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Immunomodulatory effects of detoxification agents on dendritic cell populations in methamphetamine addiction

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Abstract

Background and aim Drug abuse can impact the function of immune cells, leading to a compromised immune system response. This study aimed to investigate the immunomodulatory effects of Methamphetamine and its detoxification agents on peripheral blood dendritic cells.

Methods A total of 60 participants were enrolled, including 30 individuals with Methamphetamine addiction and 30 matched healthy controls. Participants were assessed at three time points: at the beginning of detoxification, at the end of detoxification, and one-month post-detoxification. Flow cytometry was employed to analyze dendritic cell subsets (CD11c + myeloid dendritic cells and CD123 + plasmacytoid dendritic cells) and surface marker expression (HLA-DR, CD11c, CD123).

Results The percentages of both CD11c + and CD123 + dendritic cells in peripheral blood were significantly lower in Methamphetamine addicts compared to the control group. Detoxification with Risperidone corrected this reduction, while the combination of Risperidone and Methylphenidate failed to produce any change in the percentage of dendritic cells. The expression of HLA-DR, CD11c, and CD123 markers was downregulated in the dendritic cells of Methamphetamine addicts. Treatment with Risperidone restored these markers, whereas the combination therapy further exacerbated the downregulation of these markers.

Conclusion The findings suggest that detoxification with Risperidone may help ameliorate the immunological disorders associated with Methamphetamine use.

Keywords Dendritic cells, Methamphetamine, Risperidone, Methylphenidate

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Introduction

Narcotics profoundly influence various body systems, particularly the immune system [1]. This effect is observed regardless of the duration of use, whether short-term or long-term. The underlying mechanisms primarily involve three key opioid receptors: μ (MOR), κ (KOR), and δ (DOR) opioid receptors [2].

Narcotics are known to suppress immune function, which is a significant factor contributing to the increased prevalence of infectious diseases and cancers among individuals with substance use disorders [3–5]. Additionally, the immunosuppressive effects of these substances can exacerbate the severity and prolong the duration of infections [6]. Conversely, some studies suggest that short-term use of narcotics as analgesics may stimulate certain aspects of the immune system [7].

Methamphetamine (METH) is a highly addictive central nervous system stimulant [8]. Its widespread use presents substantial public health and economic challenges globally [9]. It induces feelings of euphoria, excitement, and weight loss—effects comparable to those produced by cocaine. Methamphetamine functions as a substrate for the dopamine transporter, leading to increased levels of extracellular dopamine [10]. It achieves this by competing with dopamine for uptake and promoting the reverse transport of dopamine through the transporter [11].

The impacts of METH on the immune response have however to be completely determined,

be that as it may, there is developing proof that METH suppresses and modulates the immune system [12]. METH has critical impacts on both the innate and adaptive immune responses, with reported diminishments within the numbers of T cells, B cells, natural killer (NK) cells, and dendritic cells (DCs). METH leads to phenotypic alterations and an increase in macrophage proinflammatory responses, and expanded levels of the proinflammatory cytokine [13].

Detoxification is the initial step for individuals entering rehabilitation programs for substance use disorders. During this process, antipsychotic medications such as Risperidone—an antagonist of both opioid receptors and dopamine D2 receptors—are often administered to alleviate withdrawal symptoms associated with METH use [14, 15]. Methylphenidate was identified as a psychostimulant in 1954. It inhibits the reuptake of dopamine and norepinephrine [16, 17]. The addition of Methylphenidate was considered due to its stimulant properties, which may help mitigate fatigue and improve cognitive function and clinical outcomes during detoxification [18]. This combination aims to address both psychological and physical aspects of withdrawal, enhancing overall treatment efficacy [19–21]. Studies have shown that both Risperidone and Methylphenidate can be effective in treating Methamphetamine dependence [20], and a case study has suggested that Methylphenidate provided long-term support for METH use [22].

Historically, research on immunomodulatory effects has focused on lymphocytes. However, recent findings indicate that dendritic cells (DCs) mediate immune responses [23]. Dendritic cells are pivotal in presenting antigens to T lymphocytes and are essential for innate and adaptive immune responses [24–26]. They exhibit unique responses to various pathogens due to their diverse subgroups and strategic distribution throughout the body [27]. In humans, dendritic cells are classified into two major subgroups: CD11c + myeloid dendritic cells (mDCs) and CD123 + lymphoid dendritic cells (plasmacytoid DCs, pDCs) [28, 29].

While extensive research has been conducted on the effects of Methamphetamine in animal models [30], our understanding of its impact on human immune systems remains limited [12].

The objective of this study was to investigate the immunomodulatory effects of Methamphetamine and its detoxification agents on the dendritic cell population.

