



## Grape juice increases the BDNF levels but not alter the S100B levels in hippocampus and frontal cortex from male Wistar Rats

CAROLINE DANI<sup>1,2</sup>, ANA CRISTINA ANDREAZZA<sup>3</sup>, CARLOS ALBERTO GONÇALVES<sup>4</sup>,  
FLÁVIO KAPIZINSKI<sup>4</sup>, JOÃO A.P. HENRIQUES<sup>1</sup> and MIRIAN SALVADOR<sup>1</sup>

<sup>1</sup>Instituto de Biotecnologia, Universidade de Caxias do Sul/UCS, Rua Francisco  
Getúlio Vargas, 1130, 95070-560 Caxias do Sul, RS, Brazil

<sup>2</sup>Centro Universitário Metodista IPA, Rua Joaquim Pedro Salgado, 80, Rio Branco, 90420-060 Porto Alegre, RS, Brazil

<sup>3</sup>Department of Psychiatry, University of Toronto, 1 King's College Circle, Toronto, ON, M5S 1A8 Canada

<sup>4</sup>Universidade Federal do Rio Grande do Sul/UFRGS, Avenida Ramiro Barcelos, 2350, 90035-903 Porto Alegre, RS, Brazil

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### ABSTRACT

Several studies have shown that a high consumption of vegetables and fruits is consistently associated with a low risk of oxidative stress-induced diseases, which includes some degenerative diseases such as amyotrophic lateral sclerosis, Alzheimer and Parkinson. Therefore, the objective of this study is to verify the effects of conventional and organic grape juice in the modulation of the neurotrophic factor (BDNF) and astrocytic markers protein (S100B) in hippocampus and frontal cortex of Wistar rats. In this study, 24 male Wistar rats were divided into three groups. To the first one, it was given organic purple grape juice; to the second, conventional grape juice, while the last one received only saline. After 30 days, all rats were sacrificed and hippocampus and frontal cortex were dissected. The animals that received organic and conventional grape juice showed, in frontal cortex, an elevated BDNF levels in relation to saline group. However, S100B levels did not change. These results showed that grape juices are able to modulate important marker in brain tissue, and could be an important factor to prevent brain diseases.

**Key words:** brain, grape juice, neuroprotection, polyphenol.

### INTRODUCTION

Several studies have shown that a high consumption of vegetables and fruits is consistently associated with the protection to some important diseases (Castro et al. 2013, Mamluk et al. 2016, Mennella et al. 2016), probably by the antioxidant and anti-inflammatory properties of the polyphenolic compounds found in these fruits and vegetables

(Rice-Evans and Miller 1996). Grape juice is a very rich source of polyphenols, such as flavonoids, anthocyanins, and resveratrol (Dani et al. 2007). Grape juices could be obtained from organic or conventional vineyards (Dani et al. 2007). Organic grape juice is the juice produced with grapes cultivated without pesticides or genetic engineering, certify as an organic product, while the conventional juice is produced with traditional grapes, that receive pesticides during their growth. Other studies from our group showed that purple

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Correspondence to: Caroline Dani  
E-mail: [carolinedani@yahoo.com.br](mailto:carolinedani@yahoo.com.br)

grape juices, both organic and conventional, were capable to reduce the oxidative stress induced by carbon tetrachloride (CCl<sub>4</sub>) in hippocampus, cortex, striatum and substantia nigra in rats (Dani et al. 2008), and the grape juice improved the antioxidant defense in brain damage provoked by a high fat diet (Cardozo et al. 2013). It was already demonstrated that Concord grape juice is beneficial to reverse the course of neuronal and behavioral aging in rats (Shukitt-Hale et al. 2006), and in humans this juice was capable to improve the memory and cognitive function for older adults with early memory decline (Krikorian et al. 2010) and also in older adults with mild memory decline (Krikorian et al. 2012).

BDNF is a dimer protein that plays an important role in neuroplasticity and neuronal maturation (Poo 2001, Suzuki et al. 2014) as well exert an important role in both learning and memory abilities (Binder and Scharfman 2004). It is found throughout the brain, especially in some specific regions like the hippocampus (Binder and Scharfman 2004). Indeed, by the fact that BDNF can be found peripherally, cross the blood brain barrier and have peripheral levels that present a strong correlation with the level of cerebrospinal fluid (Pan et al. 1998), this has been used as a biomarker in clinical studies. It is involved in development, maintenance and function of the central nervous system (Yamamoto et al. 1996) BDNF is the most widely distributed neurotrophic factor in the central nervous system (CNS), and performs many biological functions such as neural survival, differentiation, and plasticity (Qian et al. 2007).

