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Neuroprotective effect of anthocyanins on acetylcholinesterase activity and attenuation of scopolamine-induced amnesia in rats

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ABSTRACT

Anthocyanins are a group of natural phenolic compounds responsible for the color to plants and fruits. These compounds might have beneficial effects on memory and have antioxidant properties. In the present study we have investigated the therapeutic efficacy of anthocyanins in an animal model of cognitive deficits, associated to Alzheimer's disease, induced by scopolamine. We evaluated whether anthocyanins protect the effects caused by SCO on nitrite/nitrate (NO_x) levels and Na^+,K^+-ATPase and Ca^{2+}-ATPase and acetylcholinesterase (AChE) activities in the cerebral cortex and hippocampus (of rats. We used 4 different groups of animals: control (CTRL), anthocyanins treated (ANT), scopolamine-challenged (SCO), and scopolamine + anthocyanins (SCO + ANT). After seven days of treatment with ANT (200 mg kg^{-1}; oral), the animals were SCO injected (1 mg kg^{-1}; IP) and were performed the behavior tests, and submitted to euthanasia. A memory deficit was found in SCO group, but ANT treatment prevented this impairment of memory ($P < 0.05$). The ANT treatment *per se* had an anxiolytic effect. AChE activity was increased in both in cortex and hippocampus of SCO group, this effect was significantly attenuated by ANT ($P < 0.05$). SCO decreased Na^+,K^+-ATPase and Ca^{2+}-ATPase activities in hippocampus, and ANT was able to significantly ($P < 0.05$) prevent these effects. No significant alteration was found on NO_x levels among the groups. In conclusion, the ANT is able to regulate cholinergic neurotransmission and restore the Na^+,K^+-ATPase and Ca^{2+}-ATPase activities, and also prevented memory deficits caused by scopolamine administration.

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1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder characterized by a progressive deterioration of memory and of other cognitive functions that lead to dementia (Scarpini and Cogiamanian, 2003; Scarpini et al., 2003). The neuropathological features of this disease include: the extracellular deposition of amyloid plaques, the development of intraneuronal neurofibrillary tangles, neuroinflammation and neuronal loss in limbic cortical regions such as the hippocampus (Lacor, 2007; Palop and Mucke, 2010). Although multiple neurotransmitter systems appear to be affected in AD, the cholinergic dysfunctions have received particular attention and most of the therapies for this disease are directed to this system. The acetylcholinesterase (AChE) is an important enzyme that rapidly hydrolyses acetylcholine (ACh), regulating the levels of this neurotransmitter in the synaptic cleft, thus being involved in cognitive function of learning and memory (Gron et al., 2006; Hut and Van der Zee, 2011). Although AChE has a major role in the regulation of cognitive functions, this enzyme is not limited to cholinergic transmission (Blokland, 1995; Paleari et al., 2008), it is also implicated in several non-cholinergic actions including cell proliferation (Appleyard,

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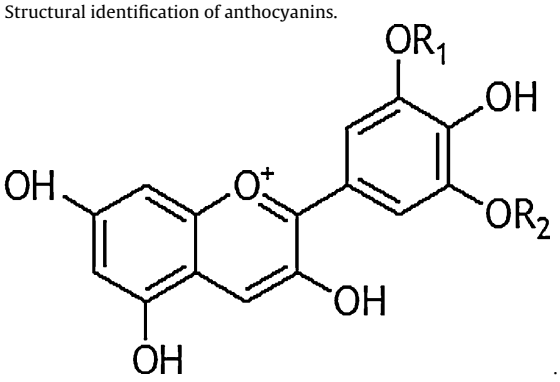
Table 1
Structural identification of anthocyanins.



Anthocyanins	R1	R2	Formula	M.W.
Cyanidin	OH	H	C15H11O6	322.72
Malvidin	OCH3	H	C16H13O6	336.74
Delphinidin	OH	OH	C15H11O7	338.72
Petunidin	OCH3	OH	C16H13O7	352.74
Malvidin	OCH3	OCH3	C17H15O7	366.77

1994) and neurite outgrowth (Chacon et al., 2003). In this way, the AChE activity has been the target of emerging therapeutic strategies for diseases associated to cognitive deficits; and the consumption of red wine with high content in polyphenols has been noted to be beneficial for neurodegenerative diseases, like AD (Ibach and Haen, 2004; Musial et al., 2007).

Anthocyanins (ANT) are flavonoids found in grape juice and red wine, with phenolic groups present in their chemical structure (Table 1) (Veitch and Grayer, 2008; Williams and Grayer, 2004; Yoshida et al., 2009). It is known that ANT are potent antioxidants (Kahkonen and Heinonen, 2003; Kahkonen et al., 2001) and have neuroprotective properties (Del Rio et al., 2010), being beneficial for animal models of Parkinson's (Kim et al., 2010) and Alzheimer's diseases (Shih et al., 2010). In fact, it was shown that ANT improves memory of aged rats, (Andres-Lacueva et al., 2005) and also of elderly humans (Krikorian et al., 2010b).

