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Research Article

Differential Immunomodulatory Potential of Silver Nanoparticles and Effect on the Kynurenine Pathway in Male Wistar Rats

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Silver nanoparticles are increasingly being used in a wide variety of ways that may lead to frequency of exposure for humans and the environment. Thus, it is necessary to understand the biological effect(s) of these nanoparticles. Previously, we showed that AgNPs activated the kynurenine pathway in rat brain independently of oxidative stress in rats. This present study is aimed at evaluating the effect of AgNPs on some selected cytokines, redox parameters, and on the kynurenine level in rats. Male Wistar rats (130-150 g) were divided into 4 groups. Rats were grouped into control, AgNPs only (50 mg/kg bw), coadministration of AgNPs (50 mg/kg bw), and dexamethasone (100 mg/kg bw) and dexamethasone only (100 mg/kg bw). Results indicated that AgNPs did not significantly elevate MDA levels in rat plasma and brain relative to the control group. AgNPs caused a significant alteration in the level of rat brain and plasma total protein concentration. Meanwhile, AgNPs led to an elevation in the level of reduced glutathione (GSH) in rat plasma but decreased plasma kynurenine level significantly. Furthermore, IFN-γ level was reduced following AgNPs administration, IL-1β decreased across the treatment groups, while NF-κB was reduced in the dexamethasone only and AgNPs + dexamethasone groups when compared with the control. AgNPs led to increased IL-4 levels, while IL-10 levels decreased across the treatment groups. Taken together, our data showed a differential immunomodulatory potential of AgNPs in rats.

1. Introduction

Nanoparticles (NPs) are small substances with sizes ranging from 1 –100 nm; there are different types of nanoparticles differentiated by sizes, shapes, or properties [1]. Amongst metal nanoparticles, silver nanoparticles (AgNPs) have been known for better and broader usage [2]. AgNPs have been used in various products such as wound bandages as well as sterilizers, disinfectants, balms, clothing, and as food additives, bed sheets, washing machines, water purification, feeding bottles,

deodorizers, cutleries, and humidifiers [3]. Silver nanoparticles have been proved to possess unique characteristics such as biological properties and high electrical conductivity [4]. AgNPs are useful as drug-delivery carriers [5]. Also, AgNPs have a remarkable prospect for biomedical applications including the performance-enhanced therapeutic alternatives, detection and diagnosis platforms, enhancement of complex healthcare conditions, biomaterial device coatings, regeneration materials, and also novel antimicrobial agents [6].

Regardless of their biomedical prospects, AgNPs could harmfully interact with cellular biomolecules, thus, making them inherently toxic. Some toxic effects of AgNPs include oxidative stress and cell membrane rupture [7]. Besides, studies have shown that AgNPs could impact a number of cellular targets such as the kynurenine pathway activation, modulation of cytokine, and immune system, and stimulation of mitochondria function which may increase free radical production, thus, resulting in oxidative stress [8]. On the other hand, studies have shown that the production of ROS (oxidative stress) affects the activities of the immune system and the levels of neurotransmitters by prompting the synthesis of the neurotransmitter [9]. Adaptive immune responses can be stimulated by the generation of free radicals which impacts the metabolism of L-tryptophan. The adaptive immune response also may stimulate an increase in the levels of proinflammatory cytokines, which may eventually increase the activity of indoleamine 2,3, dioxygenase (IDO), a rate-limiting enzyme in the oxidative degradation of L-tryptophan of the kynurenine pathway. Increased IDO activity leads to reduced L-tryptophan levels available for serotonin synthesis. The decreased level of serotonin has been linked to conditions such as anxiety, insomnia, and depression. Together, these facts link free radical production and cytokine modulation to kynurenine pathway activation [10]. More so, the kynurenine pathway can be activated in presence of oxidative stress and inflammation [11]. In contrast, recent studies revealed that kynurenine pathway activation in the rat brain by AgNPs was independent of oxidative stress [11]. This finding may indicate that kynurenine pathway activation in the rat brain may be through other means including the inflammatory signalling processes. It has been shown that L-tryptophan breakdown through the kynurenine pathway may be activated via proinflammatory cytokines [12].

Therefore, this study is aimed at determining the effect of AgNPs on proinflammatory or anti-inflammatory cytokine, redox parameters, and the kynurenine pathway.

