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A newly discovered neurotoxin ADTIQ associated with hyperglycemia and Parkinson's disease

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ABSTRACT

Background: Diabetes is associated with an increased risk of Parkinson's disease (PD). Number of studies have suggested that methylglyoxal (MGO) induced by diabetes is related to PD. However, very little is known about its molecular mechanism. On other hand, 1-acetyl-6, 7- dihydroxyl-1, 2, 3, 4- Tetrahydroisoquinoline(ADTIQ) is a dopamine (DA)-derived tetrahydroisoquinoline (TIQ), a novel endogenous neurotoxins, which was first discovered in frozen Parkinson's disease human brain tissue. While ADTIQ precursor methylglyoxal was also found in diabetic patients related to the glucose metabolism and diabetic patients.

Methods: LC-MS/MS, 1H NMR and infrared spectroscopy identified the structure of ADTIQ. The Annexin V-FITC/PI, MTT and western blot analysis were used to measure the neurotoxicity of ADTIQ. The levels of ADTIQ and methylglyoxal were detected by LC-MS/MS.

Results: Here we report the chemical synthesis of ADTIQ, demonstrate its biosynthesis in SH-SY5Y neuroblastoma cell line and investigate its role in the pathogenesis of PD. In addition, a significant increase in the level of ADTIQ was detected in the brains of transgenic mice expressing mutant forms (A53T or A30P) of α-synuclein. ADTIQ also reduced the cell viability and induced mitochondrial apoptosis in dopaminergic cells, suggesting that ADTIQ acts as an endogenous neurotoxin and potentially involved in the pathogenesis of PD. Methylglyoxal, a major byproduct of glucose metabolism and abnormalities in glucose metabolism could influence the levels of ADTIQ. Consistent with the hypothesis, increased levels of ADTIQ and methylglyoxal were detected in the striatum of diabetic rats and SH-SY5Y cells cultured in the presence of high glucose concentrations.

Conclusions: Increased levels of ADTIQ could be related with Hyperglycemia and death of dopaminergic neurons.

General significance: The increased levels of ADTIQ could be a reason of dopamine neuron dysfunction in diabetes. Therefore, ADTIQ may play a key role in increasing the risk for PD in patients with diabetes.

1. Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disorder [1].The pathology of PD is associated with the death of dopaminergic neurons in the nigrostriatal pathway and the presence of Lewy bodies in the surviving substantianigra neurons [2]. Type 2 diabetes is one of the fastest growing public health problems worldwide, and it is associated with multiple complications, including neurodegenerative diseases such as diabetic neuropathy and Alzheimer's disease [3,4]. Recent studies have shown that diabetes is significantly associated with an increased risk of developing PD, particularly in young-onset Parkinson's disease

Abbreviations: ADTIQ, 1-acetyl-6,7-dihydroxyl-1,2,3,4-tetrahydroisoquinoline; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Salsolinol, 1-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline; NM-salsolinol1(R), 2(N)-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolin; TIQ, tetrahydroisoquinoline.

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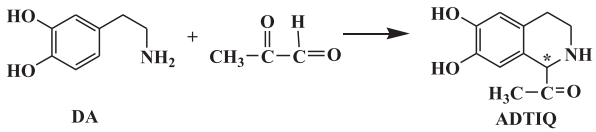
[5–7]. However, the underlying molecular mechanism responsible for the association between diabetes and PD is unknown.

