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Dopamine modifies oxygen consumption and mitochondrial membrane potential in striatal mitochondria

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Abstract Dopamine is a neurotransmitter that has been related to mitochondrial dysfunction. In this study, striatal intact mitochondria and submitochondrial membranes were incubated with different dopamine concentrations, and changes on mitochondrial function, hydrogen peroxide, and nitric oxide production were evaluated. A 35% decrease in state 3 oxygen uptake (active respiration state) was found after 1 mM dopamine incubation. In addition, mitochondrial respiratory control significantly decreased, indicating mitochondrial dysfunction. High dopamine concentrations induced mitochondrial depolarization. Also, evaluation of hydrogen peroxide production by intact striatal mitochondria showed a significant increase after 0.5 and 1 mM dopamine incubation. Incubation with 0.5 and 1 mM dopamine increased nitric oxide production in submitochondrial membranes by 28 and 49%, respectively, as compared with control values. This study provides evidence that high dopamine concentrations induce striatal mitochondrial dysfunction through a decrease in mitochondrial respiratory control and loss of membrane potential, probably mediated by free radical production.

Keywords Striatal mitochondria · Dopamine · Membrane potential

Introduction

Mitochondrial dysfunction plays a central role in the induction of cell death pathways in a subset of human diseases [1, 2]. Specifically in brain, Alzheimer's, Parkinson's, and Huntington's diseases involve mitochondrial defect at different respiratory chain complexes [3]. Growing evidence indicates that changes in mitochondrial membrane permeability are involved in several forms of neuronal death including apoptosis, excitotoxicity and ischemia [4, 5].

Dopamine plays an important role in the physiopathology of several psychiatric and neurological disorders such as Parkinson's disease and schizophrenia, and in those cases disruption of mitochondrial processes was observed [6]. The most commonly described mechanism of dopamine toxicity is its own enzymatic oxidation by monoamine oxidase, leading to hydrogen peroxide (H_2O_2) generation which causes oxidative stress and increases lipid and protein oxidation [7]. Several studies on mitochondrial function following exposure to dopamine have produced variable results. An inhibition of respiration and a decrease in complex I activity after incubation with dopamine have been reported as a result of the deleterious actions of H_2O_2 and oxyradicals [6, 8–10]. Also, Khan et al. [11] reported that extended periods of incubation with dopamine produce mitochondrial dysfunction by dopamine oxidation products.

It has been described that nitric oxide (NO) regulates mitochondrial function. It is well known that NO exerts a modulatory effect on mitochondrial respiration through the reversible inhibition of cytochrome oxidase [12]. Previous results from our laboratory have shown that dopamine is able to induce brain mitochondrial dysfunction and increased NO production [13].

Taking into account that nigrostriatal pathway is one of the four major dopamine pathways in brain, the aim of this study was to evaluate the effects of different high dopamine concentrations on striatal mitochondrial function

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through determinations of oxygen consumption and mitochondrial membrane potential. Mitochondrial free radicals production was also assayed by determination of H_2O_2 production rates and by NO generation measurements, associated to mitochondrial membranes.

Materials and methods

Animals

Three months female Sprague-Dawley rats (200 g) from the animal facility of the School of Pharmacy and Biochemistry were used. Animal treatment was carried out in accordance with the guidelines of the National Institute of Health (USA) for the care and use of laboratory animals (NIH Publ. 8023, 1996). All efforts were made to minimize suffering and reduce the number of animals used.

Preparation of mitochondria

Striatum from three rats was pooled for each experimental point. Tissues were weighed and homogenized (1:5 w/v) in a medium consisting of 0.23 M mannitol, 0.07 M sucrose, 10 mM Tris–HCl, and 1 mM EDTA, pH 7.4. Homogenates were centrifuged at $700\times g$ for 10 min, and the supernatant obtained was centrifuged at $8{,}000\times g$ for 10 min. The resulting pellet containing mitochondria was washed and resuspended in the same buffer [14]. All the procedures were carried out at 0–2°C. For some experiments, mitochondria were subjected to two freeze–thaw cycles and passed through hypodermic needle [15]. The preparation obtained, called submitochondrial membranes, consisted in a fraction of outer and inner membranes which do not present restriction to substrate access.

