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Daily consumption of methylene blue reduces attentional deficits and dopamine reduction in a 6-OHDA model of Parkinson's disease

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Highlights

- Daily administration of low-dose methylene blue preserved some signal dopamine cells after 6-OHDA infusion.
- The mild neuroprotection by methylene blue did not yield an improvement of foregaw functions and attentional disengagement.
- However, attentional performance in the five-choice task was significantly improved by the same methylene blue treatment.

Abstract

Recently, alternative drug therapies for Parkinson's disease (PD) have been investigated as there are many shortcomings of traditional dopamine-based therapies including difficulties in treating cognitive and attentional dysfunction. A promising therapeutic avenue is to target mitochondrial dysfunction and oxidative stress in PD. One option might be the use of methylene blue (MB), an antioxidant and metabolic enhancer. MB has been shown to improve cognitive function in both intact rodents and rodent disease models. Therefore, we investigated whether MB might treat attentional deficits in a rat model of PD induced by 6-hydroxydopamine (6-OHDA). MB also has neuroprotective capabilities against neurotoxic insult, so we also assessed the ability of MB to provide neuroprotection in our PD model. The results show that MB could preserve some dopamine neurons in the substantia nigra par compacta when 6-OHDA was infused into the medial forebrain bundle. This neuroprotection did not yield a significant behavioral improvement when motor functions were measured. However, MB significantly improved attentional performance in the five-choice task designed to measure selective and sustained attention. In conclusion, MB might be useful in improving some attentional function and preserving dopaminergic cells in this model. Future work should continue to study and optimize the abilities of MB for the treatment of PD.

Introduction

Currently, Parkinson's disease (PD) is most commonly treated pharmacutically with levodopa (L-dopa), which is effective in alleviating many motor symptoms, however L-dopa is often ineffective in restoring certain cognitive functions compromised in PD (Dujardin et al., 1999, Cools et al., 2003, Lewis et al., 2005, Schneider et al., 2013, Robbins and Cools, 2014). Impairments in attentional processes including attention shifting, selective attention, and sustained attention show varied responses to L-dopa in patients with PD. For example, the reduced ability to shift attention to a new rule or task in PD patients is improved with L-dopa (Cools et al., 2002, Cools et al., 2003). However among patients with mild PD, L-dopa has no impact on selective and sustained attention (Lewis et al., 2005, Moustafa et al., 2008). Furthermore, chronic L-dopa administration in patients and in animal models of PD can result in the development of L-dopa-induced dyskinesia (LID) and impulse control disorders (Kaput et al., 2002, Weintraub, 2008, Leeman and Potenza, 2011, Poletti and Bonuccelli, 2013). In a recent study with a rat model of PD (Smith et al., 2016), we also showed that short-term L-dopa treatment was able to restore motor deficits as well as deficits in attentional shifting but prolonged treatment resulted in LID. In the same study L-dopa treatment did not improve performance deficits in a five-choice task that measures selective and sustained attention. For these reasons it is pertinent to investigate alternative treatments for PD.

Here we investigated the possibility of using methylene blue (MB) to treat behavioral and neuronal deficits in a rat model of PD. MB is an antioxidant compound that also increases cell metabolism through the enhancement of mitochondrial activity at the cytochrome oxidase complex (Lindahl and Öberg, 1961, Scott and Hunter, 1966, Visarius et al., 1997). MB has been shown to enhance cognitive function in both intact and disease-modeled rodents. A low dose of MB can facilitate learning and memory of intact rats in both appetitive and aversive contexts by increasing mitochondrial respiration (Callaway et al., 2002, Callaway et al., 2004, Martinez et al., 2013). Additionally, chronic MB administration enhanced spatial learning in a mouse model of Alzheimer's disease (Medina et al., 2011) and discrimination learning in a rat model of cerebral hypoperfusion (Auchter et al., 2014). MB was shown to restore motor function and preserve striatal cellular function in a common property of neurodegeneration in PD patients as well as animal models of PD (Janetzky et al., 1994, Mizuno et al., 1998, Fukae et al., 2007, Subramaniam and Chesselet, 2011, Subramaniam et al., 2014), and oxidative stress is considered the primary cause of dopaminergic apoptosis in PD (Kumar et al., 1994, Pallanck and Greenamyre, 2006, Schapira, 2008). Therefore, MB has the potential to be an effective neuroprotective agent by enhancing cell metabolism and reducing reactive oxidative species (Poteet et al., 2012). As a proof of concept, infusion of MB into the striatum directly after an infusion of rotenone to the same site significantly attenuated cell loss at the lesion site (Rojas et al., 2009).

