Physiologic Regulation of Arterial Pressure
An Overview

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SUMMARY Research of the past 30 years has produced information showing the close interrelationships of neural mechanisms, the renin-angiotensin-aldosterone system, and salt balance as determinants of arterial pressure, both normal and elevated. Contemporary emphases are on central sites of neural regulation of arterial pressure, and an interesting sidelight of the conventional approaches is the possibility that the endorphin-enkephalin system may have a role in hypertension. Salt balance is critically important for people with salt-dependent hypertension; mechanisms of this dependency have not been defined but possible candidates are activation of the sympathetic nervous system, release of a natriuretic factor that causes vasoconstriction as well as salt loss, and renal-neural interactions. (Hypertension 4 (supp III): III-62-III-67, 1982)

KEY WORDS • salt • neural mechanisms • opioid peptides

ANY demonstration of a role for nutritional factors in hypertension immediately raises the question of mechanisms for the elevated arterial pressure. It has been amply shown that hypertension is associated with obesity, that high salt intake can produce hypertension in experimental animals, and that rigid salt restriction normalizes arterial pressure in a fair proportion of hypertensive patients, but the mechanisms for these effects are not yet fully known. This presentation will focus on factors regulating arterial pressure and will discuss how these factors may be influenced by excess calories and salt.

Hemodynamics of Normotension and Hypertension

It is by now axiomatic that arterial pressure is a function of flow and resistance, but it is surprising that this realization has come about only in the last 15 or so years.1 2 For 30 years before that, elevated vascular resistance was considered the only hemodynamic abnormality (other than high pressure), because cardiac output was considered to be normal.3 The simple formula, P = F x R, was interpreted as showing that resistance (R) alone was abnormal and that flow (i.e., cardiac output) was either not affected or played no role in hypertension. Now we recognize that cardiac output can be elevated in hypertension,1 and that in such circumstances arterial pressure rises because vascular resistance does not decrease normally.2

Cardiac output and vascular resistance are the direct determinants of arterial pressure, but the formula, P = F x R, tells us nothing of the various systems that we know influence pressure. These can be called “indirect determinants” because they influence pressure by affecting cardiac output and/or vascular resistance. These indirect determinants are: neural mechanisms, sodium balance, the renal pressor system, and aldosterone. These are known with certainty, but mention should be made also of the current interest in hormones that influence electrolyte composition of vascular smooth muscle because they may play a role in determining vasoconstriction. Although other factors, such as prostaglandins and the kallikrein-kinin system, may be important, their functions in regulating arterial pressure have not yet been fully defined. Also vasopressin and opioid peptides may play a part.

Neural Mechanisms

As will be detailed in subsequent presentations in this symposium, a variety of neural controls regulate arterial pressure normally and seem to be abnormal in hypertension. Interestingly, the possibility of neural mechanisms for hypertension has been a recurrent feature for research over the past many years. This interest can be summarized by a simple listing: 1) In 1924, Hering postulated that carotid sinus reflexes play a role in arterial hypertension in man; 2) neurogenic hypertension was the first experimental model to be developed; 3) pheochromocytoma was the first secon-
Opioid Peptides and Arterial Pressure Control

The endorphins and enkephalins are widely distributed within the central nervous system and there is a growing body of evidence that they function in arterial pressure control. Three recent papers exemplify some of the research that is aimed at understanding these mechanisms.

Schatz et al. studied the effects on pressure and heart rate of two enkephalins given intravenously (i.v.) into the lateral brain ventricles (i.v.t.) or into the cisterna magna of the fourth ventricle (i.c.i.) of cats, SHR, WKY controls, and rats with hereditary hypothalamic diabetes insipidus (DI). These studies were carried out because of evidence suggesting that opioid peptides influence the autonomic nervous system, pituitary hormone secretion and arterial pressure: 1) pain and stressful stimuli have hemodynamic effects and release opioid peptides; 2) opioid peptides are found in brain regions that regulate secretion of hypothalamic and pituitary hormones; 3) enkephalins are found in nerve fibers connecting the hypothalamus to the posterior pituitary and could function in vasopressin release; 4) enkephalin-like material has been found in the NTS.
and could influence its cardiovascular control mechanisms and 5) changes in heart rate and arterial pressure that are produced by morphine are blocked by morphine antagonists.

