*BEHAVIOR ANALYSIS AND THE SEARCH
FOR THE ORIGINS OF HYPERTENSION*

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Hypertension is a disorder of sodium regulation that develops over time in a context of the interactions of the individual with the environment. Experimental hypertension can be induced in laboratory animals and normotensive humans via increases in sodium intake under conditions of aversive behavioral control. Readiness for avoidance contingencies includes a breathing pattern characterized by subnormal rate and normal tidal volume. Studies with humans have shown that this inhibitory breathing pattern is associated with increased plasma acidity, increased renal sodium reabsorption, increased secretion of digitalis-like hormones that inhibit sodium-pump activity, and increased vasoconstriction and blood pressure. Behavioral research is needed that defines the necessary and sufficient conditions for inhibitory breathing and its role in the development of hypertension.

Key words: avoidance conditioning, blood pressure, hypercapnia, hypertension, preavoidance, respiration, sodium, dogs

We can convince 'em more with our data than
with our logic.

J.V. Brady, ca. 1970

This article reviews research on behavioral regulation of blood pressure relevant to the search for the causes of primary hypertension. Primary hypertension is a disorder of elevated blood pressure that affects as many as 20% of American adults. It is generally agreed that multiple genetic factors and environmental influences can contribute to its genesis (Cowley, 1992; Folkow, 1982). Despite extensive investigation over the past century, however, the causes of primary hypertension still are not fully understood. The following discussion proposes that one form of chronic hypertension can evolve in individuals on a diet high in sodium chloride under conditions of aversive behavioral control. Models of experimental hypertension are described that show that sodium loading can elevate resting blood pressure of laboratory animals behaving on avoidance schedules and normotensive humans preparing for examinations. It will be suggested that behavioral interactions can mediate the development of these hypertensive adap-

tations via an inhibitory breathing pattern that influences acid-base balance and secretion of hormones involved in sodium transport.

Blood-Pressure Effects of High Sodium Intake

It has been known for many years that a high dietary intake of sodium chloride is associated with an increased incidence of hypertension and that cultures with low sodium intake tend to have a low prevalence of hypertension (MacGregor, 1985). However, the healthy kidney can rapidly excrete a sodium load to maintain a stable sodium balance (Guyton, 1990), and most humans can ingest large quantities of sodium chloride over extended intervals with no significant changes in blood pressure (Sullivan & Ratts, 1983). Thus, most investigators agree that a high salt intake by itself is not sufficient to produce chronic hypertension in humans.

Blood-pressure response to high sodium intake depends on endocrine activity. For example, experimental hypertension can be produced in small (Berecek, Stocker, & Gross, 1980) and larger (Turkkan & Goldstein, 1987) animals by salt feeding in combination with administration of synthetic adrenocorticosteroids. Hypertension does not develop in response to steroid administration alone, indicating that the hormone treatment alters sodium regulation. Furthermore, the classic studies of Mason, Brady, and co-workers (Mason et al., 1968) have shown clearly that secretion of adrenal hormones varies as a function of systematic interactions of the individual with the environment.

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Blood-Pressure Effects of Aversive Stimulation

Epidemiological surveys indicate that the prevalence of hypertension is high in societies that have experienced major changes in customs and values in the lifetimes of their members (Henry & Cassel, 1969), whereas a low incidence of hypertension occurs in reclusive groups that maintain stable and traditional life-styles (Timio et al., 1988). Longitudinal studies have shown that young, normotensive people who reported decreased activity level as a "habit of nervous tension" (Thomas & Greenstreet, 1973) or who were described as "nonassertive" (Perini, Muller, & Buhler, 1991) were more likely to develop hypertension than were control groups. These studies paint a picture of a behavioral component of hypertension that is distinct from the so-called Type A personality and that involves chronic inhibition of emotional behavior.

