Natriuretic Hormone Linked to Hypertension

According to a new theory, excess salt in the diet may indirectly produce hypertension by causing the release of natriuretic hormone

Nearly everyone agrees that salt causes hypertension. Agreement on how this happens is less easy to come by. Louis Tobian, of the University of Minnesota Medical Center, said last month at a symposium,* "A high-salt diet does seem to account for a great deal of hypertension in man. What is quite mysterious is how this works."

Recent evidence, some of which was also presented at the symposium, may help to clear up the mystery. The new data suggest that a hormone, called natriuretic hormone because it increases the secretion of sodium ions into the urine, might be a link between excessive dietary salt and at least some forms of high blood pressure.

At first glance, the suggestion that an agent that enhances sodium secretion might increase blood pressure seems paradoxical. Getting rid of the offending ions would seem to be beneficial, especially since water loss usually accompanies sodium elimination. The result ought to be a decrease in blood pressure.

The key to the dilemma is in the mechanism of action proposed for natriuretic hormone. It apparently acts on sodium ion transport, not just in the kidney, where it allows more of the ions to be lost in the urine, but also in other cells of the body. In particular, the theory holds that natriuretic hormone may cause changes in the ion content of smooth muscle cells that make them contract more readily. Enhanced smooth muscle contraction in the small blood vessels called arterioles would then raise the blood pressure.

Over the years there have been several hints that some agent in the blood, distinct from such known elevators of blood pressure as angiotensin and norepinephrine, might be contributing to the development of hypertension. For example, the late Lewis K. Dahl, in a report published in 1969, suggested that this might be the case, although he apparently did not follow up on the idea.

The possibility that natriuretic hormone might be the unidentified agent did not arise until about 5 years ago. One of the pioneers in the hormone research, Hugh de Wardener of Charing Cross Hospital Medical School in London, says, "I have been studying natriuretic hormone for 20 years; I didn't know that I was studying hypertension until a few years ago."

The early evidence for the existence of the hormone came from studies of experimental animals and human patients with expanded blood volumes. Several investigators, including de Wardener, showed that animals, whose blood volumes were experimentally increased, contained a blood factor that increased sodium ion excretion by the kidney.

Neal Bricker and his colleagues at the University of California at Los Angeles (UCLA) identified a similar factor in the blood of humans who were suffering from uremia, a condition in which a diseased kidney cannot rid the body of toxic materials and water. "At first," Bricker says, "we thought we might just have a uremic toxin—not an essential control element." After further studies on both animals and human patients, they concluded that their factor was a normal control agent.

The evidence suggests that natriuretic hormone increases sodium ion excretion by inhibiting reuptake of the ions by the kidney. This sodium ion transport is performed by a "pump," using the energy released during the hydrolysis of adenosine triphosphate (ATP) by an enzyme called sodium-dependent, potassium-dependent adenosinetriphosphatase (Na^+,K^+-ATPase). Natriuretic hormone apparently works by inhibiting this enzyme. For example, Harvey Gonick and his colleagues at UCLA showed that extracts of plasma from volume-expanded rats inhibited test tube preparations of Na^+,K^+-ATPase. More recently, Vardamen Buckalew and Kenneth Gruber of the Bowman Gray School of Medicine at Wake Forest University showed that a natriuretic hormone–like material in the plasma of volume-expanded dogs also inhibits the enzyme.

One problem with all this research is that it was not carried out with preparations of pure material, which are just now becoming available. For this reason, there is still some uncertainty about whether all the groups are studying the same thing. Nevertheless, the properties of the agents are similar with regard to the conditions under which they can be detected, their proposed activities, and their size. The active materials are small, with molecular weights of less than 1000 and perhaps of a few hundred.

The sodium pump is found not just in kidney tubule cells, but in all the cells of the body. About the same time that researchers were coming to the view that natriuretic hormone inhibits the sodium pump in kidney tubules, Henry Overbeck of the University of Alabama Medical Center in Birmingham and Francis Haddy, who is now at the Uniformed Services University in Bethesda, Maryland, were developing evidence that the pump is inhibited in the blood vessels of dogs with certain types of experimental hypertension. They observed decreased pump activity only in hypertension characterized by expanded blood volumes and low renin concentrations—conditions like those in which natriuretic hormone is formed. Low-renin hypertension, which constitutes about one-quarter of the total cases in man, "has always been the most difficult to explain," Haddy says.

