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EFFECTS OF NICOTINE ON GLUTAMAT-GLUTAMINE CYCLE AND PURINE METABOLISM IN A MOUSE MODEL OF PARKINSON'S DISEASE

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ნიკოლოზ ჟღენტი, ოთარ ბიბილაშვილი, ნანა კოშორიძე

ნიკოტინის გავლენა გლუტამატ-გლუტამინურ ციკლსა და პურინულ მეტაბოლიზმზე პარკინსონის დაავადების თაგვის მოდელში

ივ. ჯავახიშვილის სახელობის თბილისის სახელმწიფო უნივერსიტეტი

რეზიუმე

პარკინსონის დაავადება ნეიროდეგენერაციული დაავადებაა, რომელიც ხასიათდება დოფამინერგული ნეირონების მკვეთრი კვდომით და მეტაბოლური დისბალანსით. აღნიშნული კვლევის მიზანს წარმოადგენდა დაგვედგინა მოდულირებს თუ არა ნიკოტინი გლუტამატ-გლუტამინურ ციკლსა და პურინულ მეტაბოლიზმზე MPTP-ით გამოწვეული პარკინსონიზმის მქონე თაგვებში. BALB/c თეთრი ლაბორატორიული თაგვები დაიყო ოთხ საკვლევ ჯგუფად: საკონტროლო, ჯგუფი, რომელიც იღებდა მხოლოდ ნიკოტინს, ჯგუფი რომელიც იღებდა MPTP-ს, ჯგუფი, რომელიც იღებდა MPTP+ნიკოტინს. ექსპერიმენტული ცხოველების შავი სუბსტანციის უჯრედების კვლევამ აჩვენა, რომ მპტპ იწვევდა დოფამინერგულ დეფიციტს, ასევე არღვევდა გლუტამატურ და პურინურ მეტაბოლიზმს, მაშინ, როცა ნიკოტინი ნორმალიზებდა ყველა ზემოაღნიშნულ პროცესს.

შეჯამებისთვის, შეიძლება ითქვას, რომ ნიკოტინს გააჩნია პროტექტორული ეფექტი პარკინსონის დაავადების დროს მიმდინარე გლუტამატური და პურინული მეტაბოლიზმის დარღვევების წინააღმდეგ.

1. Introduction. Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by dopaminergic neuron loss in the substantia nigra and striatal dopamine depletion. In addition to motor symptoms, PD involves cognitive, emotional, and gastrointestinal disturbances. Metabolic dysfunction and neuroinflammation play critical roles in its pathogenesis [1,2].

Disruptions in glutamate-glutamine cycle and purine metabolism, particularly glutamate–glutamine cycling and purine nucleotide turnover, have been implicated in excitotoxicity, oxidative stress, and mitochondrial impairment in PD [3,4]. Altered activity of enzymes such as glutaminase, glutamate dehydrogenase, AMP-deaminase, and IMP-dehydrogenase contributes to neuronal damage [5]. Uric acid, a purine end-product with antioxidant properties, has shown inverse associations with PD severity [6].

Nicotine, though widely known as a tobacco alkaloid, has demonstrated neuroprotective effects in PD models. It interacts with nicotinic acetylcholine receptors, modulating inflammation, oxidative stress, and dopaminergic survival [7]. However, its impact on some metabolic pathways remains unclear.

This study explores nicotine's influence on glutamatergic and purinergic metabolism in a mouse model of PD induced by MPTP, focusing on neurotransmitter levels, enzyme activity, and metabolic intermediates.

2. Materials and Methods. Eighty 8-week-old BALB/c male mice (~22 g) were housed under controlled conditions (12 h light/dark cycle, ad libitum food and water). After 7 days of acclimatization, mice were randomly divided into four groups (n=20/group): control (saline injections ×4 at 2-h intervals), nicotine (200 μg/mL in drinking water for 14 days), MPTP (20 mg/kg ×4, intradermally every 2 h), and MPTP+nicotine (nicotine starting 72 h after MPTP). Nicotine dose and duration followed established neuroprotective protocols; solutions were freshly prepared daily.

