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SHORT COMMUNICATION

The Flavonoid Agathisflavone from *Poincianella pyramidalis* Prevents Aminochrome Neurotoxicity

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Abstract

Flavonoids have been suggested to protect dopaminergic neurons in Parkinson's disease based on studies that used exogenous neurotoxins. In this study, we tested the protective ability of agathisflavone in SH-SY5Y cells exposed to the endogenous neurotoxin aminochrome. The ability of aminochrome to induce loss of lysosome acidity is an important mechanism of its neurotoxicity. We demonstrated that the flavonoid inhibited cellular death and lysosomal dysfunction induced by aminochrome. In addition, we demonstrated that the protective effect of agathisflavone was suppressed by antagonists of estrogen receptors (ERα and ERβ). These results suggest lysosomal protection and estrogen signaling as mechanisms involved in agathisflavone neuroprotection in a Parkinson's disease study model.

Keywords Parkinson's disease · Dopamine · Flavonoid · Neuroprotection

Introduction

The discovery of genes associated with familial forms of Parkinson's disease has had a great impact on the basic research for the understanding of their role in the neurodegeneration of nigrostriatal dopaminergic neurons containing neuromelanin. However, mutations in these genes, which include alpha-synuclein, pink-1, parkin, DJ-1, and ATP13A2 that encodes for a component of the lysosomal acidification machinery, cannot explain the degenerative process in the sporadic form of the disease. They provide important information, and it is generally accepted that the aggregation of alpha-synuclein, dysfunction of protein degradation, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, and neuroinflammation are involved in the degeneration of the nigrostriatal dopaminergic neurons (KalinderI et al. 2016; Kazlauskaite and Muqit 2015; Klein and Mazzulli 2018; Hopfner et al. 2020). Lysosome dysfunction appears to be also associated with idiopathic Parkinson's disease since the mutation in GBA1, a gene that encodes for the lysosomal β-glucocerebrosidase, is a risk factor for the development of this disease (Sidransky et al. 2009). Furthermore, it is known that lysosomal function is crucial for the degradation of α-synuclein, and disruptive lysosomal gene variants result in the formation of pathogenic α-synuclein oligomers and fibrils (Klein and Mazzulli 2018). However, what triggers these alterations in dopaminergic neurons containing neuromelanin is still unknown.

It has been proposed that aminochrome is involved in Parkinson's disease pathogenesis. It is naturally existing in the human brain, since aminochrome is formed inside dopaminergic neurons during dopamine oxidation to neuromelanin (Bisaglia et al. 2007; Segura-Aguilar et al. 2014; Herrera et al. 2017). This molecule induces in vitro the death of dopaminergic neurons and induces a slow and progressive loss of dopaminergic neuronal functions in rats. The neurotoxicity of aminochrome in animal model is different from that of

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commonly used exogenous toxins 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and rotenone, since they induce a fast and extensive loss of dopaminergic neurons (Herrera et al. 2017; Segura-Aguilar et al. 2016). Furthermore, in vitro, it induces protein degradation dysfunction of both lysosomal and proteasomal systems (Zhou and Lim 2009; Huenchuguala et al. 2014), mitochondrial dysfunction (Paris et al. 2011), aggregation of alpha-synuclein to neurotoxic oligomers (Muñoz et al. 2015), oxidative stress and endoplasmic reticulum stress (Xiong et al. 2014), formation of adducts with tubulin (Briceño et al. 2016), and neuroinflammation and loss of neurotrophic factors (Santos et al. 2017; de Araujo et al. 2018).

A protective role of flavonoids has been proposed in Parkinson's disease study models induced by exogenous neurotoxins (Wang et al. 2015; Lou et al. 2014). Studies show that quercetin has the ability to regulate the complex-I mitochondrial activity in injured dopaminergic neurons and the ability to eliminate OH radicals resulting from rotenone damage (Karuppagounder et al. 2013). The combined treatment of quercetin and desferrioxamine was effective in reducing the 6-OHDA-induced oxidative stress and neuronal damage by increasing the antioxidant enzymes in the striatum (Haleagrahara et al. 2013). Other studies have showed that rutin, a glycosylated form of quercetin, inhibits 6-OHDA-induced cytotoxicity in PC-12 cells by increasing antioxidant enzymes. Rutin also regulates multiple protective genes, particularly through the suppression of Park2, Park5, Park7, Casp3, and Casp7 (Magalingam et al. 2013).

