The High Blood Pressure-Malaria Protection Hypothesis

Julio Gallego-Delgado, Thomas Walther,* Ana Rodriguez*

Rationale: **A recently proposed hypothesis states that malaria may contribute to hypertension in endemic areas,[1] but the role of angiotensin II (Ang II), a major regulator of blood pressure, was not considered. Elevated levels of Ang II may confer protection against malaria morbidity and mortality, providing an alternative explanation for hypertension in malaria endemic areas.**

Objective: **To discuss a possible alternative cause for hypertension in populations who have been under the selective pressure of malaria.**

Methods and Results: **We reviewed published scientific literature for studies that could establish a link between Ang II and malaria. Both genetic and functional studies suggested that high levels of Ang II may confer protection against cerebral malaria by strengthening the integrity of the endothelial brain barrier. We also describe strong experimental evidence supporting our hypothesis through genetic, functional, and interventional studies.**

Conclusions: **A causal association between high levels of Ang II and protection from malaria pathogenesis can provide a likely explanation for the increased prevalence in hypertension observed in populations of African and South Asian origin. Furthermore, this potential causative connection might also direct unique approaches for the effective treatment of cerebral malaria. (*Circ Res*. 2016;119:1071-1075. DOI: 10.1161/CIRCRESAHA.116.309602.)**

Key Words: angiotensin II ■ blood pressure ■ epidemiology ■ hypertension ■ malaria

For decades, researchers have been fascinated by the idea of a causative connection between hypertension and malaria as the prevalence of hypertension is higher in populations who have been exposed to malaria for long periods. A recently published hypothesis in this journal proposes that malaria is a cause for hypertension in low- and middle-income countries, where this infection is endemic.[1] This hypothesis is based primarily on 3 associations of malaria with: (1) hypertensive disorders in pregnancy, (2) stunting and malnutrition in childhood that are, in turn, associated with high blood pressure later in life, and (3) with elevated levels of angiopoietin-2 that are also associated with high blood pressure in adults.

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However, epidemiological data indicate that individuals with African and South Asian genetic background also have a higher prevalence of hypertension compared with whites in malaria-free areas, regardless of their socioeconomic status.[2,3] This observation does not support the idea that malaria causes hypertension in low- and middle-income countries because high blood pressure is maintained in these populations after living in malaria-free areas for generations.

Indeed, more frequently occurring hypertension in populations who have strongly experienced the selective pressure of malaria evokes the well-characterized phenomenon of evolutionary adaptation where mutations that increase genetic resistance to malaria are preserved despite detrimental effects on other aspects of human health.[4]

On the basis of genetic and functional evidence linking malaria severity to the most important regulatory factors for blood pressure in humans, the renin–angiotensin system and its principal effector hormone, angiotensin II (Ang II), we propose an alternative hypothesis where hypertension is a lesser evil because it would be compensated by a major survival advantage: the protection against malaria-induced pathology.

Here, we present data to support this hypothesis based on the published literature and our own experimental data in preclinical models of cerebral malaria.

The High Blood Pressure-Malaria Protection Hypothesis

We propose the hypothesis that high levels of Ang II, which cause hypertension, protect against cerebral malaria.

Genetic Evidence

Cerebral malaria is a clinical complication involved in most of the fatalities because of infection with *Plasmodium*

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Nonstandard Abbreviations and Acronyms	
Ang II	angiotensin II
ACE	angiotensin-converting enzyme

falciparum, the malaria parasite causing nearly all the deaths associated with this disease.[5] Cerebral malaria is mediated by the adhesion of parasitized erythrocytes to brain endothelium interrupting blood flow in small brain capillaries. Loss of endothelial cell junctions and ultimately the disruption of the blood–brain barrier are characteristic of cerebral malaria, causing edema and hemorrhages in the brain tissue.[6]

P falciparum malaria has coexisted with humans for more than 50 000 years and has profoundly shaped the genetic composition of our species.[7] It is well known that polymorphisms causing diseases, such as sickle cell, glucose-6-phosphatase deficiency, ovalocytosis, and thalassemia, have been selected for the protection that they confer against severe malaria.[8]

Ang II regulates blood pressure by inducing sustained cellular contraction in vascular smooth muscle cells, which results in increased vascular resistance and consequently in higher blood pressure. One of the main enzymes, which are responsible for the steady state concentration of Ang II, is the angiotensin-converting enzyme (ACE), which converts Ang I into Ang II and thus plays an essential role in the regulation of blood pressure. Polymorphisms in this enzyme lead to elevated circulating levels of ACE[9] and Ang II,[10] which have been associated with higher prevalence of hypertension.[11–13] One of these polymorphisms leading to higher levels of Ang II (the I/D polymorphism in intron 16) has also been associated with mild malaria,[14] suggesting that elevated levels of Ang II are protective against severe malaria.