On day 17, mice were euthanized under deep anaesthesia. Brains were rapidly removed, and the substantia nigra was dissected as described earlier, using a brain matrix and stereomicroscope guided by a mouse brain atlas [8]. Samples were immediately frozen and stored at –80 °C.

Dopamine, tyrosine hydroxylase, and dopa-decarboxylase were measured using ELISA kits (Cat# MBS761192, MBS926829, MBS2125304). Glutamate and glutamine (Cat# MBS8309696, MBS169323), glutaminase, glutamate dehydrogenase, and aspartate aminotransferase (Cat# MBS8243221, MBS4504306, MBS4504237), and ammonia (Cat# ab83360) were quantified. AMP, IMP, and uric acid levels, along with AMP-deaminase and IMP-dehydrogenase activities (Cat# MBS7238172, MBS3807500, MBS7226239, MBS9921208, MBS2540398), were analysed according to manufacturers' instructions using mouse-specific reagents.

3. Results and Discussion. Dopamine levels were significantly reduced by MPTP administration ($F(3,76) = 10.55$, $p < 0.001$), reflecting the neurotoxic damage to dopaminergic neurons. Nicotine treatment effectively restored dopamine concentrations ($F(3,76) = 9.76$, $p < 0.001$), suggesting its neuroprotective role. Similarly, the activities of tyrosine hydroxylase and dopa-decarboxylase, key enzymes in dopamine synthesis, were decreased following MPTP exposure ($F(3,76) = 13.08$, $p < 0.001$ and $F(3,76) = 5.64$, $p < 0.01$, respectively) but normalized by nicotine administration ($F(3,76) = 3.88$, $p < 0.05$ and $F(3,76) = 6.01$, $p < 0.01$). No significant effects were seen in the nicotine-only group, indicating that nicotine's restorative effects are primarily evident under neurodegenerative conditions (Figure 1).

As shown in Figure 2, MPTP significantly increased glutamate levels ($F(3,76) = 16.71$, $p < 0.001$), which were reduced by nicotine ($F(3,76) = 3.55$, $p < 0.05$). Glutamine, which was decreased by MPTP ($F(3,76) = 7.01$, $p < 0.001$), was restored by nicotine ($F(3,76) = 5.43$, $p < 0.01$). Similarly, the elevated ammonium levels ($F(3,76) = 9.12$, $p < 0.001$) were normalized by nicotine ($F(3,76) = 10.88$, $p < 0.001$).

These changes correlated with enzyme activities: nicotine enhanced glutaminase ($F(3,76) = 8.69$, $p < 0.001$) and aspartate aminotransferase ($F(3,76) = 15.44$, $p < 0.001$), and normalized the reduced glutamate dehydrogenase activity ($F(3,76) = 12.08$, 21.03, 17.89, and 15.91; all $p < 0.001$).

Purine metabolism studies (Figure 3) showed that AMP levels increased in the MPTP group ($F(3,76) = 11.14$, $p < 0.001$), which was normalized by nicotine ($F(3,76) = 8.39$, $p < 0.001$). In contrast, IMP levels, which were reduced by MPTP ($F(3,76) = 5.44$, $p < 0.01$), were normalized in the nicotine group ($F(3,76) = 16.04$, $p < 0.001$). In parallel, the activity of AMP-deaminase, which was decreased in the MPTP group ($F(3,76) = 7.16$, $p < 0.001$), increased after nicotine administration ($F(3,76) = 6.00$, $p < 0.01$). As for IMP Dehydrogenase, no significant changes were observed in its activity. Uric acid concentration was decreased in MPTP (group three) animals ($F(3,76) = 4.99$, $p < 0.01$) and increased in group four animals ($F(3,76) = 9.37$, $p < 0.001$). It is noteworthy that in the animals of the second group (nicotine only) no changes were observed in any of the studied parameters.

Figure 1. Dopamine levels (μmol/mg) (A), tyrosine hydroxylase activity (U/mg) (B), and dopa-decarboxylase activity (U/mg) (C). Data represent mean ± SEM. Significance annotations: P ≤ 0.05, P ≤ 0.01, P ≤ 0.001 compared to Control group (Group I); #P ≤ 0.05, ##P ≤ 0.01, ###P ≤ 0.001 compared to MPTP group (Group III).