Some flavonoids act as estrogen-mimic molecule to promote neuroprotection against stroke-related damage, suppression of cancer cell growth, and neurogenesis (Mak et al. 2006; Schreihofer and Oppong-Gyebi 2019; Dos Santos et al. 2018). Agathisflavone (FAB) is a phytoestrogen biflavonoid extracted from *Poincianella pyramidalis* (Tul.), an abundant plant in northeastern Brazil, which presents neurogenic and antioxidant properties (Dos Santos et al. 2018; Andrade et al. 2018), as well as reduced neuronal death induced by glutamate or LPS or IL-1β in primary cocultures of neurons and glial cells (Dos Santos et al. 2018; de Almeida et al. 2020). These neuroprotective effects were associated with anti-inflammatory activity, increased expression of glutamine synthetase (GS), and excitatory amino acid transporter 1 (EAAT1), as well as increased neuroprotective trophic factors such as BDNF, NGF, NT4, and GDNF (Dos Santos et al. 2018). These properties are important for an anti-neurodegenerative drug for Parkinson's disease. However, the effects of FAB have never been investigated in Parkinson's disease study models (Amorim et al. 2018).

Therefore, the aim of this study was to test the ability of agathisflavone (FAB) to prevent lysosomal dysfunction and cell death in a Parkinson's disease study model induced by aminochrome.

Materials and Methods

Cell Culture and Treatments

SH-SY5Y cells were incubated in Dulbecco DMEM/Ham F12–modified medium (Sigma-Aldrich Co., St. Louis, USA), containing 2.7 g/L glucose (Merck, Darmstadt, Germany), 1.2 g/L sodium bicarbonate (Merck, Darmstadt, Germany), and pH 7.4, and supplemented with 10% adult bovine serum (Biological Industries, Cromwell, CT, USA), 10% fetal bovine serum (Biological Industries, Cromwell, CT, USA), 1% non-essential amino acids (Biological Industries, Cromwell, CT, USA), and 1% antibiotic/antimycotic mix (US biological, Swampscott, USA). The cells were cultivated at 37 °C under 5% CO_2.

Aminochrome was prepared by oxidizing dopamine with tyrosinase (Sigma-Aldrich, Cat. nos. T3824-50KU and H8502-10G, respectively) and purified according to what has been previously described by (Huenchuguala et al. 2017). Agathisflavone (FAB) was extracted from *Poincianella pyramidalis* (Tul.) leaves as previously described (Mendes et al. 2000), stored at 100 mM in dimethyl sulfoxide (DMSO; Sigma Chemical Co.) and kept out of light at − 20 °C until use.

Confluent cultures were maintained in culture medium or treated with DMSO (0.01%) under control conditions or treated with FAB (0.1–1 μM) and/or aminochrome (10 μM) for 24 h. In all experiments, no difference was observed between the DMSO-treated group and cells maintained with medium. In order to establish whether the neuroprotective effect of FAB was mediated through estrogen receptors (ER), cultures were treated with specific ER antagonists, starting 2 h before and concomitant with the FAB treatment, for 24 h. In this study, we used selective antagonists for ER-α 1,3-Bis(4-hydroxyphenyl)-4-methyl-5-[4-(2-piperidinylethoxy)phenol]-1H-pyrazole dihydrochloride (MPP dihydrochloride; 2.5 nM, from Sigma) or for ER-β 4-[2-Phenyl-5,7-bis(trifluoromethyl)pyrazolo[1,5- a]pyrimidin-3-yl]phenol phenol (PHTPP) at 1 μM (Tocris). Control cells were treated with the vehicle of dilution of FAB (DMSO 0.01%).

