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ANTI-NEUROINFLAMMATORY AND NEUROPROTECTIVE EFFICACY OF N-(2-HYDROXY PHENYL) ACETAMIDE IN RESPONSE TO LPS-STIMULATED PRIMARY CELL CULTURE

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Abstract

The irreversible and continuing loss of neurons is the fundamental cause of neurodegenerative diseases (ND). The most common age-associated neurodegenerative condition is Alzheimer's disease (AD), and its etiology appears to have a chronic inflammatory component. The stimulation, proliferation, phenotypic and functional modifications in glia can be brought on by a variety of stresses in the central nervous system (CNS), and these modifications are modulated by anti-neuroinflammatory substances. This study evaluated the anti-neuroinflammatory and pro-neurogenic effects of N-(2-hydroxy phenyl) acetamide (NA-2) in primary neuronal and glial co-cultures using in vitro model of neuroinflammation associated with neurodegenerative disorders. Neurons and glial cells were co-cultured from the pup's brain of wistar rats. In primary neuronal/glial co-culture, the MTT assay was performed to assess the pro-neurogenic and anti-neuroinflammatory properties of test compound. The proportion of viable cells were increased at 50µM dose of NA-2 as compared to the untreated control, which shows its proneurogenic potential at low dose. Lipopolysaccharide (LPS) was used to induce the neuroinflammatory response. It was observed that treatment group at 50µM of NA-2 followed by LPS stimulation demonstrated anti-neuroinflammatory potential when compared to the LPS treated cells. Furthermore, it reduces oxidative stress induced by H_2O_2 and significantly inhibits the generation of ROS. These results demonstrated that NA-2 possesses anti-neuroinflammatory and neuroprotective properties in in-vitro model of neuroinflammation and could potentially be an important neuroimmunomodulatory compound in the management of neurodegenerative disorders.

Keywords: Anti-neuroinflammatory, Lipopolysaccharide (LPS), MTT, neuroinflammation, N-(2-hydroxy phenyl) acetamide, NA-2, Neurons

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1. INTRODUCTION

The prevalence of age-related neurodegenerative diseases has increased as the population gets older, and represent a serious public health concern. These disorders are associated with a progressive loss of neurons with age [1], and scientific evidence suggests that the main cause of neurodegeneration, is an augmented inflammatory response [2]. Neuroinflammation, which is mainly attributed to the release of various inflammatory mediators as a result of the stimulation of microglia and astrocytes, is the condition that initiates a number of neurodegenerative conditions, including Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) [3,4]. The resident immune cells of the central nervous system, known as microglia [5], are considered to constitute up the majority of the immune system in the brain [6]. Microglia are subjected to morphological changes and produce a variety of toxic mediators during neuroinflammation, including nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), reactive oxygen species (ROS), prostaglandin E2, interleukin-1(IL-1) and various other; the increased levels of these inflammatory mediators are toxic to neurons which initiates a vicious cycle of neuronal cell death [7]. Therefore, using LPS to stimulate microglia and induce neuro-inflammation, is an effective approach for investigating potential therapeutic agents to slow the degeneration of neurons in neurodegenerative diseases. The production of pro-inflammatory mediators increases substantially by LPS. The onset and course of neurodegenerative ailments would be accelerated by an ongoing escalation of this unmanaged inflammation and oxidative stress [8,9].

Targeting neuroinflammation may be a possible therapeutic approach for AD or various other neurodegenerative conditions, according to an epidemiology data that suggests using non-steroidal anti-inflammatory medicines may be able to reduce the chance of getting AD. The evidence indicates a potential reduction in the risk of AD in cognitively normal individuals consuming long-term treatments of NSAIDs for other medical reasons [10].

N-(2-hydroxy phenyl) acetamide (NA-2), a Salicylic acid derivative, belong to NSAIDs group, was preferred for our experiment since previous literature has shown that it has anti-inflammatory properties [11,12]. To date, no previous study has been conducted to show anti-neuroinflammatory potential of NA-2. The objective of our research is to find out whether NA-2 has pro-neurogenic, anti-neuroinflammatory and anti-oxidative potential. Since it is evident that neuroinflammation plays a significant role in the pathogenesis of neurodegenerative disorders, there is an urgent need for new treatments or medications that target this condition and NA-2 could possibly be a potential candidate.