The dopamine (DA)-derived tetrahydroisoquinolines(TIQ) 1-acetyl-6, 7- dihydroxyl-1, 2, 3, 4- tetrahydroisoquinoline (ADTIQ) was recently discovered in frozen human PD brain tissues [8]. The structure of ADTIQ (SI-1) is similar to that of 1-methyl-4–phenyl-1,2,3,6-tetrahydropyridine (MPTP), which causes symptoms of PD [9,10]. Recently published evidence suggests that a number of TIQ analogs, such as1-methyl-4-phenyl-1, 2, 3, 4-tetrahydroisoquinoline (salsolinol) 1(R),2(N)-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolin(NM-salsolinol) may act as endogenous neurotoxins that cause PD [11,12]. Salsolinol can transfer to N-methyl-salsolinol in brain and it will be oxidized to DMDHIQ + consequently by nonenzymatic reaction or cytochrome P450 [13]. Salsolinol and N-methyl-salsolinoloxidized causing oxidative stress and contribute to the progress of apoptosis in dopaminergic cells [14,15]. The similar structure of ADTIQ makes it a candidate of endogenous neurotoxin for dopamine neurons. To evaluate this hypothesis, we investigated the toxicity of ADTIQ for SH-SY5Y cells, and attempt to establish a relationship between ADTIQ and PD, we detected ADTIQ level in brain samples of control mice and transgenic PD mice, which express either human wild-type (wt) or mutated (A53T, or A30P) forms of α-synuclein (α-Syn) respectively [16,17]. 1-Methyl-4-phenyl-1, 2, 3, 4-tetrahydroisoquinoline (salsolinol), is produced from dopamine and acetaldehyde by Pictet–Spengler reaction [18]. ADTIQ was endogenously synthesized from dopamine and methylglyoxal in the brain by a reaction mechanism similar to that which generates salsolinol (SI-2). Here, the Pictet–Spengler reaction was employed to synthesize ADTIQ (Scheme 1). Methylglyoxal is a precursor of ADTIQ that is a reactive dicarbonyl compound produced endogenously mainly from glycolytic intermediates [19,20]. The physiological concentration of Methylglyoxal in human blood is approximately 338 ± 62 nmol/l [21]. Methylglyoxal formation is increased under conditions of hyperglycemia and impaired glucose utilization. Its level is increased from 3 to 6-fold in patients with diabetes mellitus and found remain elevated for several months and even years [22,23]. Therefore, methylglyoxal might be the principal endogenous precursor of ADTIQ; consequently, increases in its concentration may generate more ADTIQ in the brain of patients with diabetes. To assess this idea, this hypothesis, ADTIQ levels were measured in a rat model in which diabetes is induced by streptozotocin as well as in an in vitro system employing SH-SY5Y cells cultured in the presence of excess glucose to mimic hyperglycemia.



Scheme 1. Synthesis of ADTIQ.

2. Materials and methods

2.1. Materials

The following chemicals were used: Dulbecco's modified eagle's medium (GIBCO, Germany); trypsin-EDTA (GIBCO, Karlsruhe, Germany); fetal calf serum (Seromed, Berlin, Germany); glucose, HPLC-grade formic acid and acetonitrile (Edmonton, Canada); Isoproterenol (ISTD) (Sigma, USA); Automated cell counter (Millipore); Authentic standard 1-acetyl-6, 7-dihydroxy-1, 2, 3, 4-tetrahydroisoquinoline (ADTIQ) was obtained via synthesis and purification in our lab. Water was obtained from a Milli-QWater Plus purification system (Bedford, MA, USA). All other reagents were analytical grade.

2.2. Cell culture and MTT assay for cells viability

SH-SY5Y cells were cultured in Dulbecco's modified Eagle's Medium (DMEM) supplemented with 10% fetal calf serum, penicilline/streptomicine (100 U/ml; 100 μg/ml), and 2 mM L-glutamine at 37 °C in a humidified atmosphere containing 5% CO_2/95% air. Cells viability was determined by MTT assay. Briefly, cells were seeded at 5×10^3 per well in a 96-well flat bottom plate. After different administrations, 0.5 mg/mL MTT was added into the culture medium for another 4 h. After MTT incubation, DMSO was added, and the absorbance was measured at 570 nm (Thermo Labsystems MK3, USA). Cell viability was calculated as follows: ~% survival = (mean experimental absorbance/mean control absorbance) × 100%.