Measurement of oxygen consumption

A two-channel respirometer for high-resolution respirometry (Oroboros Oxygraph, Paar KG, Graz, Austria) was used. Mitochondrial respiratory rates were measured in a reaction medium containing 0.23 M mannitol, 0.07 M sucrose, 20 mM Tris–HCl (pH 7.4), 1 mM EDTA, 4 mM $MgCl_2$, 5 mM phosphate, and 0.2% bovine serum albumin at 30°C. Malate 6 mM and glutamate 6 mM were used as substrates to measure state 4 respiration (resting or controlled respiration), and 1 mM ADP was added to measure state 3 respiration (active respiration, the maximal physiological rate of O_2 uptake, and ATP synthesis) [16]. The respiratory control ratio (state 3 respiration/state 4 respiration) was determined [17].

Evaluation of mitochondrial membrane potential

Mitochondria (0.25 μg/ml) were loaded with 30 nM of the potentiometric cationic probe $DiOC_6$ during 20 min at 37°C, and immediately events were acquired by a FACSCAN flow cytometer equipped with a 488-nm argon laser and a 615-nm red diode laser [18]. Mitochondrial fluorescence with no probe and after FCCP (carbonyl cyanide *p*-trifluoromethoxyphenylhydrazone) treatment was measured as negative and positive controls, respectively. Data from the experiments were analyzed using the CellQuest software (Becton & Dickinson).

Measurement of hydrogen peroxide production

Hydrogen peroxide generation was determined in intact striatal mitochondria (0.1–0.3 mg protein/ml) by the scopoletin-HRP method, following the decrease in fluorescence intensity at 365–450 nm (λ_{exc}–λ_{em}) at 37°C [19]. The reaction medium consisted of 0.23 M mannitol, 0.07 M sucrose, 20 mM Tris–HCl (pH 7.4), 0.8 μM HRP, 1 μM scopoletin, 6 mM malate, 6 mM glutamate, and 0.3 μM SOD.

Measurement of nitric oxide production

Nitric oxide production was measured in striatal submitochondrial membranes using a spectrophotometric method by following the oxidation of oxyhemoglobin to methemoglobin at 37°C. The NO assay was performed using a Beckman-Coulter Serie DU 7400 diode array spectrophotometer in which the active wavelength is set at 577 nm and the reference wavelength at the isosbestic point at 591 nm ($\varepsilon = 11.2\ mM^{-1}\ cm^{-1}$) [15]. The measurements were carried out in a reaction medium containing 50 mM phosphate buffer pH 5.8, 1 mM $CaCl_2$, 50 μM L-arginine, 100 μM NADPH, 10 μM DTT, 4 μM Cu–Zn superoxide dismutase (SOD), 0.1 μM catalase, 0.5–1.0 mg submitochondrial membranes protein/ml, and 25 μM oxyhemoglobin (expressed per heme group).

Evaluation of dopamine quinones formation

Quinones formation was measured in striatal intact mitochondria and submitochondrial membranes incubated with dopamine by following the increase in absorbance at 303 nm during 20 min [20]. The reaction medium consisted in 50 mM HK_2PO_4/H_2KPO_4 buffer, pH 7.4 at 37°C, and 0.5–1.0 mg submitochondrial membranes protein per ml. Appropriate blanks were kept and turbidity due to mitochondria was suitably corrected for this assay.

Statistics

Results are expressed as mean values ± SEM using 3–6 individual samples, each obtained from a pool of three rats. Student's *t*-test was used to analyze the significance of differences between paired groups. ANOVA was used to analyze differences between mean values of more than two groups, as described at the bottom of the tables.

Results

Dopamine incubation inhibited oxygen consumption

Oxygen consumption is an important parameter to characterize mitochondrial function. We measured malate–glutamate-dependent oxygen consumption rate in state 4 (resting or controlled respiration) and in state 3 (active respiration, the maximal physiological rate of O_2 uptake and ATP synthesis) and calculated the respiratory control ratios (state 3 respiration/state 4 respiration) [21].

