Potassium Infusion Attenuates Avoidance-Saline Hypertension in Dogs

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SUMMARY Previous studies have shown that a combination of avoidance conditioning schedules and increased intake of salt and water results in progressive hypertension in dogs within 14 days. The present experiments investigated the effects of increasing potassium intake upon blood pressure and heart rate of dogs made hypertensive by avoidance conditioning and salt-water loading. Two daily 30-minute sessions of free-operant avoidance conditioning were presented for 36 days during which isotonic saline was continuously infused into the arterial circulation (1.2 liters/day; 185 mEq Na+). Daily mean levels of systolic (22 ± 5 mm Hg) and diastolic (12 ± 4 mm Hg) pressure increased progressively in each dog during Days 1-14. Infusion of potassium chloride (100 mEq/day) from Days 15-28 resulted in progressive decreases in daily mean levels of systolic (— 11 ± 2 mm Hg) and diastolic (— 8 ± 1 mm Hg) pressure in each dog over this period. From Day 29-36, systolic (8 ± 1 mm Hg) and diastolic (5 ± 1 mm Hg) pressure increased. Normotensive dogs not on the avoidance schedule showed no change in arterial pressure in response to 14 days of potassium chloride infusion. These experiments show that the level of potassium, as well as sodium, intake significantly determines blood pressure levels in this form of experimental hypertension. (Hypertension 5: 415—420, 1983)

KEY WORDS • potassium • arterial pressure • avoidance conditioning • dogs • hypertension

EXPOSURE of chronically-instrumented dogs to a combination of free-operant avoidance conditioning schedules and continuous infusion of isotonic saline results in progressive hypertension within 14 days, accompanied by no consistent changes in heart rate levels. By contrast, exposure of dogs to avoidance schedules under conditions of normal sodium intake, or salt-water loading without avoidance stress, typically produces no significant blood pressure changes over the same time periods. This new model of rapidly-developing hypertension requires no specific genetic bias, surgical alteration of kidney functions, or administration of steroids.

Several models of experimental hypertension have been developed previously in rodents which involve increases in salt intake but no systematic aversive stimulation. For example, significant blood pressure elevations have been observed as a function of salt feeding in rats with genetic bias, surgical alteration of renal functions, and steroid administrations, and over much longer time periods, with no other intervention. In each of these models, it has also been observed that the hypertensive adaptation is prevented, attenuated or reversed by administrations of potassium chloride. By contrast, it has been shown that potassium infusion does not decrease blood pressure levels in normotensive dogs.

The present study was designed to investigate the effects of continuous intraarterial infusion of potassium chloride on 24-hour blood levels of dogs made hypertensive by concurrent exposure to avoidance schedules and saline infusion. Results of these experiments were compared with effects of potassium infusion upon blood pressure levels of non-stressed, normotensive dogs. In addition, the magnitude of acute cardiovascular responses to the onset of individual avoidance sessions were examined as a function of presence or absence of potassium infusion.

Methods

Subjects and Apparatus

The subjects of these experiments were four adult female mongrel dogs (mean weight, 17 kg). Each resided in an experimental environment throughout the course of the study. Continuous cardiovascular monitoring and infusion of electrolytes were enabled in this
environment by a custom-fitted leather vest worn by the subject, connected to a flexible, hollow, metal conduit, which ascended vertically to a swivel attached to an overhead, counterbalanced boom assembly. The boom was affixed to a wall of the enclosure via a universal joint 7 feet above floor level. The boom moved in concert horizontally and vertically with the dog, maintaining minimal tension on the tether, and permitting freedom of movement in the kennel as well as protection for cardiovascular monitoring and stimulation apparatus.