2.3. Transgenic α-synuclein gene Parkinson's disease mice model

Alpha-synuclein gene has recently been associated with familial PD, where the disease was caused by over expression of α-synuclein. Here over expressed α-synuclein mice model were used, the model included over expressed α-synuclein (WT), and mutate α-synuclein. One of mutations in α-synuclein gene (G209A), leading to a change from alanine to threonine at the position 53 (Ala53Thr); and the other was a mutation in α-synuclein gene (G88C), leading to a change from alanine to prolineat the position 30 (Ala30 Pro); The transgenic mice models which expressing human wild-type (WT), A53T, and A30P α-synuclein were purchased from Human Diseases Comparative Medicine Laboratory of Chinese Academy of Medical Sciences. Control and transgenic PD mice, were housed under standard laboratory conditions. The transgenic mice models need 8 months or more time to grow and show Parkinson's disease characters. In our research, the mice were grown up to11 months. The level of α-synuclein and behavior detection in transgenic mice were shown in SI-11 and SI-12.

2.4. Type 2 diabetes Sprague–Dawley rats model

Sprague–Dawley rats were obtained from the Animal Institute of the Medical Science Academy (Beijing, China), and were housed under standard laboratory conditions. All animals used in the current study were handled and treated in accordance with prescribe guidelines approved by Beijing Institute of Technology. Male Sprague–Dawley rats (n = 11, 1 weeks old), were fed normal chow (12% of calories as fat), or high-fat diet (40% of calories as fat) for 4 weeks and then injected streptozotocin (STZ, 25 mg/kg intravenously) two times. Then the rats were fed for another 4 weeks with high-fat diet. In the end, the glucose level and insulin stimulation in plasma were measured. The result showed that in Table.S1, the level of glucose level and insulin resistance in plasma showed that Type 2 diabetes SD rats model were succeed.

2.5. Sample preparation and LC-MS/MS analysis of ADTIQ [24]

The cells Sample was collected after centrifugation, and resuspended in PBS containing protease inhibitor solution. The cells were broken by sonication for 40 s (2 s on, 1 s off). The brain tissues was measured by the balance and resuspended in PBS (3 mg tissues+2.4 μl PBS, pH = 7.2), homogenates and broken by sonication for 1 min (2 s on, 1 s off). The protein concentration was determined and 0.1 M perchloric acid was added to remove the protein. The prepared cells and brain tissues were centrifuged at 4 °C and 17,000 g for 20 min and collected the supernatant. The

sample was filtered through 0.22 μm membrane for LC-MS/MS. The conditions of LC-MS/MS were: Chromatographic separation was achieved on an HS-F5 column (3 μm, 150 mm × 2.1 mm, Discovery ® Company, American) maintained at 30 °C. The mobile phase consisted of methanol–water (25/75 v/v) with 10 mM ammonium formate (pH 3.5) and was delivered at a flow rate of 0.15 ml/min. The injection volume was 10 μl. The column eluent was coupled to an electrospray ionization triple quadrupole mass spectrometer (Agilent 6460, USA) that was run in the multiple-reaction-monitoring mode (MRM) where a precursor ion is fragmented in the second quadruple (Q2), and the resulting fragments are detected in the third quadruple (Q3). MS was operated in the positive mode with a capillary voltage of 3500 V. The nebulizer gas was set at 35 psi, drying gas was set at 6 l/min, and drying gas temperature was kept at 300 °C. The $[M+H]^+$ precursor ions were used for isoproterenol (*m*/*z* 212.1) and ADTIQ (*m*/*z* 208.1). The product ions selected for the MRM scans were *m*/*z* 107.1 for isoproterenol (ISTD) and *m*/*z* 190.1 for ADTIQ.