2. Materials and Methods

2.1. Chemicals and Reagents. Silver nanoparticles (AgNPs) were given by the nanomedicine group at NRCPD, Obihiro University of Agriculture and Veterinary Medicine, Obihiro, Japan. Dexamethasone, kynurenine, and Ehrlich reagent were products of Sigma Chemicals (St. Louis, MO, USA). The cytokine kits were the product of Cusabio (Cusabio Biotech, Wuhan, China). All other reagents were of analytical grade and used as supplied. The synthesis and characterization of the AgNPs have been previously reported [11, 13].

2.2. Animal Treatments and Grouping. Twenty-four (24) male Wistar rats (130-150 g) were obtained from the Department of Biochemistry, University of Ilorin, Kwara State, Nigeria. They were accommodated in a well-ventilated environment and placed in plastic cages with ad libitum access to pellet feed and clean water. Animals were distributed into four (4) groups containing six (6) rats and allowed to acclimatize for 14 days. Rats were distributed into groups; control, AgNPs, AgNPs plus dexamethasone (Ag + DEX) group, and dexamethasone (DEX) group. The rats were orally administered 50 mg/kg AgNPs based on previous reports [14] and 100 mg/kg dexamethasone [15] for 7 days. Dexamethasone was chosen because it is a modulator of IFN-gamma and it may have an effect on the kynurenine pathway. AgNPs and dexamethasone were dissolved in distilled water for daily oral administration.

2.3. Preparation of Organ Homogenates and Plasma. After cessation of treatments, the rats were placed mildly anesthetized using diethyl ether and sacrificed. The blood and the brain were collected. The blood collected in EDTA bottles was centrifuged at 5,000 rpm for 10 minutes using a centrifuge (model C5, LW Scientific, USA) to obtain plasma. The brain was homogenized in ice-cold sucrose solution (0.25 M) using a mechanical homogenizer, and the homogenates obtained were used for the biochemical analysis.

2.4. Biochemical Assays. Biochemical assays were carried to determine the concentrations of total protein, malondialdehyde (MDA), reduced glutathione (GSH), kynurenine, and nitric oxide. Also, the cytokine levels (interleukin 1β (IL 1β), IFN gamma (IFN-γ), nuclear factor-kappa B (NF-κB), interleukin 4 (IL-4), and interleukin 10 (IL 10)) were determined.

Total protein concentration using biuret was measured as described by Gornall et al. [16]. The method of Bentler [17] was used to evaluate the level of lipid peroxidation. The procedure for the determination of reduced glutathione (GSH) level was as stated by Jollow et al. [18]. Kynurenine concentration was determined as described by the method of Adeyemi et al. [13]. The nitric oxide level was as determined by Ilavarasan et al. [19]. The cytokine levels were determined according to the manufacturer's instruction (Cusabio Biotech, Wuhan, China) by using the quantitative sandwich principle.

2.5. Statistical Analysis. Data are presented as the mean ± standard error of mean (SEM) and analyzed using the one-way ANOVA and Tukey's multiple comparison test using GraphPad Software Inc., San Diego, CA, USA. Mean values at $p < 0.05$ were considered significant.

3. Results and Discussion

3.1. Results

3.1.1. Effects of AgNPs and Dexamethasone on Average Body Weights of Rats. The difference between the mean of weight of the rats in the various experimental groups was not statistically different before the commencement of treatment (data not shown). However, oral administration of

dexamethasone only and/or in combination with AgNPs caused a significant decrease ($p < 0.05$) in the average weight of rats compared with control (Figure 1).

3.1.2. Effects of AgNPs and Dexamethasone on Protein Concentration in Rat Brain and Plasma. The effects of AgNPs and dexamethasone treatment singly or in combination on the rat brain and plasma protein concentration are shown in Figures 2(a) and 2(b), respectively. The protein levels in rat plasma were significantly increased in the AgNPs treatment group, DEX, as well as the Ag + DEX ($p < 0.05$), and dexamethasone ($p < 0.01$). In contrast to the events in the plasma, protein concentration in the brain was significantly ($p < 0.001$) decreased as shown in Figure 2(a).

3.1.3. Effects of AgNPs and Dexamethasone on Rat Redox Status. Figure 3 shows the malondialdehyde (MDA) levels in both the rat brain and plasma. There was no significant ($p > 0.05$) difference in the MDA levels in rat brain and plasma across all the treatment groups.

Nevertheless, AgNPs, DEX ($p < 0.05$), or a combination of both treatments Ag + DEX ($p < 0.01$) caused a significant increase in the GSH level in rat plasma (Figure 4). However, GSH level was not significantly different in the rat brain after oral exposure to AgNPs, DEX, or a combination of both treatments Ag + DEX (Figure 4).

