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Novel application of brain-targeting polyphenol compounds in sleep deprivation-induced cognitive dysfunction

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ABSTRACT

Sleep deprivation produces deficits in hippocampal synaptic plasticity and hippocampal-dependent memory storage. Recent evidence suggests that sleep deprivation disrupts memory consolidation through multiple mechanisms, including the down-regulation of the cAMP-response element-binding protein (CREB) and of mammalian target of rapamycin (mTOR) signaling. In this study, we tested the effects of a Bioactive Dietary Polyphenol Preparation (BDPP), comprised of grape seed polyphenol extract, Concord grape juice, and resveratrol, on the attenuation of sleep deprivation-induced cognitive impairment. We found that BDPP significantly improves sleep deprivation-induced contextual memory deficits, possibly through the activation of CREB and mTOR signaling pathways. We also identified brain-available polyphenol metabolites from BDPP, among which quercetin-3-O-glucuronide activates CREB signaling and malvidin-3-O-glucoside activates mTOR signaling. In combination, quercetin and malvidin-glucoside significantly attenuated sleep deprivation-induced cognitive impairment in -a mouse model of acute sleep deprivation. Our data suggests the feasibility of using select brain-targeting polyphenol compounds derived from BDPP as potential therapeutic agents in promoting resilience against sleep deprivation-induced cognitive dysfunction.

1. Introduction

Chronic sleep loss is a common problem in our society; an estimated 50–70 million adults in the United States have sleep or wakefulness disorder (Institute of Medicine, 2006). Insufficient sleep is co-morbid with chronic problems such as heart disease, kidney disease, high blood pressure, diabetes, obesity, and mental illness (Ford and Kamerow, 1989; Gillin, 1998; Knutson and Van, 2008; Hirotsu et al., 2010; Vijayan, 2012; Palagini et al., 2013; Najafian et al., 2013). Sleep loss can also contribute to irritability, aggression, inattentiveness, and diminished psychomotor vigilance (Rajaratnam, 2001; Van Dongen et al., 2003; Kamphuis et al., 2012). The negative impacts of sleep loss on physical and mental health place a strain on our healthcare system (Kapur et al., 2002) and a large financial burden on our economy (Goel et al., 2009). Unfortunately, many people are unable to obtain sufficient sleep on a daily basis. Therefore, it is important to explore the molecular and cellular impacts of sleep loss in an effort to identify novel therapeutic approaches to counteract these effects.

A number of studies indicate that sleep deprivation (SD) disrupts the consolidation period and impairs memory (Fishbein, 1971; Graves et al., 2003). It has been reported that SD inhibits

Abbreviations: AD, Alzheimer's disease; BDPP, bioactive dietary polyphenol preparation; BW, body weight; cAMP, cyclic adenosine monophosphate; CREB, cAMP-response element-binding protein; EC, epicatechin; Glc, glucoside; Gluc, glucuronide; GSE, grape seed extract; LTP, long-term potentiation; MeO, Methyl-O; MRM, multiple reaction monitoring; mTOR, mammalian target of rapamycin; PAC, proanthocyanidins; PKA, protein kinase A; SD, sleep deprivation.

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the induction of long-term potentiation (LTP) in the hippocampus of rodents (Campbell et al., 2002) and that the LTP deficit induced by SD may be rescued by increasing cAMP/PKA signaling (Vecsey et al., 2009), which is known to play an important role in memory consolidation. Recent studies suggest multiple molecular mechanisms by which SD disrupts memory consolidation, including down-regulation of the cAMP-response element-binding protein (CREB) and down-regulation of mammalian target of rapamycin (mTOR) signaling (Vecsey et al., 2012).

Synaptic efficacy mediating memory storage requires the activation of specific gene expression programs. For example, CREB signaling is essential for long-lasting changes in synaptic plasticity that mediate the conversion of short-term memory to long-term memory. The crucial role of CREB signaling as a cellular mechanism underlying synaptic plasticity and memory has led to the hypothesis that targeting CREB signaling could be a therapeutic approach for memory disorders (Tully et al., 2003). mTOR is a protein kinase involved in translation control and long-lasting synaptic plasticity. While the importance of mTOR signaling in synaptic plasticity has mostly been derived from studies using rapamycin (Beaumont et al., 2001; Tang et al., 2002), more specific genetic targeting of the mTOR signaling cascade has also suggested that mTOR couples receptors to the translation machinery to establish long-lasting synaptic changes (Shima et al., 1998; Pende et al., 2004; Goorden et al., 2007). Disruption of mTOR signaling appears to be a common physiological feature of many neurological disorders, including Alzheimer's disease (AD), autism spectrum disorders, and mental retardation syndromes (Hoeffer and Klann, 2010; Ma et al., 2010).