2.6. Western blot analysis

The cells were lysed in RIPA buffer and mixed with loading buffer (200 mMTris-HCl pH 6.8, 50% glycerol, 2% SDS, 20% β-mercaptoethanol, 0.04% bromophenolbule), boiled for 5 min. Aliquots of cell lysates (100 μg total protein/sample) were separated on 12% SDS-PAGE, electro transferred to a polyvinylidenedifluoride (PVDF) membrane (Bio-Rad, CA, USA), blocked with 5% non fat milk in TBS-Tween buffer for 1.5 h at room temperature, and incubated overnight at 4 °C with the primary antibody against caspase-3 (1:800, Boisynthesis, China), Bcl-2 (1:800, Boisynthesis, China), Bax (1:800, Santa Cruz. USA) and β-actin (1:7000, Abcam). After washing, the membranes were incubated with the second antibody (Boisynthesis, China) for 1 h at room temperature. After extensive washing, the bands were visualized with enhanced chemiluminescence reagents (Thermo scientific) and exposed to X-ray film (Kodak scientific imaging film, MA, USA). The densitometry of the bands was analyzed by Bio-rad imaging system using Quantity One®.

2.7. Determination of methylglyoxal

To determine the methylglyoxal in brain sample,o-Phenylenediamine was added as a derivatizing agent for methylglyoxal. Here, 2 mM o-phenylenediamine including the homogenation buffer to facilitate the trapping of methylglyoxal. The homogenate (50 μl) was incubated for 60 min at 37 °C with 50 μl of 10 Mm 6-methylquinoxaline that was used as an internal standard. After incubation, 0.1 M perchloric acid was added to remove the protein. Following centrifugation at 4 °C and 17,000 g for 20 min and was detected by HPLC-ECD. Samples were separated on HS-F5column (5 μm, 250 mm × 4.6 mm, Discovery ® Company, American) with a mobile phase of citric acid (40 mmol/L), Na_2HPO_4(20 mmol/L), Na_2EDTA (0.3 mmol/L) and 15% (v/v) methanol mixture (adjusted to pH 4.0) at a flow rate of 0.8 mL/min. The voltage of a model 6210 analytical cells was set at-50, 50, 300, and 450 mV.

2.8. Statistics analysis

Data is expressed as mean ± SEM from at least three independent experiments with duplicate wells. Statistical differences between mean values in two groups were evaluated using T-test analysis. The differences between more than two groups were analyzed by one-way ANOVA and Tukey's post-hoc test. The differences were considered statistically significant at a p-value <0.05 (*) or <0.01 (**).

3. Results

3.1. The chemical synthesis and biosynthesis of ADTIQ in SH-SY5Yneuroblastoma cells

Pictet–Spengler reaction is a direct approach, yields were low, ADTIQ was readily oxidized in buffer solution, and the reaction products were too complex to purify. We optimized the reaction conditions. The Pictet–Spengler reaction requires a strong-acid buffer system for catalysis that protects against oxidation. Further, the proton can activate the aldehyde carbonyl group and increase the reaction yield. Therefore, we decided to synthesize ADTIQ from dopamine and methylglyoxal in trifluoroacetic acid buffer (SI-3, SI-4) at 37 °C for 24 h (SI-5). Although increased temperature improves the reaction yield, and generates more side reactions. There are two unstable phenolic hydroxyl groups in the ADTIQ molecule, therefore conventional purification methods, such as recrystallization, standard chromatography, and silica gel column fractionation was not used. Instead, we used an F5-SH semi-preparative liquid column to purify ADTIQ using 20% (v/v) methanol in aqueous ammonium formate (pH 3) as the mobile phase to prevent oxidation of ADTIQ. (SI-6) The product was freeze-dried and identified using high-performance liquid chromatography electrospray triple quadrupole mass spectrometry (HPLC-ESI-QQQ (MS/MS)) (SI-7), 1H NMR(SI-8)and infrared spectroscopy (SI-9).