3.1.4. Effects of AgNPs and Dexamethasone on Kynurenine Concentration in Rat Brain and Plasma. Compared to the control, the rat plasma had a significant ($p < 0.001$) decrease in kynurenine level across all the treatment groups. In the rat brain, there was a nonsignificant change in the concentration of kynurenine in treated groups when compared to control groups. AgNPs only group had increased brain kynurenine concentrations, while the DEX or Ag + DEX groups had decreased kynurenine concentration (Figure 5).

3.1.5. Effects of AgNPs and Dexamethasone on Nitric Oxide (NO) Levels in Rat Brain and Plasma. Figure 6 shows a significant ($p < 0.001$) decrease in NO levels in the group administered DEX only, while a significant increase ($p < 0.01$) occurred in the plasma of rats administered Ag + DEX. There was a significant ($p < 0.05$) increase in NO levels in rat brain in groups administered AgNPs, DEX, or Ag + DEX compared to the control group.

3.1.6. Effects of AgNPs and Dexamethasone on Cytokines. Figures 7 and 8 show the effect of treatment with AgNPs and DEX on cytokine levels in the plasma of rats. There was a significant decrease ($p < 0.01$) in IFN-γ levels in the AgNPs group, while IFN-γ levels decreased nonsignificantly ($p > 0.05$) in the group administered Ag + DEX as compared to the control group (Figure 7(a)).

Figure 7(b) shows the effect of AgNPs and DEX on NF-κB levels in rat plasma. There was a significant increase ($p < 0.01$) in NF-κB levels in DEX and Ag + DEX groups as compared to the control group. Compared to the AgNPs, the Ag + DEX group had a significantly ($p < 0.05$) raised level of NF-κB in rat plasma. The IL-1β level decreased significantly ($p < 0.001$) in the AgNPs group, DEX, and Ag + DEX groups compared to the control (Figure 7(c)). Interleukin-four (IL-4) levels increased significantly ($p < 0.05$) in the group administered AgNPs compared with the control (Figure 8(a)). On the other hand, interleukin-10 (IL-10) levels decreased significantly ($p < 0.001$) in all the groups compared with the control (Figure 8(b)).

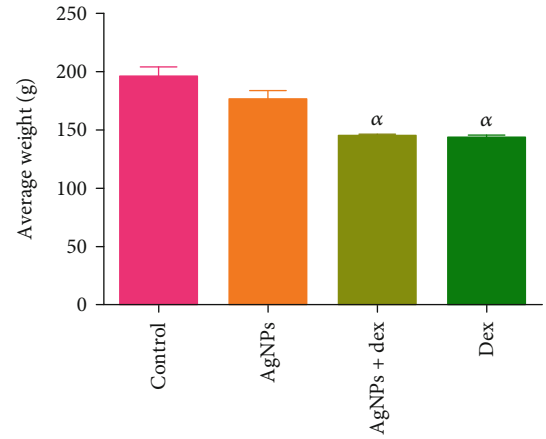

Figure 1: Effects of AgNPs and dexamethasone (DEX) on average body weights of rats. Data are expressed as mean of four replicates ± SEM. α versus control is significant at $p < 0.05$ in rats.

4. Discussion

AgNPs are regarded as safe and effective preservative agents in the cosmetic industry. They have been reported to exert cytostatic and antimicrobial effects, and consequently, they are used for a wide variety of medical purposes, e.g., wound bandages, prostheses, surgical instruments, and contraceptives [20]. In spite of the increasing number of benefits attributed to AgNPs, there are a handful of literature that suggest that they cause ROS production and oxidative damage [5, 11, 13, 14]. Reactive oxygen species are known to cause several human diseases via modification of macromolecules (proteins, lipids, and DNA) as well as activate biological pathways. One of such pathways is the kynurenine pathways responsible for the metabolism of about 95% of L-tryptophan in living cells. The kynurenine pathway produces a set of compounds collectively known as "kynurenines" which have immunomodulatory and psychiatric properties. Recently, we showed that silver nanoparticles activated the kynurenine pathway in the rat brain independently of oxidative stress [11]. In furtherance of our curiosity to understand the interaction of AgNPs with biomolecules in living cells, this present study investigated its effect on the activation of the kynurenine pathway in rat brain, redox parameters, and some pro/anti-inflammatory cytokines.