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2. MATERIALS AND METHODS

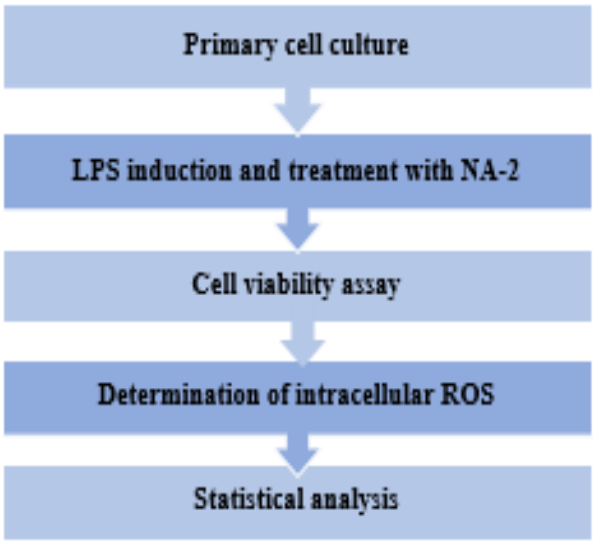

Figure 1: Schematic representation of research methodology used in this study.

2.1. Primary cell culture.

Wistar rat's pups two days old were collected, brains were dissected, and the blood vessels and meninges were removed. Isolated cerebral cortices were minced and digested with the help of 0.25 percent trypsin-EDTA. Afterwards minced tissues were placed in a serum free culture medium (Dulbecco's modified Eagle medium [DMEM] with 10% Fetal bovine serum [FBS]). Isolated cortical mixed neuronal glial cells were cultured in 75cm^2 flasks at 75,000 viable cells/ml culture medium; then, the culture flasks were incubated at 37 °C with 5% CO2V [13]. The stock solution of test compound was prepared in DMSO at concentration of 500µg/ml. Freshly prepared stock solutions were used for all the experiments conducted. The compound was finally diluted in PBS (Phosphate buffer saline). The experiment was accomplished in conformity with the International Standards for the Use and Care of Laboratory Animals set by National Institute of Health (US). Experiment was approved by Animal Ethics Committee (AEC) of Ziauddin University, Karachi, Pakistan.

2.2. LPS Induction and pre-treatment with NA-2

For activation of cell culture with LPS (Lipopolysaccharides), the cultured cells were seeded in 96-well plates for 24 hours, Next day (or after 24 h) the confluent cells were pretreated with various doses of test compounds for 2h and later on incubated in the absence and presence of LPS (10 µg/ml) for 24h. Next day or after 24h, the cell viability assay was performed as described in section 2.3 [14]. LPS-stimulated and without LPS-stimulated cells represent positive and negative controls, respectively. Stock solution of LPS were prepared by dissolving LPS in PBS (Phosphate-buffered saline) at a concentration of 1 mg/mL.

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2.3. Cell viability assay

Cytotoxicity of test compounds on cell cultures were detected by [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] MTT assay (sigma, USA). After 24h of incubation with different concentrations of NA-2 and LPS, the supernatants were collected and stored at -80 °C (as described in section 2.2) for further experimentation (if needed) and the cells in 96 well plate were incubated with 0.5 mg/ml MTT in phosphate-buffered saline (PBS) for 2 hours. Later on, dye was removed and resoluted with 150µL of DMSO (Dimethyl sulfoxide). The purple formazan crystals were detected for the absorbance at 570 nm on spectrophotometer (Multiskan SkyHigh microplate reader, Thermoscientific) [14]. Viable cells were expressed as percentage of control, represented by untreated group, which were set at 100%.

2.4. Determination of Intracellular ROS

The ROS concentration were estimated by placing cultured cells with 10µM of DCFH-DA (2,7-dichlorofluorescein diacetate) for 30 minutes at 37°C in phenol red-free DMEM. Afterwards, DCFH-DA was removed from wells and cells were treated for 1 hour with test compounds in phenol red–free DMEM in the existence of H_2O_2 at the absolute concentration of 100 µM. H_2O_2 treated cultured cells or DCFH-DA treated cultured cells denoted the positive (H_2O_2) and negative controls, respectively. Cells were rinsed with PBS after incubation and fluorescence was measured at 495nm and 525nm as excitation and emission wavelength using fluorescence spectrophotometer.