Another enzyme determining the concentration of Ang II is ACE2, which converts Ang II to Ang (1–7).[10] A polymorphism associated with less ACE2 protein that results in higher Ang II concentrations and hypertension[12] was also associated with mild malaria,[14] again implicating that gene polymorphisms resulting in higher Ang II concentrations protection against more severe forms of malaria.

Functional Evidence

There are different possible mechanisms that could mediate the protective effect of Ang II. The most obvious is the direct killing of *Plasmodium* by Ang II. Although with moderate efficacy, Ang II inhibits *Plasmodium* growth in vitro[15] and in mice.[16] This effect may have relevance in decreasing the parasitic load, which is in turn, associated with the development of cerebral malaria in mice[17] and possibly in humans.[18]

Another possible effect of Ang II in malaria may be mediated by its effects on brain endothelial cells, regulating the integrity of the blood–brain barrier and the susceptibility to cerebral malaria. Ang II binds to 2 receptors, AT1 and AT2, which have counteractive effects in regulating vascular homeostasis and permeability through interendothelial cell junctions[19] and are both expressed in brain endothelial cells.[20] Although the AT2 receptor is mainly expressed in fetal tissues, it has been shown that its expression remains significant in a few tissues during adulthood, including the brain.[21] Moreover, analysis of isolated arteries of human and animal origin suggests that the endothelium is functionally one of the most important sites for AT2 receptor expression.[20]

Although high levels of Ang II are associated with endothelial dysfunction,[22] this effect has been linked to the activation of the AT1 receptor.[23] In contrast, AT2 stimulation has demonstrated to produce a vasodilator effect in the aorta via bradykinin-nitric oxide synthase.[24] Also, AT2 stimulation has a protective role on focal cerebral ischemia by modulating the cerebral blood flow and decreasing superoxide production.[25] In fact, there is growing evidence suggesting a unique protective role of AT2 stimulation in different brain diseases, such as neural injury,[26] ischemia,[27] X-linked mental retardation,[28,29] and Alzheimer disease.[30] Accordingly, AT1 blockers, which tip the balance in favor of stimulation of AT2, have been proposed for the treatment of brain disorders.[31]

Testing the Hypothesis

Genetic and Biological Studies

Similar to the studies in Indian adults,[14] where an association was found between ACE and ACE2 polymorphisms and susceptibility to cerebral malaria, other proteins involved in the synthesis and metabolism/degradation of Ang II, its receptors on endothelial cells (AT1 and AT2), and downstream mediators, could be analyzed for polymorphisms and possible associations with susceptibility to cerebral malaria and their impact on blood pressure.

Following Etyang et al,[1] that malaria is a possible cause of hypertension, it would be expected that individuals who experienced the disease would have higher blood pressure levels than individuals with same genetic background who were not exposed to malaria. Conversely, if malaria has been an evolutionary driving force selecting for genetic predisposition to develop hypertension, both groups should present similar incidence of high blood pressure. The latter one is substantiated by a significant number of epidemiological studies showing elevated blood pressure and higher incidence in hypertension in African Americans who had no contact to malaria for generations. Interestingly, they do not only have a higher burden to hypertension but also have a higher risk of hypertension-related comorbidities as stroke or heart failure,[32] all were significantly promoted by higher Ang II concentrations.[33]

Nevertheless, it could also be that malaria acts in both ways, as a causative agent for individual hypertension and as a genetic driving force to develop high blood pressure in a population exposed to *P falciparum*.

Functional Studies

In vitro studies using human brain microvascular endothelial cells and erythrocytes infected with *P falciparum* have shown that the parasite promotes the disruption of interendothelial cell junctions between these cells.[34] An important role for Ang II in malaria is supported by the finding that the activation of AT2 or blockade of AT1 receptors preserves human brain endothelial cells junctions from the disruption induced by *P.*