Many attempts have been made to produce chronic hypertension in genetically normotensive laboratory animals. Early reports of the effects of social stress on rodents were encouraging (Henry, Meehan, & Stephens, 1967), and subsequent studies of avoidance conditioning of chronically instrumented large animals also provided tantalizing results (Forsyth, 1969; Harris, Gilliam, Findley, & Brady, 1973; Herd, Morse, Kelleher, & Jones, 1969). However, other studies showing that aversive stimulation per se did not reliably elevate blood pressure or that intermittent increases in blood pressure produced by other means did not increase resting blood pressure (Julius & Cottier, 1983) resulted in a consensus that aversive stimulation alone is not sufficient to produce hypertensive adaptations in genetically normotensive animals (Herd et al., 1987; Krantz et al., 1987).

Interactions of Sodium Intake and Aversive Interactions

Within the past decade, a series of studies with chronically instrumented dogs revealed a model of experimental hypertension that combines free-operant avoidance schedules with high sodium intake (reviewed in Anderson, 1986). The conditioning procedure involved presentation of three daily 30-min avoidance sessions (Sidman, 1962), each scheduled 7.5 hr apart. The well-trained dogs learned to maintain steady, effective avoidance behavior

during the sessions and to remain relatively inactive between sessions. Blood pressure and heart rate were stably increased during the avoidance sessions but fell rapidly following the end of each session. As the onset of the next session approached, however, blood pressure increased progressively, while heart rate decreased progressively (Anderson & Brady, 1971; Anderson & Tosheff, 1973). With normal sodium intake, the 24-hr mean level of blood pressure remained relatively stable over weeks on this schedule. As shown in Figure 1 however, the 24-hr mean level of blood pressure increased progressively over days if sodium intake was increased to a level comparable to the upper end of the human dietary range. This hypertensive effect did not develop in response to sodium loading in the absence of avoidance schedules, and could be rapidly reversed by either discontinuation of the saline infusion or by increases in intake of potassium chloride, even though the avoidance schedules remained in effect. The combination of avoidance schedules and sodium loading produced an increase in renal sodium reabsorption that preceded the elevation in 24-hr blood pressure that developed over the next 2 weeks. Although it had been proposed that sodium-sensitive experimental hypertension is mediated by increased renal sympathetic activity (e.g., DiBona, 1991), neither sodium retention nor experimental hypertension were prevented by either surgical or pharmacological blockade of the sympathetic nervous system. Recently, these findings have been confirmed and extended in baboons trained on a conflict procedure in which an operant produced food and/or electric shock (Turkkan & Goldstein, 1991a). Blood pressure increased when animals on the conflict procedure also drank a hypertonic saline solution. No changes in plasma catecholamines or atrial natriuretic peptides were observed under these conditions, and beta adrenergic blockers did not lower the elevated blood pressure (Turkkan & Goldstein, 1991b).

Experimental hypertension has also been developed in normotensive humans on a high sodium diet during a "high stress" period (Haythornthwaite, Pratley, & Anderson, 1992). Medical students were assigned to a high or normal sodium intake condition for 2 weeks immediately preceding examinations or for 2 weeks in the summer when academic demands were minimal. Blood pressure in-

creased in subjects with high salt intake preceding examinations, but sodium feeding produced no such changes during the summer. The control group showed no changes in blood pressure under either condition. A subsequent replication of these findings showed, in addition, that subjects with low potassium intake had greater blood-pressure response to the salt-loading procedure (Haythornthwaite, in press). As in the studies with dogs, plasma renin activity and aldosterone concentrations of medical students were decreased by sodium loading.