The blood pressure depends mainly on two factors—the total volume of the blood and the resistance to its flow through the circulatory system, which is in turn determined by the degree of constriction of the arterioles. Renin is an enzyme produced by the kidney that initiates a series of events culminating in the production of angiotension, an extremely potent constrictor of the vessels. Increased arteriolar resistance caused by angiotensin ought not to be a factor in low-renin angiotensin. "It also can't be explained," Haddy continues, "by increased blood volume. There is an increase, but not enough to raise blood pressure directly. We think that the extra water acts indirectly to release natriuretic hormone." Salt is involved because excess consumption will lead to water retention and expanded blood volume, if sodium ions are not excreted efficiently by the kidney.

In more recent work, carried out with Motilal Pamnani and David Clough of the Uniformed Services University, Haddy has extended the earlier findings to rats. He says, "We see a significant

*The Lewis K. Dahl Symposium: The Interrelationship of Salt and Hypertension, held at Brookhaven National Laboratory on 7 and 8 May.

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reduction in the pump of the arteries of the hypertensive rats. Moreover, we get it in normal arteries incubated in supernates from hypertensive rats." The supernates are prepared by boiling plasma from the animals and removing the solids.

In addition, Haddy and Pamnani found that normal rats, whose blood volumes have been expanded also have reduced sodium pump activity in their tail arteries. Supernates prepared from the plasma of these animals inhibited the pumps of normal arteries just as did those from the blood of hypertensive animals. All this has led Haddy to suggest that the form of hypertension he is studying is caused by natriuretic hormone.

In contrast, Overbeck does not see decreased pump activity in the tail arteries of rats with experimental hypertension of the same type that Haddy is studying. If anything, he sees an increase. The reason for the discrepancy between the results of the two laboratories is currently unclear.

However, experiments with human subjects that were performed by the de Wardener group during the past year produced results analogous to those of Haddy. Some of the subjects had hypertension of the type described as "essential," which means simply that the cause is unknown. The description applies to about 90 percent of all cases of hypertension. De Wardener says, "When we incubate normal white cells in plasma from normal or hypertensive people, we get a big increase in the salt content of cells incubated with the plasma from hypertensive people." The increase is caused by inhibition of Na^+,K^+-ATPase, with the result that fewer sodium ions are moved out of the cells.

An additional biochemical consequence of the inhibition of this enzyme is an increase in the activity of another enzyme, glucose-6-phosphate dehydrogenase (G6PD). De Wardener thinks that the activity of G6PD, which is easier to measure than that of Na^+,K^+-ATPase, might be used as a marker for what is happening to the pump. He has shown that plasma from hypertensive patients produces a much bigger stimulation of G6PD activity in kidneys than does plasma from normal individuals. In addition, the ability of plasma from both normal and hypertensive people to stimulate activity of G6PD increases as the amount of salt in their diet increases. These results provide additional evidence for the hypothesis that a high salt intake contributes to the development of hypertension by triggering increased production of natriuretic hormone.

Finally, Buckalew and Gruber have found increased levels of natriuretic hormone in the blood of two species of monkeys with either essential or experimentally induced hypertension. In both types there was a correlation between the concentration of the hormone and the blood pressure of the animals.

By itself, however, natriuretic hormone probably does not cause hypertension. Most investigators think that a genetic predisposition is required for the disease to develop. According to this view, too much dietary salt can produce hypertension in people with the genetic defect, but those without it can eat as much salt as they wish.

Too much salt, incidentally, is usually considered to be an amount in excess of about 3 grams (50 millimoles) per day. Hypertension is virtually nonexistent in cultures in which less salt than this is eaten. The average American eats more than 10 grams of salt per day.

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The likely site of the genetic defect, or perhaps of its consequences, is the kidney. As pointed out by de Wardener (who sprinkled a copious amount of salt on his turkey sandwich during lunch), "It is not the rat; it is the kidney of the rat, so to speak." Several investigators, including Tobian and Dahl, have shown that a normal rat becomes hypertensive when it receives a kidney transplant from a rat with genetic hypertension. Replacement of the kidneys of a hypertensive rat with those from a normal animal relieves the recipient's high blood pressure. The kidney defect is presumed to be inadequate salt excretion.