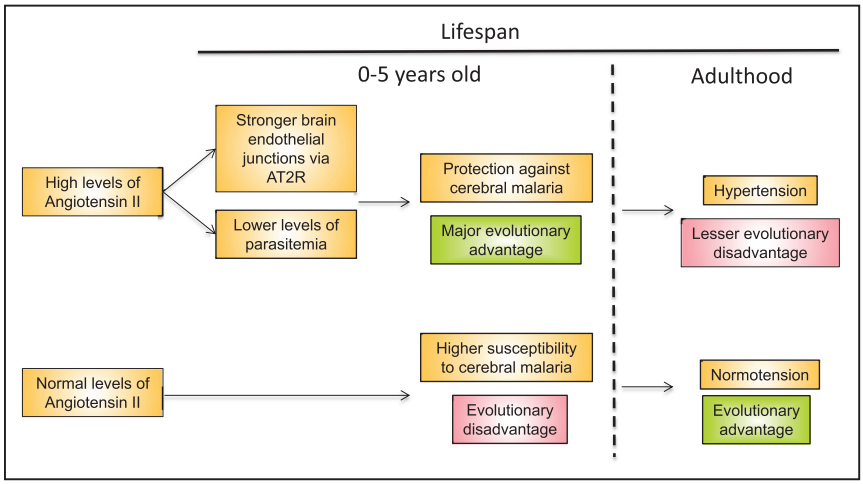

Figure The high blood pressure-malaria protection hypothesis. Malaria has been a major cause of death for humans throughout evolution, with most fatalities occurring in children <5 years of age. Several genetic polymorphisms have been selected because they conferred some degree of protection against malaria. We propose that elevated levels of angiotensin II (Ang II), which cause hypertension, also confer partial protection against cerebral malaria and have, therefore, been preserved in the human populations who have been under the selective pressure of malaria. AT2R indicates AT2 receptor

falciparum in vitro.[35] This protective effect is mediated by the inhibition of β-catenin activation that is otherwise induced by *P. falciparum* and leads to the disruption of endothelial junctions. Recently, a similar protective effect of AT1 blockers and AT2 activators is observed against experimental cerebral malaria in mice.[35]

However, further in vitro and preclinical studies are needed to dissect the role of Ang II on endothelial cells and its effects on barrier permeability mediated through its receptors.

Interventional Studies

After solid evidence for a direct role of Ang II receptors, AT1 and AT2, in the regulation of cerebral malaria is acquired in vitro and in mice models, adjunctive treatment of cerebral malaria patients with blockers of AT1, also called angiotensin receptor blockers or sartans, could be explored immediately, as these drugs have been extensively used as a first line therapy for the treatment of hypertension and are approved for use in humans.[36] Agonists of AT2, which have been developed by different companies over the past decade, would be expected to exert a similar protective role against cerebral malaria, but these compounds are still in an early clinical testing.[37]

These studies would not only provide evidence for the role of Ang II in protection from cerebral malaria but could constitute the basis for establishing an effective adjunctive treatment for cerebral malaria, which is urgently needed.

Implications of the Hypothesis

In the latest years, hypertension is alarmingly increasing in Africa with average blood pressure being significantly higher than in developed countries.[38] Differences found in the response to hypertensive therapies in black people strongly suggest that ethnicity determines blood pressure responsiveness to different classes of treatments.[39–41] If malaria is, at least in part, responsible for genetic polymorphisms in the renin–angiotensin system protecting from severe malaria in endemic areas, those polymorphisms should still be present in blacks. Therefore, it is likely that Africans in endemic areas of malaria will respond similarly to African Americans to antihypertensive therapies.

A causal association between Ang II and the pathogenesis of cerebral malaria would have a major impact in our perspective on cerebral malaria treatment, but also could have important implications on diseases where the integrity of the endothelium plays a critical role in the pathology. Indeed, angiotensin receptor blockers have been already used successfully as adjunctive treatment in infectious diseases, such as Ebola[42] and pneumonia,[43] with significant reductions in mortality in both diseases. Furthermore, it is important to consider that angiotensin receptor blockers, by shifting circulating Ang II to stimulate the AT2 receptor, may be protective against cerebral malaria, whereas ACE inhibitors would reduce the levels of Ang II, possibly increasing the likelihood of developing cerebral malaria on infection with *P falciparum*. In this context, it may be preferable to use angiotensin receptor blockers rather than ACE inhibitors for the treatment of hypertension in malaria endemic areas or at least in hypertensive patients with malaria.

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Disclosures

None.

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Novelty and Significance

What Is Known?

- Populations of African and South Asian origin present elevated blood pressure levels even after living out of these areas for generations.
- Angiotensin II is a major driver of hypertension.
- Polymorphisms in genes that result in higher levels of angiotensin II have been associated with protection against severe malaria.

What New Information Does This Article Contribute?

- Hypertension in populations of African and South Asian origin may be a protective against severe malaria because of its association with elevated levels of angiotensin II.
- The proposed mechanism of protection against severe malaria points to new and unique pharmacological strategies for the treatment of severe malaria.

The causes for the elevated blood pressure that is observed in populations of African and South Asian origin remain unknown. Here, we provide epidemicological, genetic, and experimental evidence that the hypertension protects from severe forms of malaria whereby the reason is not elevated blood pressure but higher concentrations of the peptide angiotensin II that causes vasoconstriction, thirst, and sodium retention, all leading to hypertension. However, the high levels of angiotensin II protect against more severe forms of malaria (eg, cerebral malaria). Thus, evolutionary, people with malaria and higher angiotensin II concentrations were more likely able to generate offspring (because of lower mortality rates), increasing the angiotensin II concentrations in the population and consequently the incidence of higher blood pressure over generations. Thus, the causative cascade of such selection pressure provides a likely explanation for the increased prevalence in hypertension observed in populations of African and South Asian origin. These findings could provide insights into new strategies for the treatment of severe malaria by targeting the angiotensin II receptors without increasing the blood pressure.

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