# Profile of Sérgio Ferreira

Few scientists can take credit for substantial discoveries involving a drug helping millions of people. Sérgio Ferreira, who was elected as a Foreign Associate of the National Academy of Sciences in 2006, has contributed trailblazing discoveries relating to not one drug, but three. He identified the importance of angiotensin-converting enzyme blockers in treating hypertension, unraveled aspirin's mechanism of action, and discovered the peripheral action of morphine. His Inaugural Article, published in this issue of PNAS, poses a challenge for the understanding of peripheral pain neurons and could lead to new methods of pain management (1).

Ferreira is currently a professor of pharmacology at the School of Medicine of Ribeirão Preto, of the University of Sao Paulo in Brazil. He was born in Franca, Sao Paulo and educated at the University of Sao Paolo Medical School. He entered medical school with the intention of becoming a psychiatrist, but discovered that "public psychiatry care in Brazil was rather poor, so I decided to become a scientist, not a psychiatrist. I went to work with a good Brazilian scientist."

Sérgio Ferreira

## Venom Connection

Neurophysiology was Ferreira's primary interest when he finished medical school in 1961, but there were no neurophysiologists at his medical school, or for that matter, in all of Brazil. So he moved to Ribeirão Preto to begin research with Mauricio Oscar Rocha e Silva, the pharmacologist who discovered bradykinin, a peptide hormone that lowers blood pressure, in the venom of the Brazilian pit viper *Bothrops jararaca*.

At the time, bradykinin had recently been made synthetically, and bioassays of the pure hormone showed it was less active than the natural form. Rocha e Silva gave Ferreira the task of finding out why. The project became the basis for Ferreira's thesis.

"I started working with the venom and I discovered the bradykinin potentiating factor, BPF," Ferreira says. "That was the beginning of the inhibition of the angiotensin converting enzyme (ACE), and the beginning of my career" (2).

The pit viper's venom is a mixture of proteolytic enzymes and small peptides. When injected in an animal, the venom generates bradykinin, which is potentiated by bradykinin-potentiation factor (BPF), causing intense hypotension and death. BPF acts by inhibiting bradykinin inactivation in the circulation. "It is much more potent when you have both things," Ferreira says. "So the snake was very, very clever."

Ferreira found that uncovering the mixture of peptides that constitute BPF was also useful for studying bradykinin's physiological effects. The components revealed a second important action for BPF. By purifying and synthesizing the smallest BPF peptide, composed of 5 amino acids, Ferreira's research team discovered that BPF normalizes blood pressure in a rat model of rennin hypertension by inhibiting the conversion of angiotensin I to its active form, angiotensin II (3).

Angiotensin I has no physiological effects; it must be converted in the lungs to angiotensin II. BPF has these two important physiological effects because the same carboxypeptidase enzyme that inactivates bradykinin is the same one that converts angiotensin I.

"At that moment nobody paid too much attention to angiotensin because it was thought that adrenaline and other mediators were much more important in causing hypertension," Ferreira says.

"The venom peptide called attention to the fact that the angiotensin system was important in hypertension," Ferreira continues, "particularly when one of the BPF peptides was shown to control human hypertension. But there was no drug there, because the peptides couldn't be taken by mouth."

Based on BPF5 scientists at Bristol-Myers Squibb synthesized the drug Captopril (under the pharmaceutical name Capoten), which was the first oral converting enzyme inhibitor and, at the time, was considered a breakthrough because of its mechanism of action and its structure-based drug design.

After its US Food and Drug Administration approval in 1981, Captopril was one of the first successful drugs that was purposely designed to mimic the shape of a natural molecule. Capoten was widely prescribed after it was introduced on the market in the early 1980s to treat hypertension, and a dozen other ACE inhibitors have followed. A generic equivalent of the drug has been available since 1996.

## Abroad and Back

Ferreira's early research was done in Brazil, but two political revolutions destabilized the country and sent him overseas. He first went to England for postdoctoral fellowships with John Vane at the Royal College of Surgeons (London) from 1964 to 1967 and 1970 to

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 19038.

Ferreira in his laboratory.

1973, and then at Wellcome Laboratories (London) from 1974 to 1975.

During his first stint in England, Ferreira participated in research on prostaglandin metabolism and BPF5's physiological effects. He later studied how aspirin inhibits the synthesis of proinflammatory prostaglandins, which prevents sensitization of pain neurons. This work culminated in Vane's sharing the Nobel Prize in Physiology or Medicine in 1982 (4).