Materials and methods

Participants

A total of 30 individuals with Methamphetamine addiction and 30 healthy control subjects were enrolled in the study (Table 1). The sample size was determined based on the statistical advice from a biostatistician with experience in immunological studies. The control group was closely matched to the addicted group in terms of age, sex, weight, height, and body mass index (BMI). Control subjects were selected from a population of university staff and students who had never used psychotropic drugs. The general health of the control group was confirmed through physical examinations and routine biochemical and hematological tests. The study was approved by the Ethics Committee, and all participants provided informed consent.

All volunteers were free from infectious diseases, active inflammatory conditions, and other disorders affecting the immune system. Urine samples collected from the control group tested negative for morphine and Methamphetamine.

Table 1 Demographic characteristics of volunteers included in the study

Sex	Control group	Experiment group
	Male	Male
Age (Mean of years ± SD)	30.57 ± 3.21	30.17 ± 5.47
Height (Mean of cm ± SD)	172.29 ± 6.07	171.13 ± 6.04
Weight (Mean of kg ± SD)	73.80 ± 5.63	69.85 ± 12.26
Body Mass Index (Mean ± SD)	24.87 ± 1.57	23.912 ± 4.11

The addicted group was selected based on specific criteria: individuals who consumed more than 500 mg of Methamphetamine daily for over one year, had a history of addiction to other drugs for no longer than three months in the past, and exhibited positive urine test results for Methamphetamine above the detection threshold. Those who were positive for HBV, HCV, and HIV and showed psychiatric illnesses other than addiction were excluded from the study.

The group of 30 addicted volunteers was divided into two subgroups of 15 individuals each. One subgroup received Risperidone, while the other subgroup was administered both Risperidone and Methylphenidate concurrently. The initial dose of Risperidone was 5 mg, which was increased to 7.5 mg by the end of the study. Methylphenidate was administered in a tapering manner over ten days (10 mg every 8 h). In this study, we assessed changes in dendritic cell populations in individuals addicted to Methamphetamine at three distinct time points: at the beginning of the trial (before treatment with the detoxification agents), at the end of detoxification, and up to one month following detoxification.

Flow cytometry

Mononuclear cells were isolated from peripheral blood samples using Ficoll density gradient centrifugation. A concentration of 25×10^6 cells was obtained, and 20 µl (equivalent to 5×10^5 cells) was transferred to FACS tubes. Each tube received 15 µl of a cocktail containing anti-CD3, CD14, CD16, CD19, CD20, and CD56 antibodies labeled with FITC (Lin-1), along with 5 µl of anti-CD34 antibody labeled with FITC (to exclude CD34 + HLA-DR + precursors) and 5 µl of HLA-DR antibody labeled with PerCP.

For three-color flow cytometry analysis, 5 µl of PE-labeled CD123 antibody was added to identify Lin-/HLA-DR+/CD123 + plasmacytoid dendritic cells (pDCs). In comparison, another tube received 5 µl of PE-labeled CD11c antibodies to identify Lin-/HLA-DR+/CD11c + myeloid dendritic cells (mDCs). Samples were analyzed using a FACScan flow cytometer (BD Biosciences, San Jose, CA), and data were processed using FlowJo software [31].

Statistical analysis

One-way analysis of variance (ANOVA) was employed to assess statistical significance between experimental groups. Post-hoc tests were performed using Tukey's HSD (Honestly Significant Difference) test to determine specific group differences when ANOVA indicated significant effects. All data are presented as mean ± SEM. P-values < 0.05 were considered statistically significant ($^*p < 0.05$, $^{**}p < 0.01$).

Results

Determination of the frequency of peripheral blood dendritic cells in volunteers

This study identified two major dendritic cell (DC) subsets in peripheral blood mononuclear cells (PBMCs): Lin – HLA-DR + CD11c + myeloid dendritic cells (mDCs) and Lin – HLA-DR + CD123 + plasmacytoid dendritic cells (pDCs) (Fig. 1).

To quantify the number of dendritic cells, 100,000 cells were counted within the gate of mononuclear cells. The percentage of peripheral blood dendritic cells in Methamphetamine addicts was significantly lower compared to the control group (Fig. 2A). The percentage of CD11c + DCs in the peripheral blood of Methamphetamine addicts also showed a significant decrease compared to controls (Fig. 2B). Similarly, the percentage of CD123 + DCs in the peripheral blood of Methamphetamine addicts was lower than that of the controls (Fig. 2C).