2.5. Statistical analysis

The statistical package for social science (SPSS) version 20 was used for data analysis. The results of tests were expressed as mean ± SEM at 95% confidence interval. Statistical analysis was done by using ANOVA (One-way analysis of variance) followed by post hoc Tukey's test. p value less than 0.05 was considered significant.

3. RESULTS

3.1. Pro-neurogenic effect of NA-2 on primary cell culture

The cell viability of NA-2 was determined at concentration of 50µM and 100µM using MTT assay. The number of viable cells were slightly decreased at concentration of 100µM and did not show any significant results as compared to untreated control ($p>0.05$). However, at low concentration (50µM), the proportion of viable cells were increased ($p<0.001$) as compared to untreated control which displayed pro-neurogenic potential (Figure 2).

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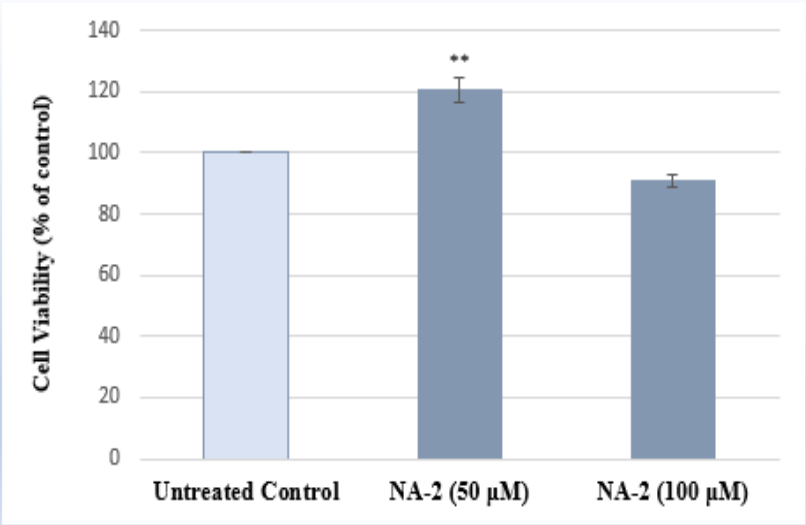

Figure 2: Percent cell viability of NA-2 in primary mixed cortical/glial cell culture. Cells were treated with 50µM and 100µM of NA-2 for 24 h. Values are expressed as mean ± SEM of three separate experiments. **, p < 0.005 vs. Untreated control cells.

3.2. Anti-neuroinflammatory effect of NA-2 on cell viability against LPS stimulation

The anti-neuroinflammatory effect of NA-2 was determined at concentration of 50µM and 100µM against LPS activated cells. The cortical/glial mixed cells were pretreated with different concentrations of NA-2 for two hours. Later on, all groups were exposed to LPS (10µg/ml) and re-incubated for 24 hours. In LPS treated cells, the initial cell population was diminished up to 20 percent which showed significant results ($p<0.05$) as compared to untreated control group. While pretreatment with NA-2 at 100µM did not show any effect on proportion of viable cells compared to LPS treated cells ($p>0.5$). However, our test compound showed promising results at concentration of 50µM and significantly increased the viability of cells ($p<0.001$) as compared to LPS treated cells. In the presence of LPS, the number of viable cells was exceptionally increased at 50µM which indicate the anti-neuroinflammatory potential of NA-2 against LPS stimulated cortical/glial cell culture (Figure 3).

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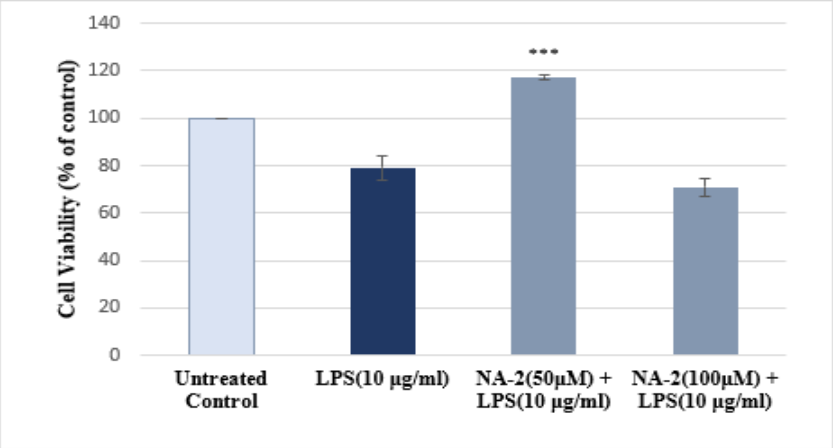