To test the effect of dopamine, intact striatal mitochondria were incubated with 1 mM dopamine at 30°C during 5 min. As shown in Table 1, dopamine inhibited state 3 oxygen consumption by 35%, as compared with control values (69 ± 2 ng atoms O/min/mg protein). No significant changes were observed in state 4 after dopamine incubation as compared with control values (16 ± 1 ng atoms O/min/mg protein). Respiratory control is a parameter of integrity and mitochondrial functionality [16]. A significant decrease in mitochondrial respiratory control ($P < 0.05$) was observed after incubation with 1 mM dopamine (1.87 ± 0.06) as compared with control mitochondria (4.31 ± 0.07), indicating mitochondrial dysfunction.

Dopamine produced striatal mitochondrial depolarization

Mitochondrial membrane potential represents another parameter of mitochondrial function. The effect of dopamine on striatal mitochondrial membrane potential is shown in Fig. 1. Unloaded control mitochondria present low auto fluorescence as observed in Fig. 1b. After incubation with 0.5 and 1 mM dopamine an important decrease in FL-1-DiOC$_6$ fluorescence was observed (Fig. 1e, f) as compared with control mitochondria (Fig. 1c), indicating mitochondrial depolarization. However, incubation with 0.1 mM dopamine did not disturb mitochondrial polarization (Fig. 1d). As expected, addition of the ionophore FCCP (0.5 μM) to striatal mitochondria showed stronger mitochondrial depolarization (Fig. 1g).

Statistical values of the relative fluorescence intensity showed that control mitochondria presented a mean value of 69 ± 2%, and after 0.1, 0.5, and 1 mM dopamine incubation and FCCP addition, FL-1-DiOC6 fluorescence mean values were 63 ± 3%, 55 ± 2%, 49 ± 2%, and 9.7 ± 0.6%, respectively (Fig. 1h).

Interesting to observe was that the level of polarization of the mitochondrial sample decreased to 49% after incubation with 1 mM dopamine as compared with 69% in the control or untreated mitochondria. Mitochondrial pretreatment with CsA before 1 mM dopamine was able to restore the level of mitochondrial polarization to 60 ± 1%; however, in these conditions the basal levels were not reached.

Dopamine incubation increased striatal H_2O_2 production

The effect of dopamine incubation on striatal H_2O_2 production rate was evaluated after incubation of striatal intact

Table 1 Dopamine effect on striatal mitochondria respiration

Condition	Oxygen consumption (ng atoms O/min/mg protein)	Respiratory control
Control (state 4)	16 ± 1	
+ADP (state 3)	69 ± 2[#]	4.31 ± 0.07
1 mM Dopamine (state 4)	21 ± 1	
+ADP (state 3)	45 ± 2*	1.87 ± 0.06*

Values represent the mean ± SEM of 3–6 individual mitochondria samples, each obtained from a pool of striatum of three rats