Arterial blood pressure was monitored 24 hours per day from an indwelling polyvinyl chloride catheter, covered with silastic, which had been placed during aseptic surgery in the ascending aorta via a carotid artery. The catheter exited from the body in the mid-scapular region, and was protected by the leather vest. The catheter was attached to a pressure minitransducer (Statham P50 Gould-Statham, Oxnard, California) located in the vest, whose cable ascended through the hollow tether and swivel, along the boom, to monitoring equipment in an adjacent room. Patency of the arterial catheter was maintained by slow but continuous infusion of lightly-heparinized saline via a peristaltic pump (Harvard model 1201, Harvard Apparatus Company, Millis, Massachusetts) through an infusion line, which also passed through the swivel and tether, to a valve located at the pressure minitransducer. Phasic arterial pressure and a carotidhemodynamic record of heart rate were displayed continuously on a polygraph (Grass model 7C, Grass Medical Instruments, Quincy, Massachusetts). A DEC PDP8E minicomputer recorded systolic and diastolic pressure at each heart beat, and provided online averages of each cardiovascular measure over successive 10-minute and 60-minute intervals on a teletype (DEC model LA36). The transducer to polygraph to computer systems were calibrated three times per week against a mercury manometer. Calibration error averaged 0.1 ± 0.6 mm Hg at 125 mm Hg (center baseline) and 0.6 ± 0.6 mm Hg at 50 mm Hg (sensitivity or gain).

Procedures

Before instrumentation, each dog was trained on a 30-minute free-operant shock-avoidance task. The task required the dog to press a 4 × 4 in. plexiglas response panel located on a wall of the kennel to postpone the occurrence of electric shock (2–10 mA for 0.3 seconds). A stimulus lamp located behind the response panel was illuminated for 30 minutes twice a day (at 8 a.m. and 4 p.m.). A recycling timer was set to present an electric shock at the completion of a 20-second cycle. Each panel-pressing response reset the timer in midcycle, and postponed the onset of the next shock for 20 seconds. By maintaining response rates in excess of one per 20 seconds, the dog could avoid all shocks during the 30-minute session. This procedure generated highly stable performance in each dog, resulting in an average of less than one shock per hour. Repeated exposure to the avoidance schedule resulted in gradual decreases in behavioral activity preceding the onset of each avoidance session, followed by a prompt initiation of panel-pressing responses at the onset of the stimulus light, and steady repetition of the response during the 30-minute avoidance session.

After several weeks of avoidance training, catheterization of the aorta was performed, and one week was permitted to elapse prior to reinstatement of the subject in the tether system in the kennel. Following this recovery period, the schedule of two daily avoidance sessions was presented for at least two additional weeks of practice. Acute and sustained increases in systolic (range of 8–30 mm Hg) and diastolic (range of 6–14 mm Hg) pressure and heart rate (16–43 bpm) were observed consistently during the 30-minute avoidance sessions. Between sessions, systolic and diastolic pressure and heart rate decreased in the first hours after the session, but while heart rate levels continued to decrease over successive hourly intervals preceding the next avoidance sessions (range 7–15 bpm), systolic pressure leveled off or increased somewhat (range 1–5 mm Hg). Typically, these patterns developed within 14 days of exposure to this schedule.

Experimental Protocol

Two, daily 30-minute sessions of free-operant shock-avoidance conditioning were programmed for 36 successive days, one at 8 a.m. and one at 4 p.m. Under these conditions, isotonic saline was continuously infused into the arterial circulation at a constant rate (1.2 liters/24 hrs.), resulting in an infusion of 185 mEq sodium/24 hrs. During Days 15–28, potassium chloride was added to the saline solution so that each dog received 100 mEq potassium intraratively per 24 hours. During Days 29–36, the avoidance sessions and increased saline infusion procedures remained in effect, but potassium chloride was no longer presented. The purpose of Days 29–36 was to ensure that any decreases in blood pressure associated with potassium infusion were due to this procedure. Daily consumption of Wayne dogfood resulted in additional intake of approximately 15 mEq sodium and 10 mEq potassium.

Following the completion of these experiments, avoidance sessions were discontinued, and the saline infusion rate was adjusted to 0.1 liter/24 hrs. After recovery of pre-experimental, normotensive blood pressure levels, two dogs were again exposed to a continuous infusion of potassium chloride for 14 successive days. During this time, no avoidance sessions were scheduled. One dog received 100 mEq of potassium in isotonic saline which was infused at a rate of 0.1 liter/24 hrs. The other dog received the same amount of potassium per day (100 mEq) but in a saline solution that was infused at a rate of 1.2 liters/24 hrs., as had occurred during the earlier avoidance experiments.