The Na^+,K^+-ATPase and Ca^{2+}-ATPase are crucial enzymes involved in the control of ionic homeostasis, generation of membrane potential and synaptic neurotransmission. Na^+,K^+-ATPase is responsible for the active transport of Na^+ and K^+ and maintains the ionic gradient for neuronal excitability (Jorgensen et al., 2003; Kaplan, 2002). Moreover, Na^+,K^+-ATPase might play a relevant role in neuronal and synaptic plasticity (Glushchenko and Izvarina, 1997; Scuri et al., 2007) and decreased enzyme activity or expression directly impairs signaling, with deleterious consequences on memory and anxiety in rats (dos Reis et al., 2002; Moseley et al., 2007), increases Ca^{2+} influx in brain slices (Fujisawa et al., 1965) and causes death in rats (Lees et al., 1990). Ca^{2+}-ATPase is responsible for control of intracellular Ca^{2+} homeostasis. Furthermore, the decreased activity of Ca^{2+}-ATPase has been associated with production of reactive oxygen species and neurodegenerative diseases (Clarke and Fan, 2011; Kodavanti, 1999; Skou and Esmann, 1992).

Changes in the activity of Na+,K+-ATPase and Ca2+-ATPase, which are crucial enzymes involved in the control of ionic homeostasis and synaptic transmission, were shown to underlie alterations in memory and anxiety (dos Reis et al., 2002; Moseley et al., 2007) and also with neurodegenerative processes related with excessive production of reactive oxygen species (ROS) and Ca^{2+} homeostasis deregulation (Ashmore et al., 2009; Giacomello et al., 2013).

Scopolamine (SCO) is a non-selective muscarinic receptor antagonist used to induce memory deficits in animal models (Klinkenberg and Blokland, 2010). It was also reported that SCO reduces frontal cortex perfusion in young humans (Honer et al., 1988) and impairs the energetic metabolism, reducing the ATP levels in cerebral cortex of rats (Blin et al., 1994; Ray et al., 1992). Mitochondrial dysfunction and ATP levels reduction are pathological events associated with neurodegenerative diseases, linked to cognitive decline, like AD (Ferrer, 2009; Hauptmann et al., 2009).

In this context, since ANT has an important function as antioxidant and neuroprotective compound, in this study we investigated whether this natural compound is able to prevent memory deficits found in animals administrated intraperitoneally with SCO. Moreover, we evaluated the nitrite/nitrate (NO_x) levels, as well as the activities of enzymes important for neurotransmission such as AChE, Na^+,K^+-ATPase and Ca^{2+}-ATPase, which are known to be altered in Alzheimer's disease.

2. Materials and methods

2.1. Chemicals

Acetylthiocholine, Trizma Base, Acetonitrile, Percoll, Coomassie Brilliant Blue G and Scopolamine (SCO) were purchased from Sigma Chemical Co (St Luis, MO, USA). Anthocyanins were purified from grape skin (AC-12-R-WS-P/10120/Gin:601412) and are commercially available by Christian Hansen A/S. All other reagents used in the experiments were of analytical grade and of the highest purity.

2.2. Animals

Male Wistar rats (3 month year old) weighing 350–400 g were used in this study. They were kept in the Central Animal House of Federal University of Santa Maria in colony cages at an ambient temperature of 25 ± 2 °C and relative humidity 45–55% with 12 h light/dark cycles, with free access to standard rodent pelleted diet and water *ad libitum*. All procedures were carried out according to NIH Guide for Care and Use of Laboratory Animals, and Brazilian Society for Neuroscience and Behavior (SBNeC) recommendations for animal care. This work was approved by the ethical committee of Federal University of Santa Maria (23081.003601/2012-63).

2.3. Drug administration

The animals were divided into two groups of analysis; the first analysis consisted in treat 7–10 animals per group with anthocyanins (200 mg kg^{-1} body weight; by gavage around 10 a.m.) for 7 days, and in last day the animals received anthocyanins 30 min before the training in inhibitory avoidance apparatus. Scopolamine (1 mg kg^{-1}) was dissolved in saline and injected intraperitoneally (i.p.) 30 min after the training in inhibitory avoidance apparatus, as previously described (Ali and Arafa, 2011; Marisco et al., 2013); the second group of animals were submitted to same treatment and sacrificed 2 h post training, with seven animals per group (see Scheme 1). The dose of anthocyanins used was chosen on the basis of previous studies indicating neuroprotection (Gutierres et al., 2012b; Manach et al., 2004; Saija et al., 1990; Varadinova et al., 2009). In addition, the daily intake of anthocyanins in residents of the United States is estimated to be about 200 mg or about 9-fold higher than that of other dietary flavonoids, and this also served as a basis for this study (Manach et al., 2004; Wang and Stoner, 2008).

2.4. Behavioral analysis

2.4.1. Inhibitory avoidance task

In the last day of treatment with anthocyanins (7th day), the animals were trained in a step-down inhibitory avoidance apparatus, as previously described (Marisco et al., 2013; Rubin et al., 2000b), and 30 min after this training received scopolamine (1 mg kg^{-1}; IP).

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