ANOVA followed by Tukey tests was used $F_{(3;14)} = 222.39$

[#] $P < 0.01$, as compared to state 4 control value

* $P < 0.05$, as compared to state 3 or respiratory control value

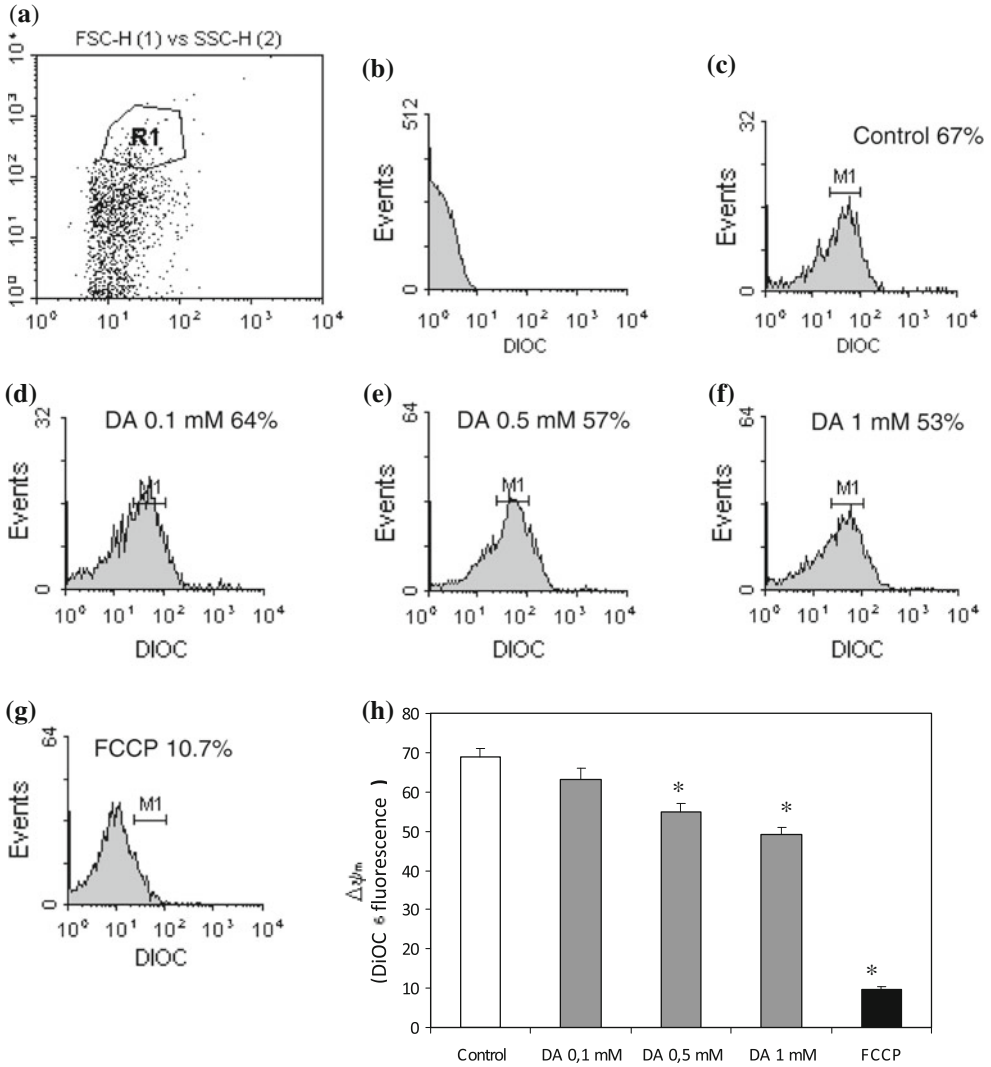

Fig. 1 Dopamine effect on striatal mitochondrial membrane potential. Histograms of gated events (R1) versus relative fluorescence intensity (FL-1) of mitochondrial membrane potential described by $DiOC_6$. **a** Dot blot of FSC-H versus SSC-H indicating a gated mitochondrial population (R1), **b** unloaded, **c** control, **d** 0.1 mM dopamine (DA), **e** 0.5 mM DA, **f** 1 mM dopamine, **g** 0.5 μM FCCP, and **h** *bars* scheme of $\Delta\psi$ mitochondrial ($\Delta\psi_m$) versus different DA treatments (mean values ± SEM) (* $P < 0.01$, $F_{(4;15)} = 246.73$. Each *histogram* represents a typical experiment, which was performed in triplicate)

mitochondria with different dopamine concentrations at 37°C during 5 min. Mitochondrial H_2O_2 production rate was increased after dopamine incubation; increases of 35 and 90% were observed after incubation with 0.5 and 1 mM dopamine, respectively, as compared with control mitochondria (0.92 ± 0.02 nmol H_2O_2/min/mg protein) (Fig. 2).

Nitric oxide production was increased by dopamine incubation

To determine whether dopamine can modulate NO production, striatal submitochondrial membranes were incubated during 5 min at 37°C with different dopamine concentrations. As shown in Fig. 2, dopamine increased NO production in a concentration-dependent manner. Incubation of submitochondrial membranes with 0.5 and 1 mM dopamine significantly increased NO production by 28 and 49%, respectively, as compared with control values (1.06 ± 0.03 nmol/min/mg protein). However, no changes were observed in NO production when submitochondrial membranes were incubated with low dopamine concentrations (0.1 mM).