In the present study, AgNPs significantly increased protein concentration in rat plasma, but there was a decline in protein concentration in the brain (Figure 2). Studies have shown that AgNPs could cross the blood-brain barrier and induce changes in metabolism in the central nervous system [8, 21–23]. For example, Khan et al. [24] demonstrated that AgNPS induced the expression of proteins related to oxidative stress and neurodegeneration in an *in vitro* human

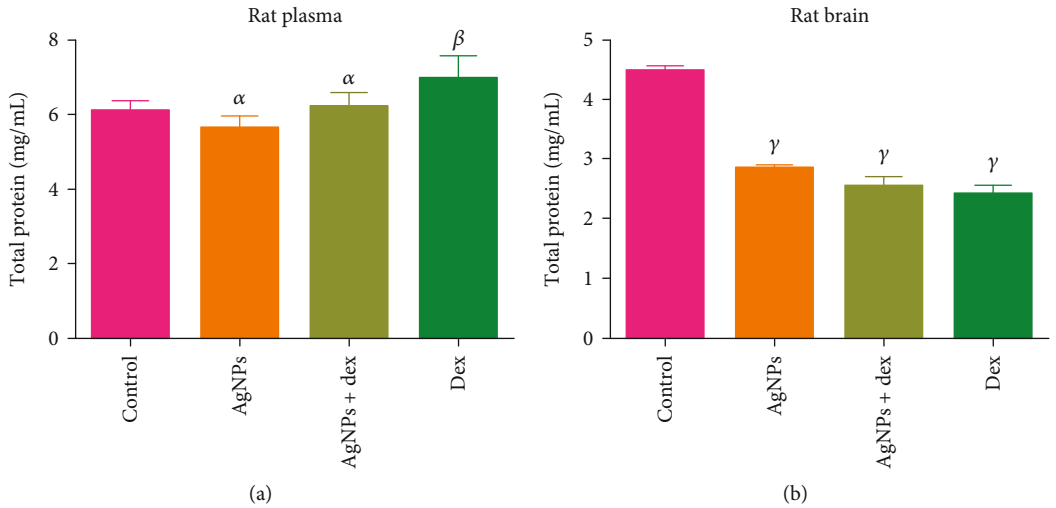

Figure 2: Effects of AgNPs and dexamethasone on total protein concentration in plasma (a) and brain (b) of rats. Data are shown as mean of four replicates ± SEM. α signifies $p < 0.05$, β signifies $p < 0.01$, and γ signifies $p < 0.001$ versus control.

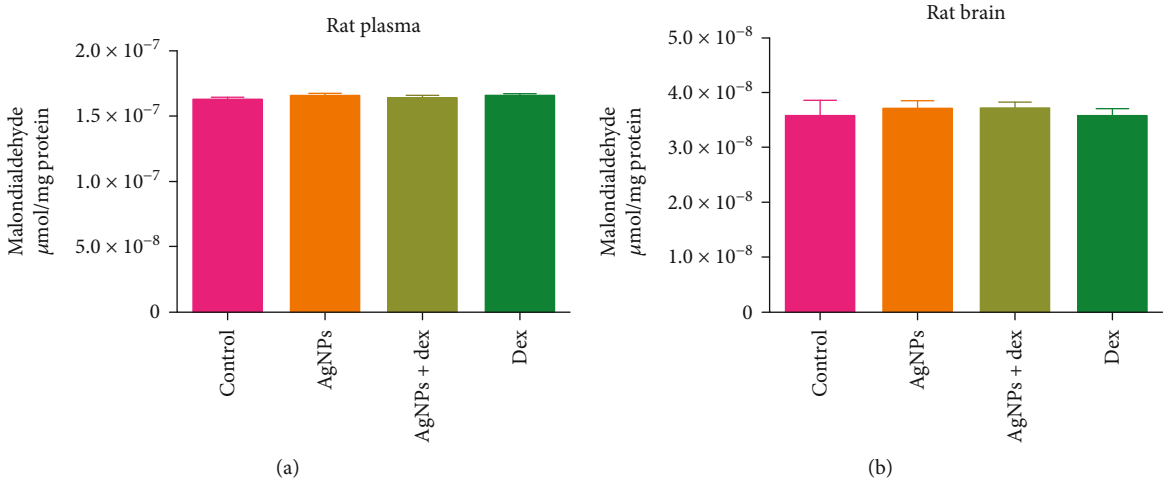

Figure 3: Effects of AgNPs and dexamethasone on MDA levels in plasma (a) and brain (b) of rats. Data are shown as mean of four replicates ± SEM.