Changes in dendritic cell populations in Methamphetamine addicts were assessed at three distinct time points: at the beginning of the trial (before treatment with the detoxification agents), at the end of detoxification, and up to one month after detoxification (prior to the onset of withdrawal symptoms). Detoxification with Risperidone restored the percentage of peripheral blood dendritic cells in Methamphetamine addicts. However, detoxification with both Risperidone and Methylphenidate did not reverse this reduction (Fig. 3A).

As illustrated in Fig. 3B, detoxification with Risperidone corrected the percentage of CD11c + DCs in the peripheral blood of Methamphetamine addicts. In contrast, detoxification with Risperidone and Methylphenidate did not restore the reduced percentage of CD11c + DCs in these individuals.

Risperidone treatment led to a significant increase in the previously reduced percentage of CD123 + dendritic cells in the peripheral blood of Methamphetamine addicts. However, when compared to the control group, detoxification with both Risperidone and Methylphenidate resulted in a significant decrease in the percentage of CD123 + DCs in the peripheral blood of addicts (Fig. 3C).

The expression of HLA-DR, CD11c and CD123 markers on CD11c + and CD123 + dendritic cells in volunteers

This study evaluated the mean fluorescent intensity (MFI), which represents the expression level of cell surface markers, for HLA-DR, CD11c, and CD123 on dendritic cells in the peripheral blood of volunteers. As depicted in Fig. 4A, the expression level of HLA-DR on the surface of peripheral blood dendritic cells from Methamphetamine addicts was significantly decreased compared to that in the control group.

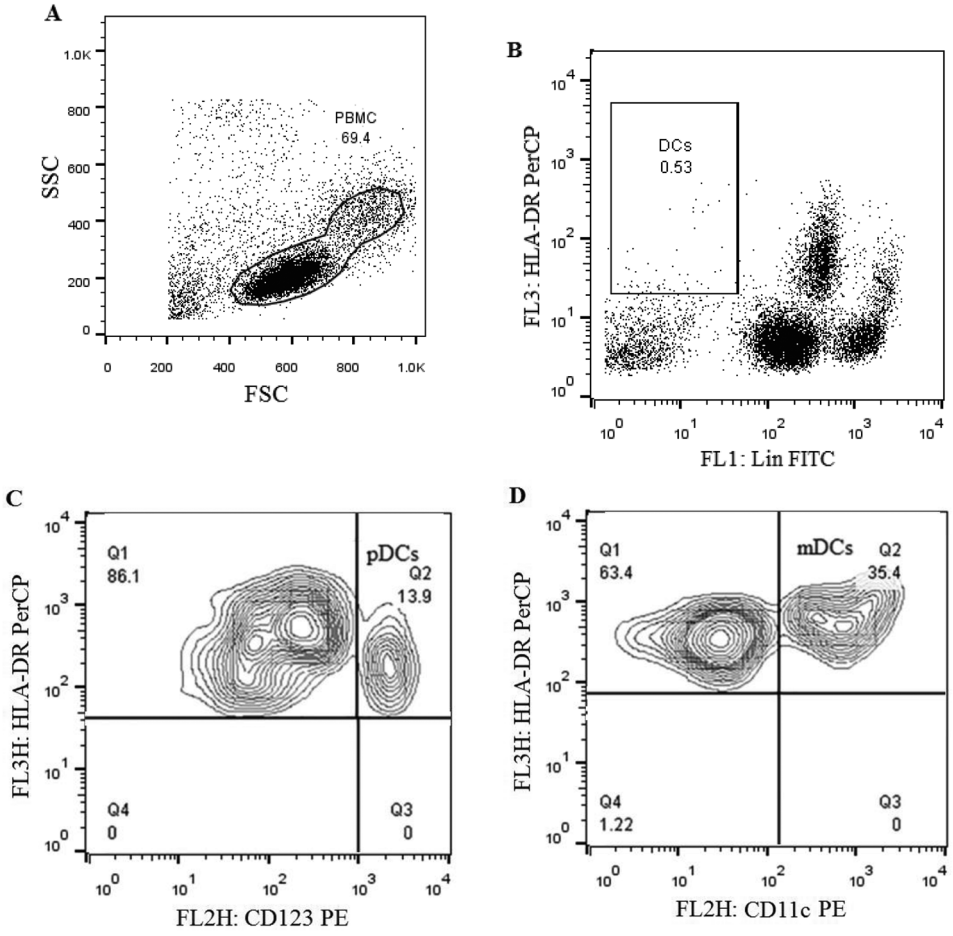

Fig. 1 Example of flow cytometry analysis and gating strategy for identifying and quantifying blood dendritic cell subsets. The PBMC (peripheral blood mononuclear cell) population is identified by a combination of forward/side scatter characteristics (**A**), and DC was identified within the lineage (CD3, CD14, CD16, CD19, CD20, CD56, and CD34)-negative (Lin–) HLA-DR+ (**B**). One representative experiment demonstrates the gating strategy for identifying DC subsets (**C** and **D**). mDCs: myeloid DCs (CD11c+), pDCs: plasmacytoid DCs (CD123+)