Cell Viability

Cell viability was accessed with the Trypan blue exclusion test in cultures exposed to aminochrome (10 μM) and/or FAB (0.1–1 μM) or exposed to control conditions (DMSO 0.01%) for 24 h. Floating and adherent cells were harvested after trypsinization (trypsin 0.05%, EDTA 0.02%) and centrifuged at 1300×*g* for 5 min. The cells were suspended in 200 μL PBS and stained with Trypan blue (0.1%). The proportion of dead cells was determined by manual count in a hemocytometer.

Lysosomal Function

The cells were stained with 1 μM LysoSensor™ Blue DND-167 (Molecular Probes by Life Technologies, Invitrogen) for 30 min. Afterwards, they were washed 3 times with PBS and immediately observed on a fluorescence microscope (Axiovert-100; Zeiss, Göttingen, Germany) with wavelength of 425 nm. Relative fluorescence was plotted as a percentage of the control.

Statistical Analysis

The data were expressed as the mean ± SEM values, and statistical significance was assessed using analysis of variance (ANOVA) for comparison between multiple groups.

Results

We studied the effect of agathisflavone (FAB) on aminochrome-induced death in SH-SY5Y cells using Trypan blue exclusion test. No toxic effects on cell viability were observed when SH-SY5Y cells were incubated with FAB in concentrations of 0.1 or 1 μM for 24 h. On the other hand, aminochrome (10 μM, for 24 h) induced cell death in SH-SY5Y cells (24.3 ± 3.8%; $p < 0.001$) when compared with SH-SY5Y cells in control conditions (DMSO 0.01%) (0.8 ± 0.3%). This reduction in cell viability was attenuated by the treatment with 0.1 μM FAB (7.6 ± 2%; $p < 0.001$), but not by the treatment with 1 μM FAB (19.3 ± 3%) when compared with SH-SY5Y cells exposed to aminochrome (24.3 ± 3.8%) (Fig. 1).

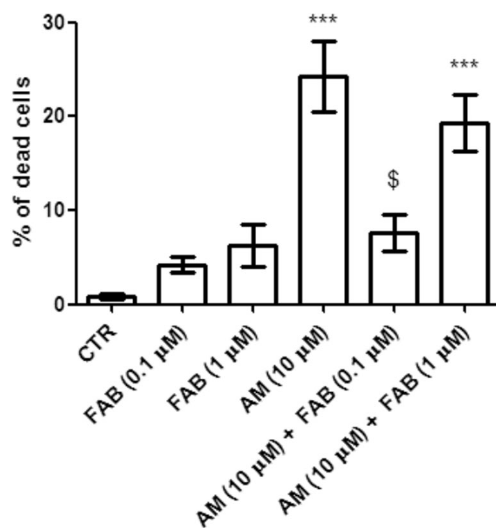
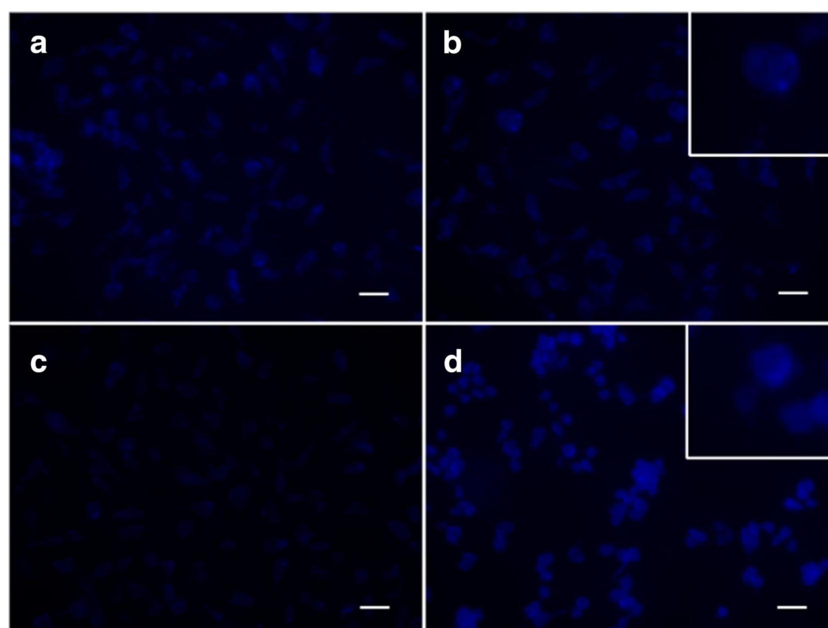