blood-brain barrier model. To be particular, AgNPs downregulated protein responsible for brain homeostasis including glutathione peroxidases, while proteins involved in neurodegeneration were upregulated. Contrary to other reports that suggested a role for AgNPs in oxidative stress, in the present study, MDA and GSH levels were not significantly altered compared with the control. Considered together, this finding may indicate that AgNPs might not have caused oxidative stress nor altered the redox homeostasis in the rat brain (Figures 3 and 4). However, when AgNPs were coadministered with dexamethasone, there was an elevation of GSH levels in rat plasma. This may indicate a differential potentiating effect of dexamethasone on AgNPs in the plasma. It further emphasizes that the oxidative stress may not be involved in downstream effects of AgNPs which include the activation of kynurenine as suggested by Adeyemi et al. [11]. Furthermore, considering that the tripeptide GSH could be inducible in response to oxidative stress, it may be plausible to infer that elevated and/or sustained GSH concentration comparable to that of the control was an adaptive mechanism to counteract ensuing oxidative stress. In other words, having a sustained GSH level as seen in the present study could have led to the mopping-up of available ROS thereby responsible for the near absence of lipid peroxidation or low MDA concentration.

The relationship between inflammation and the brain kynurenine pathway is unclear and requires further investigation. In the present study, the effect of AgNPs on inflammatory markers such as nitric oxide (NO) and the kynurenine level was measured, in the presence and absence of dexamethasone exposure. Results revealed that the administration of AgNPs caused a significant increase in inflammatory marker nitric oxide (NO) in the rat brain (Figure 6). Although the kynurenine concentration increased in rat plasma, this was

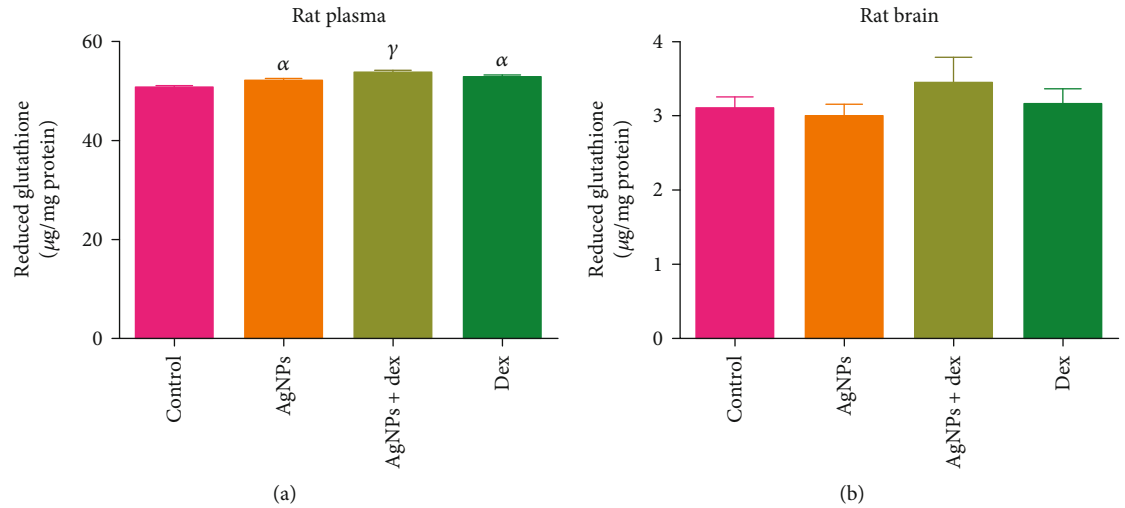

Figure 4: Effects of AgNPs and dexamethasone on the level of GSH in plasma (a) and brain (b) of rats. Data are shown as mean of four replicates ± SEM. α signifies $p < 0.05$, and γ signifies $p < 0.001$ versus control.