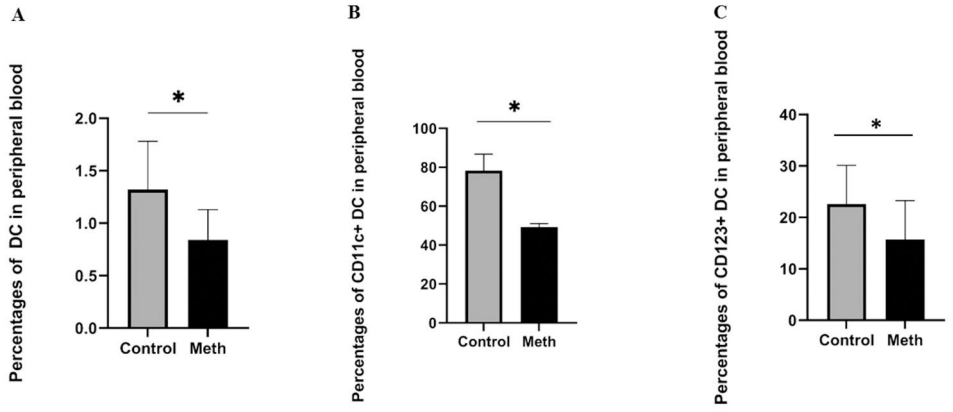

Fig. 2 Percentage of peripheral blood dendritic cells, CD11c, and CD123 dendritic cells in the control group and Methamphetamine addicts. Percentage of peripheral blood dendritic cells (**A**), peripheral blood CD11c+ (**B**), and peripheral blood CD123 + dendritic cells (**C**) in the control group and Methamphetamine addicts. DC = Dendritic cell, Meth = Methamphetamine. Data are presented as mean ± standard error. The results were extracted from the analysis of 100 thousand mononuclear cells. The sign * indicates $P < 0.05$ compared to the control