Figure 3: Anti-neuroinflammatory effect of NA-2 in LPS stimulated primary mixed cortical/glial cell culture. Cells were Pretreated with 50µM and 100µM of NA-2 for 2 h later on stimulated with LPS 10 µg/ml for 24 h. Values are expressed as mean ± SEM of three separate experiments. ***, p < 0.001 vs. LPS treated cells.

3.3. Anti-oxidative potential of NA-2

The anti-oxidative effect of NA-2 was determined by using DCFH-DA dye. The ROS production was estimated at concentration of 50µM and 100µM of NA-2. The primary cell culture was pretreated with DCFH-DA for 30 minutes followed by treatment with different concentrations of NA-2 for 1h then exposed with H_2O_2. The H_2O_2 positive cells showed enhanced ROS production as compared to the control; While, pretreatment of cells with NA-2 reduced the production of ROS at all concentration and showed significant results in comparison with LPS ($p< 0.001$) (Figure 4).

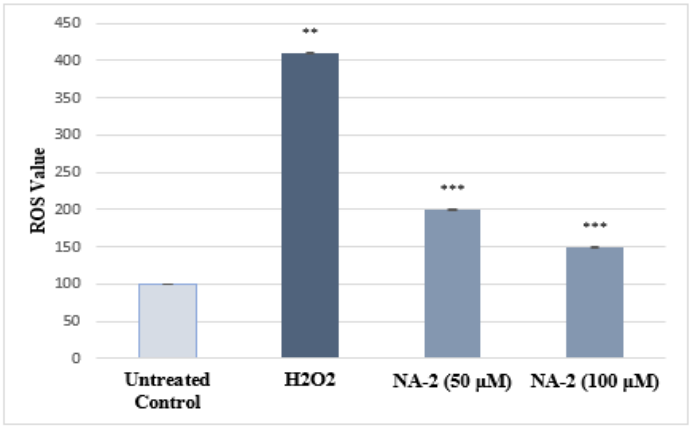

Figure 4: Anti-oxidative effect of NA-2 in primary mixed cortical/glial cell culture. Cells were pretreated with DCFH-DA for 30 minutes followed by treatment with 50µM and 100µM of NA-2 for 1h in the presence of H_2O_2. Values are expressed as mean ± SEM of three separate experiments. *** $p< 0.001$ vs. H_2O_2; **, $p< 0.001$ vs. untreated control.

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4. DISCUSSION

According to earlier research, neurodegenerative illnesses primarily affect the elderly population and are attributed to continuous neuroinflammation [15,16,17]. The most significant brain cell, microglia, is responsible for the initiation and progression of chronic inflammation in the central nervous system. Suppression of reactive microglia may have a significant therapeutic impact on a variety of neurodegenerative diseases. Various evidences suggests that neuroinflammatory pathways as contributing to the development of neurodegenerative conditions including Parkinson's and Alzheimer's. Additionally, in animal models of dementia, extensive inflammatory mechanisms, such as the stimulation of microglia and astrocytes, have been observed [18]. The endotoxin theory of neurodegeneration has been studied in this aspect previously. The blood and CNS cells of Alzheimer's patients have greater LPS concentrations, and having more of these endotoxins induces degeneration of neurons followed by neuroinflammation [19].

The aberrant expression and release of pro-inflammatory cytokines by microglia, which can be generated by LPS, contributes to neuroinflammation and the progression of neurological conditions. If abnormal responses generated by microglia are suppressed, neurodegenerative disorders may be minimized [20]. The increased expression of IL-6, TNF-α, PGE2, and IL-1β in the central nervous system may trigger and intensify an inflammatory response [21].