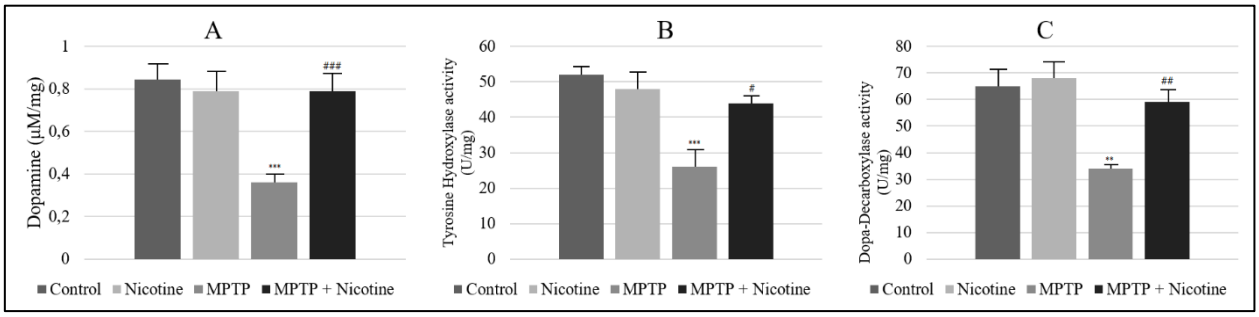


Figure 2. Glutamate (A), Glutamine (B), and Ammonia (C) levels (μmol/mg). Glutaminase (D), Glutamate Dehydrogenase (E), and Aspartate aminotransferase (F) activity (U/mg). Data represent mean ± SEM. Significance annotations: P ≤ 0.05, P ≤ 0.01, P ≤ 0.001 compared to Control group (Group I); #P ≤ 0.05, ##P ≤ 0.01, ###P ≤ 0.001 compared to MPTP group (Group III).