Statistical Analysis

Data were analyzed in terms of linear regression of 24-hour mean levels of systolic and diastolic pressure (mm Hg) and heart rate (bpm) across successive days of exposure to each experimental condition (i.e.,
avoidance and saline; avoidance, saline and potassium; avoidance and saline). In addition, means and standard errors of the acute changes in each cardiovascular measure during avoidance performance sessions (relative to the immediately preceding hour) were calculated for each dog. Analyses of variance were performed to evaluate the hypothesis that potassium infusion decreased the magnitude of acute cardiovascular responses to avoidance sessions. A chi-square test was also performed to assess the probability that potassium infusion would decrease the mean response of each cardiovascular measure to avoidance session onset in all four dogs by chance.

Results

Potassium Effects upon Cardiovascular Levels in Hypertensive Dogs

Table 1 shows the mean levels of systolic and diastolic pressure and heart rate of each dog during the first day of each experimental condition, and the change in each measure over succeeding days of exposure to that condition, determined by linear regression analysis of 24-hour means across days. Systolic pressure increased significantly in each dog during Days 1–14 of avoidance and saline (range, 9–51 mm Hg). Diastolic pressure levels also increased significantly in each dog over this period (range, 9–25 mm Hg). Heart rate levels decreased in three dogs, but the change was statistically significant in only one (range, −2 to −27 bpm). During Days 15–28 of potassium infusion, systolic pressure levels decreased significantly in all four dogs (range, 9–18 mm Hg). Diastolic pressure levels decreased in all four dogs, significantly in three (range, 5–9 mm Hg). Heart rate levels increased in three dogs, and significantly in two (range, −7 to 13 mm Hg). During Days 29–36, following termination of potassium infusion, systolic pressure levels increased again in all four dogs, significantly in one (5–13 mm Hg). Diastolic pressure levels increased in all four dogs, significantly in two (range, 3–8 mm Hg).

A summary of these results is provided in Figure 1, which shows the mean 24-hour levels of systolic and diastolic pressure and heart rate for each day of the 36-day experiment, averaged for the group of four dogs. Systolic and diastolic pressure levels increased progressively from an initial mean value of 125 ± 5.5 mm Hg on day 1 to 147 ± 6.6 mm Hg on Day 14 (r = 0.96; p < 0.01). Diastolic pressure levels increased from a mean value of 83 ± 5.3 mm Hg on Day 1 to 95 ± 3.5 mm Hg on Day 14 (r = 0.94; p < 0.01). Heart rate levels decreased from 86 ± 5.2 bpm on day 1 to 77 ± 10.1 bpm on day 14 (r = 0.80; p < 0.01).

Figure 1 also shows that the addition of potassium chloride over the next 14 days resulted in a reversal of the upward trend in group mean blood pressure and heart rate changes. Systolic pressure levels decreased by 10.8 ± 2.3 mm Hg (r = 0.79; p < 0.01), which represented a 47% attenuation of the hypertensive response to avoidance and saline. Diastolic pressure levels decreased by 7.5 ± 0.8 mm Hg (r = 0.77; p < 0.01), an attenuation of 58%. By contrast, heart rate levels increased by 5.0 ± 4.3 mm Hg (r = 0.51; p < 0.05).

Figure 1 also shows that the termination of potassium chloride infusion resulted in a resumption in the upward trend in arterial pressure as the subjects continued to be exposed to the avoidance schedule and saline infusion. During Days 29–36, systolic pressure levels increased by a mean of 8.0 ± 1.8 mm Hg (r = 0.93; p < 0.01), diastolic pressure levels increased by 5.4 ± 1.2 mm Hg (r = 0.85; p < 0.01), and heart rate levels increased by a mean of 5.3 ± 3.0 bpm (r = 0.85; p < 0.01).

| Table 1. Twenty-Four-Hour Mean Levels of Systolic and Diastolic Pressure (mm Hg) and Heart Rate (bpm) During First Day (BL) and Change Over Successive Days (Δ) for Each Experimental Condition for Each Dog |

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Na⁺ = avoidance and saline; Na⁺.K⁺ = avoidance, saline, and potassium; r = linear regression coefficient.

*p < 0.05.
Potassium Effects upon Cardiovascular Levels in Normotensive Dogs

Table 2 shows the effects of potassium chloride infusion upon arterial pressure levels averaged for two days who were not on avoidance contingencies for 14 days. The data show that neither systolic nor diastolic pressure levels changed significantly in these two dogs over this time period, and confirm previous experiments which showed that the depressor effects of potassium intake were limited to experimental conditions which maintained elevated blood pressure levels.