We determined whether SH-SY5Y dopaminergic cells could synthesize ADTIQ by exposing them to dopamine andmethylglyoxal for 24 h. The intracellular concentration of ADTIQ was measured using LC-MS/MS. ADTIQ was either undetectable or present at very low levels when the cells were incubated with either methylglyoxal or dopamine, respectively, and dramatically increased when both substrates were added simultaneously (SI-10). These results indicate that dopamine and methylglyoxal are endogenous precursors of ADTIQ.

3.2. The increase of ADTIQ in Parkinson's disease mouse brain

Here, to attempt to establish a relationship between ADTIQ and PD, we demonstrate the detection of ADTIQ in brain samples of control mice and transgenic PD mice, which express either human wild-type (wt) or mutated (A53T, or A30P) forms of α-synuclein (α-Syn) [16,17]. The levels of α-synuclein and the behaviors of the transgenic mice are shown in Figs. SI-11 and SI-12, respectively. Compare with the control mice, the concentration of ADTIQ increased significantly in brain samples obtained from transgenic mice expressing A53T or A30P α-synuclein, but not in the mice expressing wild-type (Fig. 1). Accumulating evidence demonstrates that mice bearing mutated α-synucleins show enhanced tendencies to accumulate α-synuclein and are more susceptible to oxidative stress than wild-type both in vivo and vitro [25]. We suggest, therefore, that the differences in ADTIQ levels between mice expressing wild-type human α-Syn, A53T,and A30P α-synucleins correlate with characteristic pathological features of α-synuclein mutations.

3.3. ADTIQ caused mitochondrial damage in SH-SY5Y neuroblastoma cells

Endogenous neurotoxins salsolinol and NM-salsolinol could inhibition of complex I of the electron transport chain, damage mitochondrium and cause oxidative stress [26,27]. The similar structure of ADTIQ makes it candidate endogenous neurotoxin for dopamine neurons due to the affinity for complex I. To support this thesis, we investigated the toxicity of ADTIQ for SH-SY5Y cells using the MTT reduction assay. Treatment with ADTIQ (0–2 mM) for 24 h,

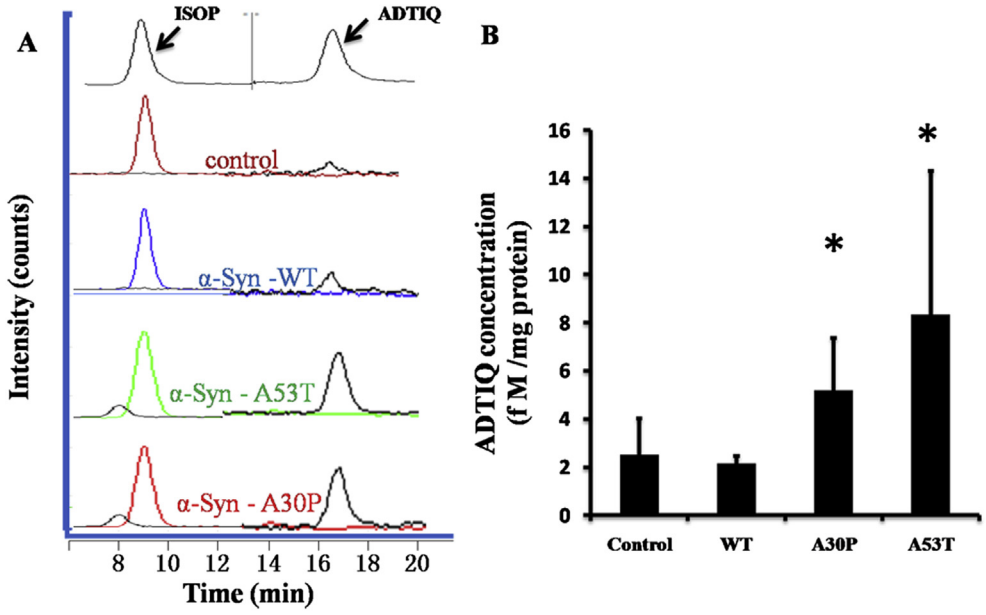


Fig. 1. ADTIQ concentrations in a transgenic mouse model of Parkinson's disease. (A) Representative extracted ion chromatograms of isoproterenol (standard) and ADTIQ in brain. (B) ADTIQ levels in brains of transgenic mice expressing A53T or A30P mutants of α-synuclein were significantly increased. Data represent mean ± S.E.M. (n = 5). *p < 0.05 vs. control.