In cats they found that D-alanine enkephalin given i.v.t. increased arterial pressure and attenuated baroreceptor sensitivity. In rats, both SHR-stroke prone (SHR-sp) and WKY, leucine enkephalin given intravenously raised arterial pressure and the response was greater in SHR-sp than in WKY. Naloxone given i.v. lessened the pressor response but given i.v.t. it had no effect. When leucine enkephalin was administered i.v.t. pressure rose and the increase was greater in SHR-sp than in WKY. Naloxone when injected i.v.t. did not reduce the response whereas i.v.t. propranolol did. When given into the cisterna magna, leucine enkephalin produced equal pressor responses in SHR-sp and WKY, both of which were blocked by similarly administered naloxone. In DI rats, leucine enkephalin i.v.t. had a depressor effect.

From these results the authors concluded that there are many central opiate receptors that mediate the arterial pressure and heart rate responses to opioid peptides. This study also confirmed that SHR-sp has increased pressor responsiveness to centrally acting agents.

In another report, Szilagyi and Ferrario investigator the effect of morphine on the pressor response to angiotensin II (AII) given into vertebral arteries. This study was an extension of much earlier work by Ferrario et al which had shown that use of morphine was necessary to elicit the pressor response to vertebrally administered AII. In the recent study, they postulated that the AII response is dependent upon activation of opiate receptors. Thus, they found that AII injected into vertebral arteries of dogs anesthetized with chloralose-morphine caused a dose-dependent rise in arterial pressure and heart rate that could be blocked with naloxone. With chloralose anesthesia alone, the pressor response to AII was much less and was unaltered by naloxone. However, when morphine was added to chloralose, the AII pressor responses were similar to those found when the chloralose-morphine anesthetic combination had originally been used. Since AII exerts its central pressor effects through the area postrema and since enkephalin-containing neurons are found there, they concluded that the endogenous opiate system is important in inducing the AII-mediated rise in arterial pressure.

Clonidine and alpha methyldopa are well recognized as having a central mechanism for their antihypertensive effects. Since clonidine and morphine both decrease arterial pressure and heart rate, Kunos et al investigated the possibility of an interaction between central opiate and alpha receptor systems. They superfused brain stem slices from SHR and WKY rats and measured the amounts of beta-endorphin immunoreactive material that was released when various alpha-agonists, alpha-antagonists, and opiate antagonists were added to the superfuse. They found that both clonidine and L-alpha methyl noradrenaline caused a marked release of beta-endorphin immunoreactive material from brain stems of SHR but not WKY. Yohimbine, an alpha-antagonist, reduced release of the beta-endorphin material from untreated brains and blocked the anticipated clonidine release. Naloxone, which blocks the depressor effect of clonidine in SHR, did not inhibit the clonidine-induced release of beta-endorphin-like material. Clonidine has little hypotensive effect in WKY and this was not affected by naloxone. Further, destruction of the NTS abolished the depressor response to clonidine in SHR but did not modify the small response in WKY. These results indicate a role for opioid peptides in arterial pressure control in SHR that is lacking in WKY.

**Body Sodium Stores**

There is no question that salt intake influences the arterial pressure of some proportion of hypertensive patients but the prevalence of salt-dependent hypertension is unknown, nor is the mechanism understood. Sodium balance determines extracellular fluid volume, plays an important role in renin release, and affects the activity of the sympathetic nervous system. Hypertension that is normalized by salt deprivation differs in certain of these functions from that which is not affected, but this tells us little about why a high salt intake produces hypertension.

**Salt-Dependent, Salt-Sensitive, and Salt-Resistant Hypertension**

There are two hypertensions that are clearly salt-dependent: primary aldosteronism and that accompanying chronic renal failure treated by dialysis. As far as essential hypertension is concerned, there is work going on to determine the functional characteristics of those patients who become normotensive with salt restriction (salt-dependent hypertension), those whose arterial pressure rises with salt-loading (salt-sensitive hypertension), and those in whom salt-loading has no effect (salt-resistant hypertension).