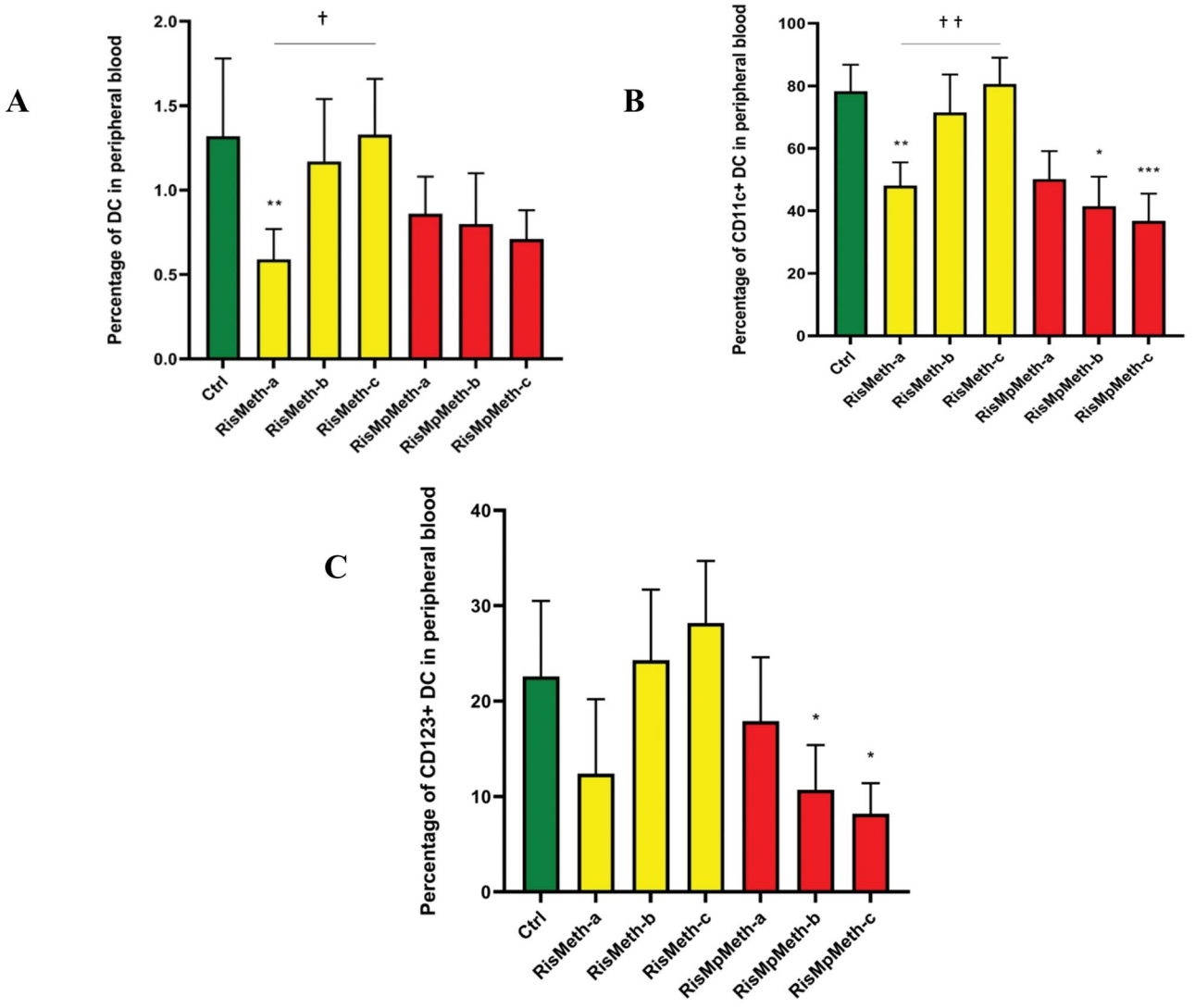

Fig. 3 The percentage of dendritic cells, CD11c + dendritic cells, and CD123 + dendritic cells in the peripheral blood of Methamphetamine addicts during the detoxification period. The percentage of dendritic cells (**A**), CD11c + dendritic cells (**B**), and CD123 + dendritic cells (**C**) in the peripheral blood of Methamphetamine addicts during the detoxification period compared to control group. DC = Dendritic cell, RisMeth = Methamphetamine addicts treated with Risperidone, RisMpMeth = Methamphetamine addicts treated with Risperidone and Methylphenidate, a = beginning of the trial, b = End of detoxification, c = no more than one month after detoxification. Data is presented as mean ± standard deviation. The results are obtained from the analysis of 100,000 mononuclear cells. The signs *(†) **(††) and ***(†††) indicate $P < 0.05$, $P < 0.005$, and $P < 0.0005$, respectively. The * sign for comparisons to the control, and the † sign denotes group comparisons

The level of CD11c expression on the surface of peripheral blood CD11c DCs in Methamphetamine users was notably less than what was seen in the control group as depicted in Fig. 4B.

Furthermore, the expression level of CD123 on the surface of peripheral blood CD123 + DCs from Methamphetamine addicts was significantly lower than that observed in the control group (Fig. 4C).

As shown in Fig. 5A, detoxification with Risperidone significantly altered the reduced expression of the HLA-DR molecule on the surface of peripheral blood dendritic cells in Methamphetamine addicts. However, the combination of Risperidone and Methylphenidate did not restore the decreased expression of HLA-DR on peripheral blood dendritic cells in this group.

Detoxification with Risperidone resulted in a significant increase in the expression of the CD11c molecule on CD11c + dendritic cells in the peripheral blood of Methamphetamine addicts. In contrast, the combination of Risperidone and Methylphenidate did not improve the reduced expression of CD11c on the surface of these CD11c + dendritic cells (Fig. 5B).

Neither detoxification regimen was able to correct the diminished expression of the CD123 molecule on the

