to decrease for periods of immersion up to 120 min.

The simplest explanation for a decrease in tissue wet weight in hypertonic solution would seem to be a decrease in cell volume. Replacement of extracellular or cellular fluid with a denser hypertonic solution would increase tissue weight. Therefore a decrease in weight must indicate a decrease in volume of some tissue compartment and the decrease in wet weight observed in these experiments is probably an underestimate of tissue shrinkage. There is no reason why hypertonic solutions should cause a decrease in extracellular volume, whereas such solutions would be expected to extract water from cells.

The simplest explanation for the changes in gains in weights of the uterus during prolonged immersion in hypertonic solutions might be the slow penetration of sucrose and mannitol and the somewhat faster initial penetration of choline chloride. After 120 min, however, tissues made hypertonic with choline chloride had not regained a higher proportion of their initial
weight loss than tissues in the other media (Fig. 1). Penetration of sucrose into a portion of the cellular water of frog stomach muscle has been demonstrated (Bozler, 1967). If this explanation is correct, then the permeability of the vas deferens to these agents must be considerably less than that of the uterus.

When hypertonic solutions were added to the central compartment of the triple bath, conduction of excitation in the uterus was blocked. If cell volume, as evidenced by changes in tissue wet weight, can be taken as an indication of the ability of the uterus to conduct a response to stimulation, then the magnitude of conducted responses should be depressed in proportion to the decrease in tissue wet weight. This was indeed the case for responses to electrical stimulation and for spontaneous contractions in single bath experiments. Furthermore, there was a close correlation between tissue wet weight and the magnitude of the response of the uterus to stimulant drugs. This result supports the idea that conduction of excitation may make a significant contribution to the drug-induced responses of this organ.

Contractions in response to KCl were slightly depressed by hypertonic solutions in both preparations. In the vas deferens this decrease was paralleled by the decrease in response to acetylcholine. Since conduction could not be demonstrated in the vas deferens, and since KCl probably acts on all smooth muscle cells, this result is also in accordance with the idea that the much more marked effect of hypertonic solutions on drug responses of the uterus was due to blockade of conduction. This result also implies that the large concentrations of acetylcholine required to stimulate the vas deferens were acting on all smooth muscle cells. An increase in drug concentration could partially antagonize the effects of hypertonic solutions in the uterus—presumably by activating a larger number of smooth muscle cells directly and so countering the loss or depression of conduction.

Depression of responses to KCl in both smooth muscles, and depression of responses to acetylcholine in the vas deferens may have been due to the effect of hypertonic solutions on excitation-contraction coupling (see Hodgkin and Horowicz, 1957; Howarth, 1958) or to the possibility that KCl caused a smaller depolarization in hypertonic solution due to an increase in the concentration of intracellular K.

The mechanism by which hypertonic solutions block conduction remains to be studied. In the triple compartment bath experiments conduction block by hypertonic solutions could be reversed by the addition of KCl, as previously observed in the rat portal vein by Johansson and Ljung (1967) and Mellander et al. (1967). Johansson and Jonsson (1968) have discussed the mechanism of these effects. This result suggests that cell shrinkage may have caused hyperpolarization due to an increase in intracellular K concentration which could be counteracted by an increase in external K (see Tomita, 1966). Electron
microscope studies and measurement of the electrical resistance of the uterus for longitudinal current will be needed to decide whether or not the disruption of intercellular connections is also involved.

This work was supported by a Life Insurance Medical Research Grant to Dr. Carroll.

Received for publication 20 May 1968.

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