High-Pressure Hormone

Mysterious blood compound may plant seeds of hypertension

By KATHY A. FACKELMANN

Members of certain East African tribes gather seeds of the tropical vine *Strophanthus gratus* and extract a lethal poison to smear on their arrow tips. Some accounts describe murderers slathering the poison on a prickly fruit, then placing the fruit on a jungle path minutes before their barefoot victim arrives.

The toxic agent is ouabain (pronounced *wah*-bane), a well-known steroid hormone produced by plants and belonging to a class of drugs called cardiac glycosides. Tiny doses of cardiac glycosides increase the force of the heartbeat while slowing its rate, and physicians have long prescribed these drugs for patients with heart failure. In large amounts, however, cardiac glycosides can trigger erratic heart contractions that kill within minutes.

Researchers have now detected small amounts of ouabain or a chemical lookalike in blood samples from people not known to have taken such drugs, suggesting that the human body manufactures its own ouabain-like substance. Moreover, their findings hint that elevated levels of this substance may play a role in the development of high blood pressure, and perhaps in heart disease as well.

For many years, scientists suspected that a human hormone circulating in the bloodstream underlies at least some cases of hypertension. Early data suggested that the unidentified hormone slowed the activity of cellular sodium pumps – membrane proteins that help transport sodium out of cells. Researchers speculated that a persistent slowdown of pump activity would allow both sodium and calcium to accumulate within the cells lining blood vessels, narrowing the vessels to create hypertension.

The first direct evidence of such a hypertension hormone surfaced in the Dec. 16, 1982 NATURE, where Mordecai P. Blaustein and John M. Hamlyn of the University of Maryland Medical School in Baltimore reported that people with hypertension showed elevated blood levels of a sodium-pump inhibitor. While the chemical identity of the inhibitor remained a mystery, the team's data suggested the compound had physiological effects similar to those of a cardiac glycoside called digitalis. This drug, extracted from the leaves of the flowering foxglove plant, had largely replaced ouabain as a treatment for heart failure.

Walter H. Lewis/Washington University

Extracts from the seeds of a Strophanthus *vine contain ouabain, a potent plant steroid traditionally used in East Africa as an arrow poison. Other plant sources of ouabain include the bark of a tropical tree.*

The 1982 findings spawned an eight-year collaboration between the Maryland team and scientists at Upjohn Laboratories in Kalamazoo, Mich., who began testing blood samples from hospital patients and outpatients undergoing evaluations for a wide range of disorders. After an exhaustive analysis of hundreds of gallons of plasma (the clear portion of blood), they finally unmasked the compound. To the surprise of everyone involved, mass spectrometry scans at Upjohn revealed what appeared to be ouabain.

W. Rodney Mathews of Upjohn reported the discovery in September at the American Heart Association's 44th scientific sessions on high blood pressure, held in Baltimore. There is a "slim chance," he told SCIENCE NEWS, that the compound isolated from human plasma is not ouabain itself but an isomer – a substance sharing the same molecular formula but varying slightly in its three-dimensional structure. However, he adds, all tests conducted so far point to a substance identical to plant-derived ouabain.

"We had no idea that humans are capable of making ouabain," says Blaustein. He recalls that when a senior scientist at Upjohn first told him of the preliminary evidence for ouabain, he assumed the scientist was joking, since researchers routinely reach for a bottle of commercial ouabain to conduct experiments involving cellular sodium pumps.

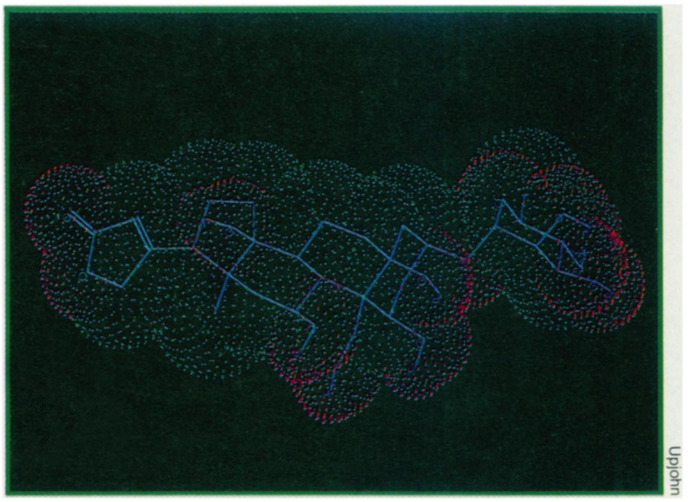
And Hamlyn says he nearly fell off his chair when he heard the news. "We thought that certainly some of the characteristics of the material were similar [to ouabain]," he says. "But I don't think in our wildest dreams we ever thought it would be the same thing."

Scientists attending the September conference responded with similar astonishment. "People who heard the talk are taking a very cautious approach to this finding," says Vardaman M. Buckalew Jr., a nephrologist at the Bowman Gray School of Medicine of Wake Forest University in Winston-Salem, N.C. Buckalew adds that the discoverers have yet to prove that the human body actually synthesizes the substance rather than extracts it from plant foods.

The Upjohn/Maryland collaborators share that uncertainty, but they say their evidence favors a bodily source. For example, they found that people on intravenous, ouabain-free diets continued to show high blood levels of the compound a week after the liquid diets began. In addition, the Maryland researchers found that rats, cows and humans share similar blood concentrations of the com-

pound – an observation that points away from a dietary source of ouabain because these three mammals differ radically in the foods they eat.