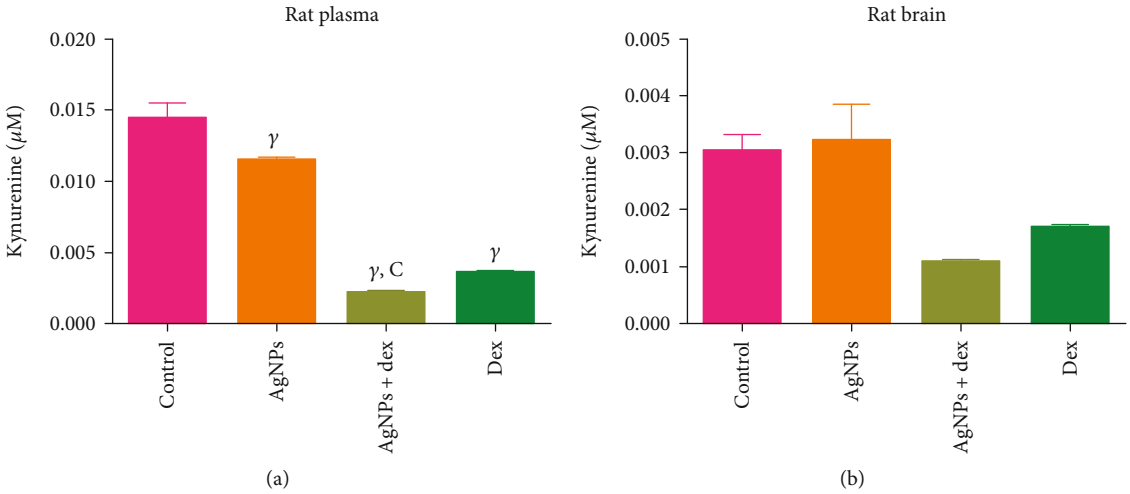

Figure 5: Effects of AgNPs and dexamethasone on kynurenine concentration in plasma (a) and brain (b) of rats. Data are shown as mean of four replicates ± SEM. γ signifies $p < 0.001$ versus control. c signifies $p < 0.001$ versus AgNPs.

not significant compared to control (Figure 7). In addition, there was a concomitant increase in NO level which may well correlate with kynurenine level, thus, suggesting that nitrosative stress/inflammation may likely play a role in the activation of the kynurenine pathway. Nitric oxide is a known IDO-1 inhibitor, thus, increased NO will lead to a decrease in kynurenine level.

In the present study, we also investigated the modulatory role of AgNPs on selected proinflammatory (IFN-γ and IL-1β) and anti-inflammatory (IL-4 and IL-10) cytokines. It has been shown previously that AgNPs possess immunogenicity property [25]. Also, earlier studies by Dantzer [26] showed that inflammation and modulation of IFN-γ are factors that drive L-tryptophan breakdown via the kynurenine pathway. IFN-γ stimulates macrophages and boosts the microbicidal activity of human cells to kill intracellular pathogens via the generation of RNS and ROS [27]. The kynurenine pathway has been observed to be upregulated by proinflammatory cytokines such as IFN-γ, and also the most potent activator of IDO-1 is IFN-γ suggesting that IFN-γ increases the level of kynurenine [28]. Additionally, it has been observed that AgNPs increased IFN-γ levels [27], and dexamethasone is a well-known suppressor of IFN-γ production [29]. Taken together, this may suggest that AgNPs increased kynurenine levels by elevating IFN-γ levels and also suggest that IFN-γ plays an intermediary role in the kynurenine pathway activation by AgNPs. However, in this present study, for reasons that are not clear, AgNPs decreased IFN-γ levels, while dexamethasone increased IFN-γ levels. In contrast, AgNPs caused increased levels of NF-κB though not statistically significant. NF-κB is known to be a potent regulator of cellular behavior, in particular, inflammatory responses, cellular growth, and apoptosis. NF-κB is an essential transcription factor necessary for the