Potassium Effects upon Acute Responses to Avoidance Session Onset

Figure 2 shows mean changes in systolic and diastolic pressure and heart rate from the hour immediately preceding the avoidance session to the levels of each measure evoked by the avoidance session, averaged for all sessions for each dog under conditions of avoidance and saline, and of avoidance, saline and potassium. For all four dogs, the average increase in systolic pressure and heart rate were smaller under conditions of potassium-loading, as was the case for diastolic pressure effects in three of the four dogs. Analyses of variance of the changes for each individual dog were not statistically significant. However, a chi-square test showed that decreases in mean response on these measures in 11 of 12 instances (4 of 4 systolic pressure, 3 of 4 diastolic pressure, 4 of 4 heart rate) occurs by chance less than once in 100 occasions ($X^2 = 8.33$).

| Table 2. Systolic and Diastolic Pressure and Heart Rate During the First 2 Days and Last 2 Days of a 14-Day Period of Intraarterial Infusion of Potassium Chloride (6 mEq/kg/24 hrs) for Each of Two Normotensive Control Subjects |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Dog** | **Systolic pressure (mm Hg)** | **Diastolic pressure (mm Hg)** | **Heart rate (bpm)** | **Systolic pressure (mm Hg)** | **Diastolic pressure (mm Hg)** | **Heart rate (bpm)** |
| 1 **X** | Days 1,2 13,14 | Days 1,2 13,14 | Days 1,2 13,14 |
| SEM | 1.1 | 1.2 | 1.1 | 1.2 | 0.7 | 0.7 | 1.9 | 2.4 |
| 2 **X** | 115 | 119 | 77 | 77 | 101 | 98 |
| SEM | 1.1 | 1.0 | 0.8 | 0.8 | 1.1 | 1.2 |

Figure 2. Mean changes in systolic and diastolic pressure and heart rate from the hour immediately preceding to the hour of the avoidance session, averaged for all sessions under conditions of saline infusion (Days 1-14) and saline and potassium infusion (Days 15-28).
Discussion

Results of this study show that continuous infusion of potassium chloride significantly attenuated the elevations in 24-hour mean levels of arterial pressure produced in dogs by exposure to avoidance conditioning and saline infusion. When the potassium infusion procedure was terminated, arterial pressure began to rise again in response to continuation of avoidance sessions and saline infusion. In addition, the magnitude of the acute increases in arterial pressure and heart rate evoked by the onset of an avoidance session was consistently smaller during the potassium infusion condition than during the preceding period of avoidance and saline only.

These findings are consistent with the results of previous research showing that potassium administration decreased blood pressure levels in other forms of experimental hypertension. Potassium-loading significantly attenuated the development and maintenance of hypertension occurring over periods of months in rats on a high salt diet. In addition, 2 weeks of potassium-loading decreased blood pressure levels of hypertensive rats with a renal artery clip, prevented the development of DOCA-salt hypertension that otherwise occurred over a 14-day period, and attenuated the magnitude of hypertension produced by two previous weeks of DOCA-salt injections. The data from these studies parallel the results of the experiments described in the present study in terms of the time course over which hypertension developed, and over which the effects of potassium were observed. However, more prolonged potassium feeding also has been shown to attenuate the exacerbation of hypertension in the spontaneously hypertensive rat which otherwise occurred over an 8-month period in response to increases in dietary sodium intake. In addition, diets fed to salt-sensitive rats for 6 months containing the same sodium but different potassium concentrations were associated with lower blood pressure in rats receiving more potassium. The same study showed that diets with different absolute concentrations of sodium and potassium, but varying ratios of sodium/potassium ratio, were associated with higher blood pressure levels in the rats on the higher absolute sodium levels. Therefore, the development of hypertension was clearly a function of the sodium to potassium ratio, as well as of the absolute levels of salt intake.

