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NEW HYPOTHESES IN CLINICAL MEDICINE:

The High Blood Pressure-Malaria Protection Hypothesis

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Abstract

Rationale—A recently proposed hypothesis states that malaria may contribute to hypertension in endemic areas¹, but the role of angiotensin (Ang) II, a major regulator of blood pressure, was not considered. Elevated levels of Ang II may confer protection against malaria morbidity and/or mortality, providing an alternative explanation for hypertension in malaria endemic areas.

Objective—To discuss a possible alternative cause for hypertension in populations that 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.

Keywords

Blood pressure; malaria; epidemiology; angiotensin II; angiotensin II receptor blocker; hypertension

INTRODUCTION

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 that

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DISCLOSURES

None.

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 three 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 Angiotensin-2 that are also associated with high blood pressure in adults.

However, epidemiological data indicate that individuals with African and South Asian genetic background also have a higher prevalence of hypertension compared to Caucasians 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, since high blood pressure is maintained in these populations after living in malaria-free areas for generations.

Indeed, more-frequently occurring hypertension in populations that have strongly suffered 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.

Based on genetic and functional evidence linking malaria severity to the most important regulatory factors for blood pressure in humans, the renin-angiotensin system (RAS) and its principal effector hormone, angiotensin (Ang) II, we propose an alternative hypothesis where hypertension is a 'lesser evil' since 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 published literature as well as 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 due to infection with *Plasmodium 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.

Plasmodium 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 plays thus an essential role in the regulation of blood pressure. Polymorphisms in this enzyme lead to elevated circulating levels of ACE⁹ and Ang II¹⁰, which have been associated with higher prevalence of hypertension^{11,12,13}. One of these polymorphisms leading to higher levels of Ang II (the I/D polymorphism in intron 16) has also been associated with mild malaria¹⁴, 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 hypertension¹², was also associated with mild malaria¹⁴, again implicating that gene polymorphisms resulting in higher Ang II concentrations protect 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 vitro¹⁵ and in mice¹⁶. This effect may have relevance in decreasing the parasitic load, which is in turn, associated with the development of cerebral malaria in mice¹⁷ and possibly in humans¹⁸.

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 two receptors, AT1 and AT2, which have counteractive effects in regulating vascular homeostasis and permeability through inter-endothelial cell junctions¹⁹ and are both expressed in brain endothelial cells²⁰. While 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 brain²¹. 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 expression²⁰.

Although high levels of Ang II are associated with endothelial dysfunction²², this effect has been linked to the activation of the AT1 receptor²³. In contrast, AT2 stimulation has demonstrated to produce a vasodilator effect in the aorta via bradykinin-NO synthase²⁴. Also, AT2 stimulation has a protective role on focal cerebral ischemia by modulating the cerebral blood flow and decreasing superoxide production²⁵. In fact, there is growing evidence suggesting a unique protective role of AT2 stimulation in different brain diseases such as neural injury²⁶, ischemia²⁷, X-linked mental retardation^{28,29}, and Alzheimer's disease³⁰. Accordingly, AT1 blockers, which tip the balance in favor of stimulation of AT2, have been proposed for the treatment of brain disorders³¹.

Testing the Hypothesis

Genetic and biological studies—Similarly to the studies in Indian adults¹⁴, 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 as well as their impact on blood pressure.

Following Etyang *et al.*¹, that malaria is a possible cause of hypertension, it would be expected that individuals that suffered 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 Afro-Americans who had no contact to malaria for generations. Interestingly, they do not only have a higher burden to hypertension but also higher risk for hypertension-related comorbidities as stroke or heart failure³², all significantly promoted by higher Ang II concentrations³³.

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 *Plasmodium falciparum*.

Functional studies—In vitro studies using human brain microvascular endothelial cells and erythrocytes infected with *Plasmodium falciparum* have shown that the parasite promotes the disruption of interendothelial cell junctions between these cells³⁴. An important role for Ang II in malaria is supported by the finding that activation of AT2 or blockade of AT1 receptors preserves human brain endothelial cells junctions from the disruption induced by *P. falciparum* in vitro³⁵. 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. Very recently, a similar protective effect of AT1 blockers and AT2 activators is observed against experimental cerebral malaria in mice³⁵.

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 (ARBs) or sartans, could be explored immediately, since these drugs have been extensively used as a first line therapy for the treatment of hypertension and are approved for use in humans³⁶. Agonists of AT2, which have been developed by different companies over the last decade, would be expected to exert a similar protective role against cerebral malaria, but these compounds are still in an early clinical testing³⁷.