led to decrease the cell viability (upto an extent of 44%) in a concentration-dependent manner. (SI-13). To assess whether ADTIQ mediated mitochondrial apoptosis in SH-SY5Y cells, the expression of key apoptotic protein involved in mitochondrial apoptotic Bax, Bcl-2 and caspase3were analyzed by western blot assay (Fig. 2). The results showed that ADTIQ could activate Bax, decrease anti-apoptosis protein Bcl-2, that releases Cytochrome C from mitochondria into cytosol. Consequently it cause up-regulation of Caspase-3 expression that lead to mitochondrial damage and cause apoptosis (Fig. 2). We also found LC-3A, a kind of protein assigned with autophagy gene, was increased which could be due to mitochondrial damage. ADTIQ reduced cell viability and induced mitochondrial apoptosis in dopaminergic cells, suggesting that ADTIQ acts as an endogenous neurotoxin potentially involved in the pathogenesis of PD.

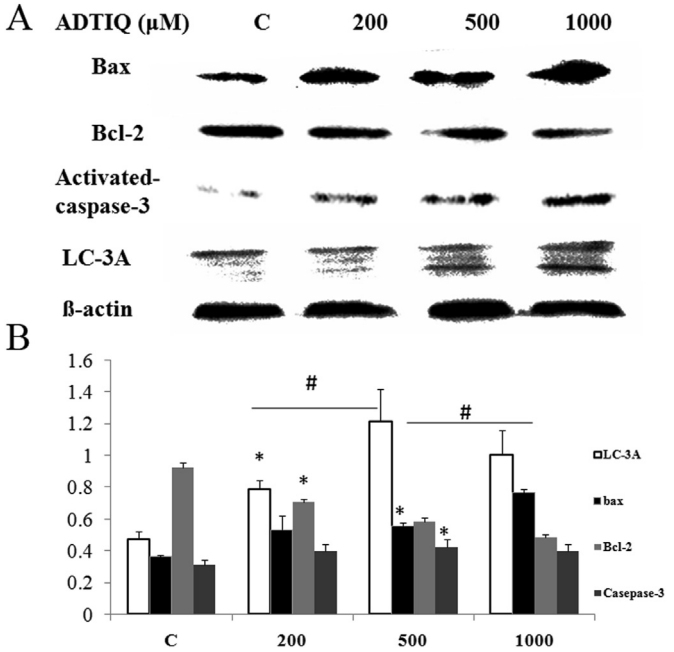


Fig. 2. ADTIQ-induced mitochondrial apoptosis in SH-SY5Y cells. (A) Western blot analysis for key apoptotic protein expression level. The protein levels relative to β-actin (as an internal standard), were expressed as the percentage of control. (B) Statistics for protein expression. Data represent mean ± S.E.M. (n = 5). *p < 0.05 vs.control.

3.4. The increase of ADTIQ level in type 2 diabetes SD rats and Hyperglycemic induced SH-SY5Y neuroblastoma cells

ADTIQ levels were measured in a rat model in which diabetes is induced by streptozotocin and in an in vitro model employing SH-SY5Y cells cultured in the presence of excess glucose to mimic hyperglycemia. Diabetes is characterized by hyperglycemia, and the levels of blood glucose and insulin resistance in the strptozoticin-treated rats are shown in Table S-1. ADTIQ levels were determined in the striatum, a component of the dopaminergic nigrostriatal pathway. Compared with the controls, a significant increase in ADTIQ and methylglyoxal levels were observed in the striatum, suggesting that diabetic hyperglycemia promotes the production of ADTIQ in the brain (Fig. 3).