Dopamine incubation did not produce quinone formation

In order to evaluate quinone formation, striatal intact mitochondria and submitochondrial membranes were

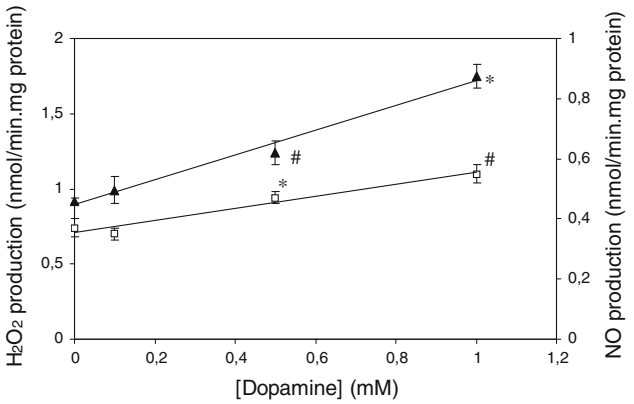

Fig. 2 Dopamine effects on striatal H_2O_2 production and NO production. H_2O_2 production (*triangle*): values represent the mean ± SEM of 3–6 individual samples, each obtained from a pool of striatum of three rats. ANOVA followed by Dunnet test was used. * $P < 0.05$, as compared with control mitochondria. $F_{(4;10)} = 4.493$. NO production (*square*): values represent the mean ± SEM of 3–6 individual samples, each obtained from a pool of striatum of three rats. ANOVA followed by Dunnett test was used. $^{\#}P < 0.01$, as compared with control submitochondrial membranes. $F_{(3;14)} = 11.830$

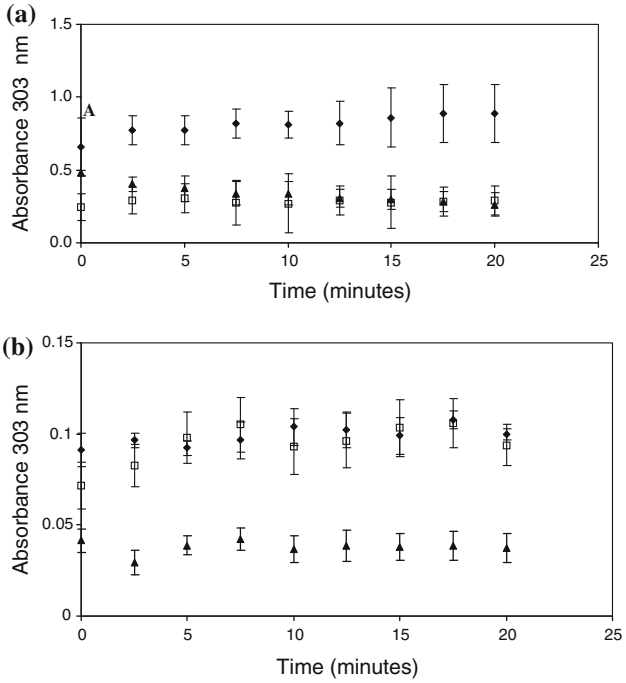

Fig. 3 Production of dopamine quinones. **a** Striatal intact mitochondria. **b** Striatal submitochondrial membranes. *Triangle* 0.1 mM dopamine, *square* 0.5 mM dopamine, and *diamond* 1 mM dopamine. Values represent the mean ± SEM of 3–6 individual samples, each obtained from a pool of striatum of three rats. ANOVA followed by Dunnet test was used

incubated with different dopamine concentrations during 20 min.

Figure 3a shows that no dopamine auto-oxidation was observed along incubation of intact mitochondria for 20 min, indicating that at 5 min, which is the incubation time used for the evaluation of mitochondrial function parameters, no dopamine quinones are formed. Similar results were observed when submitochondrial membranes were incubated with 0.1, 0.5, and 1 mM dopamine (Fig. 3b).

Discussion

Disruption of mitochondrial processes was observed in the pathophysiology of several psychiatric and neurological disorders such as schizophrenia and Parkinson's disease where dopamine plays an important role [6]. Due to the fact that the nigrostriatal pathway is one of the four major dopamine pathways in brain, in this study we investigated the effects of incubation of striatal mitochondria with different dopamine concentrations.