The theory now is that if a susceptible individual eats more salt than his kidney can handle, his blood volume will increase, thus stimulating release of natriuretic hormone. The hormone inhibits the sodium pump of kidney tubules and facilitates salt excretion, but not enough to restore blood volume completely to normal. Although this should tend to lower the blood pressure, at the same time, natriuretic hormone inhibits the pump in other types of cells, including those of smooth muscle in the arterioles, causing them to contract more readily and increasing the blood pressure. After long periods of enhanced contraction, the arterioles may undergo permanent structural changes that make them more rigid. Investigators have observed such alterations in the arteriolar walls of hypertensive animals and patients.

An explanation of how inhibition of the sodium pump might lead to enhanced contractility was provided in 1977 by Mordecai Blaustein of the University of Maryland Medical Center. Several years ago he discovered an ion transport system in which sodium ions are exchanged for calcium ions. This does not require an immediate source of energy as does the sodium pump. Instead it depends on the maintenance of a gradient of sodium ion concentrations between the cell interior and exterior, for which the pump is largely responsible. Normally, the pump helps to keep sodium ion concentrations much higher outside than inside. Because the cell membrane is permeable to the ions they tend to leak back inside, and as they move in, an equivalent number of calcium ions move out. However, if the internal sodium ion concentration is increased for any reason, such as by pump inhibition, calcium ions may fail to move out and their concentration may build up inside, according to Blaustein.

This finding suggested a link between abnormally high intracellular sodium ion concentrations and high blood pressure. "Calcium ions are the immediate trigger for muscle contraction," Blaustein explains, "and one problem in hypertension is that the small arterioles are contracted. Here was a link between sodium and calcium ions in the muscle." He finds that "anything we do to increase the sodium [ion concentration] causes smooth muscle to contract more."

Many investigators besides those mentioned here have noted high intracellular sodium ion concentrations in a variety of cell types from humans and animals with hypertension, although they do not all agree that inhibition of Na^+, K^+-ATPase is at fault. Other possibilities include increased membrane permeability, allowing more sodium to leak back in, and defects in transport systems other than the sodium pump (*Science*, 27 February, p. 911). For example, Philippe Meyer of INSERM Unite 7 at the Hôpital Necker in Paris has found a large decrease in another sodium-potassium transport system in red blood cells from hypertensive patients. This system can be distinguished from the pump because the Na^+, K^+-ATPase that drives the pump is inhibited by ouabain, a chemical that is structurally related to the heart stimulant digoxin, whereas the transport system Meyer finds to be inhibited in the patients is not affected by ouabain. Meyer says that he never finds a defect in the

ouabain-sensitive pump. De Wardener notes that Meyer's assay conditions differ from those he uses, however.

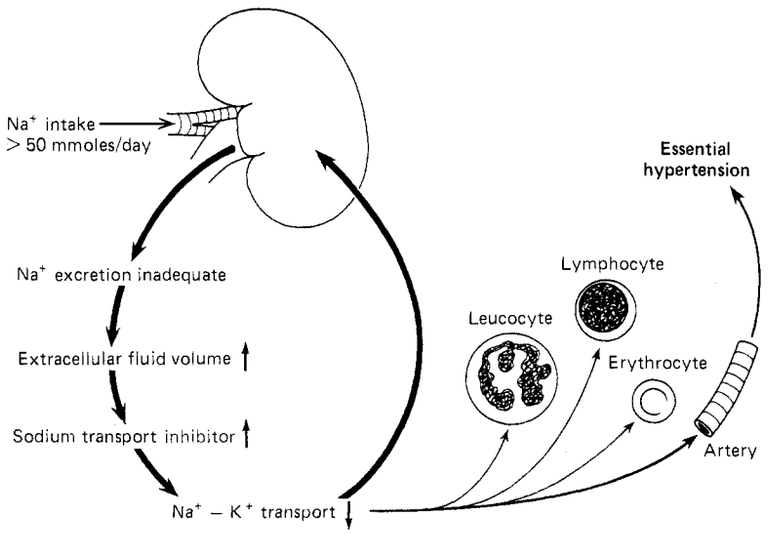
Whether or not a sodium ion increase is caused by natriuretic hormone inhibiting the sodium pump, the result still might be hypertension. Blaustein says, "For the peripheral mechanism [of hypertension], it wouldn't make any difference how the sodium ion concentration was elevated. As long as the sodium goes up, the muscle ought to contract more." But, he continues, "The data on the inhibition of the ouabain-sensitive pump look good. Enough people have done it that I believe it."