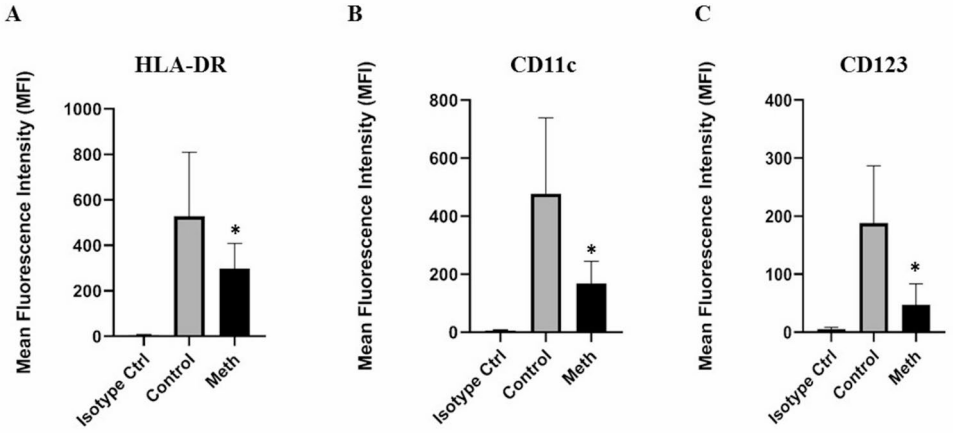

Fig. 4 Mean fluorescence intensity (MFI) of HLA-DR, CD11c, and CD123 peripheral blood dendritic cells. Mean fluorescence intensity (MFI) of the HLA-DR peripheral blood dendritic cell molecule on the surface of peripheral blood dendritic cells (**A**), the CD11c molecule on the surface of CD11c + dendritic cells (**B**), and the CD123 molecule on the surface of CD123 + dendritic cells (**C**) of Methamphetamine addicts. DC = Dendritic cell, Meth = Methamphetamine. Data are presented as mean ± standard error. The results were extracted from the analysis of 100 thousand mononuclear cells. The sign * indicates $P < 0.05$ compared to the control

surface of CD123 + dendritic cells in the peripheral blood of Methamphetamine addicts when compared to the control group (Fig. 5C).

Discussion

Dendritic cells are crucial for processing and presenting antigens, stimulating naïve T cells, and regulating subsequent immune responses. In the bone marrow, newly generated dendritic cells migrate through the bloodstream to various peripheral tissues [23]. Consequently, the presence of circulating blood dendritic cells can provide insights into the overall status of the immune system. For example, a study by Lissoni et al. found that decreased levels of circulating blood dendritic cells were strongly associated with suppressed immune function in patients with advanced malignant tumours [32].

In the current study, we assessed the overall percentages of two main subgroups of dendritic cells in the peripheral blood of Methamphetamine addicts and examined their surface markers.

We found that individuals addicted to Methamphetamine exhibited significantly lower total dendritic cell counts, as well as reduced numbers of CD11c + and CD123 + dendritic cells compared to healthy controls. Harms et al.. have shown a decrease in both proportion and number of DCs in Methamphetamine addicts [33]. This finding suggests a potential defect in the immune system. The observed decrease in dendritic cell percentages could stem from several factors, including reduced production rates in the bone marrow, disruptions in monocyte responses to differentiation signals, inhibition of factors that promote dendritic cell differentiation, or the induction of apoptosis in dendritic cells [34]. Our results align with previous studies indicating that drug-induced immunosuppression can lead to adverse health outcomes in substance users [35, 36]. Although further studies are needed to confirm these possibilities, our findings suggest that dendritic cells are involved in the immunopathogenesis of disorders associated with Methamphetamine use.

In Methamphetamine addicts, detoxification with Risperidone restored the total percentage of dendritic cells as well as the numbers of CD11c + and CD123 + dendritic cells to levels comparable to those of the control group. This restoration highlights Risperidone's potential role in reversing some immunosuppressive effects associated with Methamphetamine use. In a study by Chen et al., Risperidone modulates the cytokine and chemokine release of DCs [37]. Risperidone, as an antagonist of both dopamine and opioid receptors, may exert its immunomodulatory effects by influencing cytokine production and T cell activation [38]. Specifically, blockade of dopamine receptors can reduce the production of pro-inflammatory cytokines, while opioid receptor antagonism can enhance immune cell function [39]. In contrast, treatment with a combination of Risperidone and Methylphenidate did not yield similar benefits; instead, it exacerbated reductions in dendritic cell counts.

HLA-DR is a critical molecule expressed on the surface of antigen-presenting cells. It stimulates T cells and serves as an indicator of dendritic cell activity [26]. Our data indicate that the expression of HLA-DR is decreased in the dendritic cells of individuals addicted to Methamphetamine, suggesting compromised antigen presentation capabilities. This reduction may further increase susceptibility to infectious diseases among this population [40]. In a study by Akbari et al., it was indicated that HLA-DR is downregulated in dendritic cells of heroin addicts [31]. The decreased expression of HLA-DR in Methamphetamine addicts was restored following