Fig. 1 Agathisflavone (FAB) protects SH-SY5Y cells against aminochrome cytotoxicity. SH-SY5Y cells were exposed to control condition (CTR; DMSO 0.01%) or 0.1–1 μM agathisflavone (FAB) and/or 10 μM aminochrome (AM) for 24 h. Afterwards, cell death was assessed with the Trypan blue exclusion test. The values are the mean ± SEM (n = 6), and the statistical significance was assessed by using one-way ANOVA test. The p value was represented by $^{***}p < 0.001$ compared to CTR group (DMSO 0.01%) and $^{\$}p < 0.05$ compared to AM group (10 μM aminochrome)

Lysosomes play an important role in mitochondrial normal function due to the removal of damaged mitochondria by mitophagy (Segura-Aguilar et al.2018; Huenchuguala et al. 2017); therefore, lysosomes have been suggested as an important target to neuroprotective compounds for Parkinson's disease. In this study, the LysoSensor™ assay revealed that the treatment with agathisflavone (0.1 μM) for 24 h induced an increase in lysosomal acidification in SH-SY5Y cells, measured as fluorescence intensity (426.8% ± 9.1%; $p < 0.01$) when compared with cells in control condition (DMSO 0.01%) (358.3 ± 11.8). It was also observed that cells exposed to aminochrome (10 μM, for 24 h) presented a reduction in lysosomal acidification (167.6% ± 8.8%; $p < 0.001$) when compared to the control condition (DMSO 0.01%). This reduction in lysosomal acidification was inhibited by treatments with 0.1 μM FAB (419.6% ± 21.8%; $p < 0.001$), which presented higher lysosensor fluorescence than that observed in cells under control condition (DMSO 0.01%) (358.3 ± 11.8) (Fig. 2 a and b).

In order to investigate the involvement of the estrogen receptor (ER) signaling on the effects of FAB on neuroprotection, we carried out experiments with antagonists to ERα and ERβ subtypes. We observed that pharmacological antagonism of ERα with methyl-piperidinopyrazole (MPP) inhibited the protective effect of FAB against aminochrome cytotoxicity. Cell death in cultures exposed to aminochrome plus FAB plus MPP (30.2 ± 2.5%) was higher than in cultures treated with aminochrome plus FAB (3.4 ± 1.1%; $p < 0.05$). In the groups treated with aminochrome plus FAB plus MPP, cell death was higher than in cells exposed to DMSO 0.01% alone (0.8 ± 0.5%; $p < 0.001$) or than in cells exposed to DMSO plus MPP (0.9 ± 0.5%; $p < 0.01$), suggesting that cell death is not induced by MPP (Fig. 3a).

Similarly, blocking ERβ with pyrazolo[1,5-a] pyrimidine (PHTPP) resulted in the inhibition of neuroprotective effects of FAB. Cell death induced by exposures to aminochrome plus FAB plus PHTPP (39.6 ± 4.1%) was higher than in cultures exposed to aminochrome plus FAB (7.6 ± 2%; $p < 0.01$) or to aminochrome alone (25.9 ± 3%; $p < 0.01$). In the group exposed to aminochrome plus FAB plus PHTPP, cell death was also higher than in cells exposed to 0.01% DMSO alone (0.8 ± 0.5%; $p < 0.001$) or than in cells treated with DMSO plus PHTPP (2.4 ± 1%; $p < 0.01$)(Fig. 2b). In addition, we observed that FAB plus PHTPP was cytotoxic to SHSY-5Y cells, which induced 23.3 ± 1.4% of cell death when compared with control conditions 0.01% DMSO (0.8 ± 0.5%; $p < 0.001$) or DMSO plus PHTPP (2.4 ± 1%; $p < 0.01$) (Fig. 3b).



