HHS Public Access

Author manuscript

J Hypertens. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

J Hypertens. 2015 November ; 33(11): 2368–2370. doi:10.1097/HJH.0000000000000724.

A central role of H_4B deficiency in eNOS uncoupling in hypertension, Reply to "Creatine synthesis demands the majority of the bioavailable L-arginine"

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We highly appreciate the quick responce from Mr. Karamat [1]. His letter provides a novel research area in regard to the relationship between creatine kinase (CK) and nitric oxide (NO), and his group have given some evidences that CK system is associated with blood pressure [2, 3]. However, our review mainly focused on the role of H_4B deficiency in eNOS uncoupling in hypertension.

As we discussed in our review [4], H_4B deficiency plays a key role in determining eNOS uncoupling-dependent hypertension, which really exists and has been confirmed by many independent groups including us [5–9]. Therefore, the enzymes involved in H_4B biosynthesis, including de-novo synthetic pathway and salvage pathway, become significantly important for eNOS coupling states. In de novo synthetic pathway, H_4B is formed from guanosine-5′-triphosphate (GTP), through a sequence of enzymatic steps carried out by GTP cyclohydrolase I (GTPCHI), 6-pyruvoyl tetrahydropterin synthase (PTPS) and sepiapterin reductase (SPR) [10]. In the salvage pathway, the exogenous pterin precursor sepiapterin is firstly metabolized by SPR to H_2B, and further to H_4B by dihydrofolate reductase (DHFR) [11]. In hyperphenylalaninemia (hph)-1 mice, which display 90% deficiency of GTPCHI, the intracellular levels of H_4B as well as NO bioavailability are significantly lower in hph-1 mice than in WT mice [12]. In angiotensin II (Ang II)- infused mice, eNOS uncoupling contributes to high blood pressure, where aortic nitric oxide production was markedly decreased. The molecular mechanism involves a rapid and transient activation of endothelial NOX, subsequent H_2O_2-dependent down-regulation of DHFR, and persistent H_4B deficiency [13]. Therefore, DHFR overexpression or folic acid restoration of DHFR function effectively recoupled eNOS to reduce blood pressure [5, 14]. Furthermore, SPR was lost in the endothelium of DOCA-salt-induced hypertensive mice, and combined treatment of H_4B and a NOX inhibitor apocynin fully restored nitric oxide bioavailability. All these evidences emphasize the central role of H_4B for maintaining eNOS coupling in hypertesnion.

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Competing Interests

The authors have no conflicts of interest to report.

On the other hand, we can not deny the possible role of CK system in the development of hypertension. However, it is still unknown whether its effect on hypertension is through affecting NO production. Although creatine synthesis demands nearly 10 times the flux of plasma L-arginine represented by NO synthesis [1], the concentration of plasma L-arginine rarely falls below 60 mmol/l in pathological conditions, which is much higher than the amount need for eNOS (K_m=3 mmol/l). In this way, ADMA is considered as a much more influencing factor than CK. Moreover, there are evidences that multiple pathways for L-arginine uptake are present in vascular cells and L-arginine transport and NO formation are differentially controlled in these cells [15]. For example, the selective stimulation of L-arginine uptake in BAECs shows that L-arginine transport is dissociated from NO generation in these cells [15]. Therefore, the concentration of plasma L-arginine seems not that important. In addition, high levels of NO are known to stimulate apoptosis [16], which should be accurately controlled by the organism.

In conclusion, our review paper is maily focused on a central role of H_4B deficiency in eNOS uncoupling in hypertension. Based on the major regulatory mechanisms, preserving eNOS coupling activity will be considered as a novel therapeutics for the treatment of hypertension.

Acknowledgments

This study was supported by National Institute of Health National Heart, Lung and Blood Institute (NHLBI) Grants HL077440 (HC), HL088975 (HC), HL108701 (HC, DGH), HL119968 (HC), an American Heart Association Established Investigator Award (EIA) 12EIA8990025 (HC), and an AHA Postdoctoral Fellowship Award 14POST20380966 (QL).

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