Physiology & Behavior 142 (2015) 66–78

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Melatonin receptor and K_{ATP} channel modulation in experimental vascular dementia

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HIGHLIGHTS

- Renovascular hypertension (2K1C) has induced vascular dementia.
- 2K1C has induced endothelial dysfunction, brain damage & oxidative stress.
- MT_1/MT_2 receptor modulation has attenuated endothelial dysfunction & brain damage.
- K_{ATP} channel modulation has reduced endothelial dysfunction & brain damage.
- Agomelatine & nicorandil have attenuated oxidative stress & offer neuroprotection.

ARTICLE INFO

Article history:
Received 22 February 2014
Received in revised form 3 February 2015
Accepted 4 February 2015
Available online xxxx

Keywords:
Acetylcholinesterase
Agomelatine
Nicorandil
Donepezil
Mitochondrial enzyme complex
Myeloperoxidase

ABSTRACT

Cerebrovascular and cardiovascular diseases are stated as important risk factors of vascular dementia (VaD) and other cognitive disorders. In the central nervous system, melatonin (MT_1/MT_2) as well as serotonin subtype 2C ($5\text{-}HT_{2C}$) receptors is pharmacologically associated with various neurological disorders. Brain mitochondrial potassium channels have been reported for their role in neuroprotection. This study has been structured to investigate the role of agomelatine, a melatonergic MT_1/MT_2 agonist and nicorandil, a selective ATP sensitive potassium (K_{ATP}) channel opener in renal artery ligation (two-kidney-one-clip: 2K1C) hypertension induced endothelial dysfunction, brain damage and VaD. 2K1C-renovascular hypertension has increased mean arterial blood pressure (MABP), impaired memory (elevated plus maze and Morris water maze), endothelial function, reduced serum nitrite/nitrate and increased brain damage (TTC staining of brain sections). Furthermore, 2K1C animals have shown high levels of oxidative stress in serum (increased thiobarbituric acid reactive species—TBARS with decreased levels of glutathione—GSH, superoxide dismutase—SOD and catalase—CAT), in the aorta (increased aortic superoxide anion) and in the brain (increased TBARS with decreased GSH, SOD and CAT). 2K1C has also induced a significant increase in brain inflammation (myeloperoxidase—MPO levels), acetylcholinesterase activity (AChE) and calcium levels. Impairment in mitochondrial complexes like NADH dehydrogenase (complex-I), succinate dehydrogenase (complex-II) and cytochrome oxidase (complex-IV) was also noted in 2K1C animals. Administration of agomelatine, nicorandil and donepezil significantly attenuated 2K1C-hypertension induced impairments in memory, endothelial function, nitrosative stress, mitochondrial dysfunction, inflammation and brain damage. Therefore, modulators of MT_1/MT_2 receptors and K_{ATP} channels may be considered as potential agents for the management of renovascular hypertension induced VaD.

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1. Introduction

Vascular dementia (VaD), manifested by loss of memory and cognitive function resulting from vascular lesions in the brain, is the second-most-common cause of dementia [1]. Cardiovascular diseases are reported to have a negative impact on the brain and contribute to the development of neurodegenerative diseases such as Alzheimer's disease (AD) and VaD [2]. Accordingly, new therapies are urgently required to recover cognitive deficits associated with VaD.

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http://dx.doi.org/10.1016/j.physbeh.2015.02.009
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In the recent times, we have developed VaD with the help of deoxycorticosterone acetate (DOCA)-hypertension, arsenic-toxicity, L-methionine-hyperhomocysteinemia–hyperlipidemia, streptozotocin-diabetes and chronic cerebral hypoperfusion [3–8]. The two-kidney-one-clip (2K1C) model has already been established for the induction of renovascular hypertension [9]. In the present study, we have utilized the 2K1C-hypertension model to induce endothelial dysfunction, brain damage and associated VaD in rats.

Previously, it has been reported that reduction of circulating melatonin in the central nervous system (CNS) is involved in various neurological disorders, including AD and in depressive conditions [10]. Agomelatine is a selective melatonergic (MT_1/MT_2) agonist and a 5-HT_{2C} antagonist [11]. Agonistic modulation of melatonin receptors has been reported to improve locomotor activity and protect cholinergic system [12], as well as attenuation of mitochondrial oxidative damage [12]. Agomelatine has been reported to possess antioxidant [13], anti-inflammatory [14] and memory facilitating properties [12]. Dagyte and colleagues have observed that agomelatine restores hippocampal neuronal activity, increases expression of several neuroplasticity-associated molecules and promotes adult hippocampal neurogenesis [15].

Activation of K_{ATP} channels in the inner mitochondrial membrane of the brain has been reported to play an important role in modulating neuronal excitability, cell survival, cerebral vascular tone [16], and exacerbating brain injury [17]. Opening of K_{ATP} channels has been demonstrated to exert significant neuroprotection in in vivo and in vitro models of Parkinson's disease [18]. Nicorandil, an ATP sensitive potassium (K_{ATP}) channel opener, is known to have protective effects on ischemic injury in the brain [19]. Activated microglial cells are important effectors of demyelination and neurodegeneration, by secreting cytokines and other neurotoxic agents. It has been suggested that microglia express K_{ATP} channels whose pharmacological activation can provide neuroprotective and anti-inflammatory effects [20]. K_{ATP} channel openers have been reported to stimulate hippocampal neurogenesis [21].