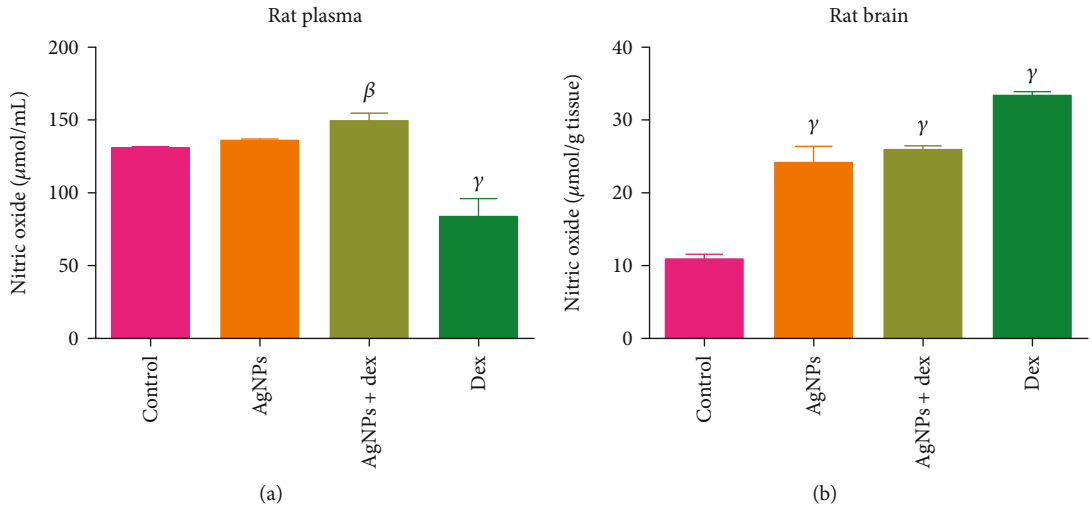

Figure 6: Effects of AgNPs and dexamethasone on NO levels in plasma (a) and brain (b) of rats. Data are shown as mean of four replicates ± SEM. β signifies $p < 0.01$, and γ signifies $p < 0.001$ versus control.

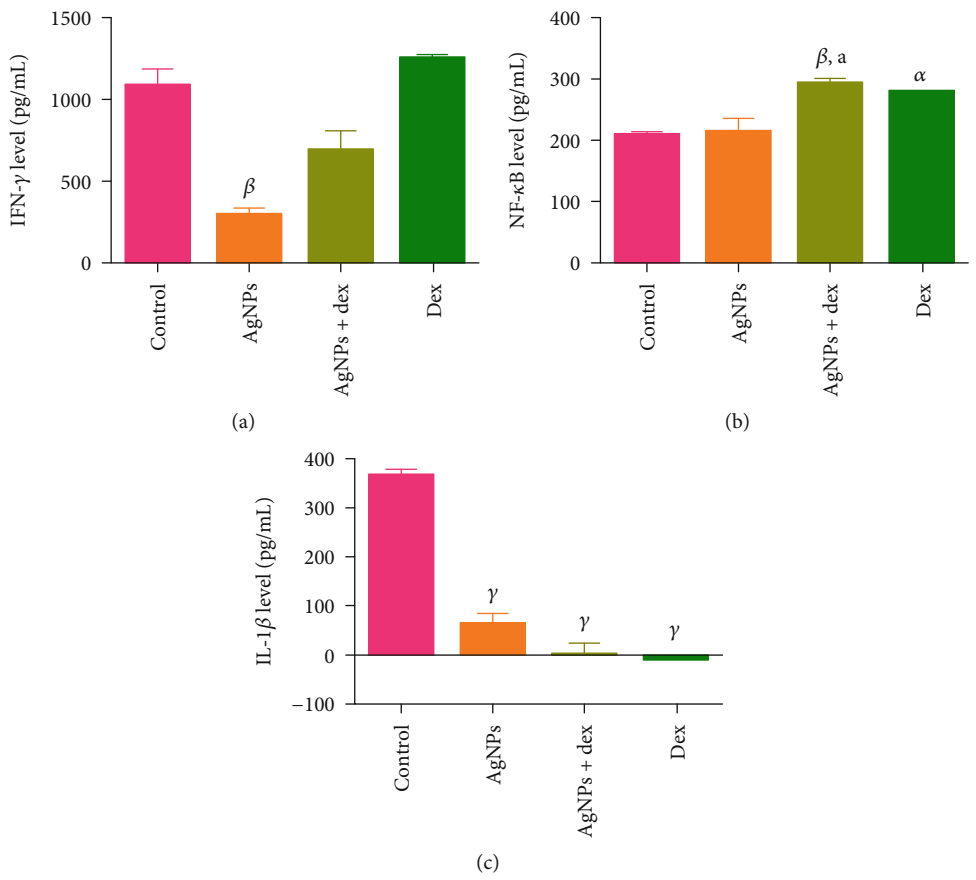

Figure 7: Effects of AgNPs and dexamethasone on IFN-γ (a), NF-κB (b), and IL1β (c) levels in rat plasma. Data are shown as mean of four replicates ± SEM. α signifies $p < 0.05$, β signifies $p < 0.01$, and γ signifies $p < 0.001$ versus control. a signifies $p < 0.05$ versus AgNPs.

upregulation of genes important for inflammatory responses [30]. The kynurenine pathway is upregulated by proinflammatory cytokines such as NF-κB, and also the NF-κB is a potent activator of IDO-1, suggesting that NF-κB may increase kynurenine levels [31]. In the present study, AgNPs did not alter NF-κB level differently from the control but DEX might have potentiated the effect of AgNPs on NF-κB causing an increase in the level of the cytokine. Nevertheless, there was no corresponding increase in rat brain and plasma kynurenine level, and therefore, no clear role could be ascribed to NF-κB in the present study.