Interaction effects on blood pressure of increases in sodium and potassium intake have also been reported in studies with normotensive humans. Luft et al. found that increasing salt intake to 800 mEq/day resulted in significant blood pressure elevations. McCarron et al. replicated the study, and found that these changes were prevented by maintaining potassium balance. Increases in dietary potassium intake, alone or in combination with moderate decreases in sodium intake, have also been shown to decrease blood pressure levels in human essential hypertension. Increases in systolic pressure in mildly hypertensive patients produced by 12 weeks on a high sodium diet were attenuated by 12 subsequent weeks of increased potassium intake. In another study, addition of potassium to the diet (with normal sodium intake) for 4 weeks resulted in significant decreases in blood pressure in a group of students with a history of parental hypertension, but not in a control group. By contrast, addition of sodium to the diet increased the blood pressure levels of both groups. A low sodium-high potassium diet (50 mEq sodium, mEq potassium for 2 weeks) has been reported to decrease arterial pressure significantly even in normotensive humans. In addition, the acute blood pressure increase to norepinephrine infusion and to mental arithmetic stress was smaller on this diet than under control conditions. These findings are consistent with the results of the present study showing that the acute cardiovascular responses to the avoidance stimulus were decreased by increasing potassium intake.

By contrast, previous experiments have shown that levels of potassium infusion at levels equal to or greater than those utilized in this study did not significantly alter arterial pressure in normotensive dogs. These experiments reported that potassium intake of up to 9–10 mEq/kg/24 hrs also resulted in no sustained changes in plasma potassium levels. The depressor effects observed in the present experiments apparently depend, therefore, on sustained changes in physiological functions produced by the experimental procedures.

The nature of the physiological mechanisms mediating the observed potassium effects upon blood pressure in experimental and essential hypertension remains to be determined. It is well established that potassium, injected intraarterially, causes vasodilation, which occurs even after denervation or adrenergic blockade with phentolamine, and which decreases vasoconstriction of skeletal muscle vessels induced by stimulation of the sympathetic nervous system. These observations indicate that potassium may act directly on the vascular smooth muscle wall, and attenuate elevations in total peripheral resistance occurring between avoidance sessions. It has been suggested that potassium causes vasodilation by stimulating an electrogenic sodium-potassium pump in the vascular smooth muscle cell, and that this sodium-potassium pump works less effectively in hypertensive individuals. Recent experiments have indicated that pump activity is suppressed in volume-expanded types of experimental hypertension. Previous studies with normotensive rats have shown that symptomatically-mediated pressor responses to intracerebral infusions of hypertonic saline or angiotensin II were enhanced by increased sodium intake, and attenuated by increased potassium intake. Recently, it has been found that Dahl salt-sensitive (S) rats show more marked acute pressor responses to intracerebral infusion of hypertonic saline or angiotensin II than salt-resistant (R) rats, and that this difference is significantly reduced by potassium-feeding. These relationships continue to be observed even if the blood pressure of the S rats is kept normotensive by maintaining the rats on a low salt diet.

It is also clear that potassium has diuretic properties, however, and that increasing potassium intake can in-
crease renal excretory functions. Previous experiments have shown that potassium infusion significantly decreases sodium balance and increased sodium excretion in normotensive dogs and in DOCA-salt hypertensive rats. This response was observed even though the potassium administration did not significantly increase plasma potassium levels. In addition, potassium administration is associated with alterations of various hormones which could participate in long-term blood pressure control. Suzuki et al. showed that potassium administrations which prevented the development of DOCA-salt hypertension also prevented the significant fall in plasma renin activity and plasma aldosterone concentrations which normally occur in response to DOCA and salt. In addition, potassium loading of rats with a renal artery clip was found to result in an increase in urine volume, and increased excretion of sodium and potassium. It also attenuated the increase in plasma renin activity which is typically observed under these conditions, but further enhanced the plasma aldosterone concentrations. Studies of fluid and sodium balance in dogs with avoidance-saline hypertension will be useful to determine the role of the kidneys in the effects of potassium under these conditions.

In summary, the data from the present study show clearly that increasing potassium intake decreases the magnitude of blood pressure elevation in dogs produced by avoidance conditioning and saline infusion. In addition, it appears to reduce the acute increases in blood pressure and heart rate in response to an excitatory stimulus (i.e., onset of the avoidance session). Whatever the physiological mechanisms by which these potassium-induced alterations occur, it is clear that the ratio of potassium to sodium intake, as well as the absolute intake of sodium, should be considered in analysis of the environmental conditions that influence both long-term blood pressure and acute cardiovascular response to stressful stimulation.

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References

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