**Primary Aldosteronism**

Bravo et al showed some years ago that the hypertension of primary aldosteronism could be reduced to normal by a 9 mEq Na diet and use of a mercurial diuretic. This result points to the primacy of sodium in this type of hypertension which could be abolished in the face of continuing hyperaldosteronism; it also underlines the importance of aldosterone excess in interfering with sodium homeostasis.

**Renoprival Hypertension**

Patients with chronic renal failure maintained by dialysis frequently have hypertension, and this is now recognized to be either renin-dependent, salt-dependent, or a mixture of the two types. Bilateral nephrectomy removes the renin component and when hypertension persists, it is then salt-dependent. Onesti and colleagues have provided landmark data concerning this type of hypertension. They showed that hypertension in anephric patients was positively correlated with
total exchangeable sodium so that it depended on the degree of positive sodium balance that persisted following dialysis or accumulated between dialysis. In contrast, there was a small group of anephric patients who never became hypertensive regardless of the degree of positive sodium balance. Experience with the hypertension of chronic renal failure has uncovered two important aspects about sodium in hypertension. One is the fact that, whereas the prevalence of hypertension is 15% to 20% in the overall U.S. population, it rises to about 80% in renal failure. The other is that salt alone does not produce hypertension; a susceptibility to the pressor effect of sodium must be present for hypertension to develop. The nature of this susceptibility is unknown, but I am tempted to ascribe it to differences in the contractile apparatus of vascular smooth muscle such that salt excess causes vasoconstriction.

Essential Hypertension

Some years ago, we described a group of patients who became normotensive (i.e., blood pressure less than 140/90) during 4 days of salt deprivation. We called this "volume-dependent essential hypertension," but a better term seems now to be "salt-dependent hypertension." In this study, patients took a 9 mEq sodium diet for 4 days, and a mercurial diuretic was given on the first day. In those with salt-dependent hypertension, the arterial pressure response was striking, with reduction to, or toward, normal on the first day. Average control pressure was 161/103 mm Hg and during the 4 days of deprivation was 131/86 mm Hg. This response was in sharp contrast to that obtained in the salt-resistant group: control, 161/107 mm Hg; deprivation, 151/103 mm Hg. Three of the seven salt-resistant patients studied had some reduction in pressure but not to normotensive levels. A salt-loading period of 3 days followed the 4 days of sodium deprivation, and on each day, the patients received 0.9% sodium chloride solution intravenously (25 ml/kg or 3.88 mEq Na/kg). Arterial pressure of the salt-resistant patients did not change (151/102 mm Hg) while that of the salt-dependent patients rose somewhat and averaged 162/99 mm Hg on Day 3 of salt-loading. We looked for differences between the salt-dependent and salt-resistant hypertensives that would distinguish them. In the control period, those with salt-dependent hypertension had lower plasma volume and lower plasma renin activity than the salt-resistant ($p < 0.01$ and $p < 0.05$, respectively). Aldosterone excretion rates were not different. With salt deprivation, plasma volume decreased the same amount in the two groups so that a significant difference persisted. Plasma renin activity (PRA) was increased and, although the average level achieved in the salt-dependent group was less than in the salt resistant group, the difference was not statistically significant. Aldosterone excretion rates responded similarly in the two groups.

Thus, we were unable to say that salt-dependent hypertension is characterized by subnormal compensatory increases in renin and aldosterone. With salt-loading, the patients with salt-dependent hypertension retained significantly more sodium and gained more weight than those whose hypertension was salt-resistant. This could have been because of the lower arterial pressure in the patients with salt-dependent hypertension. The major finding of this study was the identification of a group of patients who became normotensive with salt deprivation, and the impressive factor was the rapidity with which arterial pressure fell.