We previously reported that dietary supplementation with a Bioactive Dietary Polyphenol Preparation (BDPP), a combination of 3 bioactive and commercially available polyphenol products (Concord grape juice, grape seed extract (GSE), and resveratrol), is effective in protecting against diverse mechanisms associated with cognitive function and general brain health (Wang et al., 2008, 2010, 2013; Ho et al., 2013), including oxidative stress and inflammation, and of promoting neuroplasticity. We found that the grape-derived polyphenolic preparation significantly improved cognitive function through the activation of the CREB signaling pathway in a mouse model of AD (Wang et al., 2012). The current study was designed to test the hypothesis that BDPP can attenuate SD-induced cognitive impairments through activation of the CREB and mTOR signaling pathways, and to identify bioactive components of the BDPP that promote resilience against SD-mediated cognitive decline (Fig. 1).

2. Material and methods

2.1. Materials

Food grade resveratrol was purchased from ChromaDex (Irvine, CA). GSE was purchased from Supplement Warehouse (UPC: 603573579173). Only one lot of the resveratrol and one lot of the GSE were used for this particular study. Both resveratrol and GSE have been shown to be very stable when stored at 4 °C in the dark. Welch Concord purple grape juice was purchased at a local market. Quercetin-3-O-glucuronide was purchased from Sigma (St. Louis, MO). Malvidin-3-O-glucoside chloride, delphinidin-3-O-glucoside, and cyanidin-3-O-glucoside chloride were purchased from ChromaDex (Irvine, CA). 3′-O-methyl-epicatechin-5′-O-glucuronide was synthesized as previously described (Blount et al., 2012; Wang et al., 2012). All extraction and LC solvents were HPLC certified and were obtained from J.T. Baker (Phillipsburg, NJ).

2.2. Animals and treatment

C57BL6/J mice were purchased from Jackson's laboratory and housed in the centralized animal care facility of the Center for Comparative Medicine and Surgery at the Icahn School of Medicine at Mount Sinai. For the BDPP treatment, the calculated daily intake of GSE was 200 mg/kg body weight (BW) (Wang et al., 2012; Blount et al., 2012), resveratrol was 400 mg/kg BW (Lagouge et al., 2006; Vingtdeux et al., 2010), and the total polyphenols from juice extract was 183 mg/kg BW (Krikorian et al., 2010). These doses were chosen based on the equivalent doses used in the studies that showed efficacy either in humans or in animal models for each component. Mice were given BDPP delivered through their drinking water for two weeks and the drinking solution was changed once every two days. For short-term dose finding experiments, animals were treated with different doses of quercetin (0.02, 0.2, 2, 20, and 200 mg/kg/day) or malvidin-3-O-glucoside (0.05, 0.5, 5, and 50 μg/kg/day) for 10 days. Animals were then sacrificed and brains were dissected for further analyses. For combinational polyphenol compound treatment, quercetin (0.2 mg/kg/day) and malvidin-3-O-glucoside (5 μg/kg/day) were delivered in the drinking water for 6 weeks. Drinking solution was changed once every two days. All animals were maintained on a 12:12-h light/dark cycle with lights on at 07:00 h in a temperature-controlled (20 ± 2 °C) vivarium, and all procedures were approved by the Mount Sinai ICAUC.

2.3. Sleep deprivation and cognitive assessment by contextual fear conditioning test

A contextual fear conditioning test was performed as previously described (Steele et al., 2013).

During conditioning, mice were trained and tested in conditioning chambers on 3 consecutive days in the cued and contextual fear conditioning paradigm. On Day 1, mice were placed into Context A (gray walls, grid floor, houselights at 50% with lemon scent) and allowed to explore for 180 s (baseline) prior to 3 tone/shock pairings (30 s 4.0 kHz pure tone co; terminating with a 2 s

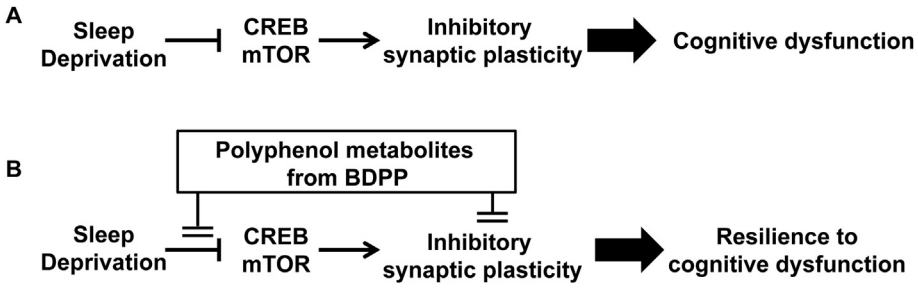

Fig. 1. Scheme of the working hypothesis. (A) Sleep deprivation inhibits CREB signaling and mTOR signaling, thus leading to cognitive impairment. (B) Polyphenol metabolites activate the CREB and mTOR signaling pathways, thus promoting resilience to sleep deprivation-induced cognitive dysfunction.