Ferreira returned to Ribeirão Preto in 1975, whereupon he devoted himself to pain research, specifically on analgesia and the sensitization of pain receptors. His behavioral studies of rats have revealed that morphine has peripheral, as well as central nervous system, effects.

"By injecting in the paw, we could show—during inflammation or during prostaglandin nociception—that we could block [central nervous system effects] with peripheral morphine," Ferreira recalls (5).

At that time, morphine was thought to act only on neurons in the central nervous system, and Ferreira's discovery was not initially accepted. "Nobody believed it at first, but after a period everybody knew morphine has a peripheral effect." He has since shown that other opiates have similar peripheral analgesic activity (6).

Ferreira followed the discovery of peripheral analgesia by developing a modified opiate that does not cross the blood–brain barrier. "It was experimental. Nowadays substances like this one we developed are coming to the market. They do not cross the blood–brain barrier, but they still give you analgesia, which is important for surgical uses and inflammatory pain. They're much safer because they will not give you respiratory problems or cause dependency and tolerance," he says.

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Other new drugs work in reverse. "They block the effect of morphine in the gut but do not block its effect in the brain," he says. "Ultimately, it's all based on the idea you can have a peripheral-acting antagonist."

## Managing Pain

In his Inaugural Article, Ferreira presents details of a recently discovered phenomenon he has dubbed "tele-antagonism." His research team found that the effects of morphine and other analgesics injected into a rat's spine could be canceled out by injecting an antagonist into the rat's paw. The effect also happened in reverse, with morphine delivered to the paw and the antagonist in the spine.

"We observed that if we give a drug in a neuron in the periphery, we can antagonize the effect of the drug in the central system," he says. "The neuron has two ends, one peripheral and one central. We can antagonize the drug given centrally if you give the agonist peripherally. We don't understand exactly how a drug can move in the neuron to the other end or how they can be antagonized. This is a mystery."

Ferreira thinks that the drugs may be traveling rapidly along or through the primary nociceptive neuron to a common place of action, or perhaps some kind of signal is being transmitted through the neuron. In either scenario, the drug's effects are cancelled at a distance from the sensitization site.

"It's very intriguing that some drugs can move along the neuron from the head to the spinal medulla," Ferreira says. "[The drugs] can move all of the way to the other end and have an effect. It is very intriguing because it has a practical effect. You can give the drug near the spinal cord and it will be distributed to all of the nearby neurons."

Ferreira believes that tele-antagonism could lead to new methods of pain management. "Even the small pains in aging people are very important. There are always small pains, like back pains—even if it's not terrible it's still annoying. With these kinds of pain we don't want to get inside the brain, and we need to know how to manipulate it with a little delicacy to not make people too sleepy."

Ferreira speculates that tele-antagonism may help explain the analgesic effects of acupuncture and could provide a scientific explanation for the ancient practice. He says that acupuncture needles may release small amounts of endorphins in the tissue, which like morphine, may diffuse through the primary sensory neuron.

If his tele-antagonism hypothesis is correct, the endorphins or some signal that comes with their release could travel from the periphery to the central nervous system.

## Future Directions

Ferreira credits Michel Rabinovitch, with whom he published his first paper (7), his thesis supervisor Mauricio Rocha e Silva, and John Vane for helping to guide his long and productive research career, in which he has been rewarded with memberships in the Brazilian Academy of Sciences, Brazilian Society for the Advancement of Science, Third World Academy of Sciences, British Pharmacological Society, and International Association for the Study of

Pain. He has also been recognized with numerous awards in Brazil and worldwide. "I was lucky to have good mentors," he recalls.

Ferreira, who recently turned 74, has no plans to retire soon although his wife has retired after a career as a child development psychologist.

"I believe that in five years, if I can put together all my present work, I may contribute to understanding chronic neuralgia and acute pain," he says. "I have done some pioneering work in the role of cytokine hyperalgesia. This work explains why corticoids are analgesics and shows new targets for controlling chronic pains. I also described a property of the primary sensory neuron, which was named peripheral memory of pain."

"Because researchers dedicated to chronic pain are biased toward central plasticity, they never understood our work," Ferreira says. "When the studies are isolated from one another, sometimes you can't see the overall meaning, but I expect to put them together." (8)

Philip Downey, *Science Writer*


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