More recently, Kawasaki et al. reported their results with salt deprivation and salt-loading in 19 patients with essential hypertension, studied during 1 week of a 9 mEq sodium diet followed by 1 week of a 249 mEq sodium intake. They were not so much concerned with pressure responses to salt deprivation as they were with rises in arterial pressure with loading. They defined salt-sensitive (SS) hypertension as that exhibiting a 10% or greater increase in mean arterial pressure during salt-loading when compared with values obtained during the low salt period. Nonsalt sensitive hypertension (NSS) was not changed with the addition of salt. They found that the patients with SS hypertension had less stimulation of supine PRA with salt deprivation than those with NSS hypertension although salt-loading was accompanied by equal suppression in the two groups. Plasma aldosterone concentration responses followed the same patterns as PRA. They also found that the SS hypertensives gained more weight with loading than the NSS hypertensives, but did not attribute it to the decrease in arterial pressure during the low sodium diet. We had noted a similar response to salt-loading in our salt-dependent hypertensives and thought it probably represented a lack of pressure natriuresis. In a 1980 report, Fujita and coworkers described responses of another group of SS and NSS hypertensive patients. They confirmed their earlier findings of differences in responses of PRA and plasma aldosterone to salt deprivation and, in addition, found that the SS hypertensive patients had significantly higher norepinephrine levels during the fourth day of salt loading than those with NSS hypertension.

Recently, Campese et al. have shown that hypertensive patients whose blood pressure rose with a 200 mEq sodium intake/day failed to show a suppression of plasma norepinephrine as did the normotensive control subjects and patients with salt-resistant hypertension. It seems likely that the salt-dependent hypertension that we described is equivalent to salt-sensitive hypertension and that at least one mechanism for this type is failure of an adequate stimulation of PRA to maintain pressure during negative sodium balance.

Natriuretic Hormone

A research area of much contemporary interest and activity concerns the possibility that salt-dependent hypertension results from the production of a natriuretic hormone that not only affects the kidney but also inhibits the sodium pump of vascular smooth muscle. Such an inhibitor would diminish the capacity of those cells to regulate intracellular cation concentrations, which would render them more excitable to ordi-
nary stimuli such as nerve impulses or circulating vasoconstrictor substances. A corollary to this is believed to be the abnormalities of red cell cation transport found in patients with essential hypertension,30,31 and some of their normotensive relatives.32

Renal Pressor System

The importance of the renal pressor system in renovascular hypertension is clear,33,34 but its role in essential hypertension has not yet been determined. Because the bulk of essential hypertensive patients have either normal or low PRA and little blood pressure response to captopril alone, it has seemed likely that the renal pressor system has little significance in essential hypertension. A recent report by Hollenberg et al.35 has, however, raised doubt about this conclusion. They studied the effect of captopril on renal blood flow and glomerular filtration rate in normotensive subjects and patients with essential hypertension maintained on either a low (10 mEq) or normal (200 mEq) sodium intake. The PRA of the two groups was not different during the control period. However, captopril produced a greater increase in blood flow and filtration rate in the hypertensive patients than in the normotensive patients regardless of the sodium intake, and, during sodium deprivation, a greater fall in arterial pressure. These results raise the question whether renal vasoconstriction itself sets in motion a sequence that not only initiates hypertension but also maintains it.

In this regard it is relevant to recall that Fahn et al.36 considered renal ischemia to be a cause of hypertension, that Goldblatt et al.37 undertook their classic experiment to test that hypothesis, and that Katholi et al.38 and Cowley and Lohmeier39 have shown that low dose intrarenal norepinephrine infusion could raise arterial pressure in dogs more than when it was given intravenously. It is interesting that the possibility of renal vasoconstriction as playing an important role in hypertension has been such a durable idea during the past 65 years.

Conclusions

This is an important time in our understanding of hypertension. Current research, building on the information of the past, is revealing the myriad ways in which brain centers, neural peptides, and neural endocrine hormones control arterial pressure and play a role in hypertension. The mechanisms whereby sodium produces hypertension are beginning to be understood. The importance of the kidney and its relationships to the brain are becoming tangible. Certainly this knowledge will be central to our understanding of nutritional factors in hypertension.

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