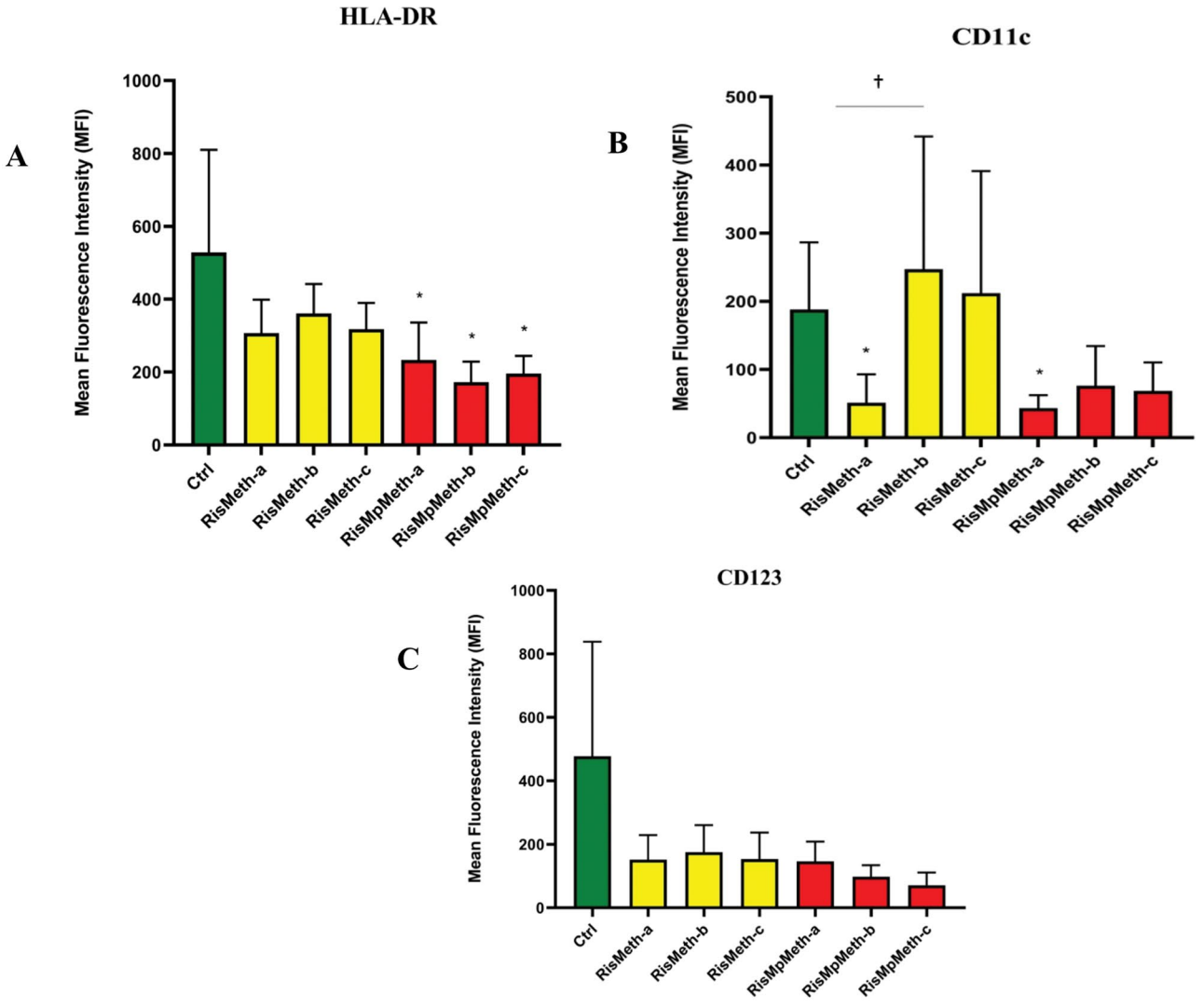

Fig. 5 Mean fluorescence intensity (MFI) of the HLA-DR, CD11c, and CD123 molecules on the surface of peripheral blood dendritic cells. The level of HLA-DR molecule expression on the surface of dendritic cells (**A**) CD11c on the surface of CD11c + dendritic cells (**B**) and CD123 molecule on the surface of CD123 + dendritic cells (**C**) in the peripheral blood of Methamphetamine addicts during the detoxification period compared to the control group. DC = Dendritic cell, RisMeth = Methamphetamine addicts treated with Risperidone, RisMpMeth = Methamphetamine addicts treated with Risperidone and Methylphenidate, a = beginning of the trial, b = End of detoxification, c = no more than one month after detoxification. Data is presented as mean ± standard deviation. The results are obtained from the analysis of 100,000 mononuclear cells. The signs *(†) **(††) and ***(†††) indicate $P < 0.05$, $P < 0.005$, and $P < 0.0005$, respectively. The * sign for comparisons to the control, and the † sign denotes group comparisons

treatment with Risperidone. In contrast, co-administration of Risperidone and Methylphenidate exacerbated the downregulation of HLA-DR expression. The decreased expression of HLA-DR in methamphetamine addicts may result from multiple factors, including oxidative stress, cytokine dysregulation, and epigenetic modifications [41, 42]. The clinical implications of these findings are significant. Reduced HLA-DR expression can increase the risk of infections, autoimmune diseases, and cancer [43]. Therefore, identifying and treating immune dysfunction in individuals addicted to Methamphetamine is of paramount importance.