S100B is a calcium binding protein physiologically produced and released mainly by astrocytes in CNS (Sorci et al. 2010). Increase in S100B may reflect either glial damage or it may belong to a body of astrocytic reactions to neural injury (Donato et al. 2013). To date, there are no study showing neuronal protection and/or modulation by the grape juices on brain-derived neurotrophic fac-

tor (BDNF) and S100 calcium binding protein B (S100B) content.

The aim of this study was to evaluate whether organic and conventional purple grape juices have the ability to alter the BDNF and S100B content in frontal cortex and hippocampus.

#### MATERIALS AND METHODS

Twenty-four male Wistar rats (60 days-old, 200±50 g) from our breeding colony were used in these experiments. The animals were handled under standard laboratory conditions of a 12-h light/dark cycle and fixed temperature (25±2°C). Food and water were available *ad libitum*. All experimental procedures were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals with the approval of the local ethics committee.

The animals were randomly allocated into one of the three experimental groups (n=8 per group). Group 1 served as control and received only saline, and conventional or organic purple grape juices were given to groups 2 and 3, respectively. Grape juice samples used in this study were produced from *Vitis labrusca*, variety Bordo, vintage 2005. The organic juices were obtained from Cooperativa Aecia (Antonio Prado, Brazil) which received the ECOVIDA certificate. ECOVIDA is a certificate to the organic agriculture, this is an associative system when there are some participants that are responsible to analyze and verify if all parameters are in accordance to the organic law. The certification will take to the company from a kind of certify organization, namely *Opacs*, and this organization is in accordance to the Brazilian Agriculture Ministry. The conventional juices were obtained from Vinhos Monte Reale (Flores da Cunha, RS, Brazil). Total phenolic content measured according to Singleton et al. (1999) and resveratrol and anthocyanidins amounts of the two purple grape juices were measured by HPLC and are presented in Table I.

TABLE I

**Total phenolic content and main phenolic compounds in organic and conventional grape juices.**

	Organic grape juice	Conventional grape juice
Total phenolic content (mg catechin/mL)	262.50±0.70	119.59±3.53*
Catechin (ppm)	33.89±1.82	2.06±0.15*
Epicatechin (ppm)	2.72±0.22	22.13±1.92*
Resveratrol amount (ppm)	0.213±0.005	0.075±0.010*
Cyanidin (ppm)	11.79±0.42	0.76±0.04*
Delphinidin(ppm)	26.30±1.15	4.10±0.40 *
Peonidin(ppm)	19.21±1.43	8.59±0.82 *
Malvidin(ppm)	232.46±4.25	95.26±1.95 *

Data are showed as media±sd \*p<0.05 if compared between organic and conventional grape juice, analyzed by *t* test. Data adapted from Dani et al. (2007).

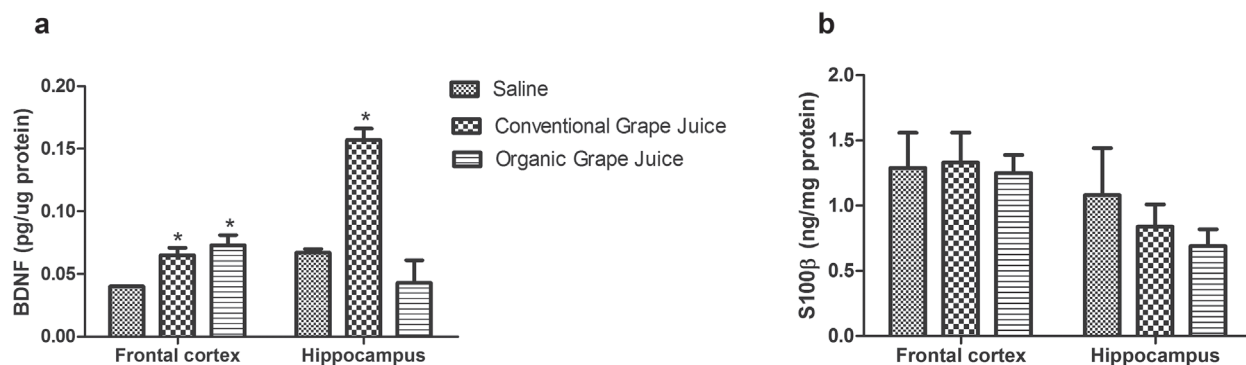
The doses of grape juice were determined by calculating the average amount of juice that would be consumed daily (about 500 mL) by a 70 Kg human person (Park et al. 2003). Juices were administered to the rats (7 µl of grape juice/g of body weight) by gavage twice a day. During the experiment, the amount was adjusted according to the animals' weight. On the 30<sup>th</sup> day, the animals were anesthetized, and then, the animals' blood was withdrawn by cardiac puncture, kept in heparin tubes and stored at -70°C until analysis.

