

Of snakes and men: the evolution of ACE inhibitors

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Key words:
ACE-inhibitors,
hypertension,
salt

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Accepted for publication
6th February 2007

JRAAS 2007;8:1–2

Journal of
the Renin-
Angiotensin-
Aldosterone
System
(Including other
Peptidergic Systems)

March 2007
Volume 8
Number 1

Introduction

Angiotensin-converting enzyme (ACE) inhibitors, developed in the late 1960s from the venom of a Brazilian pit viper, have become a mainstay of current medical therapy for essential hypertension, congestive heart failure, and chronic kidney disease. In this essay, we explore the evolutionary theory behind ACE inhibitors (ACE-Is), using the lessons of anthropology to explain why the venom of a deadly pit viper would become a balm for the modern epidemic of hypertension. Our discussion focuses on the role that salt played in the development of the renin-angiotensin-aldosterone system and how humans have not yet evolved to account for their current, relatively high salt diets.

Angiotensin-converting enzyme (ACE) inhibitors were developed in the late 1960s using an extract of the venom of the Brazilian pit viper, *Bothrops jararaca*. This toxin contained, in addition to anticoagulant proteins, bradykinin-potentiating peptides that were potent inhibitors of the ACE. The discovery of these peptides coincided with advances in the understanding of the role of the renin-angiotensin-aldosterone system (RAAS) in blood pressure (BP) regulation. Thus, from a snake's venom spring forth a mainstay of current medical therapy for essential hypertension, congestive heart failure, and chronic kidney disease. Lost amidst the controversy over who principally discovered the ACE inhibitor (ACE-I) and what roles government and industry support played in this discovery¹ is the intriguing question of why a snake's venom would contain an agent that blocks the RAAS.

Like most terrestrial animals, *Bothrops jararaca* evolved in an environment with limited salt. The natural enemies of the Brazilian pit viper evolved under similar environmental, evolutionary pressures. Among these enemies is man – in northern Brazil and southern Venezuela, the species is typified by the Yanomamo Indians. In the 1960s and 1970s, a group of researchers from the University of Michigan, led by the anthropologist Napoleon Chagnon and the geneticist James Neel, extensively studied this tribe. In Chagnon's celebrated ethnography, entitled

Yanomamo, the Fierce People,² the Yanomamo hunter-gatherers emerged as one of the most primitive, culturally intact tribes in existence.

Neel's group focused on the Yanomamo's 'no salt culture' and, in 1975, reported the mean BPs, plasma renin activities (PRAs), and urinary aldosterone excretion levels from a Yanomamo sample population.³ The mean systolic and diastolic BP, across 10-year age groups, ranged from 93.2–108.4 and 58.6–69.4 mmHg, respectively. The mean urinary aldosterone excretion was 74.52 micrograms/24 hours and mean PRA was 13.10 mg/ml/hour. In explaining these findings of low BPs despite high renin and aldosterone levels, the authors wrote: "The chronic elevation of renin (and aldosterone) without hypertension once again emphasises the importance of the level of body sodium in affecting hypertension in man." Indeed, the larger epidemiological study, the INTERNational study of SALT and blood pressure (INTERSALT), has since shown that other rural populations with low salt intake have lower BPs and rates of hypertension than populations with high-salt diets.⁴

Another interpretation of the Yanomamo data is that these hunter-gatherers, like other terrestrial animals living in a low-salt environment, had evolved a RAAS to conserve salt and maintain their BPs at liveable levels. Their elevated renin and aldosterone levels were appropriate evolutionary responses to an environment with sparse salt. Salt only became a staple of the human diet after the emergence of agriculture to enable food preservation. In the Paleolithic, pre-agricultural, period, humans consumed less than one-fourth of the salt that modern Westerners do.⁵ The subsistence patterns of the Yanomamo were pre-agricultural and dictated a reliance on RAAS-dependent normotension to ensure adequate blood flow to all organs.

Back to the Brazilian pit viper: If its prey relies on an effective RAAS to maintain its BP, then a poison that can block the RAAS, and thereby induce hypotension and syncope, would provide a strong selective advantage and likely be a

conserved trait. Over thousands of years, the same environmental pressures that forced the Yanomamo and other terrestrial animals in northern Brazil to evolve a hyperactive RAAS also led *Bothrops jararaca* to conserve an efficient killing mechanism that targeted its enemies' haemodynamic vulnerabilities. The bradykinin-potentiating peptides that would become the first ACE-Is were, in essence, the viper's weapon of choice in a predator-prey arms race.

The Yanomamo provide a glimpse of early human circulatory physiology, specifically how an efficient RAAS evolved in response to the demands of a very low sodium environment. But most humans now live in a very different environmental scenario, with plenty of salt, fat, and calories. How is our physiology responding to this mismatch? Is our relatively new high-salt culture, driven by acquired taste rather than physiologic need, interacting with an ancient salt conservation system to promote illness? If the 'thrifty genes' that our ancestors evolved to conserve nutritional resources are leading to modern epidemics of obesity and diabetes, are their 'thirsty genes,' initially designed to withstand terrestrial environments, now leading to hypertension?

Clinicians who prescribe ACE-Is and other RAAS-blocking agents such as angiotensin receptor

blockers and mineralocorticoid receptor blockers are indirectly addressing these questions because, like *Bothrops jararaca*, they are exploiting evolutionary strategies. Modern hypertension is the kidney's attempt to reconcile a mismatch between conserved RAAS activity and high dietary salt intake – the pressure natriuresis helps re-establish salt balance, albeit at the expense of hypertension-related cardiovascular and renal damage. RAAS-dependent hypertension is also the body's reminder that not all humans have evolved to accommodate salt gluttony. If patients can't heed this advice, then clinicians can opt for another evolutionary remnant, the ACE-Is born from a snake's venom.

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