The physiological mechanisms by which the stress/salt procedures elevate blood pressure in laboratory animals and human subjects remain to be clarified, but appear to involve non-adrenergic mechanisms. Experimental hypertension produced in rodents by stimulus deprivation may provide some clues. Sustained social isolation was found to elevate blood pressure and increase the ratio of intracellular sodium/potassium concentrations (Bennett & Gardiner, 1978). These effects could be prevented by prior adrenalectomy (Gardiner, Milner, & Bennett, 1981). Similarly, deprivation of auditory stimulation in rats generated elevations in blood pressure that were accompanied by decreases in urinary catecholamines, and the hypertension persisted for weeks following discontinuation of the experimental procedures (Marwood & Lockett, 1977). These studies are consistent with the view that the aspects of avoidance schedules that are important for development of hypertension in sodium-loaded animals involve sustained inhibitory behavioral states between brief periods of active behavioral response.

Studies of Inhibitory Breathing

Preavoidance procedures have effects on respiratory as well as cardiovascular functions. During intervals immediately preceding the onset of free-operant avoidance sessions, well-trained dogs showed progressive decreases in breathing rate with no compensatory increases in tidal volume. This pattern of anticipatory hypoventilation occurred only in animals who initiated avoidance responding promptly following the onset of the avoidance session, and appeared to be part of a physiological pattern accompanying attention to salient stimuli. The development of experimental hypertension in sodium-loaded dogs required repeated recur-

Fig. 1. 24-hr mean levels and standard errors of systolic and diastolic pressure and heart rate over 15 days of avoidance schedules and continuous isotonic saline infusion (1.3 L/day), averaged for 8 dogs.

rence of this preavoidance cardiorespiratory pattern. Thus, it was originally concluded that it was a correlate of an unidentified endocrine response during preavoidance periods that sensitized the dog to increased sodium intake.

Extension of these findings on preavoidance respiration to the study of human breathing was facilitated by construction of a portable, battery-powered microprocessor system for ambulatory monitoring of respiration (Anderson & Frank, 1990). Lung inflation is known to be proportional to the sum of the stretch of elastic bands worn around the thorax and abdomen (Sackner, Nixon, Davis, Atkins, & Sackner, 1980). The microprocessor detected changes in electrical inductance in thoracic and abdominal bands accompanying lung expansion, and excluded postural artifact via electronic filters that were sensitive to the probable timing of breathing and the probable magnitude of band stretch. Studies with this ambulatory monitoring system found that, under most conditions, variations in minute ventilation in ambulatory humans were achieved via concurrent changes in tidal volume with relatively stable breathing rates. For example, low levels of ventilation during sleep were accompanied by parallel changes in tidal volume, but breathing rates were comparable to those

Fig. 2. Mean levels and standard errors of end tidal CO₂, pCO₂, pH, HCO₃⁻, mean arterial pressure, and heart rate before, during, and following inhibitory breathing (i.e., end tidal CO₂ > 40 mmHg), averaged for 12 normotensive human subjects.

observed in awake subjects at rest (Stradling, Chadwick, & Frew, 1985).

However, under some conditions, breathing rate varied above and below the normal range (12 to 16 breaths per minute) for extended intervals, with little change in tidal volume (Anderson, Coyle, & Haythornthwaite, 1991). Low-rate/normal-tidal-volume breathing was termed inhibitory breathing and was differentiated from hypoxic or hypercapnic breathing in that it is sustainable over time. Inhibitory breathing was found to occur more frequently in work situations and when subjects were in social situations than when they were at home or alone (Haythornthwaite, Anderson, & Moore, 1992), and was found to be accompanied by higher blood pressure, but not

heart rate, than normal breathing (Anderson, Austin, & Haythornthwaite, 1993).