In this study, we hypothesized that melatonin receptor (MT_1/MT_2) as well as K_{ATP} channel modulators may exert protective effects on nitrosative as well as oxidative stress, mitochondrial oxidative damage, cholinergic system and neurodegeneration. So modulation of melatonin receptors and K_{ATP} channels may provide benefits in VaD. Thus, melatonin receptor and K_{ATP} channel modulation deserves investigations for their potential in renovascular hypertension induced VaD.

Donepezil, an acetylcholinesterase inhibitor (AChEI), is frequently used for the management of memory deficits and improve cognitive function [22]. We have already reported that donepezil attenuates DOCA-salt hypertension, streptozotocin-diabetes induced as well as another form of VaD [23–25]. In light of the above, the present study has been undertaken to investigate the potential of MT_1/MT_2 receptor agonist (agomelatine) as well as a K_{ATP} channel opener (nicorandil) in renovascular hypertension induced vascular dementia (VaD) in rats.

2. Material and methods

2.1. Animals

Adult male albino Wistar rats (3–5 months old), weighing 200–250 g (purchased from Indian Veterinary Research Institute, Izatnagar, India), were employed in the present study and were housed in animal house with free access to water and standard laboratory pellet chow diet (Kisan Feeds Ltd., Mumbai, India). The animals were exposed to natural light and dark cycle. The experiments were conducted between 9.00 and 18.00 h in a semi-sound-proof laboratory. The animals were acclimatized to the laboratory condition five days prior to behavioral study and were maintained in the laboratory until the completion of the study. The protocol of the study was duly approved by the Institutional Animal Ethics Committee (IAEC) and the care of the animals was taken as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India (Reg. No. 25/230/2011/AWD/CPCSEA).

2.2. Drugs and chemicals

Agomelatine was obtained from Abbott Healthcare Pvt. Ltd., India. Nicorandil was obtained from Torrent Pharmaceuticals, India. Lowry's reagent, 5,5′-dithiobis (2-nitrobenzoic acid) (DTNB), Folin–Ciocalteu reagent, bovine serum albumin (BSA) and N-naphthylethylenediamine were purchased from Sigma Aldrich, USA. 4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), ethylene glycol tetra acetic acid (EGTA), mannitol, glycyl glycine buffer, nicotinamide adenine dinucleotide (NADH), nitroblue tetrazolium (NBT) and cytochrome-C were purchased from SISCO Research Laboratory Pvt. Ltd., Mumbai, India.

All drug solutions were freshly prepared before use. Selection of doses and the dosing schedule were based on the previously published reports. Agomelatine and nicorandil were suspended in 0.5% carboxymethylcellulose (CMC). Donepezil was dissolved in 0.9% saline. Administration of agomelatine (2 and 4 mg kg^{-1} orally) [12], was performed at 15:00 (2 h prior to the dark phase), based on the circadian rhythm resynchronization properties as per the previously published reports [26]. Administration of nicorandil (2 and 4 mg kg^{-1}; orally) [27], and donepezil (0.5 mg kg^{-1} intraperitoneally) [24] was also performed at 15:00, once a day for 24 days to rats. CMC (10 ml kg^{-1}), saline (10 ml kg^{-1}), agomelatine (2 and 4 mg kg^{-1}), nicorandil (2 and 4 mg kg^{-1}) and donepezil (0.5 mg kg^{-1}) per se were administered to rats for 24 days once daily as exact drug administration to 2K1C animals was also for 24 days, starting from the 7th day of surgery till the end of the study (day 30).

2.3. Two-kidney-one-clip (2K1C) renovascular hypertension induced VaD

The 2K1C model has already been established for the induction of renovascular hypertension that increased mean arterial blood pressure (MABP) [9]. Briefly, the animals were anesthetized with chloral hydrate (450 mg kg^{-1}, intraperitoneally) and kept on a heating pad that maintained the body temperature at 37 °C to avoid hypothermia. The left renal artery was exposed through a retroperitoneal flank incision and was carefully isolated from the renal vein, nerves and connective tissues. A silk suture (4–0) was tied around the renal artery close to the abdominal aorta, which resulted in complete occlusion of renal perfusion. Then, the animal was sutured back followed by recovery under care for 24 h. For the sham group, surgeries were performed as described above, except that silk suture ligation was applied to the renal artery then removed prior to the kidney being placed back in its original position. All animals were observed for 4 h following surgery, then individually housed for 24 h and allowed access to standard laboratory feed and water ad libitum.

The animals were used on day 23rd for the behavioral and other assessments. MABP was measured by BIOPAC student lab version 3.7.7; MP36 acquisition system (BIOPAC Systems, Inc., USA).

It has been reported that 2K1C induces hypertension within one week after surgery [28]. Therefore, treatment of agomelatine, nicorandil and donepezil has been started from the 7th day onwards till the end of the study (day 30). Treatment was started from the 7th day because in starting six days after surgery, animals were allowed to develop hypertension as well as to recover from the stress of surgery. Behavioral studies were performed from the 23rd day onwards. 2K1C and 2K1C + drug treatment animals were exposed to the elevated plus maze (EPM) from day 23 to day 25 and to Morris water maze (MWM) from day 26 to day 30. Whereas, vehicles and drug per se treated animals were exposed to EPM from day 17 to day 19 and on MWM from day 20 to day 24 of surgery. After behavioral assessments, all animals were utilized for biochemical estimations.

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