To investigate the effect of glucose metabolism on ADTIQ synthesis in dopaminergiccells, SH-SY5Y cells were exposed to the high glucose concentrations, and the intracellular ADTIQ level was detected using LC-MS/MS. When glucose was added to a final concentration of 50 mM or 200 mM for 24 h, high glucose lead to the damage of mitochondrial integrity and reactive oxygen species which promotes the apoptosis. (SI-14) As well as, the concentration of ADTIQ increased significantly. Further, treatment with the same concentrations of mannitol to control for osmotic shock did not have a significant effect on ADTIQ levels. These results suggest that the ADTIQ level in dopaminergic cells increases as a function of increased glucose metabolism without inducing osmotic stress (Fig. 4). The results of these in vitro and in vivo experiments support our hypothesis that hyperglycemia in diabetes accelerates ADTIQ formation, particularly in dopaminergic neurons. This can be

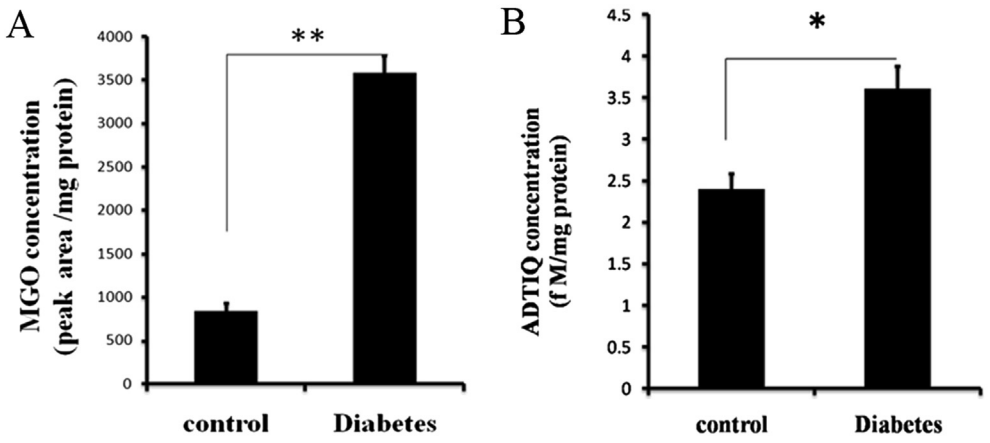


Fig. 3. ADTIQ and methylglyoxal levels in streptozotocin-treated diabetic rats. The ADTIQ and methylglyoxal levels in the striatum were determined using LC-MS/MS and HPLC-ECD. The data represent the mean ± S.E.M. (n = 5). **p < 0.05 vs. control.

explained further by alterations in glucose metabolism that lead to elevated production of methylglyoxal, a reactive α-dicarbonyl.

4. Discussion

The chemical synthesis and biosynthesis of ADTIQ indicate that dopamine and methylglyoxal are endogenous precursors of ADTIQ. The endogenous synthesis of salsolinol from dopamine and acetaldehyde is catalyzed by salsolinolsynthase [15], which has been purified from human brain [28,29]. Salsolinolis converted to N-methyl-salsolinol in brain [30]. Salsolinoland N-methyl-salsolinol can cause oxidative stress, which contributes to the induction of apoptosis in dopaminergic cells [26,27,31]. In our previous research, we found that salsolinol *N*-methyltransferase activity in peripheral lymphocytes and brain was significantly increased compared with the control in a rat model of unilateral 6-hydroxydopamine deficiency [32]. The synthesis of ADITQ in vitro requires an acidic catalyst to accelerate the condensation reaction (SI-4). High concentrations of ADTIQ were detected in the basal ganglia, which are rich in dopamine, suggesting that the reaction catalyzed by an unknown enzyme. Salsolinol is converted to N-methyl-salsolinol in brain [30], salsolinol and N-methyl-salsolinol cause oxidative stress, which contributes to the induction of apoptosis in dopaminergic cells [26,27,31]. The similar structure of ADTIQ, as a candidate endogenous neurotoxin, the increased ADTIQ level in the brain of transgenic PD mice and the toxicity of ADTIQ for dopaminergic cell suggested that this newly discovered TIQ may play an important role in the pathogenesis of Parkinson's disease.