However, as of yet, the ability of MB to restore cognitive and motor deficits and/or simultaneously provide neuroprotection in an animal model of PD has not been shown in the same experimental preparation. Therefore we examined the behavioral and neuronal effects of MB in a unilateral rat model of PD. A five-choice task was used to assess selective and sustained attention. In addition, attentional disengagement/shifting and motor functions (cylinder and pasta tests) were examined. The effects of MB on dopamine cell loss were measured in the same rats tested for attentional and motor functions.

Section snippets

Subjects

Sixty-one Sprague–Dawley male rats (350–450 g) were housed in a reversed light cycle (lights off at 10 AM for 10 h). The rats were food restricted to 90% of free-feeding weight for the duration of the five-choice task training. Water access was restricted for 24 h prior to disengagement testing only. All behavioral training and testing occurred during the dark phase of the light cycle. The rats were divided into four groups with a 2 (dopamine or sham lesion) × 2 (MB or vehicle feeding) design. All ...

TH density

The TH optical density was measured for both the intact and lesioned siders and the percentage of TH density on the lesioned side was calculated based on the intact side. The photomicrographs in Fig. 1 show TH-stained sections showing SNc and VTA on the intact (left) and lesioned (right) sides. The scatter plots show percentage of TH density reduction in each rat (Fig. 1). The plots show a wide range of TH density reduction in the lesion groups including some within the range seen among sham ...

Discussion

It is established that 6-OHDA administration causes dopamine depletion by disrupting mitochondrial function (Glinka and Youdim, 1995, Glinka et al., 1996, Glinka et al., 1998) and increasing the presence of reactive oxidative species (Perumal et al., 1989, Perumal et al., 1992, Kumar et al., 1995, Kupsch et al., 2014). Furthermore, the application of antioxidants either in vitro or in vivo after 6-OHDA results in decreased presence of reactive oxidative species (Tiffany-Castiglioni et al., 1982 ...

Author disclosure

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Author contributions

Elizabeth Smith contributed the conception, design and execution of the research project as well executing statistical analyses and writing of the manuscript, data collection and analyses, and manuscript preparation. Madeline Clark, Gwendolyn Hardy, David Kraan, and Elisa Biondo contributed to the execution of the research project. Lawrence Cormack was involved in the interpretation of data and statistical analyses. Francisco Gonzalez-Lima and Marie Monfils were integral in the ...

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New insights into the complex role of mitochondria in Parkinson's disease
2018, Progress in Neurobiology

Citation Excerpt :
... Methylene blue (MB) is a renewable electron cycler in the mitochondrial electron transport chain, with antioxidant and cell energetic enhancing properties (Rojas et al., 2018). Investigators have used acute toxin models of PD to demonstrate that MB has beneficial effects on nigrostriatal dopaminergic cell loss and motor impairment (Rojas et al., 2009; Smith et al., 2017; Wen et al., 2011). In a chronic MPTP/probenecid mouse model it was shown that olfactory dysfunction improved with MB treatment, in comparison to currently available anti-parkinsonian medication, which had no benefit (Biju et al., 2018)....

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Methylene Blue Ameliorates Olfactory Dysfunction and Motor Deficits in a Chronic MPTP/Probenecid Mouse Model of Parkinson's Disease
2018, Neuroscience

Citation Excerpt :
... Indeed, MB has significant beneficial effects in reducing nigrostriatal dopaminergic loss and motor impairment in acute toxin models of PD, such as the rat rotenone model (Rojas et al., 2009; Wen et al., 2011) and rat 6-hydroxydopamine (6-OHDA) model (Smith et al., 2017). Our demonstration of therapeutic efficacy of low-dose MB for motor coordination and nigrostriatal dopaminergic loss in the chronic MPTP/p mouse model align with the studies in rat toxin models (Rojas et al., 2009; Wen et al., 2011; Smith et al., 2017), while providing novel evidence for mitigation of olfactory dysfunction. Notably, olfactory dysfunction is an early warning sign of PD, with olfactory loss occurring in up to 90% of PD patients....

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