Peripheral Vasconstriction Associated
with Hyperpotassemia

By Frederick N. Sudak, Ph.D., and George P. Fulton, Ph.D.

Experimental conditions have been described in which constriction of the small blood vessels in the cheek pouch of the golden hamster was found in association with increased serum potassium levels. The arterioles of adrenalectomized hamsters became progressively constricted, starting three to four days after operation until death. An increase in serum potassium occurred during the same period of time. Severe vasconstriction in the cheek pouch preparation also accompanied hyperpotassemia during the terminal stages following total body x-irradiation with 1,000 r. A direct vasoconstrictor action of potassium has been postulated, but supportive evidence has not been consistent. Katz and Lindner reported constriction of perfused coronary arteries in dogs when the potassium levels in the perfusate were greatly increased. Driscol and Berne, using a similar preparation, were unable to confirm these results. Vasocostriction associated with experimental hyperpotassemia has been reported to occur in perfused hind limbs of dogs and cats. Emanuel et al. have demonstrated that potassium excess has a direct vasodilator action on arterioles in perfused fore limbs of dogs.

The present investigation is concerned with the caliber of small blood vessels in a simple vascular bed, as related to increases in serum potassium concentration produced by slow intravenous infusions of potassium salts. The membranous cheek pouch of the golden hamster was selected for the observation of blood vessels.

Methods

Male hamsters, 90 to 120 Gm. in weight, were anesthetized with either sodium pentobarbital (100 mg./Kg.) or chloralose (100 mg./Kg.), administered intraperitoneally. The cheek pouch was everted and prepared for transillumination. A circular cut (20 mm.) was made in the top layer of the cheek pouch, and blood vessels in the bottom layer (mucosal) were exposed by removing excess connective tissue. The preparation was kept moist by means of a salt solution containing 0.10 Gm. of NaCl, 0.10 Gm. of CaCl₂, 0.20 Gm. of KC1, and 0.02 Gm. of NaHCO₃ in 1,000 ml. of distilled water which had been boiled and cooled just prior to addition of salts. In several cases, the dissection was performed while the tissue was submerged in this solution; the preparation was then rinsed several times, and the exposed vessels were covered with a thin layer of paraffin oil (white, heavy, domestic). The caliber of the blood vessels in either type of preparation remained stable for periods up to four hours.

The diameters of blood vessels were measured with a Leitz screw micrometer (X 12.5) in combination with a water/oil immersion lens, providing a total magnification of 275 X. Measurements were made on large (50 to 100 μ), medium (25 to 50 μ), and small (10 to 25 μ) arterioles and medium (25 to 50 μ) venules.

Blood samples were obtained by cardiac puncture and from the orbital sinus and were analyzed for serum sodium and potassium in a Baird flame photometer. Samples taken from the orbital sinus reflect concentrations of electrolytes in venous blood draining the vascular site under observation. Potassium salts (10 per cent solutions) were slowly infused into the left femoral vein by means of a custom-built variable rate-infusion apparatus. Electrocardiograms (lead CV) continuously monitored on the face of a cathode ray oscilloscope were used to indicate changes of potassium concentrations in the circulation. Steady-state levels of serum potassium were obtained by regulating the rate of potassium infusion to sustain a given ECG pattern associated with hyperpotassemia.

Animals were bilaterally adrenalectomized in a single operation by way of a dorsolateral approach 36 hours before they were used in experiments. Sham operations were performed on a group of animals which served as controls. All animals received no special postoperative care and were allowed food and water ad libitum. Adrenergic blockade of the blood vessels in the...
Response of Hamster EKG to Hyperpotassemia

Control

Serum K = 5.1 mEq/l
Na = 140 mEq/l

Serum K = 9.02 mEq/l
Na = 131.9 mEq/l

Serum K = 11.48 mEq/l
Na = 126 mEq/l

FIGURE 1
Segments of an electrocardiogram recorded continuously during infusion of potassium chloride into an intact animal. Serum potassium and sodium were measured before (control) and twice during the infusion. The ECG pattern shown above each potassium and sodium value was maintained for a period of 10 to 14 minutes before blood samples were drawn for electrolyte analysis.
VASOCONSTRICTION AND HYPERPOTASSEMIA

TABLE 1
Correlation of Electrocardiographic Changes with Serum Electrolyte Levels

