Angiotensin II–Linked Hypothesis to Understand the Advantage of the Coevolution of Hypertension and Malaria

“Sympathy for the Devil”

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In the article “The high blood pressure-malaria protection hypothesis” published in this issue, Gallego-Delgado et al1 hypothesize that hypertension confers an evolutionary advantage and protection for populations chronically exposed to Plasmodium falciparum infection.1 The authors suggest that hypertension, which is more frequent in the areas with endemic malaria, may protect affected patients from the development of cerebral malaria, which is the most lethal complication of this disease. According to the authors1 both preclinical and clinical evidence support the possibility that the key factor in the hypertension–malaria relationship is angiotensin II (Ang II), whose levels tend to be higher in populations living in endemic areas. Indeed, Ang II seems to have beneficial effects on the brain–blood barrier integrity (most likely by binding to Ang II type 2 receptors [AT2] on endothelial cells), which might exert, through a variety of mechanisms, a cerebroprotective effect during malaria infection.1

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The evolutionary role of the renin–angiotensin system in the development of species is indeed suggested by several considerations. The renin–angiotensin system is a biological system almost ubiquitary in humans body, and it is present in the whole phylogenetic scale of animals from simple organisms to humans.2,3 Its major biological effector in mammals is Ang II. In the evolution of the human species, renin–angiotensin system may have favored the upright posture by counteracting the blood pressure–lowering effect of gravity. It has also represented a major contributing factor in the adjustments of living species to water deprivation, thirst, dramatic environmental change and heat, and blood loss. Ang II acts by binding 2 major receptors coupled to different intracellular signaling pathways: the Ang II type 1 receptor (AT1) and AT2. The AT1 receptors are more represented on cell membranes, their stimulation leading to vasoconstriction, sodium and water retention, blood pressure elevation, trophic effects, and aldosterone release. AT1 receptor stimulation also promotes oxidative and inflammatory processes and cardiovascular remodeling.4 In the 1980s, Ang II has also been suggested to have a protective effect against stroke by causing vasoconstriction of the proximal cerebral arteries and thus prevention of Charcot–Bouchard aneurysms from rupture.5 This hypothesis was later revisited on the basis of clinical trials showing that risk of stroke was reduced by antihypertensive treatments based on the administration of both Ang II–increasing and Ang II–decreasing drugs. When directly comparing Ang II–decreasing drugs (eg, β-blockers) with drugs that reduce binding to AT1 receptors and thus increase unbound circulating Ang II, such as angiotensin receptor antagonists, the last have been associated with a greater cerebroprotective effect and a reduction of stroke, for similar decreases in blood pressure.5,6 The current view is, therefore, that the beneficial effect of Ang II on stroke prevention is more likely related to the binding and stimulation of AT2 on cell of the central nervous system. AT2 receptors can be identified in the adult organisms in the vascular endothelial cells, myocardium, and central and peripheral nerve cells.4 Their main activities are opposite to those of AT1 subtypes and are mostly characterized by promotion of vasodilatation and maintenance of the cardiovascular homeostasis, counterbalancing the effects of AT1.4 In the central nervous system, in particular, the stimulation of AT1 causes disruption of cerebral blood flow, induction of inflammation, and production of reactive oxygen species in the endothelium, leading to tissue ischemia, brain damage, and cell apoptosis.9 In contrast, AT2 mediates vasodilatation and preserves cerebral vasculature. It should be emphasized that the opposite functional effects of AT1 and AT2 are far from having a constant balance, because of a cross talk between AT1 and AT2, because AT1 blockade promote AT2 overexpression.10,11 Brain damage and mortality significantly decreased in animals pretreated with the selective angiotensin receptor antagonist losartan or by the selective AT2 agonist PD 123319, but not with the converting enzyme inhibitor enalapril.12,13 Recent evidence has also shown that AT2 stimulation by a synthetic compound C21 attenuates early mortality and neurological deficits after experimental stroke.17 These results reinforce the authors’ hypothesis that angiotensin receptor antagonists may protect against major cerebral events in hypertension by blocking the binding of Ang II on AT1, thereby increasing AT2 activation (Figure).
Gallego-Delgado et al suggest, in fact, that the balance between AT1 and AT2 activation by Ang II might play a central role during the malaria infection as well. This hypothesis is firstly based on the epidemiological evidence of a higher prevalence of hypertension in the areas where malaria is endemic. Independent of socioeconomic issues, people who derived from an ancestry that has lived and grown for centuries in an area at high rate of malaria contagion generally present a greater prevalence of hypertension but usually develop less severe manifestations of malaria infection. The genome of these families is characterized by specific polymorphisms that cause an increase in Ang II levels. The authors, therefore, suggest that high concentrations of Ang II might be the reason why hypertensive populations usually develop milder form of malaria when infected. Gallego-Delgado et al have previously reported in a rodent model of malaria that increased levels of Ang II result in a moderate decrease in the incidence of cerebral malaria. Recently, preclinical studies have explained, at least in part, the possible underlying mechanisms. Indeed, Ang II can inhibit the \textit{P. falciparum} growth and erythrocyte invasion.\textsuperscript{15} Moreover, Ang II seems to play a beneficial effect on the endothelium of vessels in the central nervous system. It has been suggested that AT2 stimulation might inhibit endothelial dysfunction during malaria infection, thereby preventing the loss of integrity of the blood–brain barrier and avoiding the severe and lethal cerebral infection.\textsuperscript{14} The antioxidant and anti-inflammatory actions of AT2-mediated effects of Ang II may also contribute to the preservation of endothelium and blood–brain barrier.\textsuperscript{16} Finally, treatment of \textit{Plasmodium}-infected mice with losartan decreases endothelial cell migration and lowers disruption of interendothelial cell junctions,\textsuperscript{17} aligned with the hypothesis of a beneficial effect of Ang II/AT2 pathway in malaria severity.

In conclusion, evidence collected to date, as Gallego-Delgado et al suggest, may open a new perspective on the evolutionary beneficial role of hypertension. The authors also propose a preferential use of angiotensin receptor blocker–based therapy in specific conditions, such as malaria. Even though it is too early to propose AT1 inhibitors or AT2 agonists as first-line therapy for the infection by \textit{P. falciparum}, there is in fact a rationale to further investigate the potentially favorable role of the cross talk between AT2 stimulation/AT1 inhibition and its therapeutic effects on diseases of the central nervous system.

**Disclosures**

None.

**References**


Key Words: Editorials ■ angiotensin II ■ angiotensin receptors ■ blood–brain barrier ■ hypertension ■ malaria
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