Indeed, preliminary data strongly suggest that the adrenal glands manufacture ouabain or its look-alike. Adrenal glands from cows and humans contain rich concentrations of the substance, and isolated adrenal cells secrete it when cultured in a laboratory dish, Hamlyn says. But in order to confirm an adrenal source, he says, researchers must show that adrenal cells can synthesize the hormone from its chemical precursor.



Molecular structure of ouabain. Scientists have now identified ouabain or a very similar compound in the blood of humans, cows, rats and other mammals, and they speculate that it may contribute to human hypertension.

Blaustein disclosed another piece of the ouabain puzzle at the hypertension meeting. The compound isolated from human plasma, he says, intensifies heart contractions just as plant-derived ouabain does – at least in the lab. That raises important questions about this chemical's function in healthy people and whether elevated amounts cause hypertension and heart disease, Blaustein says.

He and his collaborators first placed heart tissue from guinea pigs in a saline solution and measured the force of the hearts' contractions, which they triggered with an electrical current. Then they added the ouabain-like extract from human plasma to some of the saline baths and repeated the electrical stimulation. Blaustein reports that these hearts contracted with three times the force of the untreated hearts. Moreover, he says, guinea pig hearts treated with plant-derived ouabain reacted in exactly the same way as those treated with the plasma-derived compound.

In another laboratory experiment, the team used the stimulant histamine to trigger contractions in isolated sections of guinea pig aortas, the heart's main artery. When they repeated the procedure – this time treating the tissues with both histamine and the ouabain-like compound – the contracting aortas narrowed twice as much as before, Blaustein reports. This, he says, implies that the recently isolated compound exerts the same cardiac effects as plant ouabain: strengthening the heartbeat and constricting blood vessels.

Scientists don't know what function the chemical would serve in the healthy body. Blaustein speculates, however, that a ouabain-like hormone might help maintain sufficient blood pressure by reinforcing the vessel-constricting messages of the hormone noradrenaline. This process could go awry, he suggests, when elevated levels of the amplifying compound – perhaps resulting from a high-salt diet – cause the vessels to overreact to noradrenaline, leading to chronically narrowed vessels and eventually to high blood pressure.

Researchers now wonder whether the ouabain-like compound might play a separate role in the genesis of heart disease. Hamlyn proposes that some people, after years of secreting excess levels of this heart-boosting hormone, may develop cardiac failure when the heart grows resistant to the compound's contraction-enhancing effects.

So far, the data merely hint at such a role, but Hamlyn plans to investigate his hypothesis with a new antibody test he has developed for measuring the suspect substance in blood. He and co-workers have already begun a multicenter study involving 300 people with congestive heart failure, in search of a link between potentially fatal digitalis toxicity and circulating levels of the ouabain-like cardiac glycoside. By assaying natural concentrations of the ouabain compound in patients' blood, Hamlyn hopes to identify those at risk of an adverse reaction to digitalis treatment. He says he suspects that people with high blood levels of the ouabain-like substance can develop irregular heartbeats if a dose of digitalis pushes their total blood level of cardiac glycosides into the danger zone.

The new antibody test may have applications in hypertension as well. Blaustein and others propose that it may help identify people with "white coat" hypertension, a benign condition that occurs only when the patient's blood pressure is being measured.

Physicians have trouble distinguishing between chronically elevated blood pressure and pressure that soars only during the stress of a medical exam. But Blaustein says he suspects the new assay will show that people with white coat hypertension have normal levels of the ouabain-like compound, whereas those with the chronic disease have elevated levels. Routine use of the test – which is not yet commercially available – might prevent unnecessary medication of healthy people with white coat hypertension, he asserts.

Conversely, he says, the ouabain assay might flag healthy people at risk of later developing high blood pressure, thereby allowing early intervention. Hypertension, which can increase a person's risk of heart attack, stroke or kidney disease, strikes without warning or outward symptoms. But Blaustein and others contend that people with a genetic predisposition to this "silent killer" may show rising blood levels of ouabain long before their blood pressure soars.

If studies confirm that theory, clinicians could use the new test to monitor adults and even children with a family history of high blood pressure, notes François M. Abboud, a cardiologist at the University of Iowa College of Medicine in Iowa City. Those who show rising levels of the compound might prevent hypertension by switching to low-salt diets, Abboud says. Like Blaustein, he believes high-salt diets may spur excessive secretions of the ouabain-like substance, which in turn may narrow blood vessels and elevate pressure.

"This [ouabain excess] may be a disease that starts with teenagers," adds Blaustein. "The only thing we've been able to measure up until now has been hypertension." Solid evidence of a link between high blood pressure and ouabain-like secretions would give clinicians their first reliable biochemical marker of the earliest stage of hypertension, Blaustein says.

And for people with established hypertension, such evidence might lead to new drugs that block the action of the overabundant compound, Abboud says.

Everyone involved in the unfolding story of ouabain agrees that researchers must answer a number of key questions before the new prospects for diagnosis and treatment can become reality. But the discovery of a blood ingredient that appears identical to a potent plant steroid gives scientists enough intriguing research leads to spark productive investigations for years to come.

"Over the next five to 10 years," says Blaustein, "all of this will be played out and we'll begin to get some answers." □