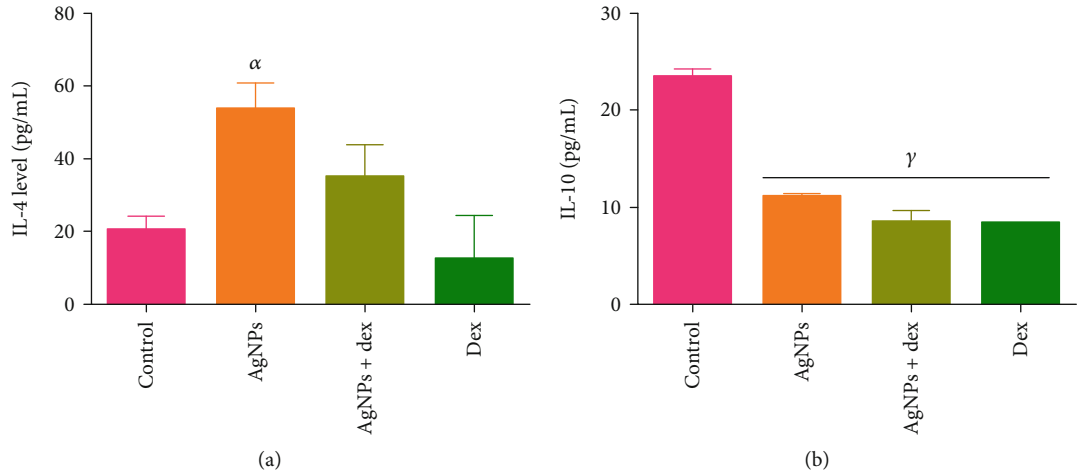

Figure 8: Effects of AgNPs and dexamethasone on anti-inflammatory cytokines IL-4 (a), and IL-10 (b) levels in rat plasma. Data are shown as mean of four replicates ± SEM. α signifies $p < 0.05$, β signifies $p < 0.05$, γ signifies $p < 0.001$ versus control.

Furthermore, reports have shown that IL-4 downregulates IDO expression by opposing IFN-γ [32]; IL-4 is known to inhibit the production of proinflammatory molecules that are normally induced as a result of the action of IFN-γ or together with other stimulants of inflammation. IL-4 inhibits the production of reactive oxygen species intermediate; thus, it opposes the activation of macrophages, consequently, and IL-4 controls levels of tissue damage during immune responses [33]. In the present study, AgNP exposure led to an increased level of IL-4 suggesting an anti-inflammatory potential. AgNPs significantly increased IL-4 level in rats administered AgNP only, but when coadministered with dexamethasone, IL-4 level was nonsignificantly decreased. In contrast, treatments with AgNPs, DEX, or Ag + DEX led to a decreased level of IL-10 in rat plasma. Although increased expression of IL-10 has been shown to suppress the activation of the kynurenine pathway [34], in the present study, however, the administration of AgNPs singly or in combination with DEX led to a lower level of IL-10 compared with the control. Considered together, it could be inferred from the results of the present study that AgNPs at the dose investigated showed a differential immunomodulatory potential, lowering the level of proinflammatory cytokines, while raising the level of anti-inflammatory cytokines.

5. Conclusions

In conclusion, our data suggest that AgNPs activated the kynurenine pathway in the rat brain but not by oxidative stress, and the elevation was not modulated by cotreatment with dexamethasone. Furthermore, AgNPs demonstrated a differential immunomodulatory potential in rats.

Data Availability

Data availability is available on request.

Conflicts of Interest

The authors declare that there is no conflict of interest.

Authors' Contributions

Conceptualization was done by OSA and DER; data collection was done by OSA, LBA, DER, DSO, TO, DOO, and TPO; formal analysis was done by OSA, LBA, DER, FA, DSO, TO, DOO, and TPO; investigation was done by OSA; methodology was done by OSA; writing—original draft was done by OSA, LBA, DER, FA, DSO, TO, DOO, TPO, AY, GMH, and GEB; writing—review and editing was done by OSA, LBA, DER, FA, DSO, TO, DOO, TPO, AY, GMH, and GEB. All authors have read and agreed to the final version of the manuscript.

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