This study revealed that Methamphetamine significantly reduced the expression of the CD11c molecule in peripheral blood CD11c + dendritic cells among addicts. CD11c is a surface protein expressed on myeloid dendritic cells (mDCs) that plays a role in cell adhesion, migration, and immune cell activation. It acts as a receptor for complement iC3b and is involved in phagocytosis and antigen presentation [44]. Reduced expression of CD11c can impair the ability of dendritic cells to perform their immune functions. In contrast to our results, Akbari et al. showed that heroin can significantly increase the expression of CD11c molecules on the surface of myeloid DCs [31]. This discrepancy may be due to differences in

the mechanisms of action of heroin and Methamphetamine, as well as differences in study populations, laboratory methods, or other factors. Risperidone treatment restored CD11c expression to levels comparable to those in the control group; however, co-administration with Methylphenidate exacerbated this reduction. Risperidone may improve CD11c expression by modulating the immune system and reducing inflammation [38, 45].

Lymphoid dendritic cells require IL-3 for differentiation, leading to high expression of the IL-3 receptor alpha chain (CD123) [46]. In our study, Methamphetamine notably decreased the expression of CD123. This reduction suggests a potential impairment in the development and function of pDCs, which are critical for antiviral and antitumor immune responses [47]. The decreased CD123 expression in Methamphetamine addicts may contribute to their increased susceptibility to infections and other immune-related complications. However, Akbari et al.. observed that heroin had no significant effect on the expression of the CD123 molecule [31]. This discrepancy may be due to differences in the mechanisms of action of heroin and Methamphetamine, as well as differences in study populations, laboratory methods, or other factors. Heroin primarily acts on opioid receptors, while Methamphetamine has a broader range of effects on the nervous and immune systems. It is possible that these different mechanisms of action lead to different effects on CD123 expression [48].

Detoxification with Risperidone increased CD123 expression; however, when combined with Methylphenidate, this expression was reduced, although these changes were not statistically significant. Risperidone, an antagonist of dopamine and serotonin receptors, may promote the differentiation and survival of pDCs, leading to increased CD123 expression [49]. The lack of statistical significance in the Methylphenidate group may be due to the small sample size or other limitations of the study. Future studies with larger sample sizes are needed to confirm these findings and to investigate the underlying mechanisms.

These results emphasize the importance of understanding drug interactions during detoxification processes. Risperidone blocks opioid and dopamine D2 receptors [50], while Methylphenidate increases dopamine levels by blocking the reuptake of dopamine and norepinephrine into neurons [18]. Methylphenidate increases dopamine levels in the synapse, potentially "overriding" the receptor blockade caused by Risperidone. The potential mechanism might explain why the effects of Risperidone diminish when combined with Methylphenidate.

In conclusion, our study demonstrates that long-term Methamphetamine use has significant immunosuppressive effects mediated through alterations in dendritic cell function. While Risperidone appears beneficial during detoxification by mitigating some negative impacts of Methamphetamine on the immune system, Methylphenidate's stimulatory properties may complicate recovery efforts. Future research should explore these interactions further and consider their implications for clinical practice.

Limitations of the study

The follow-up period in this study was limited to one-month post-detoxification, which may not adequately capture long-term changes in immune function or treatment effects. The study lacked randomization, potentially introducing selection bias and limiting causal inference. Several confounding factors, such as nutritional status and co-morbid conditions, were not controlled for, which could affect the outcomes. Although the sample size was determined based on power analysis, the relatively small size may limit the generalizability of the findings. The absence of a control group with active drug users receiving alternative detoxification treatments presents a gap in the evaluation of treatment efficacy. Lastly, the lack of double-blinding could introduce bias in evaluating outcomes and affect the objectivity of the results.

Conclusion

Dendritic cells in individuals addicted to Methamphetamine may lose their ability to respond effectively to invading pathogens, potentially increasing their susceptibility to infections. Impairments in dendritic cell function could also diminish the effectiveness of vaccines in this population. During detoxification from Methamphetamine, the administration of Risperidone was found to mitigate some of the adverse effects associated with Methamphetamine use. However, the combination of Risperidone and Methylphenidate exacerbated these adverse effects. Although this study is grounded in natural science experimentation, its findings may have practical implications for clinical practice.

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Author contributions

H.F and A.G wrote and edite the main manuscript. H.F prepared tall the figures. H.F and A.G reviewed the manuscript. M.R analysed the data. M.M, G.M and A.G supervised the work. H.S collected the samples.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The Ethics Committee of Arak University of Medical Sciences approved this study (Ethical Code: IR.ARAKMU.REC.1390.113.9) and informed consent to participate was obtained from all study participants.

Competing interests
The authors declare no competing interests.

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