BDNF levels in pre-frontal cortex and hippocampus were measured with sandwich-ELISA, using a commercial kit according to the manufacturer instructions (Chemicon, USA) (Tramontina et al. 2009). Serum S100B was measured by ELISA, as described previously (Tramontina et al. 2002). Total protein was measured by Lowry's method using bovine serum albumin as a standard (Lowry et al. 1951)

## RESULTS AND DISCUSSION

BDNF modulates neuronal plasticity, inhibits cell death cascades, and increases the cell survival proteins that are responsible for the proliferation and maintenance of CNS neurons (Yuluğ et al. 2009). In this sense, we observed that both grape juices, important polyphenols sources, increased the lev-

els of BDNF in frontal cortex. In hippocampus this parameter was significantly increased in the animals treated with conventional grape juice (Figure 1a). Several studies have shown that different polyphenols, including flavonoids such as genistein, quercetin, isorhamnetin (a flavonolaglycone) from *Ginkgo biloba* plant and acetylated flavonoid glycosides from *Scopariadulcis*, as well as resveratrol (the stilbenoid compound present in grapes and red wine) cause a significant enhancement of neurotrophin (nerve growth factor [NGF] and brain-derived neurotrophic factor [BDNF])-mediated neurite outgrowth in PC12 cells (Nakajima et al. 2011, Xu et al. 2012, Li et al. 2004, Zhang et al. 2012). Interestingly, in the hippocampus we observed that only the conventional grape juice increased the BDNF level, this result could be explained by the epicatechin level. According to the literature, several factors may influence grape juice nutritional analyses, such as grape variety, soil, climate, processing methods, etc. (Fuleki and Ricardo-da-Silva 2003). These differences could be observed in the literature, for example, Dani et al. (2007) observed that the conventional purple grape was richer in epicatechin levels than the organic one, however, Toaldo et al. (2015) showed that the organic one was richer in epicatechin level than the conventional but they analyzed grape juice from other Brazilian region and different kind of grapes.



**Figure 1** - BDNF (pg/ug protein) (a) and S100B content (ng/mg protein) (b) in cortex and hippocampus in rats treated with or without conventional grape juice (CGJ) and organic grape juice (OGJ). Data are shown as media $\pm$ EP.  $\neq$  Different letters indicate significant differences using the analysis of variance (ANOVA) and Tukey post-test ( $p \leq 0.05$ ); \* $p < 0.05$  if comparing with the organic group, analyzed by t test.

The epicatechin and catechin are compounds from the flavanol group. The increase observed only by conventional grape juice, could be explained because the higher epicatechin content could represent an important effect in this neurotrophin, showing also anxiolytic and antidepressive effect in different models (Stringer et al. 2015, Lima et al. 2016). Lima et al. (2016) showed that BDNF levels in the hippocampus were increased by a polyphenols source (hydroalcoholic extract of *Cocos nucifera* husk fiber), suggesting an antidepressant-like effect. In this study they attributed the effect to the presence of phenols in the extract, such as epicatechin (flavanol) and chlorogenic acid. Flavonoids, a large part of polyphenols obtained from plants, are speculated to be effective in the treatment of several CNS disorders such as depression (Donato et al. 2014, Souza et al. 2013). In addition, evidence suggests that natural products rich in flavonoids, which increase the BDNF levels, are promising therapeutic targets for the treatment of depression (Stringer et al. 2015).