Changes in the ionic content of smooth muscle cells might also enhance their contractility by making them more susceptible to vasocontrictive agents such as norepinephrine. Haddy's group has found that pump suppression does increase the response of blood vessels to such agents, with a resultant increase in blood pressure. And Buckalew and Gruber see an increased sensitivity to norepinephrine in the resistance arterioles of rats that were also exposed to their natriuretic hormone preparation.

Lack of a pure preparation of a characterized material has been one of the handicaps of work on natriuretic hormone and has contributed to the uncertainties about its role in hypertension. At present, a half-dozen or so groups have pure or nearly pure preparations of natriuretic substances. Everyone agrees that their agent is small and heat-stable, but there is still disagreement about its chemical nature.

According to de Wardener, the material isolated from urine by his group is pure. Preliminary characterization suggests that it is a sugar derivative, definitely not a peptide. Meanwhile, Buckalew and Gruber have been working to identify the material they find in increased amounts in the blood of volume-expanded animals. They currently think that it is a peptide, partly because its activity is destroyed by enzymes that attack peptides. To add to the confusion, both groups say that their agent binds to antibodies against digoxin.

This antibody binding was how the Bowman Gray workers, taking a tack first suggested by Sidney Spector of the Roche Institute of Molecular Biology, identified their material in the first place. The idea is that antibodies to drugs that bind to specific receptors might recognize and bind to the endogenous ligand for those receptors, even though the two substances might have different structures. Because digoxin and ouabain are chemically related and both inhibit the



How natriuretic hormone may cause hypertension

Natriuretic hormone (the sodium transport inhibitor) increases sodium excretion in the urine by inhibiting sodium-potassium transport in the kidney. But at the same time, it also inhibits the transport in other cells. The resulting ionic changes in the smooth muscle of the small arteries causes them to constrict, thus raising the blood pressure. [Reprinted with permission from Kidney International **18**, *1 (1980)].*

Na^+, K^+-ATPase affected by natriuretic hormone, Buckalew and Gruber hypothesized that they could use antibodies against digoxin as a probe for natriuretic hormone. They identified a material like the hormone, but whether it proves to be the same as that studied by de Wardener remains to be seen.

Bricker is also among the investigators who are working on the characterization of natriuretic hormone. He has a preparation that he describes as almost pure. As to its chemical nature, Bricker says, "Up until 6 months ago, we thought it was a peptide . . . but with the purest preparation, we did not recover any amino acids." Because of a possible problem with the amino acid analyzer on the day of the most recent analysis, Bricker cannot yet conclude that his material is not a peptide, however.

Another unknown is the site of formation of natriuretic hormone, although an area of the brain called the hypothalamus is a good possibility. De Wardener has identified a natriuretic substance that is also an inhibitor of the sodium pump in the hypothalamus, and, he says, "There is more [of the inhibitor] in a rat given a lot of sodium."

One region of the hypothalamus that is extremely important for regulating the blood pressure is the anteroventral third ventricle (AV3V). According to Michael Brody of the College of Medicine of the University of Iowa, destruction of the AV3V "prevents practically all kinds of hypertension." In experiments performed with A. K. Johnson, also at Iowa, he finds that animals with lesions in this part of the brain excrete less sodium in their urine and have increased concentrations of the ion in their blood.

These are just the findings that would be expected if the animal lacked natriuretic hormone. To see if this was the case, Brody and Johnson collaborated on an experiment with Buckalew and Gruber. They compared the effects of blood volume expansion in animals with AV3V destruction and in controls. As expected, the lesioned animals excreted much less sodium in the urine than did the controls. They also had no detectable amounts of natriuretic hormone in their blood, whereas the controls had a high concentration. The results suggest that destruction of the AV3V may prevent hypertension from developing by cutting off the body's supply of natriuretic hormone. But Brody points out, "We do not know whether the substance is made or stored there, or whether nerves from the AV3V region signal another part of the body to make it."

The last word is not yet in on the relation between the hormone and high blood pressure, but there is strong circumstantial evidence that the agent contributes to the development of at least the low-renin form of the disease. If that is the case, it could open new approaches for identifying those who are likely to get the disease—for example, by looking for evidence of higher than normal levels of the hormone. It could also lead to the development of new therapeutic agents for hypertension that work by counteracting the effects of natriuretic hormone on the arterioles.—JEAN L. MARX