To understand the mechanism causing neuronal death and to find better treatment targeting neuro-inflammation-related neurodegenerative disorders, numerous preclinical studies in the CNS have been carried out. We highlighted the use of neuron and glia co-culture among other in-vitro methods because it has a variety of benefits such as the capacity to produce neuronal phenotypes that effectively interact with glial cells and recreate tissue-like biological sceneries because of its high cell density [22].

Using well-established co-cultures of neurons and glial cells, we assessed the anti-neuroinflammatory and neuroprotective properties of the NA-2 in an inflammatory model generated by LPS in this study. NA-2 demonstrated improved cell viability at low dose in the MTT assay in the absence of LPS, demonstrating its potential for regeneration or neurogenesis, however in the presence of LPS, NA-2 demonstrated neuroprotective effect by reducing cell damage from LPS while improving proliferation. The generation of trophic elements like BDNF, NGF, and GDNF, which can encourage the growth and differentiation of native neurons, may be the mechanism for this response [23,24,25]. The findings demonstrated that our chemical possesses neuroprotective properties and improved neuronal survival at low concentrations.

In primary cell culture, NA-2 showed to possess antioxidant capability against oxidative damage; in fact, at both concentrations, NA-2 was able to prevent the production of ROS when H_2O_2 was present in vitro. The CNS is particularly vulnerable to oxidative stress due to its high oxygen demand and inadequate antioxidant system. It is believed that the generation of ROS and oxidative damage contribute to the development of neurological disorders like Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic

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lateral sclerosis (ALS). ROS are crucial signaling molecules responsible for initiating the CNS inflammatory response cascade. It is well known that ROS cause the activation of pro-inflammatory transcription factors like nuclear factor-κB (NF-κB) to affect the expression of numerous genes associated with neuroinflammation [26,27]. In light of the fact that NA-2 decreased the ROS production in our in vitro experiment, we can infer that NA-2 administration in vivo might result in a more notable reduction in ROS production and might be useful for the prevention and control of various neurodegenerative disorders.

An earlier study using NA-2 demonstrated the effect of decreased IL-1β and TNF-α secretions in model of arthritis, which demonstrated its anti-inflammatory response [11].

Pathological and severe neuronal loss are hallmarks of neurodegenerative disorders, which lead to cognitive decline, dementia, impaired motor function, and ultimately death. Neurodegenerative disorders are becoming a greater economic burden on the world due to their ineffective management and catastrophic nature. We need to find treatments to restore the regeneration potential of neurons in certain neuroinflammatory conditions considering everything we have learned about neuroinflammation and the damage that it causes to the process of neurogenesis [28]. We have to discover more potent and effective compounds to improve the protection of neurons or prevent the onset of neurodegeneration in order to deal with the increasing knowledge of neuroinflammation in a variety of diseases. Advances in the field of neuroprotection during neuroinflammation could improve the quality of life for people with these deadly conditions [28,29].

Recent developments have focused on whether or not lost or injured neurons in chronic inflammation or due to excessive immune response could be replaced by new neurons [28,30]. Due to an increasing aging population global, there are more cases of neurological disorders. Moreover, an increase in chronic inflammatory diseases may be one of the contributing factors. A promising field for future investigation would be the underlying mechanisms of neurodegeneration and neuroinflammation associated with systemic inflammation [28]. Our test compound (NA-2) showed anti-neuroinflammatory and neuroprotective effects against LPS-induced neuroinflammation and suppressed activated microglia at low micromolar dose, however it did not show any significant result at high dose; besides it possesses anti-oxidative potential at both doses used in the study.

5. CONCLUSION

Based on our study, we can derive the following conclusion that in our in-vitro model of neuroinflammation, NA-2 has shown to exhibit anti-neuroinflammatory, neuroprotective and anti-oxidative properties. However, the unique novelty and implication of our study lie in the fact that, as of now, no prior research has been conducted using NA-2 in model of neuroinflammation and we can say that it might represent a possible treatment for neurodegenerative diseases associated with neuroinflammation. We only performed in-vitro experiment; However, further investigation is required in future to establish whether it has an in-vivo anti-neuroinflammatory potential.

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The techniques were performed in MDRL-2, Ziauddin University, Karachi, Pakistan.

Ethical Approval

The animal procedure was performed according to standard ethical guidelines approved by Animal Ethics Committee (AEC) of Ziauddin University, Karachi, Pakistan.

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