Van Praag et al. (2007) showed that consumption of (-)-epicatechin increases memory function, hippocampal angiogenesis, and neuronal spine density. According to this authors, some studies in humans show that (-)-epicatechin-rich foods and purified (-)-epicatechin, by cocoa beverage, showed enhanced cortical blood flow (Fisher et al. 2006,

Francis et al. 2006). According to Gage (2000) and Pereira et al. (2007), the increased cerebrovascular function, especially in the hippocampus, a brain region important for memory, may facilitate adult neurogenesis. Our results in hippocampus could be explained by Praag et al. (2007), these authors showed that the hippocampus is particularly responsive to the effects of flavanols. According to microarray analysis of gene expression in hippocampal tissue after 6 weeks of daily flavanol consumption showed that (-)-epicatechin treatment alone, without running, resulted in an upregulation (and downregulation) of genes that did not change when (-)-epicatechin was combined with running. According to this study, the expression of genes associated with learning, synaptic plasticity, and angiogenesis was increased, whereas genes relevant to learning deficits and neurodegeneration were decreased.

The S100B levels did not present differences among the groups (Figure 1b). Similar to this result, Vieira de Almeida et al. (2008) observed that in astrocytes cultures the resveratrol, an important antioxidant, did not affect basal S100B secretion, showing different results according to the treatment. However, in other study with vitamin E, in a pathological aging mouse model, this compound was capable to increase the S100B (Bialowas-McGoey et al. 2008). The same result

was observed in a study with (-)-epicatechin-3-gallate (ECG) in C6 glioma cells. In this study ECG induces a significant improvement in glutamate uptake and S100B secretion in C6 cells, indicating that ECG could contribute to the neuroprotective role of astroglial cells (Abib et al. 2008).

Vieira de Almeida et al. (2008) observed that the S100B secretion was transiently increased (first hour) after H<sub>2</sub>O<sub>2</sub> insult, provoked probably by the oxidative damage. Conversely, when astrocytes were preincubated with resveratrol a decrease was observed in S100B secretion. When these authors incubated only with resveratrol, they observed that the resveratrol did not change S100B secretion during the first hour of insult, but induced a late increment (24 h afterwards) of extracellular levels of S100B. According to these authors, there is a limited knowledge about the mechanism of S100B secretion, as well as how the molecular signaling involved contributes to maintaining this doubt, however, they suggested that resveratrol stimulates S100B secretion, during the long-term, which, in turn, stimulates neuronal survival and activity during brain injury and recovery. This fact could explain our results, in our study we do not have a brain injury neither we tried to recover some damage, and maybe for this reason we do not see any change on S100B levels. Also, the absence of difference between the groups could be explained by the resveratrol amount. Vieira de Almeida et al. (2008) in a study with cells, and Meng et al. (2014) in a study with intraperitoneal injection in rats, showed effect in the S100B levels using almost 4.5mg/day of resveratrol. However, in our study the rats received almost 0.5 mg/day by the grape juice ingestion (gavage). The amount of this polyphenol and the treatment way could explain the difference observed in these studies, and could help indicating other studies to understand better the difference.

The neuroprotection by polyphenols source has been published in the last 10 years in scientific

literature. Joseph et al. (1999) showed in their study that the animals supplemented with strawberry, blueberry and spinach showed improved working memory (short-term memory). And in other study only with blueberry supplementation, the authors showed an alteration in extracellular signal regulated kinase (ERK), that may also increase hippocampal neurogenesis, suggesting that at least part of the efficacy of the blueberry supplementation may be responsible to enhancing neuronal function in areas of the brain affected by aging or disease (Casadesus et al. 2004). Recent studies showed that the grape juice was capable of improving the memory and the cognitive function in rats and humans (Shukitt-Hale et al. 2006, Krikorian et al. 2010, 2012) and also studies from our group showed an important neuroprotective action in rats that received daily purple grape juice (Dani et al. 2008, 2009, Rodrigues et al. 2012). In this way, we concluded that the grape juice, conventional and organic, could be an important alternative to promote a neuroprotection. This is the first study to show that the grape juice could increase the BDNF levels in brain, supposing that this beverage could be an alternative to improve the memory and also exert an antidepressive effect, according to the literature.

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