The metabolic and cardiovascular concomitants of sustained breath holding are well known (Mithoefer, 1964). When an individual suspends breathing, plasma levels of carbon dioxide increase, the blood flow is preferentially shunted away from the skeletal muscles to the brain and heart, and blood pressure increases while heart rate decreases. In recent years, the physiological concomitants of voluntary inhibitory breathing have been studied in our laboratory (Anderson, Austin, & Coyle, in press). Humans were trained to maintain comfortable subnormal ventilation by breathing at a low rate (six to eight breaths per minute) and to maintain a normal tidal volume by using a respiratory gas monitor that displays end tidal CO₂ on a breath-to-breath basis. As shown in Figure 2, a sustained decrease in plasma pH and a progressive increase in plasma bicarbonate levels were observed when subjects maintained end tidal CO₂ near the upper end of the normal range. Unlike breathing in a high-CO₂ environment, which produces sympathetic arousal (Somers, Mark, & Abboud, 1988), there is evidence that voluntary inhibitory breathing does not increase sympathetic nervous system stimulation of the heart or skeletal muscle (Anderson, Somers, Clary, Sinkey, & Anderson, 1991). Nevertheless, blood pressure typically increased during inhibitory breathing due to an increase in total peripheral resistance, while heart rate was slightly decreased.

Evidence has shown that inhibitory breathing that decreases pH is also accompanied by renal sodium retention (Anderson & Bagrov, 1993). Levels of urinary sodium excretion were significantly lower during 30 min of "inhibitory" breathing than during a preceding interval of normal breathing, and were also lower than in a control group of subjects who did not perform the breathing task (Figure 3). This response may have been mediated by an increase in renal exchange of sodium and hydrogen ions in response to acidification of the plasma (Mahnen Smith & Aronson, 1985). In any event, this study suggests that interactions of the organism with the environment can affect sodium balance via effects on breathing pattern.

During periods of renal sodium retention, proportional increases in circulating fluid vol-

Fig. 3. Mean levels and standard errors of urine volume, sodium, potassium, and endogenous digitalis-like factors (EDLF) during free breathing (open bars), regulated normal breathing (end tidal $\text{CO}_2 < 40$ mmHg; cross-hatched bars), and inhibitory breathing (end tidal $\text{CO}_2 > 40$ mmHg; solid bars) for 20 normotensive human subjects on a water-drinking regimen. Panel A: 10 experimental subjects; Panel B: 10 control subjects who did not perform inhibitory breathing task.

ume maintain a constant extracellular sodium concentration. The resulting expansion of plasma volume is known to stimulate increased adrenal-gland secretion of digitalis-like hormones (EDLF) that inhibit the ability of the sodium pump to maintain intracellular sodium balance and that are known to be increased in clinical and experimental hypertension (deWardener & Clarkson, 1985). Studies in our laboratory have now shown that secretion of EDLF is stimulated by inhibitory breathing (Anderson & Bagrov, 1993). Figure 3 shows

that levels of urinary EDLF doubled during 30 min of inhibitory breathing, compared with normal breathing by experimental and control groups. Inhibition of sodium-pump activity by EDLF can increase intravascular sodium levels and increase vasoconstriction via sodium-calcium exchange. Studies of the effects of inhibitory breathing on sodium-pump activity and cell sodium are needed to determine whether EDLF stimulation under conditions of high sodium intake is sufficient to result in chronic hypertension. Inhibitory breathing may

be not merely a correlate of a neuroendocrine response to behavioral stress, but a direct stimulus to expansion of plasma volume, which influences hormones regulating vascular tone and blood pressure.

Conclusions

This article has reviewed findings that are consistent with the hypothesis that preavoidance breathing contributes to the development of experimental hypertension in sodium-loaded individuals. Although it is known that decreased pH is associated with increased blood-pressure response to salt loading (Sharma, Kribben, Schattenfroh, Cetto, & Distler, 1990), much remains to be done to link inhibitory breathing to long-term regulation of blood pressure. An important question remaining for behavioral scientists concerns the necessary and sufficient stimuli for evocation of inhibitory breathing and the time course of its physiological effects. Experimental analysis of this problem is at the interface between behavioral science and physiology, but its solution will demonstrate the value of the principles and methods of the experimental analysis of behavior in the search for the origins of hypertension (Brady & Harris, 1977; Engel, Anderson, & Talan, 1993).

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