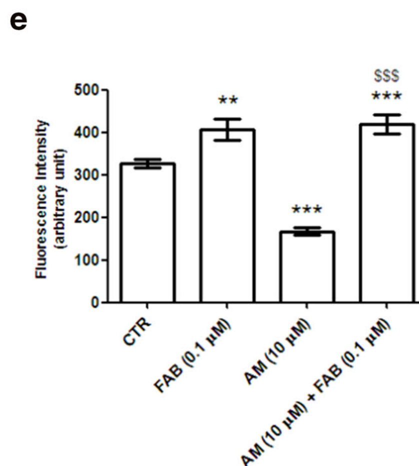


Fig. 2 Agathisflavone (FAB) increases lysosomal acidification in SH-SY5Y cells. The effect of aminochrome on lysosomal function was determined with LysoSensor™ Blue DND-167 staining after incubating SH-SY5Y cells for 24 h with 0.01% DMSO in **a**, 0.1 µM agathisflavone (FAB) in **b**, 10 µM aminochrome (AM) in **c**, or 0.1 µM FAB plus 10 µM AM in **d**. Obj. 20 × 0.70, scale bars = 50 µm. Amplified images in the upper right corner of **b** and **d**. The quantification of fluorescence was plotted in **e**. The values are the mean ± SEM ($n = 6$), and the statistical significance was assessed by using one-way ANOVA test. The p value was represented by $^{**}p < 0.01$; $^{***}p < 0.001$ compared to CTR group (DMSO 0.01%) and $^{\$\$\$}p < 0.001$ compared to AM group (10 µM aminochrome)

Discussion

The neuroprotective effect of agathisflavone has recently been discovered (Dos Santos et al. 2018; de Almeida et al. 2020) but has never been studied in Parkinson's disease models. In this study, we demonstrated the protective action of this biflavonoid in a catecholaminergic model cell line (SY-SY5Y) exposed to the endogenous neurotoxin aminochrome. Aminochrome is an *o*-quinone formed during dopamine oxidation to neuromelanin (Segura-Aguilar et al. 2016). In animal models, it induces a slow progressive dysfunction in dopaminergic neurons(Herrera et al. 2016) and, in in vitro studies, it induces disruption of actin and tubulin cytoskeleton networks and mitochondrial and mitophagy dysfunction, which are associated with a lysosomal dysfunction that results in neuronal death (Segura-Aguilar et al. 2016; Segura-Aguilar and Huenchuguala 2018).

The study shows the importance of macroautophagy and lysosomal degradation systems for the normal functioning of mitochondria and for cell survival in aminochrome-induced damage (Huenchuguala et al. 2017). These data suggest lysosomal function as an important target for neuroprotective drugs in Parkinson's disease. Among several neuroprotective mechanisms of flavonoids for Parkinson's disease, activation of endogenous antioxidant enzymes, suppression of lipid peroxidation, inhibition of inflammatory mediators, and protection against mitochondrial damage are the most reported (Magalingam et al. 2015). However, there is little knowledge about the effect of flavonoids on lysosomal function. Some studies show the effect of quercetin on lysosomal activity in an experimental model of diabetes (Chougala et al. 2012) and in tumor cells (Tomas-Hernández et al.2018; Wang et al. 2011). Another study shows that rutin protects the lysosomal