<table>
<thead>
<tr>
<th>Number of experiments</th>
<th>Heart sample</th>
<th>Orbital sinus sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na</td>
<td>K</td>
</tr>
<tr>
<td>Control</td>
<td>5</td>
<td>142 ± 5.0*</td>
</tr>
<tr>
<td>Stage 1 on ECG</td>
<td>5</td>
<td>123 ± 3</td>
</tr>
<tr>
<td>Stage 2 on ECG</td>
<td>5</td>
<td>12.3 ± 1.74</td>
</tr>
</tbody>
</table>

*Mean and standard deviation in mEq./L.

check pouch was obtained by introducing 5 mg./Kg. of phenoxybenzamine, Dibenzyline, directly into the general circulation. Experiments were not begun until one hour after injection. Sympathetic denervation of the check pouch blood vessels under observation was accomplished by cutting the sympathetic trunk to the area below the superior cervical ganglion one to one-and-one-half hours before experiments were begun.

Results

Fifteen experiments were performed to determine if the electrocardiograms of hamsters could be used as an index of serum potassium levels during infusion of potassium salts. Electrocardiographic changes which occurred during infusion of potassium chloride are shown in figure 1. Amplitudes of the P, R, S, and T waves were affected by these infusions. The pattern of ECG change was characterized by two distinct stages: Stage 1 revealed a gradual disappearance of the P wave, increase in the amplitude of the T wave, reduced R waves, deeper S waves, and an increase in the duration of the QRS complex. These permutations of the ECG became more pronounced during the period of infusion. In stage 2, the heart beats were slower and arrhythmic, P waves reappeared, and T waves were tall and "peaked." Similar ECG patterns were obtained during infusion with potassium bicarbonate, potassium nitrate, or potassium sulfate.

Blood samples drawn from the heart after maintaining each stage (KCl infusion) for 10 to 14 minutes contained an average of 9.4 mEq./L. potassium during the period just after the disappearance of the P wave in stage 1, and 12.3 mEq./L. (average) potassium during stage 2 (fig. 1 and table 1). The concentration of potassium in blood samples drawn from the orbital sinus during each of these stages did not differ significantly (P≥0.025) from those obtained from the heart (table 1). These data indicate that we were able to establish a steady state in the level of experimental hyperpotassemia in this species with some degree of accuracy. During the course of the experiments to follow, blood samples for analysis were drawn from the orbital sinus to check the venous potassium concentrations under which blood vessel caliber measurements were made.

The calibers of arterioles were markedly reduced in control and sham-operated hamsters during infusions of potassium chloride (table 2). Reduction of vessel caliber was greater at an average serum potassium concentration of 12.3 mEq./L. than at 9.0 mEq./L. (P≤0.01). Sympathetic denervation of the blood vessels one to one-and-one-half hours prior to infusion with potassium failed to prevent the vascular response. Vasoconstriction which would have occurred during stage 1 was abolished and a slight increase in the caliber of medium and large arterioles was recorded in animals adrenalectomized 30 hours earlier. This increase, however, was not statistically significant (P≥0.15). Removal of the adrenal glands reduced the degree of vasoconstriction present during stage 2. However, a significant reduction in the caliber of small arterioles occurred (P≤0.025). Figure 2 is a photomicrograph of a typical response during infusion of KCl into an adrenalectomized animal. Denervation of blood vessels in adrenalectomized animals or treatment of intact animals with Dibenzyline prevented vasoconstriction produced by hyperpotassemia.
Constriction of venules in the cheek pouch occurred when the serum potassium level was increased to an average of 12.0 mEq./L. in intact and sham-operated animals, as well as in animals in which the cheek pouches were denervated. Vasoconstriction similar in degree to that obtained during potassium chloride infusions was also recorded, using potassium nitrate, bicarbonate, or sulfate.

In view of the vasoconstrictor response to an increase in serum potassium observed in intact, untreated animals, the effect of hyperkalemia on systemic blood pressure was investigated. Blood pressure measurements were obtained directly from the carotid artery with a Statham P-23Db transducer and, after amplification, recorded directly on paper by means of an Einar polygraph. Electrocardiograms were monitored continually during the infusions to reflect serum potassium concentrations. The results are shown in Table 2. A significant (PHO.01) increase in systolic blood pressure over control values occurred in all animals during stage 1 (serum potassium between 8 mEq./L. to 10 mEq./L.), while a significant decrease (P=0.01) was manifest during stage 2 (serum potassium between 11 mEq./L. and 13 mEq./L.).

Discussion

These studies show that the vasoconstriction in the cheek pouch of the hamster which occurs concomitantly with increased serum levels of potassium is an indirect effect of this cation. The capacity of potassium to stimulate the adrenal medulla and initiate hormonal secretion has been confirmed many times (see reference 10 for review). The possibility that potassium initiated liberation of catecholamines by stimulation of sites other than the adrenal medulla is unlikely since denervation plus adrenalectomy prevented the vasoconstrictor response.