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 countries³⁸. Differences found in the response to hypertensive therapies in African American 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 RAS protecting from severe malaria in endemic areas, those polymorphisms should still be present in African Americans. 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, ARBs have been already used successfully as adjunctive treatment in infectious diseases such as Ebola⁴² and pneumonia⁴³ with significant reductions in mortality in both diseases. Furthermore, it is important to consider that ARBs, by shifting circulating Ang II to stimulate the AT2 receptor, may be protective against cerebral malaria, while ACE inhibitors would reduce the levels of Ang II, possibly increasing the likelihood of developing cerebral malaria upon infection with *P. falciparum*. In this context, it may be preferable to use ARBs 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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Nonstandard Abbreviations and Acronyms

Ang	Angiotensin
ACE	Angiotensin converting enzyme
ARBs	Angiotensin receptor blockers
RAS	Renin-angiotensin system

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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 (e.g. 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.

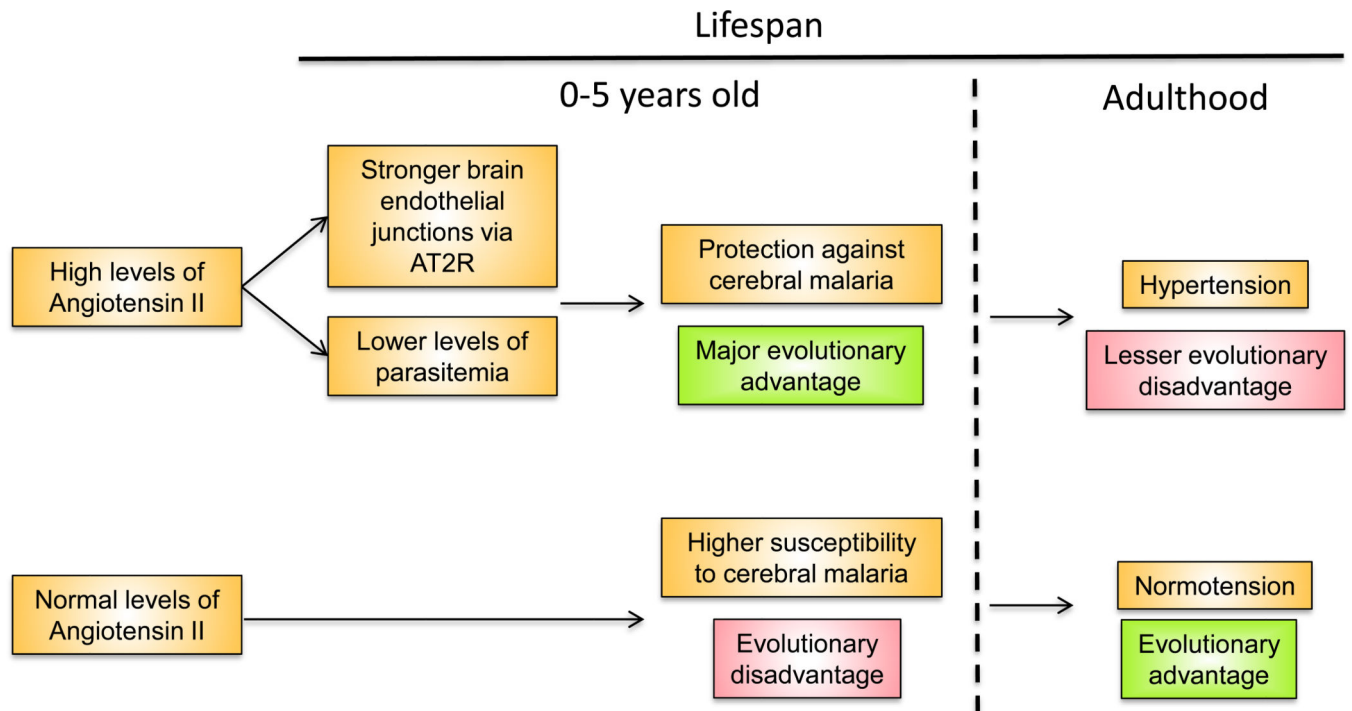


Figure 1. The high blood pressure-malaria protection hypothesis

Malaria has been a major cause of death for humans throughout evolution, with most fatalities occurring in children under 5 years of age. A number of genetic polymorphisms have been selected because they conferred some degree of protection against malaria. We propose that elevated levels of Ang II, which cause hypertension, also confer partial protection against cerebral malaria and have therefore been preserved in the human populations that have been under the selective pressure of malaria.