Methylglyoxal are the endogenous precursors of ADTIQ, the production of the toxic compound methylglyoxal is implicated in diabetic complications, such as macrovascular disease, nephropathy, neuropathy, and other neurodegenerative diseases [23]. Methylglyoxal readily cross-links amino groups in proteins forming advanced glycation end products, which are associated with serious toxic effects [33]. Further, methylglyoxal may directly damage neurons through inhibiting mitochondrial respiration, increasing reactive oxygen species production, and inducing apoptosis [34]. ADTIQ generated as the downstream product of

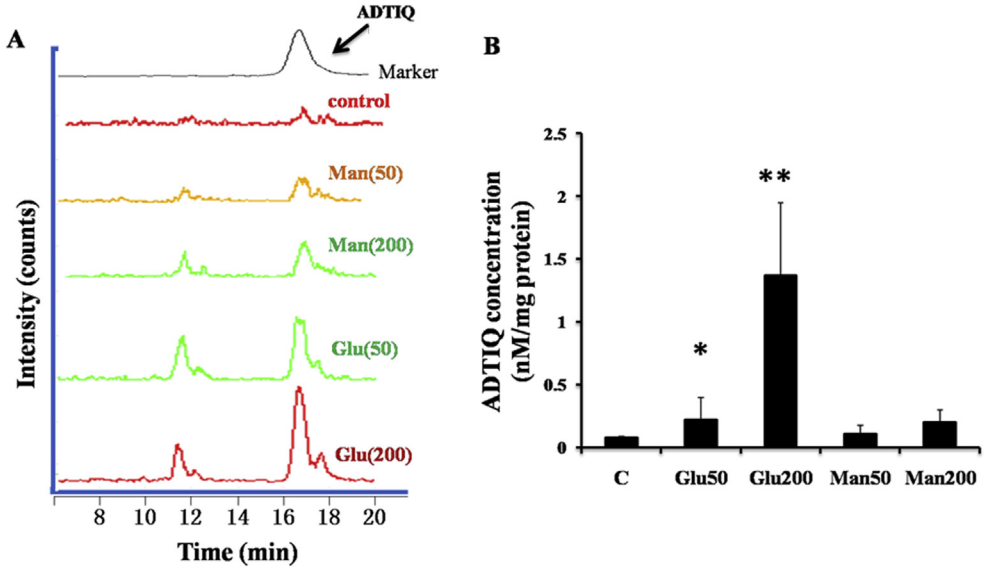


Fig. 4. The effect of high glucose on concentrations on ADTIQ in SH-SY5Y cells. (A) Representative ion chromatograms of SH-SY5Y cells exposed to vehicle (1), 50 mM mannitol (2), 100 mMmannitol (3), 50 mM glucose(4) and 200 mM glucose (5). (B) Quantitation of ADTIQ after exposure to mannitol or glucose. Data represent the mean ± S.E.M. (n = 5). **p < 0.01 vs. control.

methylglyoxal and glucose in dopaminergic neurons and is toxic to a dopaminergic cell line. Therefore, we propose that ADTIQ might be a critical downstream effect or that participates in methylglyoxal-induced dopaminergic neurotoxicity in hyperglycemia and diabetes. It provides a new insight into understanding why diabetes is significantly associated with increased risk of developing Parkinson's disease. The pathway for ADTIQ biosynthesis is suggested in SI-15. However, further work will be required to understand the biosynthesis of ADTIQ in detail.

Conflict of interest

None.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2015.02.069.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.02.069.

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