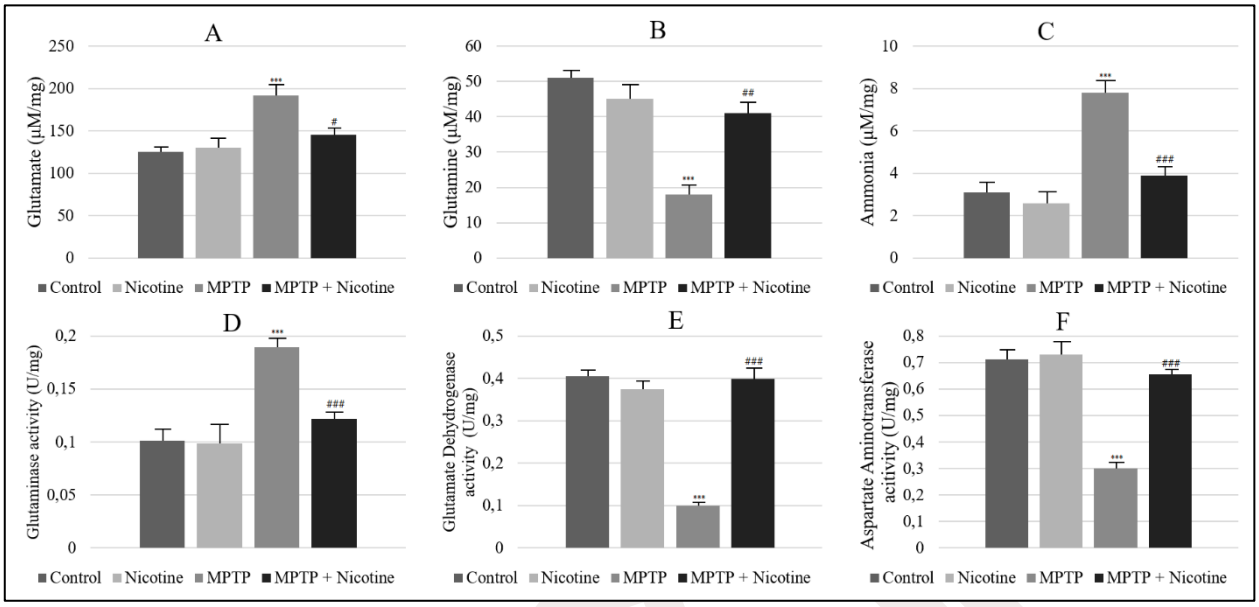
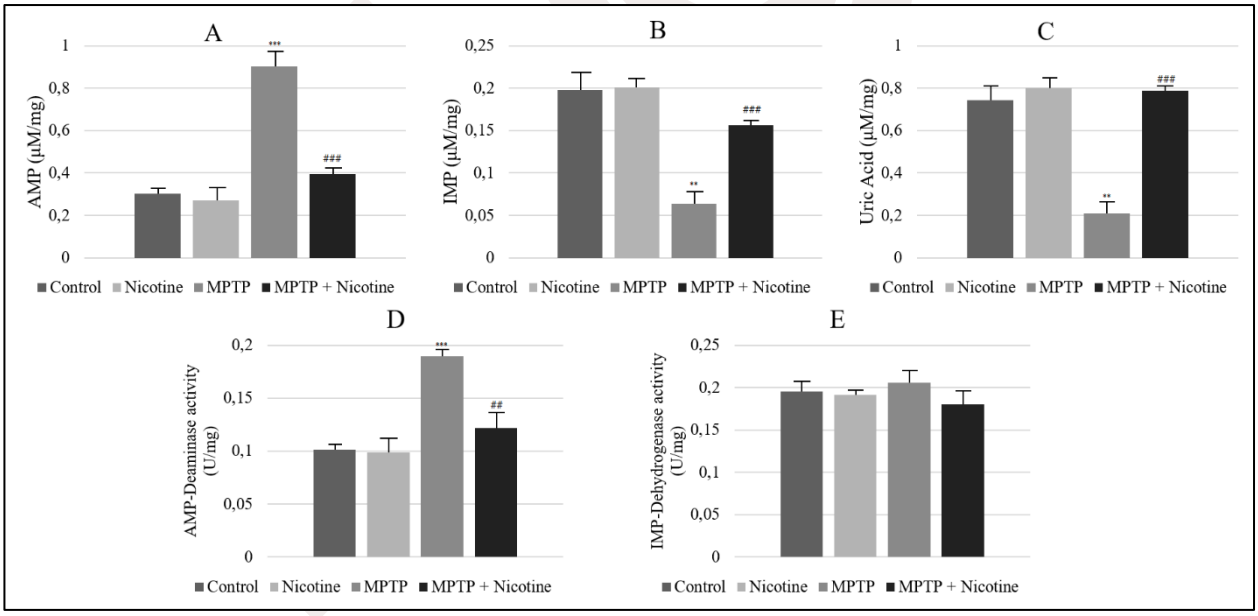


Figure 3. AMP (A), IMP (B), and Uric acid (C) levels (μmol/mg). AMP-Deaminase (D), and IMP-Dehydrogenase (E) activity (U/mg). Data represent mean ± SEM. Significance annotations: P ≤ 0.05, P ≤ 0.01, P ≤ 0.001 compared to Control group (Group I); #P ≤ 0.05, ##P ≤ 0.01, ###P ≤ 0.001 compared to MPTP group (Group III).



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SUMMARY

Parkinson's disease is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons and metabolic imbalances. This study aimed to determine whether nicotine modulates MPTP-induced parkinsonism in mice. BALB/c mice were divided into four groups: control, nicotine-only, MPTP-treated, and MPTP+nicotine. Analysis of substantia nigra tissue revealed that MPTP caused dopaminergic deficits and disrupted glutamate and purine metabolism, while nicotine treatment normalized these alterations. In conclusion, nicotine exhibits a protective effect against glutamate and purine metabolic disturbances associated with Parkinson's disease.

Keywords: Effects, nicotine, glutamate-glutamine, cycle, purine, mouse model, Parkinson's disease