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Original Research Article

Effect of dietary supplementation of ginger and turmeric rhizomes on ectonucleotidases, adenosine deaminase and acetylcholinesterase activities in synaptosomes from the cerebral cortex of hypertensive rats

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ABSTRACT

Ginger and turmeric rhizomes are used in folk medicine for the treatment of several cerebrovascular diseases with limited scientific basis for their action. Hence, in this study, we investigate the effects of two Zingiberaceae varieties (ginger and turmeric) on ectonucleotidases (NTPDase and 5′-nucleotidase), adenosine deaminase (ADA) and acetylcholinesterase (AChE) activities in synaptosomes of cerebral cortex from L-NAME induced hypertensive rats. The animals were divided into seven groups ($n = 10$): normotensive control rats; hypertensive rats; hypertensive rats treated with atenolol; normotensive and hypertensive rats treated with 4% supplementation of turmeric and ginger rhizomes, respectively. After 14 days of pre-treatment with both rhizomes the animals were induced with hypertension by oral administration of L-NAME. The results revealed an increase of ATP and AMP hydrolysis as well as ADA and AChE activities of cerebral cortex synaptosomes in induced rats when compared with the control. The supplementation of both rhizomes prevented these alterations by decreasing ATP and AMP hydrolysis and ADA and AChE activities in cerebral cortex. In conclusion, this study demonstrated that both rhizomes

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Abbreviations:
ACh, acetylcholine
AChE, acetylcholinesterase
ADAa, denosine deaminase
ADP, adenosine diphosphate
AMP, adenosine monophosphate
AT, atenolol
ATP, adenosine triphosphate
CNS, central nervous system
L-NAME, N_{ω}-nitro-L-arginine-methyl-ester-hydrochloride
NO, nitric oxide
NOS, nitric oxide synthase
RG, red rhizomes
WG, white rhizomes

interfere with the purinergic and cholinergic neurotransmission in cerebral cortex of hypertensive rats. Therefore, we can suggest that both rhizomes exert neuroprotective potential under hypertensive state.

Introduction

Hypertension is one of the major health problems of the Western world. It is a prevailing vascular risk factor for several cerebrovascular diseases and dementia (Duron and Hanon, 2008). Several studies have suggested some possible mechanisms underlying high blood pressure and cognitive impairment (Duron and Hanon, 2008; Lee et al., 2014; Toth et al., 2015) but a pathophysiological mechanistic link is still to be ascertained (Carnevale et al., 2012). Although, the negative impact of hypertension on CNS function is due to pathological alterations of both the large cerebral arteries and the cerebral microvessels (Toth et al., 2015).

The well-established mechanism for maintaining normal blood pressure is by nitric oxide (NO), a potent vasodilator which is produced in the vascular endothelial cells (Moncada et al., 1991). The chronic inhibition of NO produces volume-dependent elevation of blood pressure and its physiological and pathological characteristics resemble essential hypertension (Lerman et al., 2005; Cardoso et al., 2012, 2014). Several studies have administered *in vivo* an inhibitor of nitric oxide biosynthesis, the N-nitro-L-arginine methyl ester hydrochloride (L-NAME), which is an L-arginine analog, to induce hypertension in rats (Furstenau et al., 2008, 2010; Cardoso et al., 2012, 2014).

The brain especially the cerebral cortex is a major target of the deleterious effects of hypertension and is responsible for a large portion of the related mortality and morbidity (Dahlof, 2007; Toth et al., 2015). The existence of memory deficits correlates with the presence of hypertension, and the subsequent pathological changes of ischemic damage in deep cerebral white matter (Vermeer et al., 2003). The white matter damage may contribute to cognitive impairment and its most serious manifestation being dementia (Vermeer et al., 2003). Peoples with controlled hypertension seem to have a lesser prevalence of white matter lesions than peoples with uncontrolled hypertension (Poels et al., 2012).

In the cerebral cortex, important neurotransmitters involved in the process of cognition are acetylcholine (ACh) and adenosine triphosphate (ATP) which are synaptic modulators and paracrine or autocrine signaling substances (Zimmermann, 2008). It is interesting to note that both ATP and ACh are co-released from the same motor nerve endings (Silinsky and Redman, 1996). ATP plays important roles in the cell to cell signaling *via* the activation of specific ionotropic P2X and G protein coupled P2Y receptors (Zimmermann, 2008). It acts as a fast excitatory neurotransmitter, as a presynaptic neuromodulator and it is also involved in neuron–glial interactions with a role in neuronal development and plasticity (Burnstock, 2006; Burnstock and Pelleg, 2015). Furthermore, its breakdown product, adenosine, plays an important modulatory role in neuronal activity and neuroprotective actions in pathological conditions which are mediated by the activation of P1-purinoreceptors (Rial et al., 2014; Ferreira et al., 2015).

Different enzymes carry out the control of signaling events of these molecules in the central nervous system (CNS). The acetylcholinesterase (AChE) enzyme is responsible for the degradation of ACh in the synaptic cleft of cholinergic synapses and neuromuscular junctions into inactive metabolites such as choline and acetate (Lendvai and Vizi, 2008). This enzyme has essential role in regulating many vital functions such as learning, memory, cortical organization of movement and cerebral blood flow control which demonstrates the high degree of importance of ACh as a neurotransmitter target for the study of cerebrovascular diseases associated with hypertension (Lendvai and Vizi, 2008; Cardoso et al., 2014).

The control of the signaling of ATP neurotransmitter are performed by a family of enzymes called the ectonucleotidases, involved in the control of nucleotide and nucleoside levels in the synaptic cleft and in the control of purinergic neuromodulation and neurotransmission (Schetinger et al., 2007; Bagattini et al., 2011). The ectonucleotidase is composed from NTPDase (nucleoside triphosphate diphosphohydrolase) and ecto-5′-nucleotidase. The NTPDase hydrolyses ATP and ADP to AMP (Robson et al., 2006) while ecto-5′-nucleotidase hydrolyse AMP producing adenosine (Sträter, 2006). Another enzyme describe as the last enzyme of the purinergic cascade is the adenosine deaminase (ADA), involves in the conversion of adenosine to inosine, playing an important role in the regulation of adenosine. Since these enzymes contribute to the maintenance of physiological levels of extracellular ATP and