It has been recognized that dopamine at different concentrations inhibits brain oxygen consumption [9, 10]. Previous results from our laboratory have shown that high dopamine concentrations have deleterious effects on mitochondrial function such as a decrease in mitochondrial respiration and depolarization of mitochondrial membrane [13]. Microdialysis studies report that extracellular dopamine can range between 3 and 750 nM depending on neuronal activation and brain region [22]. Synaptic concentrations of dopamine can range between 30 and 100 mM following activation of dopamine cell bodies [23]. The striatal concentration of dopamine is estimated to be about 70 μM, whereas the dopaminergic concentration in the neuronal endings and during the phasic release is of the order of mM [24]. Cells with high dopamine concentrations such as dopaminergic neurons are highly vulnerable to degeneration. It has been proposed that if dopamine is not efficiently stored in vesicles or if vesicles are disrupted, it can achieve high intracellular concentrations and may overcome the antioxidant capacity of the cell [25]. Under pathological conditions, which are associated with massive release of dopamine, as in schizophrenia, mitochondria enriched nerve terminals are exposed to increased dopamine levels due to its increased reuptake and synthesis [26]. Also, elevated rat brain dopamine concentrations following chronic administration of L-DOPA or D-methamphetamine resulted in a reduction of the activity of the first complex of the respiratory system and ATP levels in striatum [27, 28]. Results reported in our study are related to high dopamine concentrations. High dopamine levels decreased O_2 consumption in state 3 and decreased respiratory control in striatal intact mitochondria indicating mitochondrial dysfunction, as previously reported for whole brain mitochondria [13]. In this study, decreased state 3 respiratory rate was accompanied by a tendency to

an increased state 4 respiratory rate, thus suggesting a serious uncoupling of mitochondria.

Evaluation of mitochondrial membrane potential shows that low physiological dopamine concentrations do not affect mitochondrial membrane potential, while high dopamine concentrations induce depolarization. We propose that the fact that CsA pretreatment before dopamine addition was able to restore membrane potential is an indication of the possibility that mitochondrial permeability transition could be involved as a molecular mechanism of the mitochondrial depolarization. Our data are consistent with an early study by Berman and Hastings who found that dopamine induces mitochondrial permeability transition and produces membrane depolarization [6].

According to our results, uncoupling of the respiratory chain and mitochondrial permeability transition could be the cause of dopamine-induced mitochondrial depolarization.

Hydrogen peroxide is normally formed during basal respiration [29] and also is a product of dopamine metabolism by MAO [1]. It has been proposed that metabolism of dopamine by MAO increases H_2O_2 levels and consequently inhibits mitochondrial respiration [10]. In our study, high dopamine concentrations were able to increase striatal mitochondrial H_2O_2 production in a dose-dependent manner, probably contributing to dopamine-induced mitochondrial dysfunction.

It is known that NO plays an important role in numerous physiological neuronal functions as liberation of neurotransmitters, neural development, axonal regeneration, and synaptic plasticity. However, excessive formation of NO has been implicated in the pathogenesis of various neurological disorders [30]. Figure 2 shows that low dopamine concentrations did not alter mitochondrial NO production, but high dopamine concentrations (mM range) increased NO production. This result is in accordance with a previous report by Sammut et al. [31], who found that phasic dopaminergic transmission increases NO efflux in the rat dorsal striatum via a neuronal NOS and a dopamine $D_{1/5}$ receptor-dependent mechanism.

Studies from different laboratories have proposed that high dopamine concentrations induce mitochondrial dysfunction by dopamine oxidation products [11]. In our study conditions, no dopamine quinone formation was observed, suggesting that quinone formation does not seem to be involved in dopamine-induced mitochondrial dysfunction.

Conclusions

As previously shown for brain mitochondria, this study provides evidence that high dopamine concentrations induce striatal mitochondrial dysfunction through a decrease in mitochondrial respiratory control and loss of membrane potential. Increases of H_2O_2 and NO production induced by dopamine in striatal mitochondria seem to contribute to dopamine-related mitochondrial damage. Quinone formation does not seem to be involved in the mechanism of dopamine mitochondrial dysfunction in our study conditions.

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