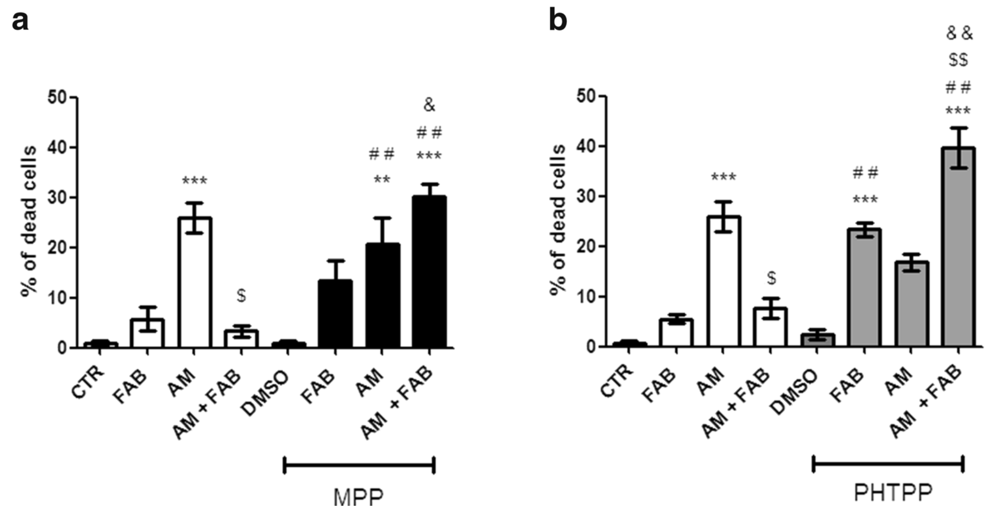


Fig. 3 ERα and ERβ antagonists inhibit the agathisflavone (FAB) neuroprotective effect against aminochrome-induced cytotoxicity. In A: SHSY-5Y cells were treated with vehicle 0.01% DMSO; 0.1 μM FAB and/ or aminochrome (10 μM) in the presence or absence of ERα antagonist methyl-piperidinopyrazole (MPP, 2.5 nM) for 24 h. In B: SHSY-5Y cells were treated with vehicle 0.01% DMSO; 0.1 μM FAB and/ or aminochrome (10 μM) in the presence or absence of ERβ antagonist pyrazolo[1,5-a]-pyrimidine (PHTPP, 1 μM) for 24 h. Afterwards, cell death was assessed by Trypan blue exclusion test. The values are the mean ± SEM ($n = 6$), and the statistical significance was assessed by using one-way ANOVA test. The p value was represented by $^{**}p < 0.01$; $^{***}p < 0.001$ compared to CTR group (DMSO 0.01%); $^{\$}p < 0.05$; $^{\$\$}p < 0.01$ compared to AM group (10 μM aminochrome); $^{\#\#}p < 0.01$ compared to the group treated with DMSO + ER antagonist (MPP or PHTPP); $^{\&}p < 0.05$; $^{\&\&}p < 0.01$ compared to the group treated with AM + + ER antagonist (MPP or PHTPP)

membrane against isoproterenol-induced cardiac damage due to the free radical scavenging, antioxidant, and membrane stabilizing (Prince and Priya 2010). On the other hand, our findings revealed an increase in lysosomal acidification induced by agathisflavone that can be associated to the neuroprotection by elimination of altered proteins or damaged organelle (Segura-Aguilar et al.2016; Huenchuguala et al.2017).

Studies have shown the involvement of estrogen pathway in lysosomal function. It has been shown that ERβ promotes Aβ degradation in SHSY-5Y cells via the modulation of autophagy (Wei et al. 2019). Another study showed that lysosome function is further involved in ERα activities (Totta et al. 2014). In our previous studies, agathisflavone acts via ERα and ERβ to promote neurogenesis (Dos Santos et al. 2018). The results of the present study show that ER signaling via ERα and ERβ is also involved in cell survival as a mechanism of agathisflavone neuroprotection against aminochrome neurotoxicity.

This is the first evidence of the protective effects of agathisflavone in a Parkinson's disease study model. Further studies should be performed to clarify the involvement of the lysosomal-induced acidity by agathisflavone in mitochondrial recovery and inhibition of alpha-synuclein accumulation. Taken together, these results suggest an in vitro protective role of agathisflavone against lysosomal dysfunction involved in aminochrome neurotoxicity and the involvement of ER signaling in the protection against aminochrome neurotoxicity.

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