The vasoconstrictor response to potassium excess may have been mediated through neural pathways. Denervation of the blood vessels in adrenalectomized animals prevented decreases in vessel caliber at the higher potassium concentrations. Several additional studies were obtained directly from the carotid artery with a Statham P-23Db transducer and, after amplification, recorded directly on paper by means of an Einar polygraph. Electrocardiograms were monitored continually during the infusions to reflect serum potassium concentrations. The results are shown in Table 2. A significant (PHO.01) increase in systolic blood pressure over control values occurred in all animals during stage 1 (serum potassium between 8 mEq./L. to 10 mEq./L.), while a significant decrease (P=0.01) was manifest during stage 2 (serum potassium between 11 mEq./L. and 13 mEq./L.).
mechanisms may have been possible. First, the observed vasoconstriction may have been a compensatory reflex response resulting from a fall in systemic blood pressure commensurate with, and resulting from, the pronounced bradycardia accompanying severe hyperpotassemia. A second possibility may have been a direct effect of the potassium ion on the vasomotor centers during a period of sustained hyperpotassemia. A rise in blood pressure in experimental animals has been demonstrated by direct intracisternal injections of potassium salts,\textsuperscript{11-13} by increasing the potassium concentration in cerebrospinal fluid,\textsuperscript{14} and by perfusing the heads of cats and rabbits with fluid containing excessive quantities of this cation.\textsuperscript{15} Possibility of a direct action of potassium on ganglion cells to produce vasoconstrictor discharge may be obviated by the fact that preganglionic denervation of the blood vessels in adrenalectomized animals prevented vasoconstriction. Vasoconstriction resulted from the action of the potassium ion and was not related to the nature of the accompanying anion. Each of four different potassium salts produced a decrease in the diameter of arterioles.

No statically significant evidence was found for a dilator action of potassium on the smooth muscle of small blood vessels of the cheek pouch, although a slight increase in diameter was recorded in adrenalectomized animals. Small increases in the concentrations of this cation in fluids perfusing isolated organs and limbs have consistently resulted in a decrease in the resistance to blood flow.\textsuperscript{4-7} Although the small diameter changes recorded in our experiments were not significant statistically, they might well be very significant in pressure-flow experiments since the resistance to blood flow is an exponential function of the blood vessel caliber.

**Summary**

Hyperpotassemia was induced in hamsters by intravenous infusions of potassium salts.

**TABLE 3**

| Effect of Potassium Chloride Infusion on Systolic Blood Pressure of the Hamster |
|---------------------------------|---------------------------------|-----------------|
| Systolic blood pressure (mm. Hg) | Systolic Blood Pressure (mm. Hg) |                  |
| Number of experiments | Control | ECG stage 1 (serum K=8 to 10 mEq./L) | ECG stage 2 (serum K=11 to 13 mEq./L) |
| 10 | 108 ± 11.5* | 141 ± 14.5 | 62.8 ± 23.8 |

*Mean and standard deviation.

Circulation Research, Volume X, April 1962
The caliber of blood vessels (10 to 100μ in diameter) in the cheek pouch was measured and comparisons were made when serum potassium concentration was maintained at 9.0 (σ = ± 1.64 mEq./L.) for 10 to 14 minutes and again at 12.3 (σ = ± 1.14 mEq./L.) for 10 to 14 minutes. In unoperated controls, a significant degree of vasoconstriction occurred in all arterial vessels at both levels of hyperpotassemia. Venular constriction was found at the higher potassium concentrations. Sympathetic denervation of the blood vessels had no effect on the vasoconstrictor response. Adrenalectomy prevented vasoconstriction at a potassium level of 9.0 mEq./L., but vasoconstriction was still evident in small arterioles at higher potassium levels. Sympathetic denervation of blood vessels in adrenalectomized animals, or treatment of intact animals with Dibenzyline, prevented vasoconstriction produced by hyperpotassemia. These data indicate that peripheral vasoconstriction associated with hyperpotassemia is an indirect effect of the potassium ion.

Acknowledgment

The authors wish to express their gratitude to the Smith, Kline and French Laboratory for their generous supply of Dibenzyline.

References

Peripheral Vasoconstriction Associated with Hyperpotassemia
Frederick N. Sudak and George P. Fulton

Circ Res. 1962;10:587-592
doi: 10.1161/01.RES.10.4.587
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1962 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/10/4/587

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/